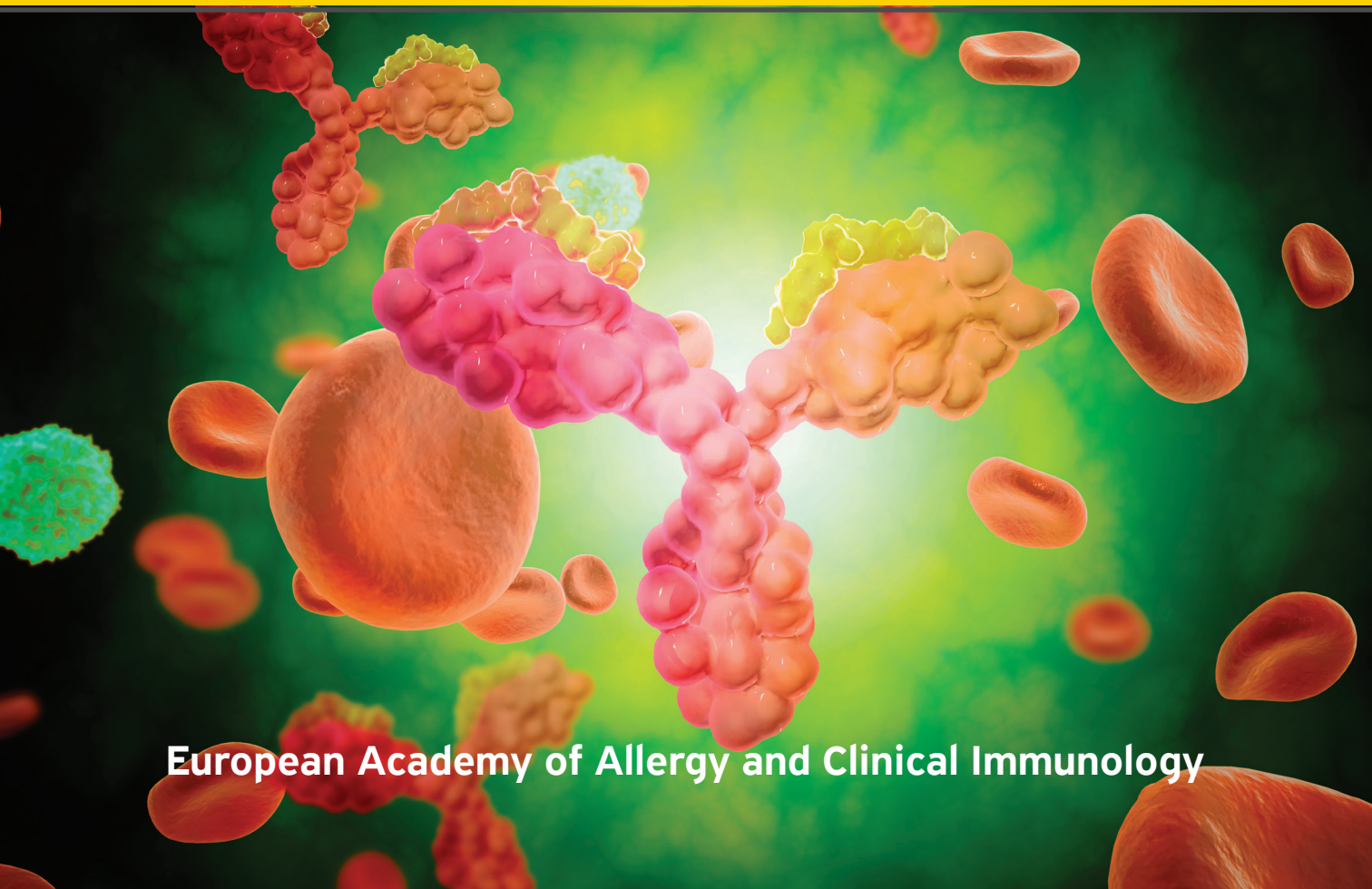
EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Food Allergy and Anaphylaxis Guidelines

Translating knowledge into clinical practice



European Academy of Allergy and Clinical Immunology

EAACI GUIDELINES

Food Allergy and Anaphylaxis

Editors

Antonella Muraro

Graham Roberts

Editorial Board

Ioana Agache

Carsten Bindslev-Jensen

Andy Clark

Anthony Dubois

Susanne Halken

Karin Hoffmann-Sommergruber

Aziz Sheikh

Thomas Werfel

Margitta Worm

EAACI
Hagenholzsltrasse 111
3rd Floor
8050 Zurich
Switzerland

The European Academy of Allergy and Clinical Immunology, EAACI, is a non-profit organisation active in the field of allergic and immunologic diseases such as asthma, rhinitis, eczema, occupational allergy, food and drug allergy and anaphylaxis. EAACI was founded in 1956 in Florence and has become the largest medical association in Europe in the field of allergy and clinical immunology. It includes over 7800 members from 121 countries, as well as 47 National Allergy Societies.

© - European Academy of Allergy and Clinical Immunology (EAACI) 2014
All rights reserved.

To all the members of EAACI
and to our patients

Contents

1 Food allergy: diagnosis and management

3 **The epidemiology of food allergy in Europe**: systematic review and meta-analysis
23 **Prevalence of common food allergies in Europe**: systematic review and meta-analysis
47 **The diagnosis of food allergy**: systematic review and meta-analysis
61 **Acute and long-term management of food allergy**: systematic review
73 **Diagnosis and management of food allergy:** EAACI guidelines

2 Primary prevention of food allergy

119 **Primary prevention of food allergy in children and adults**: systematic review
133 **Primary prevention of food allergy in children and adults**: EAACI guidelines

3 Quality of life in food allergy

153 **Disease-specific health-related quality of life instruments for IgE-mediated food allergy:** systematic review
169 **Food allergy health-related quality of life measures:** EAACI guidelines

4 Anaphylaxis

185 **The epidemiology of anaphylaxis in Europe:** systematic review
197 **Management of anaphylaxis:** systematic review
209 **Anaphylaxis:** EAACI guidelines

5 Community

239 **Managing patients with food allergy in the community:** EAACI guidelines

6 Food industry

259 **Protecting consumers with food allergies:** EAACI guidelines

7 Summary and future perspectives

273 **Summary and future perspectives**

Foreword

Food allergy is affecting the lives of millions of people around the world and is on the rise. The emergency and life-threatening nature of the disease with the burden of anaphylaxis and its increasing prevalence, makes it a major public health problem. Governments and the general public are expected to face increasing direct and indirect costs, due to its major effects on life style and quality of life. Unfortunately, a high number of unmet needs remain to be resolved because of gaps in current scientific knowledge in pathophysiology, preventive measures, standardization and patient care.

To tackle this huge global health problem, the EAACI decided to develop "EAACI Food Allergy and Anaphylaxis Guidelines". We aimed to develop a comprehensive set of documents on food allergy and severe allergic reactions, embracing all stakeholders. Our efforts during the guidelines development enabled us to establish a working model involving all related sections and interest groups of our Academy and helped to develop a network of affiliated scientists, clinicians and patient organizations across the globe.

The guidelines were drafted by more than 70 expert authors from all around the world. All sections of the EAACI, Pediatrics, Immunology, Dermatology, Asthma, Junior Members and Affiliates and Interest Groups of Food Allergy, Allied Health, Allergy Diagnosis, Insect Venom Hypersensitivity, and Primary Care were directly involved in their development. Twenty one international patient organizations were involved from the beginning within the frame of EAACI Patient Organization Committee. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the European Society of Emergency Medicine (EuSEM), and the Association for Teacher Education in Europe (ATEE) were involved as international associations. A panel of 30 international experts has reviewed the Guidelines, which have also gone through public consultation.

We would like to thank all of the authors and organizations for their contributions, the EAACI Executive Committee Members of the last two terms, and particularly Prof. Antonella Muraro for her leadership and commitment. We are certain that this effort, followed by a structured dissemination program will have a major impact on improving the wellbeing of patients with food allergy in Europe and around the world.

Cezmi A. Akdis

EAACI Past President

Nikolaos Papadopoulos

EAACI President

List of contributors

Ioana Agache
Department of Allergy and Clinical Immunology Transylvania University, Brasov, Romania

Cezmi A Akdis
Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Christine Kühne–Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

S Hasan Arshad
Clinical and Experimental Sciences Academic Unit, University of Southampton Faculty of Medicine, Southampton, SO16 6YD, UK; David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK; and NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Barbara K Ballmer-Weber
Allergy Unit, Department of Dermatology, University Hospital, Zürich, Switzerland

Abdelouahab Bellou
European Society for Emergency Medicine and Emergency Department, University Hospital and Faculty of Medicine, Rennes, France

Kirsten Beyer
Division of Paediatric Pneumology and Immunology, Charité University Hospital, Berlin, Germany

M Beatrice Bilò
Allergy Unit, Department of Immunology, Allergy and Respiratory Diseases , University Hospital Ospedali Riuniti, Ancona, Italy

Carsten Bindslev-Jensen
Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark

Luis Miguel Borrego
Centro de Alergia, Hospital CUF Descobertas and Departamento de Imunologia, NOVA Medical School, Lisboa, Portugal

Knut Brockow
Department of Dermatology and Allergy, Biederstein, Technische Universität München, Munich, Germany.

Vicky Cardona
Hospital Vall d'Hebron, Barcelona, Spain

Andrew Clark
Allergy Department, Addenbrookes NHS Foundation Trust, Cambridge, UK

Sangeeta Dhami
Evidence-Based Health Care Ltd, Edinburgh, UK

Nicolette W de Jong
Department of Internal Medicine, Section Allergology, ErasmusMC, Rotterdam, the Netherlands

Pascal Demoly
Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France

Debra de Silva
The Evidence Centre, London, UK

Anthony EJ Dubois
Department of Paediatrics, Division of Paediatric Pulmonology and Paediatric Allergy, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Audrey DunnGalvin
Department of Paediatrics and Child Health, University College, Cork, Ireland

George duToit
King's College London, King's Health Partners, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK and Department of Paediatric Allergy, Guy's and St Thomas' NHS Foundation Trust, London, UK

Philippe Eigenmann
Department of Child and Adolescent, University Hospitals of Geneva, Geneva, Switzerland

Maria Fernandez Rivas
Allergy Department, Hospital Clinico San Carlos, Madrid, Spain

Bertine MJ Flokstra-de Blok
GRIAC Research Institute and Department of General Practice, University of Groningen, University Medical Center, Groningen, the Netherlands

Matthew Geromi
The Evidence Centre, London, UK

M Hazel Gowland
Allergy Action, St Albans, UK

Kate EC Grimshaw
Clinical and Experimental Sciences Academic Unit, University of Southampton Faculty of Medicine, Southampton, UK

Susanne Halken
Odense University Hospital, Odense C, Denmark

Laurie Harada
Anaphylaxis Canada

Lennart Hickstein
Institute for Medical Informatics, Biometry and Epidemiology, University of Munich, Germany

Jennette Higgs
Health Education Trust, Greens Norton, Northamptonshire, UK

Karin Hoffmann-Sommergruber
Department of Pathophysiology and Allergy Research Medical University of Vienna, Vienna, Austria

Thomas Holzhauser
Division of Allergology, Paul-Ehrlich Institute, Langen, Germany

Arne Høst
Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense,Denmark

Jonathan O'B Hourihane
Department of Paediatrics and Child Health, University College, Cork, Ireland

Sundas Javad
School of Public Health, Imperial College London, London, UK

Penny Jorgensen
Allergy, Auckland, New Zealand

Marek Jutel
Wroclaw Medical University, Wroclaw, Poland

Edward Knol
Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

Gideon Lack
King's College London, King's Health Partners, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK and Department of Paediatric Allergy, Guy's and St Thomas' NHS Foundation Trust, London, UK

Mary J Marchisotto
Food Allergy and Anaphylaxis Research and Education-FARE

Angel Mazon
Pediatric Allergy and Pneumology Unit. Children's Hospital La Fe. Instituto de Investigacion Sanitaria La Fe, Valencia, Spain

Clare Mills
Institute of Inflammation and Repair, Manchester Academic Health Science Centre, Manchester Institute of Biotechnology, University of Manchester, Manchester, UK

Antonella Muraro
Department of Mother and Child Health Referral Centre Food Allergy Diagnosis and Treatment, Veneto Region, University of Padua, Padua, Italy

Bodo Niggemann
Division of Paediatric Pneumology and Immunology, Charité University Hospital, Berlin, Germany

Caroline Nilsson
Department of Clinical Science and Education, Södersjukhuset, KarolinskaInstitutet and Sachs' Children's Hospital, Stockholm, Sweden

Bright I Nwaru
School of Health Sciences, University of Tampere, Tampere, Finland

Liam O'Mahony
Swiss Institute of Allergy and Asthma Research, University of Zurich, Zurich, Switzerland

H van Os-Medendorp
UMC Utrecht, Department of Dermatology &Allergology, Utrecht, the Netherlands

Sukhmeet S Panesar
Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, UK

Nikos G Papadopoulos
Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece and Centre for Pediatrics and Child Health Institute of Human Development, The University of Manchester, Manchester, UK

Davide Parmigiani
Association for Teacher Education in Europe, Bruxelles, Belgium and Department of Education, University of Genoa, Genoa, Italy

Shyamal Patel
St. George's University, London, UK

Lars K Poulsen
Laboratory of Medical Allergology, Allergy Clinic, Copenhagen University Hospital, Hellerup, Denmark

Susan Prescott
University of Western Australia, Perth, Australia

Lynne Regent
The Anaphylaxis Campaign, Farnborough, Hampshire, UK

Graham Roberts
David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK; NIHR Southampton Respiratory Biomedical Research Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, UK and Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, UK

Franziska Rueff
Department of Dermatology and Allergy, Ludwig-Maximilian University, Munich, Germany

Maria Said
Allergy & Anaphylaxis Australia, Hornsby, New South Wales, Australia

Sarah A Salvilla
Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK

Alexandra F Santos
Department of Pediatric Allergy, Division of Asthma, Allergy & Lung Biology, King's College London, UK; King's College London, King's Health Partners, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK; and Immunoallergology Department, Coimbra University Hospital, Coimbra, Portugal

Sabine Schnadt
Deutscher Allergie- und Asthmabund e.V., Mönchengladbach, Germany

Alain Schoepfer
Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Aziz Sheikh
Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, UK; Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Isabela Skypala
Department of Rehabilitation and Therapies, Royal Brompton and Harefield NHS Foundation Trust, London, UK

Karla Soares-Weiser
Enhance Reviews Ltd, Wantage, UK

Yemisi Takwoingi
Public Health, Epidemiology and Biostatistics, School of Health and Population Sciences, University of Birmingham, Birmingham, UK

Frans Timmermans
Nederlands Anafylaxis Netwerk – European Anaphylaxis Taskforce, Dordrecht, the Netherlands

Berber J Vlieg–Boerstra
Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, The Netherlands

Ronald van Ree
Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, The Netherlands

Carina Venter
David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK and University of Portsmouth, Portsmouth, UK

Valerie Verhasselt
Université de Nice Sophia-Antipolis EA 6302 "Tolérance Immunitaire", Hôpital de l'Archet, Nice, France

Stefan Vieths
Division of Allergology, Paul-Ehrlich Institute, Langen, Germany

Thomas Werfel
Hannover Medical School, Hanover, Germany

Magnus Wickman
Institute of Environmental Medicine, KarolinskaInstitutet, Stockholm, Sweden; Department of Pediatrics, Sachs' Children's Hospital, Stockholm, Sweden; and Centre for Allergy Research, KarolinskaInstitutet, Stockholm, Sweden

Margitta Worm
Division of Paediatric Pneumology and Immunology, Charité University Hospital, Berlin, Germany

Allison Worth
Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK

Zaraquiza Zolkipli
David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, United Kingdom; NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK and Clinical Experimental Sciences Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK

Abbreviations

AAI	Adrenaline Auto-injector
ACE inhibitor	Angiotensin Converting Enzyme Inhibitor
AGREE II	Appraisal of Guidelines for REsearch & Evaluation
APT	Atopy Patch Test
AQLQ	Asthma Quality of Life Questionnaire
BAT	Basophil Activation Test
BCG vaccine	Bacillus Calmette–Guérin vaccine
BoT	Burden of Treatment
BP	Blood Pressure
CASP	Critical Appraisal Skills Programme
CBT	Cognitive Behavioural Therapy
CCC	Concordance Correlation Coefficient
CI	Confidence Interval
CRD	Component Resolved Diagnosis
DALY	Disability Adjusted Life Years
DBPCFC	Double-Blind, Placebo-Controlled Food Challenge
EAACI	European Academy of Allergy and Clinical Immunology
ED	Emergency Departments
EIA	Exercise-Induced Anaphylaxis
EoE	Eosinophilic Esophagitis
FA	Food Allergy
FAIM	Food Allergy Independent Measure
FAQL-PB	Food Allergy Quality of Life Parental Burden
FAQLQ –PF	Food Allergy Quality of Life Questionnaire Parent Form
FAQLQ-AF	Food Allergy Quality of Life Questionnaire Adult Form
FAQLQ-CF	Food Allergy Quality of Life Questionnaire Child Form
FAQLQ-PF	Food Allergy Quality of Life Questionnaire Parental Form
FAQLQ-TF	Food Allergy Quality of Life Questionnaire Teenager Form
FAQL-teen	Food Allergy Quality of Life Assessment Tool for Adolescents
FDEIA	Food-Dependent, Exercise-Induced Anaphylaxis
FIR	Food Information Regulation 1169/2011 EC
FPIES	Food Protein-Induced Enterocolitis Syndrome
GERD	Gastro-Esophageal Reflux Disease
GMP	Good Manufacturing Practice
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQL	Health-Related Quality of Life
HRQLQ	Health-Related Quality of Life Questionnaire
ICC	Intraclass Coefficient
ICD	International Classification of Diseases codes
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IM	Independent Measure
LR	Likelihood Ratio
LTP	Lipid Transfer Proteins
MCID	Minimal Clinically Important Difference
MID	Minimal Important Difference
NIAID	National Institute of Allergy and Infectious Diseases
NNT	Number Needed to Treat
NPV	Negative Predictive Value
NSAID	Non Steroidal Anti-Inflammatory Drugs
OAS	Oral Allergy Syndrome
OFC	Oral Food Challenge
PCP	Personalized Care Plan
PEF	Peak Expiratory Flow
PEMP	Personalized Emergency Management Plan
PFA-QL	Paediatric Food Allergy Quality of Life Questionnaire
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-Adjusted Life Years
QOL	Quality of life
RCT	Randomised Controlled Trial
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
sIgE	Specific Immunoglobulin- E
SLIT	Sublingual Immunotherapy
SPT	Skin Prick Test
UK	United Kingdom
US	United States
VIT	Hymenoptera Venom Immunotherapy

Preface

The lack of public understanding of food allergy is hugely affecting the recognition of the disease and of its impact at the community level including the quality of life and costs issues. In addition, very few people are aware that a severe allergic reaction, such as anaphylaxis, can result in death. As a consequence, anaphylaxis is still frequently mismanaged, both by patients and healthcare professionals. There is a need for better education of health professionals and the public. As part of its Mission, the European Academy of Allergy and Clinical Immunology (EAACI) initiated a project on food allergy and anaphylaxis in 2012 which combined a public campaign with the development of scientific outputs and guidelines, intended to translate best science into best practice. The EAACI Food Allergy and Anaphylaxis Guidelines are devoted to improving the overall care of the patient suffering from food allergy and anaphylyaxis. The aim has been to provide scientific update on the latest evidence in the field establishing a platform where all the stakeholders can share their knowledge and ultimately create links and networks around the patients and their families.

The EAACI Food Allergy and Anaphylaxis Guidelines group has undertaken this unprecedented project over the last 2 years. Within the group, six task forces have comprehensively reviewed food allergy and anaphylaxis in children, adolescents and adults. The activity has been grounded in evidence with the use of comprehensive systematic reviews and, where appropriate, meta-analyses of the literature. The work was carried out by a wide range of health care professionals and scientists along with the involvement of both patient groups and regulators.

This book represents a compilation of the output of the EAACI Food Allergy and Anaphylaxis Guidelines Group. The first section covers food allergy. It is based on three systematic reviews covering the epidemiology, the diagnosis and the management of food allergy; these are presented in four chapters (1.1, 1.2., 1.3, 1.4) that summarise the evidence in these areas. These data have been used to generate the food allergy diagnosis and management guidelines (Chapter 1.5). The second section focuses on prevention. A systematic review of the food allergy prevention literature (Chapter 2.1) was used to develop evidence based prevention guidelines for food allergy (Chapter 2.2). The third section focuses on quality of life in food allergy. A systematic review of the literature (Chapter 3.1) looked for food allergy quality of life instruments that were appropriately developed and validated. These data were used to generate food allergy quality of life guidelines (Chapter 3.2). The fourth section focuses on anaphylaxis. It is imbedded within two systematic reviews of the literature, the first focuses on the epidemiology (Chapter 4.1) and the second on the management of anaphylaxis (Chapter 4.2). These data were then combined to generate guidelines for anaphylaxis (Chapter 4.3). Section 5 focuses on the community where many reactions to foods take place. The last section focuses on the food industry and how it might help to reduce the burden associated with food allergy and anaphylaxis. Each of the sections also looks forward, highlighting which research gaps should be prioritised and what public health interventions are required to minimise the burden of food allergy and anaphylaxis.

All the chapters in this book represent manuscripts that have been published in the journal Allergy. Wiley has kindly given permission to reproduce these in this book. Supplementary material associated with each of the guidelines chapters can be found as appendices at the end of each chapter. The supplementary material for the other chapters is available online via the EAACI website.

This book represents the work of over 70 individuals The EAACI food allergy and anaphylaxis guidelines would not have been possible without their hard work and dedication to this activity. We would particularly like to thank the steering group leads: Ioana Agache, Carsten Bindslev-Jensen, Vicky Cardona, Anthony Dubois, Susanne Halken, Karin Hoffmann-Sommergruber, Lars Poulsen, and Thomas Werfel who ensured that the guidelines remained on track during

their development. We are hugely indebted to Aziz Sheik for leading the methodology team who were fundamental to synthesising the evidence base for this project. We would particularly like to thank Sukhmeet Panesar who project managed this element of the project. We thank all the experts, who kindly reviewed the draft manuscripts and helped us to develop them into the final documents reproduced in this book, and the patient's group representatives who were heavily involved in developing each of the chapters; they are listed at the beginning of each chapter.

We are also very grateful for all the EAACI members who responded to our call for comments about the draft documents in June 2013. The guidelines group are extremely appreciative of the support of our past President Cezmi Akdis and our current President Nikos Papadopoulos for this activity, as well as for the support of all the other Executive Committee members. We would like to thank the EAACI Headquarters staff for their support of this project. Finally we would also like to express our appreciation of our personal assistants, Lynn Reeves in Southampton and Catherine Crowley in Padua.

It has been an exciting journey. However, having scientifically robust and thoroughly researched guidelines is just the beginning; it is their application in health professionals' daily work that will make a real and tangible difference to clinicians and their patients.

Antonella Muraro and Graham Roberts

Editors

SECTION 1

FOOD ALLERGY DIAGNOSIS AND MANAGEMENT

1.1

THE EPIDEMIOLOGY OF FOOD ALLERGY IN EUROPE

SYSTEMATIC REVIEW AND META-ANALYSIS

BI Nwaru[1], L Hickstein[2], SS Panesar[3], A Muraro[4], T Werfel[5], V Cardona[6], AEJ Dubois[7], S Halken[8], K Hoffmann-Sommergruber[9], LK Poulsen[10], G Roberts[11-13], R Van Ree[14], BJ Vlieg–Boerstra[15], A Sheikh[3, 16] on behalf of The EAACI Food Allergy & Anaphylaxis Guidelines Group

EAACI Food Allergy & Anaphylaxis Guidelines Group: CA Akdis, R Alvarez, K Beyer, C Bindslev-Jensen, V Cardona, P Demoly, A Dubois, P Eigenmann, M Fernandez Rivas, A Host, E Knol, G Lack, MJ Marchisotto, B Niggeman, N Papadopolous, I Skypala, M Worm

AFFILIATIONS

[1] School of Health Sciences, University of Tampere, Finland

[2] Institute for Medical Informatics, Biometry and Epidemiology, University of Munich, Germany

[3] Allergy & Respiratory Research Group, Center for Population Health Sciences, The University of Edinburgh, UK

[4] Department of Pediatrics, Center for Food Allergy Diagnosis and Treatment, Veneto Region, University of Padua, Italy

[5] Hannover Medical School, Hanover, Germany

[6] Hospital Valld'Hebron, Barcelona, Spain

[7] Department of Paediatrics, Division of Paediatric Pulmonology and Paediatric Allergy, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[8] Odense University Hospital, Odense C, Denmark

[9] Department of Pathophysciology and Allergy Research Medical University of Vienna, Vienna, Austria

[10] Laboratory of Medical Allergology, Allergy Clinic, Copenhagen University Hospital, Hellerup, Denmark

[11] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[12] NIHR Southampton Respiratory Biomedical Research Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, UK

[13] Human Development and Health and Clinical and Experimental Sciences Academic Units, Faculty of Medicine, University of Southampton, UK

[14] Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, The Netherlands

[15] Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, The Netherlands

[16] Division of General Internal Medicine and Primary Care Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA

***Background**: Food allergy (FA) is an important atopic disease although its precise burden is unclear. This systematic review aimed to provide recent, up-to-date data on the incidence, prevalence, time-trends, and risk and prognostic factors for FA in Europe.*

***Methods**: We searched four electronic databases, covering studies published from January 1, 2000 to September 30, 2012. Two independent reviewers appraised the studies and qualified the risk of bias using the Critical Appraisal Skills Programme tool.*

***Results**: Seventy-five eligible articles (comprising of 56 primary studies) were included in a narrative synthesis and 30 studies in a random-effects meta-analysis. Most of the studies were graded as at moderate risk of bias. The pooled lifetime and point prevalence of self-reported FA were 17.3% (95% CI 17.0-17.6) and 5.9% (95% CI 5.7-6.1), respectively. The point prevalence of sensitization to ≥ 1 food as assessed by specific-IgE was 10.1% (95% CI 9.4-10.8) and skin prick test 2.7% (95% CI 2.4-3.0), food challenge positivity 0.9% (95% CI 0.8-1.1). While the incidence of FA appeared stable over time, there was some evidence that the prevalence may be increasing. There were no consistent risk or prognostic factors for the development or resolution of FA identified, but sex, age, country of residence, familial atopic history, and the presence of other allergic diseases seem to be important.*

***Conclusions**: Food allergy is a significant clinical problem in Europe. The evidence base in this area would benefit from additional studies using standardized, rigorous methodology; data are particularly required from Eastern and Southern Europe.*

Originally published as: Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, Dubois AEJ, Halken S, Hoffmann-Sommergruber K, Poulsen LK, Roberts G, Van Ree R, Vlieg-Boerstra BJ, Sheikh A. on behalf of The EAACI Food Allergy & Anaphylaxis Guidelines Group. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014;69:62–75. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

During the past 50-60 years, the frequency of asthma and other atopic diseases, such as atopic eczema/dermatitis and allergic rhinitis, has increased in many Western countries. They now represent a substantial burden to healthcare systems and the society (1-5). Whilst the incidence of these diseases may have peaked in some settings (3), it has been suggested that the frequency of food allergy (FA) appears to have increased during the last 10-20 years (6-10), leading to the thought that FA may have different risk factors (6, 8).

Despite the suggested increasing frequency of FA and the attributed public health burdens (6-10), estimates of the actual incidence and prevalence are uncertain. Relatively few epidemiological studies have utilized the gold standard of diagnosis – the double-blind, placebo-controlled food challenge (DBPCFC) in defining FA (6, 8). Most frequency estimates have been based on lay perceptions or specific Immunoglobulin E (IgE) or skin prick test (SPT) sensitization to common food allergens. Both self-perception and allergic sensitization are known to substantially overestimate the actual frequency of FA (11-13).

This systematic review is one of seven inter-linked evidence syntheses that have been undertaken to provide a state-of-the-art European synopsis of the current evidence base in relation to epidemiology, prevention, diagnosis and clinical management, and impact on quality of life. They have been used to inform clinical recommendations in the *EAACI Guidelines for Food Allergy and Anaphylaxis*. The aims of the systematic review were to: (1) estimate the frequency of FA; (2) investigate time-trends; and (3) identify potential risk and prognostic factors for the development of FA in Europe.

Methods

Protocol and registration

The protocol of this review has been published previously (14) and it is registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/prospero/, reference CRD42013003704).

Search strategy

A highly sensitive search strategy was designed (see Box E1) to retrieve all articles combining the concepts of food allergy and epidemiology from electronic bibliographic databases. See online supplement for further details.

Inclusion and exclusion criteria

The following studies were included: systematic reviews and meta-analyses, cohort studies, cross-sectional studies, case-control studies and routine healthcare studies published in Europe between January 1, 2000 and September 30, 2012. These were chosen to ensure that the highest levels of European evidence were pooled based on the aims of the review. Reviews, discussion papers, non-research letters and editorials, case studies, and case series plus animal studies and all randomised controlled trials were excluded. See online supplement for further details.

Study selection

The titles of retrieved articles were checked by two independent consultant reviewers according to our selection criteria and categorized as: included, not included, and unsure. The abstracts of papers in the unsure category were retrieved and re-categorized as above after further discussion. Full text copies of potentially relevant studies were obtained and their eligibility for inclusion was independently assessed by two reviewers (BN and LH). Any discrepancies were resolved by consensus or a third reviewer (AS) arbitrated.

Risk of bias assessment

Risk of bias in the studies was independently carried out by two reviewers (BN and LH) using adapted relevant versions of the Critical Appraisal Skills Programme (CASP) tool (http://www.casp-uk.net/). An overall grading was assigned to each study based on the grading obtained from the various components of the study (i.e., the appropriateness of the study design for the research question, the risk of selection bias, exposure and outcome assessment). Discrepancies were resolved by consensus or a third reviewer (AS) arbitrated.

Analysis, synthesis and reporting

A customized data extraction form was developed and independently used to obtain relevant data from each study by two reviewers (BN and LH). Discrepancies

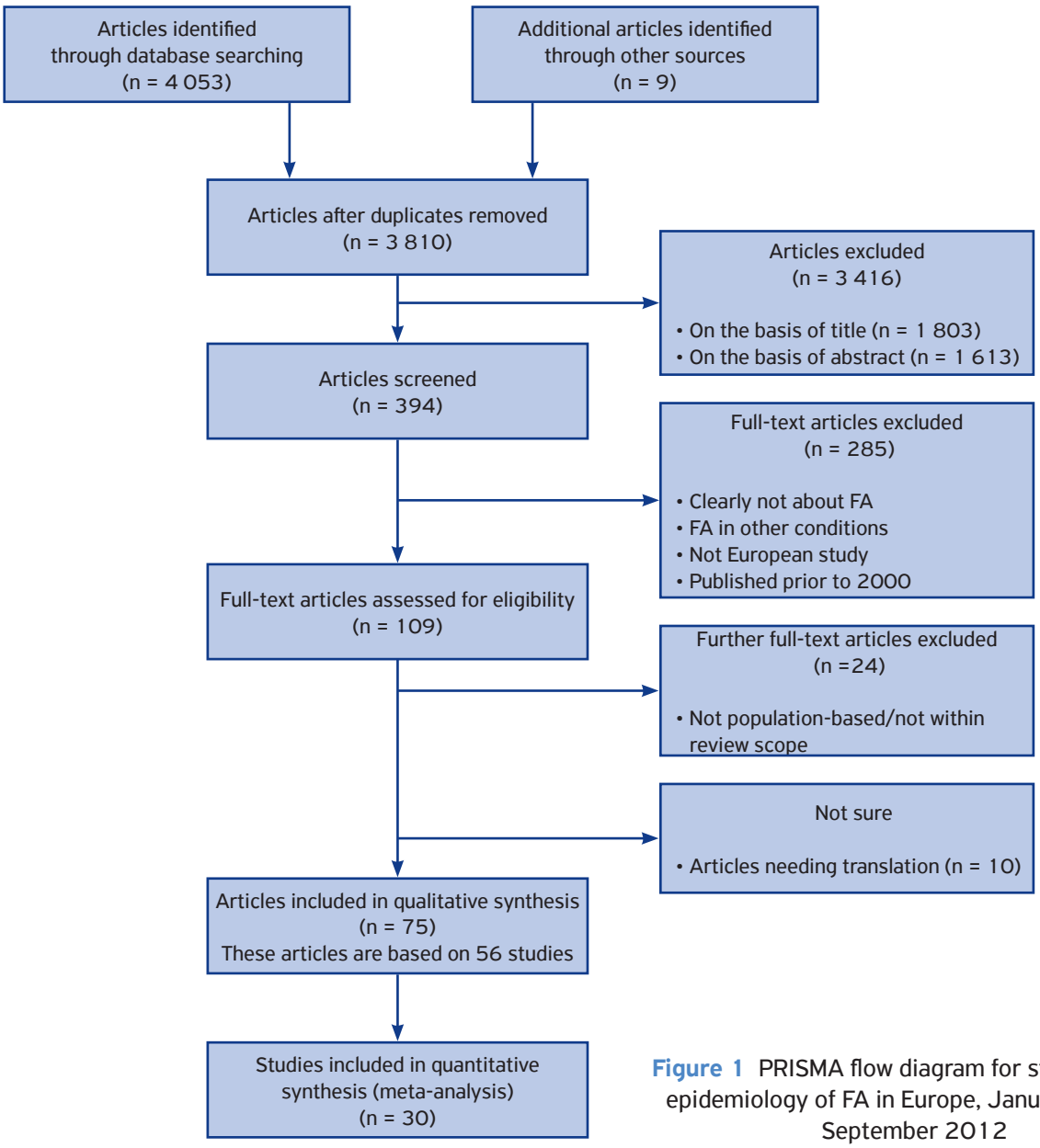


Figure 1 PRISMA flow diagram for studies on the epidemiology of FA in Europe, January 2000 – September 2012

were resolved by discussion or arbitration by a third reviewer (AS). We recalculated all the frequency estimates of any FA occurrence if adequate data were provided by authors by using minimal measured events rather than extrapolated ones. The 95% confidence intervals (95% CI) of our recalculations were computed by using the Wilson score method without continuity correction (15). We performed a random-effects meta-analysis for clinically and methodologically comparable studies to estimate the frequency of FA. We calculated the age-stratified pooled estimates for the age group 0–17 years (children) and 18 years and over (adults). We also present the pooled estimates stratified by geographical region in Europe. Statistical analysis was undertaken using STATA 11 (Stata Corp, College Station, Tx). See online supplement for further details.

Results

Study selection and characteristics

Figure 1 shows the PRISMA flowchart for our study selection and screening. Seventy-five papers (based

Table 1 Summary of range of estimates of the frequency of FA in Europe by self-report, skin prick (SPT) positivity, IgE positivity, food challenges, and symptoms or clinical history: estimates from studies published between 1 January 2000 and 30 September 2012

Frequency of FA	Age bands, years					
	≤ 1	2-5	6-10	11-17	18-60	> 60
POINT PREVALENCE						
Self-report	1.7 - 9.8%	1.6 - 38.7%	1.6 - 24.4%	1.6 - 24.4%	3.5 - 19.6%	3.3%
Positive IgE	19.4 - 20.3%	4.1 - 21.5%	4.1 - 52.0%	4.1 - 16.1%	2.0 - 21.9%	9.0 - 16.8%
Positive SPT	2.2 - 4.3%	3.2 - 4.5%	1.8 - 6.1%	1.8 - 6.1%	-	-
Symptom plus positive IgE	1.3 - 4.6%	4.6%	4.6%	4.6%	2.2%	2.2%
Symptom plus positive SPT	1.6 - 13.1%	13.1%	0.1 - 13.1%	0.1 - 13.1%	-	-
Clinical history or food challenge	2.7 - 3.0%	2.1 - 6.8%	1.1 - 2.1%	1.4 - 2.3%	-	-
Food challenge	0.3 - 4.2%	0.0 - 4.2%	0.4 - 4.2%	0.1 - 5.7%	0.1 - 3.2%	2.9%
LIFETIME PREVALENCE						
Self-report	5.7 - 38.4%	5.7 - 38.4%	5.7 - 41.8%	10.6 - 38.4%	9.5 - 35.0%	15.5 - 35.0%

on 56 primary studies) were included in the narrative synthesis (16-89), and 30 studies were included in the meta-analysis (Figure 1). Further details are found in the online supplement (Table E1).

Risk of bias assessment of studies

The overall risk of bias grading of the studies indicated that almost all of the studies (54 of 56 studies) were graded as at 'moderate' risk of bias (Table E2).

Frequency of FA

Table 1 presents the summarized ranges of estimates for different age groups, by different assessment methods of FA, and includes the point prevalence for all FA assessment methods and life-time prevalence only for self-reported FA. Detailed results are shown in Tables E1- E6.

Self-reported FA

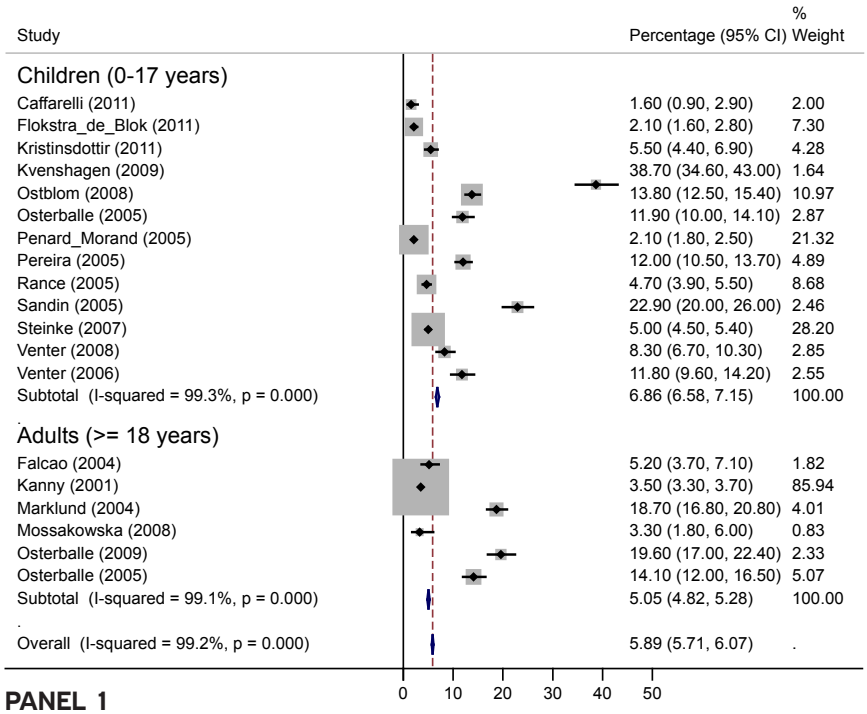
The overall pooled point prevalence of self-reported FA was 5.9% (95% CI 5.7-6.1) (Figure 2). The pooled point prevalence among children was higher than among adults and highest in Northern Europe than in other regions (Figure 2). The overall pooled life-time prevalence of self-reported FA was 17.3% (95% CI 17.0-17.6), and this was similar in children and in adults and highest in Eastern Europe than other regions and lowest in Southern Europe. High prevalences were also reported in Western and Northern Europe (Figure E1). However, even after stratification by age and region, there was still significant heterogeneity between the studies ($P < 0.001$ for I^2).

FA by positive SPT or IgE to food allergens

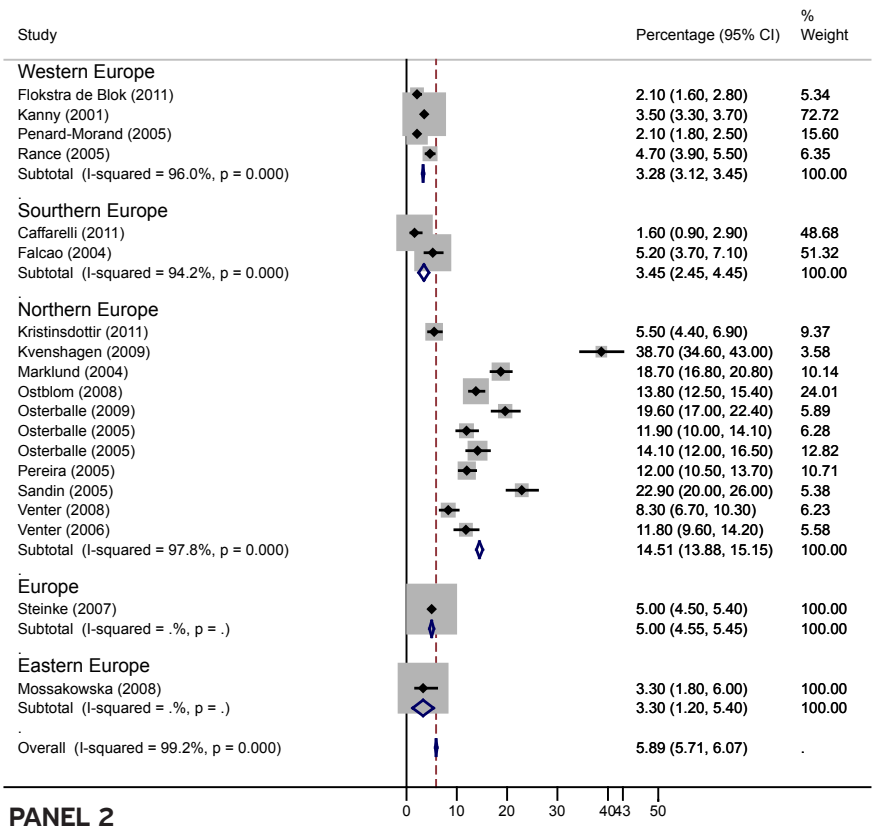
The overall point prevalence of positive specific-IgE to at least one food was 10.1% (95% CI 9.4-10.8) and higher among children than adults (Figure E2). The overall point prevalence of positive SPT to at least one food was 2.7% (95% CI 2.4-3.0) without differences between Northern and Southern Europe (Figure E3). After stratification by age and region, there was still significant heterogeneity between the studies ($P < 0.001$ for I^2).

FA defined by symptoms plus allergic sensitization and by clinical history or food challenge

The overall pooled point prevalence of symptoms plus positive IgE to at least one food was 2.7% (95% CI 1.7-3.7), and slightly higher among children than



PANEL 1



PANEL 2

Figure 2 Pooled point prevalence of self-reported FA stratified by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent the size of the study

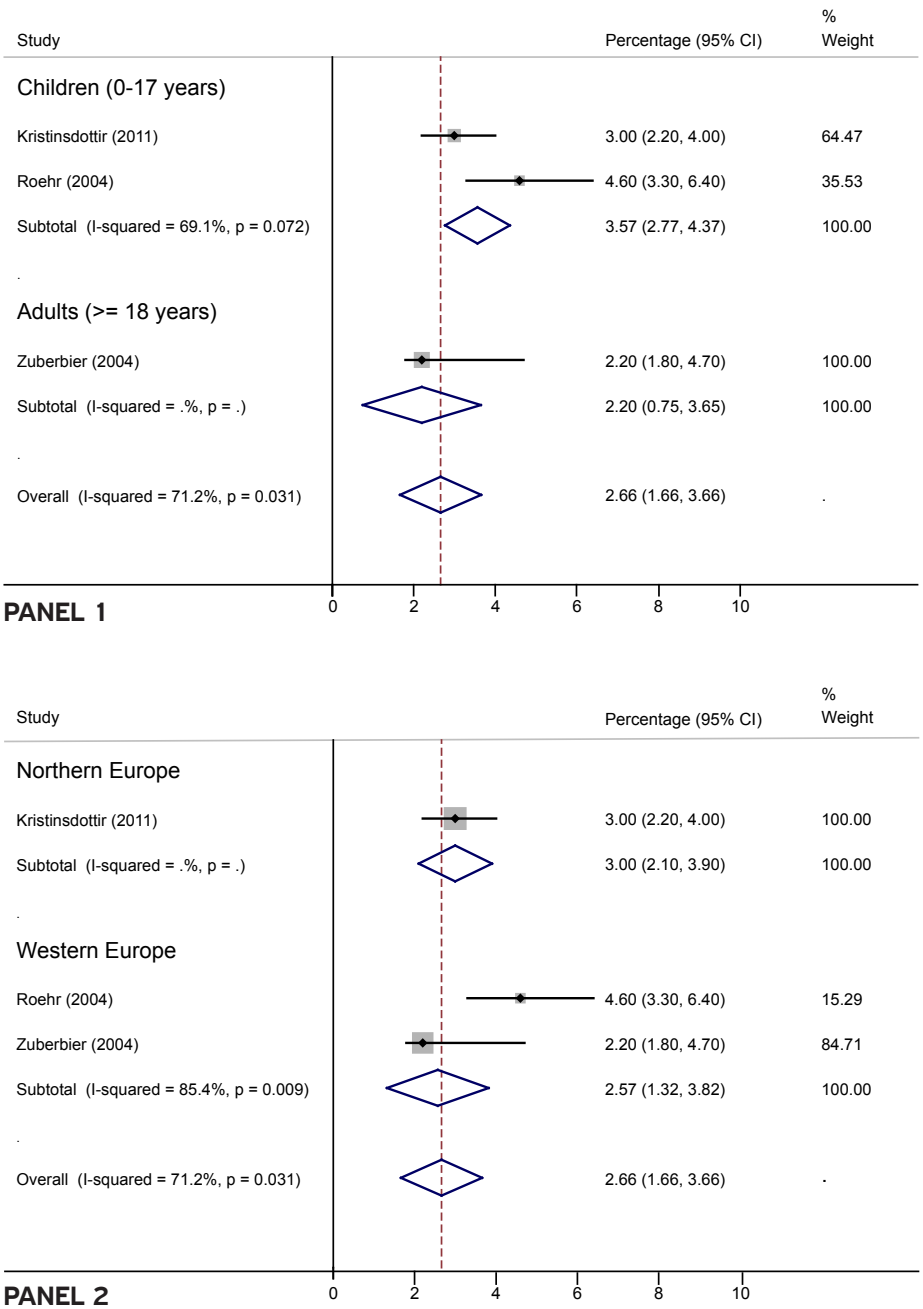
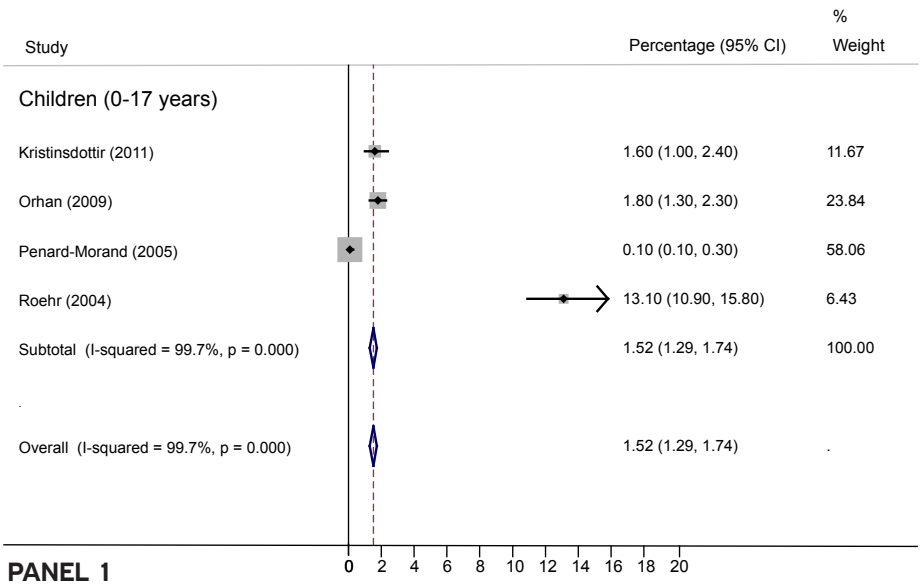


Figure 3 Pooled point prevalence of symptoms plus specific-IgE positivity to at least one food allergen by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent the size of the study

among adults (Figure 3). The overall pooled point prevalence of symptoms plus SPT positivity to at least one food was 1.5% (95% CI 1.3-1.7) and this was only among children (Figure 4). Usually, the estimates for clinical history or OFC and clinical history or DBPCFC were close to each other, hence we report the point prevalence estimates for clinical history or DBPCFC. FA-defined clinical history refers to the cases confirmed by a convincing clinical judgment by a physician, without the use of any food challenge.



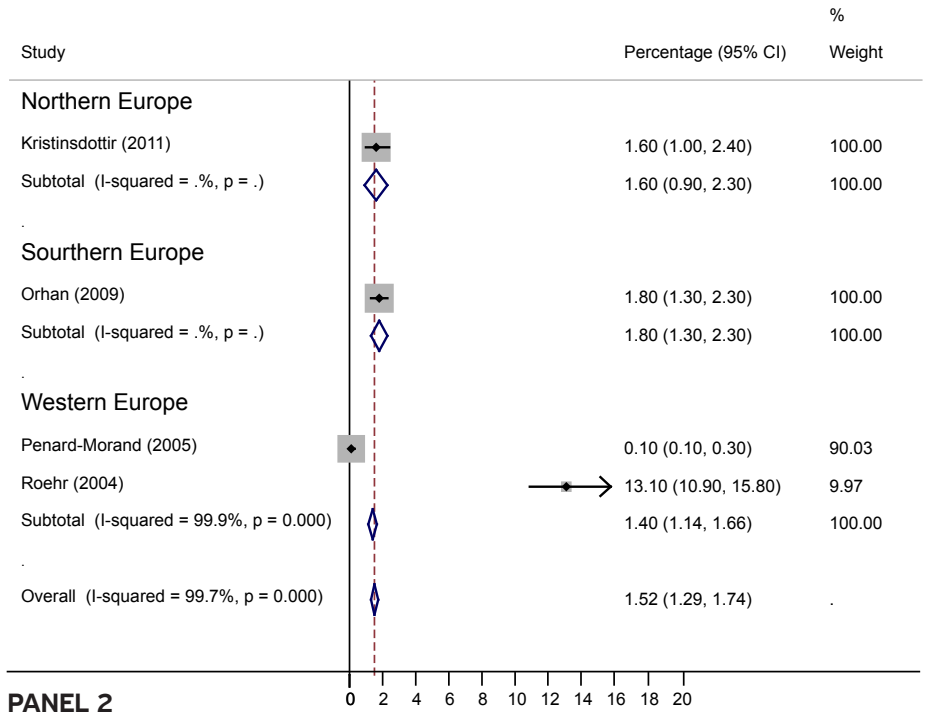


Figure 4 Pooled point prevalence of symptoms plus SPT positivity to at least one food allergen by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent the size of the study

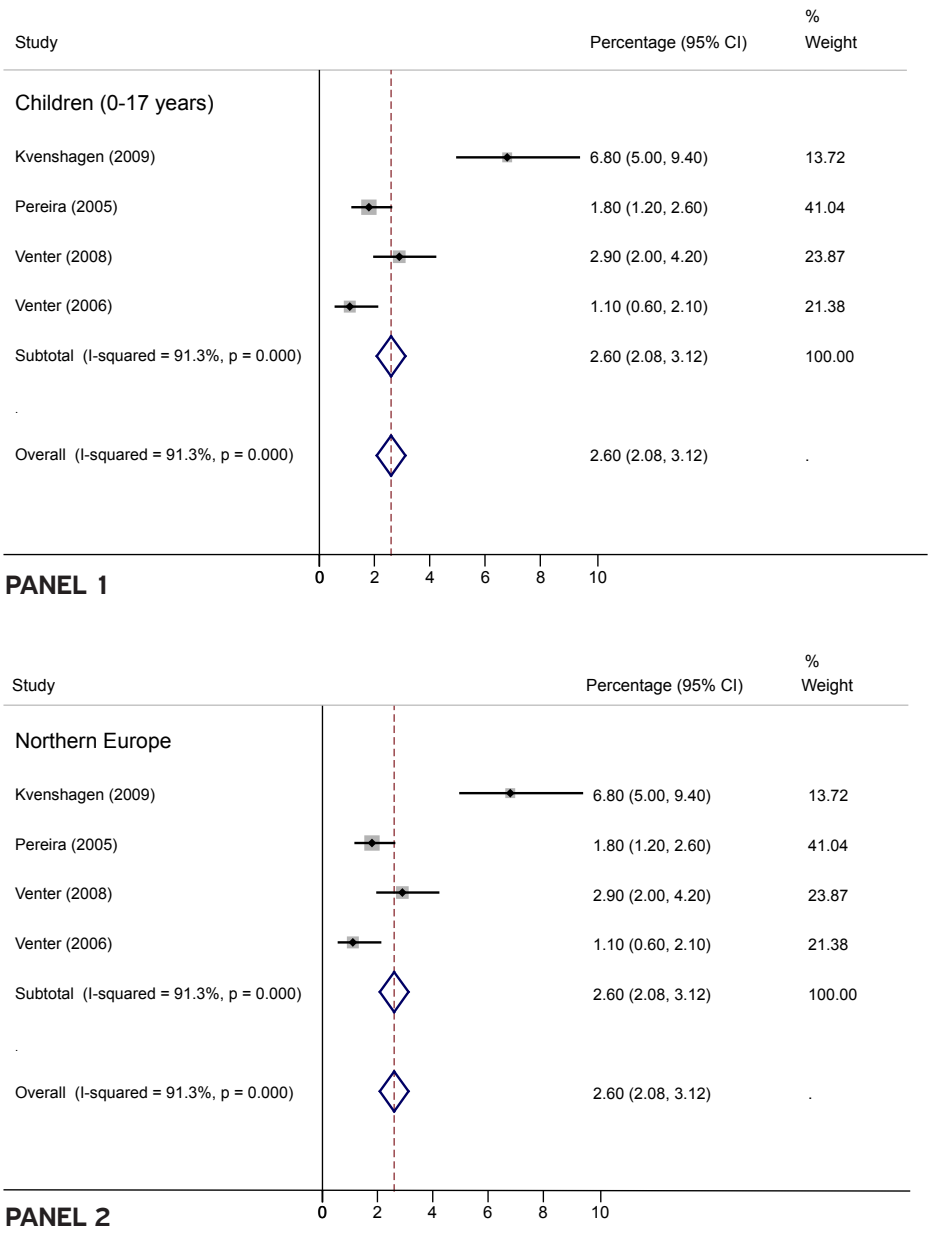
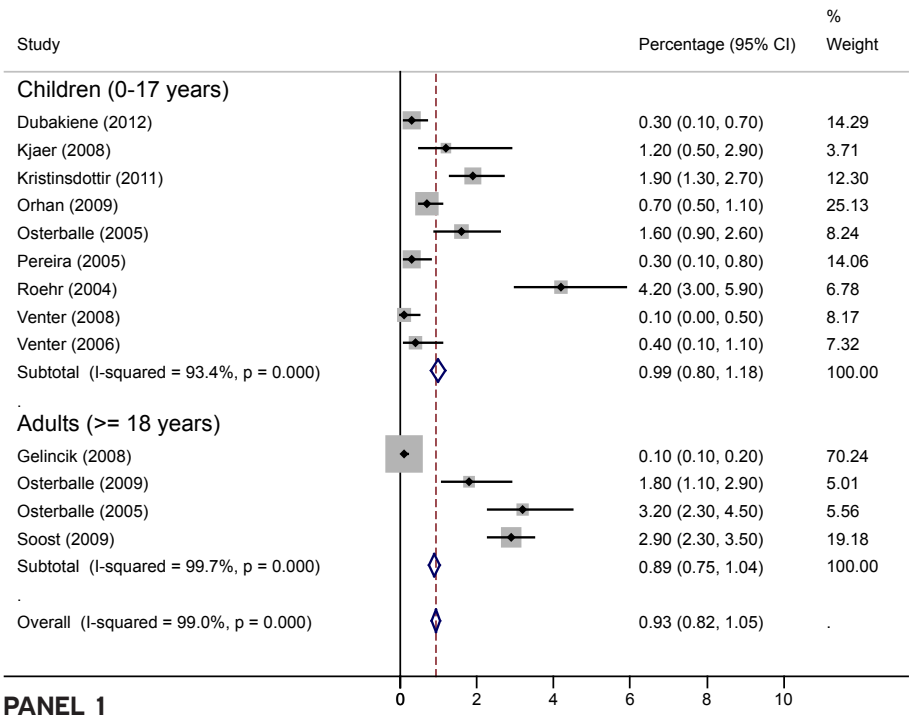


Figure 5 Pooled point prevalence of clinical history of FA or food challenge (open food challenge or double-blinded placebo-controlled) by age (only studies among children available) (PANEL 1) and geographical region (only studies from Northern Europe available) (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size

This was mostly done for subjects who refused food challenge or could not undergo food challenge due to other reasons. The overall pooled point prevalence of clinical history or food challenge positivity was 2.6% (95% CI 2.1-3.1) and this was only among children from Northern Europe (Figure 5).

Challenge-verified FA

The overall pooled point prevalence of food challenge (OFC or DBPCFC) was 0.9% (95% CI 0.8-1.1) and was similar among children and adults, but highest in Western Europe, and being higher in Northern Europe than in Southern Europe (Table 1, Figure 6).



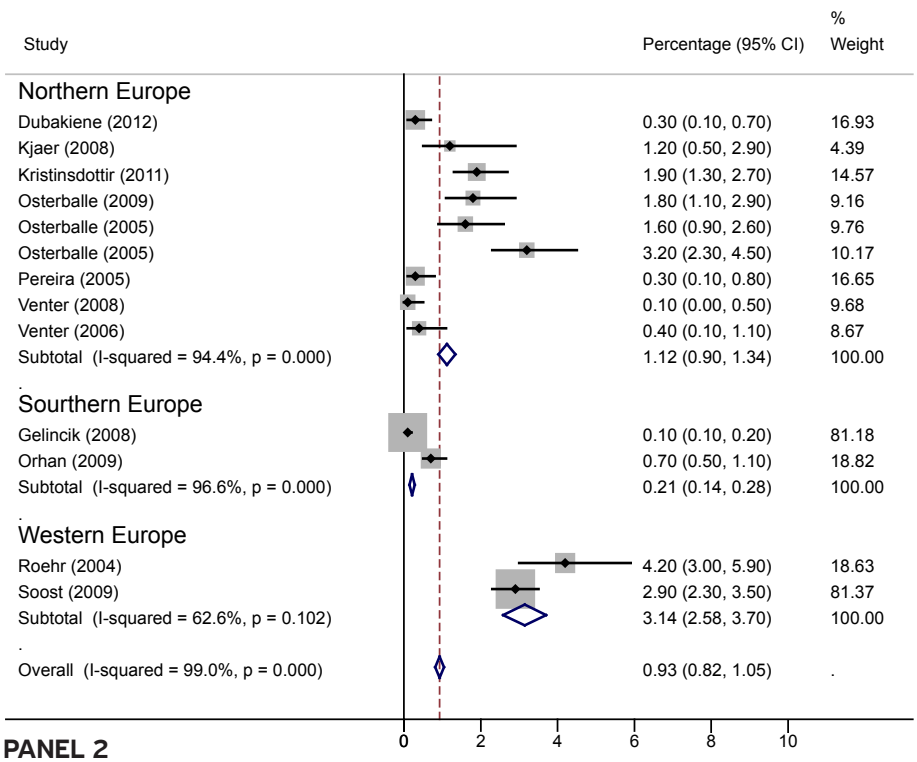


Figure 6 Pooled point prevalence of food challenge positivity (open food challenge or double-blinded placebo-controlled) by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size

Table 2 Time trends in the frequency of FA in Europe: estimates from studies published between 1 January 2000 and 30 September 2012

Age(s) of subjects	Frequency of occurrence FA					Comments
GUPTA *et al.* 2007(36), 2004(4), 2003(37), UK						
All ages		1990/1991	2000/2001	2003/2004		The increasing trends hospital admissions for FA between the study years were statistically significant. These admission data do not include period accident and emergency departments for observation and are therefore likely to underestimate the actual incidence or prevalence.
	Admissions rate for FA for all age groups	0.5	2.9	2.6		
	0-14 age group	1.6	11.8	10.7		
	15-44 age group	0.5	1.1	9.0		
	45+ age group	0.0	0.5	0.6		
KOTZ *et al.* 2011(45), UK						
All ages	2001	2002	2003	2004	2005	All estimates were age- and- sex-standardized. During the study period, while the lifetime prevalence of peanut allergy doubled, the incidence rate of peanut allergy remained fairly stable. Sex-specific, age-specific, and SES-specific estimates are also reported in the paper.
	Lifetime prevalence of doctor-diagnosed peanut allergy per 1000 patients Percentage (95% CI)					
	0.24 (0.22-0.26)	0.32 (0.30-0.34)	0.39 (0.37-0.42)	0.45 (0.43-0.48)	0.51 (0.49-0.54)	
	Incidence rate of doctor-diagnosed peanut allergy per 1000 person-years Percentage (95% CI)					
	0.06 (0.05-0.07)	0.08 (0.07-0.09)	0.08 (0.07-0.09)	0.08 (0.07-0.09)	0.08 (0.07-0.09)	
VENTER *et al.* 2010 (83), UK						
Children 3-4 years	1993		1998-2000		2004-2005	Three different cohorts were involved in the study, which were born in 1989, 1994-1996, and 2001-2002 and respectively reviewed (3-4 years after birth) in 1993, 1998-2000, and 2004-2005. SPT positivity to peanut allergen and clinical peanut allergy statistically significantly increased from 1993 to 1998-2000, but non-significantly decreased from 1998-2000 to 2004-2005.
	Point prevalence of SPT positivity to peanut allergen Percentage (95% CI)					
	1.3% (0.6-1.8)		3.3% (2.4-4.4)		2.0% (1.2-3.4)	
	Point prevalence of clinician diagnosed peanut allergy (i.e. history plus sensitization plus OFC) Percentage (95% CI)					
	0.5% (0.2-1.1)		1.4% (0.9-2.2)		1.2% (0.7-2.2)	

Time-trends in the frequency of FA

Only three studies have investigated the time-trends of FA in Europe (4, 36, 37, 45, 83) (Table 2). All these studies were from the UK and two were primarily hospital-based studies that employed only admissions data (4, 36, 37, 45), limiting the application of the findings to the general population, although the estimates were standardized to the local populations. Two focused on peanut allergy, while one considered any FA.

In the first study (45), while the incidence of doctor-diagnosed peanut allergy remained rather stable between 2001 and 2005, the life-time prevalence doubled during the study period. Using three different cohorts, Venter *et al* (2010) reported a significant increase in positive SPT to peanut allergen and clinical peanut allergy from 1993 to 1998-2000, but non-significantly decreased from 1998-2000 to 2004-2005 (83). Reviewing admissions rate for FA, Gupta and colleagues (4, 36, 37) observed an increased rate for all age groups between 1990 and 2004 (Table 2).

Risk and prognostic factors for FA

Risk factors for FA

Generally, the presence of other allergic diseases or allergic sensitization in the subjects, their parents, or siblings were strong risk factors for the development of FA (24-26, 34, 39, 57, 67-69, 72, 83-86). Increasing age appeared as a risk factor (34, 45, 68, 69). Male sex was associated with an increased risk in some studies (45, 68, 69) mainly among children, although other studies also reported no association (57). Higher socioeconomic status (45) or living in more affluent societies increased the risk (22). Caesarean section delivery and the use of antibiotics were not associated with FA (24-26, 52). In some studies, breastfeeding was not associated with the risk of FA (24-26, 57), although one study reported an increased risk (39). There was also an increased risk with the use of infant formula in one study (72). Other risk factors considered were inconsistently associated with FA across the studies.

Prognostic factors for FA

Of the various factors studied across the studies, no potential prognostic factor for the development of FA was reported, indicating that little data exist at present to indicate the prognosis of FA. Some studies have studied outgrowing (e.g. level of specific IgE) but our search strategy would not necessarily have picked up these studies.

Discussion

Statement of principal findings

The present systematic synthesis has provided estimates of the frequency of FA across different age groups and geographical regions in Europe. Almost all the studies received 'moderate' overall grading. Only a few of the studies were undertaken in Eastern and Southern Europe. The overall lifetime prevalence of self-reported food allergy was 17.3% (95% CI 17.0-17.6). Point prevalence for self-reported FA (5.9%), positive SPT to at least one food (2.7%), positive specific IgE (10.1%) and challenge-verified FA (0.9%) were lower. The highest prevalence was seen in North-western Europe and in children compared to adults. Low prevalence of self-reported and confirmed FA were found in Southern Europe, while sensitization was similar to other regions In Eastern Europe a high prevalence of self-reported FA was found with lacking data about sensitization or clinical reactivity. Although data on the time-trends of FA were weak, while the incidence of FA seemed to be stable over time, the prevalence appeared to be increasing. Finally, no consistent risk or prognostic factors for the development of FA were observed, although age, sex, and the presence of other allergic diseases seem potentially important.

Strengths and limitations

Rigorous steps were undertaken in the synthesis, including a comprehensive literature search that covered the major electronic databases; no language restriction; and rigorous screening and appraisal process undertaken. However, one of the limitations of this study is that due to the large amount of literature initially found, the review was restricted to studies published in Europe between 2000 and 2012 given the synthesis unpins the development of European guidelines. This is so far the first study to consider the frequency of FA by geographical regions and thus sets the pace for further consideration in future studies so as to clearly understand the spatial distribution of the disease. The highly significant heterogeneity in the pooled frequency estimates points to important differences among the studies in terms of differences in protocols such as food challenge and skin prick testing methodology. These differences indicate that caution should be exercised in interpreting the pooled results. The limited number of studies from Southern and Eastern Europe could also point to the fact that a majority of the studies published from these regions were done in local journals and in national languages which eventually are not indexed in the mainstream databases included in our study.

We were able to examine all possible methods that have been used to measure FA (eg self-report, specific sensitization, food challenges and their various combinations)) and different measures of occurrence of FA (eg point prevalence, lifetime prevalence incidence). We planned to additionally study case-fatality and resolution but their poor reporting made this impossible. Additionally most studies failed to make clear whether IgE or non-IgE phenotypes were being studied. Such uncertainty, in addition to the changing definition of FA, has so far also contributed to the difficulty in estimating the actual frequency of FA.

Overall, the quality of studies included in the review was moderate. The methodological quality of future studies

Table 3 Summary of evidence on the risk/prognostic factors for FA in Europe: studies published between 1 January 2000 and 30 September 2012

Reference, country	Outcomes	Risk/prognostic factors studied	Statistical analysis method	Results and comments
Du Toit *et al.* 2008 (22), UK and Israel	OFC-verified peanut, sesame, tree nut, egg, and milk allergy	Country of residence (i.e. living in the United Kingdom as compared to living in Israel)	Mantel-Haenszel, Kaplan-Meier, log-rank test, multiple logistic regression	In both unadjusted and adjusted models: ↑living in the United Kingdom (compared to living in Israel) associated with peanut, sesame, tree nut, egg, and milk allergy. Early consumption of peanuts in infancy was associated with lower risk of peanut allergy, but estimates for this were not reported in the paper.
Eggesbø *et al.* 2001a, 2001b and 2003 (24-26), Norway	History and OFC/ DBPCFC-confirmed	Cesarean section, maternal antibiotics, child antibiotics, breast feeding, maternal allergy, older siblings	Pearson Chi-square test, logistic regression,	↑ Maternal allergy, → cesarean delivery, → maternal antibiotics,→ child antibiotics, → breast feeding, →older siblings
Fox *et al.* 2009 (32), UK	SPT or sIgE positivity or DBPCFC	Environmental (household) peanut consumption, maternal peanut consumption during pregnancy and lactation, infant peanut consumption	Wilcoxon rank-sum test, multiple logistic regression,	In adjusted models: ↑higher household peanut consumption; →maternal peanut consumption during pregnancy; →maternal peanut consumption during lactation.
Gelincik *et al.* 2008 (34), Turkey	DBPCFC-verified FA	Age, familial atopy, household pets, nasal allergy, itching dermatitis/ urticaria, doctor-diagnosed asthma, smoking	Pearson's Chi-square test, multiple logistic regression	In adjusted models: ↑age < 40 years; ↑familial atopy; ↑household pets; ↑nasal allergy; ↑itching dermatitis/urticaria; ↑doctor-diagnosed asthma. Only the factors that were significant at the unadjusted level were included in the adjuste dmodels
Hourihane *et al.* 2007 (39), UK	DBPCFC-verified peanut allergy	Breastfeeding, history of eczema and allergic rhinitis	Multiple logistic regression	DBPCFC-verified peanut allergy: ↑breastfeeding; ↑history of eczema. All these results were from adjusted models.
Kotz *et al.* 2011 (45), UK	Physician-diagnosed peanut allergy	Sex, age, socioeconomic deprivation	Pearson's Chi-square test	Incidence: ↑male sex; ↑0-4 years old; ↑being in the most affluent group Prevalence: ↑5-9 years old; being in the most affluent group Only frequencies and p-values were reported; no modeling strategies were employed in the analysis.
Kvenshagen *et al.* 2009 (52), Norway	Clinician diagnosed allergy to any food	Caesarean section, use of antibiotics	Logistic regression	Unadjusted models: →caesarean section delivery, →use of antibiotics

Table 3 (continued)

Reference, country	Outcomes	Risk/prognostic factors studied	Statistical analysis method	Results and comments
Nicolaou *et al.* 2010 (57), UK	History plus OFC/ DBPCFC-verified peanut allergy	Sex, breastfeeding, maternal allergy, paternal allergy, current asthma/ wheeze, current hay fever, current eczema, other know food allergies, median serum sIgE, peanut SPT > 8 mm	Pearson's Chi-square test	→Male sex; →breastfed; →maternal allergic disease; →paternal allergic disease; ↑current asthma/wheeze; ↑current hay fever; ↑current eczema; ↑other known food allergies; ↑median serum sIgE to peanut; ↓median serum sIgE to grass; ↑median serum sIgE to peanut; ↑peanut SP weal > 8mm. Only frequencies and p-values were reported; no modeling strategies were employed in the analysis.
Pereira *et al.* 2005 (67), UK	Self-reported FA	Atopic status	Binary logistic regression	Unadjusted model: ↑atopic children compared to non-atopic children
Pyrhönen *et al.* 2011 and 2009 (68, 69), Finland	Physician diagnosed FAand OFC-verified FA	Age, sex, no. of siblings, parental allergy (FA symptoms, animal allergy, hay fever, atopic rash, allergic asthma, any allergy, positivity to milk allergy; egg allergy; essential foods allergy)	Kaplan-Meier analyses and multiple Cox proportional regression	In unadjusted model: ↑age ≥ 1 years (compared to age 1 year); ↑male sex; →one or more siblings. In adjusted model: ↑either one or both parents having FA symptoms; ↑increased number of parental FA symptoms. The factors studied in the unadjusted model were not adjusted for and vice versa for factors studied in the adjusted model.
Roberts *et al.* 2005 (72) and Lack *et al.* 2003 (73), UK	DBPCFC-verified peanut allergy	SES, environmental tobacco smoke, maternal history of asthma, eczema, hay fever, other specific allergies, atopy; maternal intake of soybean meat, nuts during pregnancy; infant's breast-feeding status, use of soy milk or soy formula in 1st 2 yrs, rashes in 1st 6 months	Multiple logistic regression	Adjusted models: ↑consumption or formula during infancy; ↑rash over joints and in skin creases; ↑Oozing, crusted rash
Venter *et al.* 2010 (83), UK	Physician diagnosed and OFC/ DBPCFC-verified peanut allergy	Having allergic diseases (wheeze, eczema) and increased SPT antibodies to food and inhalant allergens (house dust mite, grass, cat, milk, egg, wheat, and sesame)	Pearson's Chi-square test and binary logistic regression	Unadjusted models: ↑ever wheeze; ↑wheeze in past 12 months; ↑ever physician-diagnosed eczema; ↑sensitization to house dust mite, grass, cat, milk, egg, wheat, and sesame. No adjusted models were computed for the estimates.
Venter *et al.* 2008 (84); Dean *et al.* 2007 (85); Venter *et al.* 2006 (86, 87), UK	Physician diagnosed and OFC/ DBPCFC-verified FA	Sex, sibship, maternal and family history of atopy	Fisher's exact test, calculation of relative risk based on contingency tables	Estimates of associations between the risk factors and the endpoints not reported in the paper.

↑ Indicates a statistically significant increased risk (risk factor);
↓ Indicates a statistically significant decreased risk (protective factor);
→ Indicates no statistically significant association between the factor of interest and FA endpoint
DBPCFC: double-blind, placebo-controlled food challenge; OFC: oral/open food challenge;
sIgE: specific immunoglobulin E test; SPT: skin prick test for sensitization to specific food allergens

needs to be improved, for example the gold standard DBPCFC should be used. However, the OFC is more often applied as DBPCFC is not yet common practice in many settings. Additionally, using DBPCFC can be problematic because many symptomatic individuals are not challenged due to co-existing disease, lack of validated and blinded challenge materials or refusal, which could result into an underestimation of the real frequency of FA. However, the comparable DBPCFC estimates across different age groups indicate that the DBPCFC estimates obtained in this study are likely robust. Overall, using estimates where subjects with convincing clinical history and those with positive food challenge were combined as history or FC may represent the best estimates.

Due to wide variations in the definition of FA based on IgE or SPT sensitization to food allergens across the studies, comparison of estimates from studies that used these methods is also difficult. For instance, the values used for defining both positive IgE and SPT were inconsistent across a number of studies. Also, the number of specific foods tested was inconsistent across studies. Data indicates that the most common sensitized allergens are scantly represented in available commercial mixes, thus the observed frequency of FA may be an underestimation (18). Allergies to very common inhalant allergies, such as grass pollen, house dust mites, and cockroaches, may lead to non-clinically relevant SPT- or IgE-positivity to cereals, peanut, and shrimp (90-92). This may inhibit valid estimation of the frequency of FA based on sensitization to specific food allergens. Finally, the diagnostic methods used to assess FA sensitization varied widely across studies, which may also reflect geographic variability in application of diagnostic tools for defining FA sensitization.

Comparison of our findings with previous studies

We identified three previous systematic reviews that investigated the frequency of FA (16, 74, 89). Zuidmeer and colleagues focused only on the prevalence of plant food allergies and only searched the MEDLINE database, reporting estimates generally lower than our estimates (89). We searched four databases and had no restriction to the type of foods examined. The latest of the three systematic reviews (16) reported frequency of FA based on the estimates reported in a previous review (74), in which the prevalence of self-reported FA was around 12% in children and around 13% in adults (74). These compare to 6.9% and 5.1% respectively in our study. That review also reported a lower range of prevalence for positive specific-IgE to at least one food (4-6%) but a higher range of positive SPT to at least one food (7-17%). The overall pooled estimate of FA by food challenge was above 2% in that study (74), twice our estimate (0.9%). The previous systematic review excluded primary studies that examined fruits, vegetables, seeds, nuts, cereals, and meats, and included primary studies both from Europe and beyond. These may partly explain the differences in estimates found between our review and the previous ones. Only one of the previous studies examined the time-trends in the frequency of FA and concluded that it is unclear if the prevalence is increasing and that the observed increase over time could be attributed to increased awareness and improved pattern of reporting and diagnosis rather than a true increase (14). We did not identify any previous systematic review that has investigated the risk or prognostic factors for FA.

Conclusions

The present evidence indicates that the lifetime and point prevalence of self-reported FA in Europe are around 17% and 6%, respectively. The point prevalence of food challenge-confirmed FA is under 1%. The frequency of FA is higher among children than among adults and highest in North-western Europe than in other regions, while Southern Europe seems to have the lowest prevalence. Caution is required due to the heterogeneity among the studies suggesting important methodological and diagnostic differences within and across geographic regions of Europe. Whilst the incidence of FA seems stable over time, the prevalence may be increasing, possibly reflecting changes in diagnostic practices or longer time to resolution. The risk or prognostic factors for the development of FA are inconsistent, although sex, age, country of residence, the presence of other allergic diseases, and familial history of allergy may be important. Clearly, there is need to improve this evidence base in order to validly estimate the putative frequency of food allergy. Future studies need to be rigorously designed using standardized methodology including DBPCFC to limit potential sources of bias that could weaken the estimates of food allergy and more high-quality studies are needed from Eastern and Southern Europe (93, 94).

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing this systematic review. We would also like to thank the EAACI Executive Committee for their helpful comments and suggestions.

Funding

EAACI

Contributorship

AS, AM and GR conceived this review. It was undertaken by BN and LH, with the support of SSP. BN, LH, GR and AS led the drafting of the manuscript and all authors critically commented on drafts of the manuscript.

Conflicts of interest

None known

References

1. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. *PLoS One* 2012;7:e39803.
2. Anandan C, Gupta R, Simpson R, Fischbacher C, Sheikh A. Epidemiology and disease burden from allergic disease in Scotland: analyses of national databases. *J R Soc Med* 2009;102:431-442.
3. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010;65:152-167.
4. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004;34:520-526.
5. Schoenwetter WF, Dupclay L Jr, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality of life burden of allergic rhinitis. *Curr Med Res Opin* 2004;20:305-317.
6. Allen JK, Koplin JJ. The epidemiology of IgE-mediated FA and anaphylaxis. *Immunol Allergy Clin N Am* 2012;32: 35-50.
7. Sampson HA. FA: accurately identifying clinical reactivity. *Allergy* 2005; 60 Suppl 79:19-24.
8. Prescott S, Allen KJ. FA: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol* 2011;22:155-160.
9. Lack G. Update on risk factors for FA. *J Allergy Clin Immunol* 2012;129:1187-1197.
10. Sicherer SH. Epidemiology of FA. *J Allergy ClinImmunol* 2011;127:594-602.
11. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S *et al.* A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813-824.
12. Masilamani M, Commins S, Shreffler. Determinants of FA. *Immunol Allergy Clin N Am* 2012;32:11-33.
13. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M *et al.* ICON: food allergy. *J Allergy Clin Immunol* 2012;129:906-920.
14. Nwaru BI, Panesar SS, Hickstein L, Rader T, Werfel T, Muraro A *et al.* The epidemiology of food allergy in Europe: protocol for a systematic review. *Clin Transl Allergy* 2013;3:13.
15. Newcombe RG. Two-sided confidence intervals for the single proportion: Comparison of seven methods. *Stat Med* 1998;17:857-872.
16. Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al.* Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;303:1848-56.
17. Bant A, Kruszewski J. Increased sensitization prevalence to common inhalant and food allergens in young adult Polish males. *Ann Agric Environ Med* 2008;15:21-27.
18. Burney P, Summers C, Chinn S, Hooper R, Van Ree R, Lidholm J. Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: A EuroPrevall analysis. *Allergy* 2010;65:1182-1188.
19. Woods RK, Abramson M, Bailey M, Walters EH. International prevalences of reported food allergies and intolerances. Comparisons arising from the European community respiratory health survey (ECRHS) 1991-1994. *Eur J Clin Nutr* 2001;55:298-304.
20. Caffarelli C, Coscia A, Ridolo E, Povesi Dascola C, Gelmett C, Raggi V *et al.* Parents' estimate of FA prevalence and management in Italian school-aged children. *Pediatr Int* 2011;53:505-510.
21. Colver AF, Nevantaus H, Macdougall CF, Cant AJ. Severe food-allergic reactions in children across the UK and Ireland, 1998-2000. *Acta Paediatr* 2005;94:689-695.
22. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR *et al.* Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-991.
23. Dubakiene R, Rudzeviciene O, Butiene I, Sezaite I, Petronyte M, Vaicekauskaite D *et al.* Studies on early allergic sensitization in the Lithuanian birth cohort. *The Scientific World Journal* 2012;909524.
24. Eggesbø M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for FA? *J Allergy Clin Immunol* 2003;112:420-426.
25. Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of allergy to egg: a population-based study in young children. *Allergy* 2001;56:403-411.
26. Eggesbo M, Botten G, Halvorsen R, Magnus P. The

prevalence of CMA/CMPI in young children: The validity of parentally perceived reactions in a population-based study. *Allergy* 2001;56:393-402.

27. Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. FA and food sensitization in early childhood: Results from the DARC cohort. *Allergy* 2009;64:1023-1029.
28. Kjaer HF, Eller E, Host A, Andersen KE, Bindslev-Jensen C. The prevalence of allergic diseases in an unselected group of 6-year-old children. The DARC birth cohort study. *Pediatr Allergy Immunol* 2008;19:737-745.
29. Johnke H, Norberg LA, Vach W, Host A, Andersen KE. Patterns of sensitization in infants and its relation to atopic dermatitis. *Pediatr Allergy Immunol* 2006;17:591-600.
30. Falcao H, Lunet N, Lopes C, Barros H. Food hypersensitivity in Portuguese adults. *Eur J Clin Nutr* 2004;58:1621-1625.
31. Flokstra-de Blok BM, Doriene van Ginkel C, Roerdink EM, Kroeze MA, Stel AA, van der Meulen GN *et al.* Extremely low prevalence of epinephrine autoinjectors in high-risk food-allergic adolescents in Dutch high schools. *Pediatr Allergy Immunol* 2011;22:374-377.
32. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* 2009;123:417-423.
33. Frongia O, Bellomo AR, Di Giorgio G, Fiumalbi C, Frizza J, Maresca C *et al.* Food allergies and intolerance in infants and children. [Italian] Intolleranze e allergie alimentari nella prima infanzia. *Medico e Bambino* 2005;24:533-538.
34. Gelincik A, Buyukozturk S, Gul H, Isik E, Issever H, Ozseker F *et al.* Confirmed prevalence of FA and non-allergic food hypersensitivity in a Mediterranean population. *Clin Exp Allergy* 2008;38:1333-1341.
35. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;110:784-789.
36. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax* 2007;62:91-96.
37. Gupta R, Sheikh A, Strachan DP, Anderson HR. Increasing hospital admissions for systemic allergic disorders in England: Analysis of national admissions data. *BMJ* 2003;327:1142-1143.
38. Host A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol* 2002;13:23-28.
39. Hourihane JO, Aiken R, Briggs R, Gudgeon LA, Grimshaw KEC, DunnGalvin A *et al.* The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry. *J Allergy Clin Immunol* 2007;119:1197-1202.
40. Isolauri E, Huurre A, Salminen S, Impivaara O. The allergy epidemic extends beyond the past few decades. *Clin Exp Allergy* 2004;34:1007-1010.
41. Johansson SGO, Nopp A, Florvaag E, Lundahl J, Soderstrom T, Guttormsen AB *et al.* High prevalence of IgE antibodies among blood donors in Sweden and Norway. *Allergy* 2005;60:1312-1315.
42. Julge K, Vasar M, Bjorksten B. Development of allergy and IgE antibodies during the first five years of life in Estonian children. *Clin Exp Allergy* 2001;31:1854-1861.
43. Vasar M, Julge K, Bjorksten B. Development of atopic sensitization and allergic diseases in early childhood. *Acta Paediatri* 2000;89:523-527.
44. Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of FA in France. *J Allergy Clin Immunol* 2001;108:133-140.
45. Kotz D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. *J Allergy Clin Immunol* 2011;127:623-630.e1.
46. Krause TG, Koch A, Poulsen LK, Kristensen B, Olsen OR, Melbye M. Atopic sensitization among children in an Arctic environment. *Clin Exp Allergy* 2002;32:367-372.
47. Kristinsdottir H, Clausen M, Ragnarsdottir HS, Halldorsdottir IH, McBride D, Beyer K *et al.* [Prevalence of FA in Icelandic infants during first year of life]. [Icelandic] Algengifaeduofnaemishjaislenskumbornum a fyrstaari. *Laeknabladid* 2011;97:11-18.
48. Kucukosmanoglu E, Yazi D, Yesil O, Akkoc T, Gezer M, Bakirci N *et al.* Prevalence of egg sensitization in Turkish infants based on skin prick test. *Allergologia Et Immunopathologia* 2008;36:141-144.
49. Kurukulaaratchy RJ, Matthews S, Arshad SH. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. *Allergy* 2005;60:1280-1286.
50. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 2001;108:E33.
51. Tariq SM, Matthews SM, Hakim EA, Arshad SH. Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. *Pediatr Allergy Immunol* 2000;11:162-167.
52. Kvenshagen B, Halvorsen R, Jacobsen M. Is there an increased frequency of FA in children delivered by caesarean section compared to those delivered vaginally? *Acta Pædiatr* 2009;98:324-327.
53. Majkowska-Wojciechowska B, Wardzynska A, Luczynska M, Kowalski MK, Makowska J, Kowalski ML. Food hypersensitivity in the population of school children in Lodz - Results of the "EuroPrevall" surveys. *Alergia Astma Immunologia* 2009;14:35-44.
54. Marklund B, Ahlstedt S, Nordström G. Health-related quality of life among adolescents with allergy-like conditions: with emphasis on food hypersensitivity. *Health Qual Life*

Outcomes 2004;2:65.

55. Matricardi PM, Bockelbrink A, Beyer K, Keil T, Niggemann B, Gruber C *et al.* Primary versus secondary immunoglobulin e sensitization to soy and wheat in the Multi-Centre Allergy Study cohort. *Clin Exp Allergy* 2008;38:493-500.
56. Mossakowska M, Pawlinska-Chmara R, Broczek KM. Asthma, allergy, and respiratory symptoms in centenarians living in Poland. *J Physiol Pharmacol* 2008;59 Suppl 6:483-489.
57. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G *et al.* Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125:191-197.
58. Niggemann B, Schmitz R, Schlaud M, The high prevalence of peanut sensitization in childhood is due to cross-reactivity to pollen. *Allergy* 2011;66:980-981.
59. Orhan F, Karakas T, Cakir M, Aksoy A, Baki A, Gedik Y. Prevalence of immunoglobulin E-mediated FA in 6-9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. *Clin Exp Allergy* 2009;39:1027-1035.
60. Ostblom E, Lilja G, Ahlstedt S, van Hage M, Wickman M. Patterns of quantitative food-specific IgE-antibodies and reported food hypersensitivity in 4-year-old children. *Allergy* 2008;63:418-424.
61. Ostblom E, Lilja G, Pershagen G, Van Hage M, Wickman M. Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life. *Clin Exp Allergy* 2008;38:1325-1332.
62. Ostblom E, Wickman M, van Hage M, Lilja G. Reported symptoms of food hypersensitivity and sensitization to common foods in 4-year-old children. *Acta Paediatr* 2008;97:85-90.
63. Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin Exp Allergy* 2005;35:612-618.
64. Osterballe M, Mortz CG, Hansen TK, Andersen KE, Bindslev-Jensen C. The prevalence of food hypersensitivity in young adults. *Pediatr Allergy Immunol* 2009;20:686-692.
65. Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005;16:567-573.
66. Penard-Morand C, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Charpin D *et al.* Prevalence of FA and its relationship to asthma and allergic rhinitis in schoolchildren. *Allergy* 2005;60:1165-1171.
67. Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. *J Allergy Clin Immunol* 2005;116:884-892.
68. Pyrhonen K, Hiltunen L, Kaila M, Nayha S, Laara E. Heredity of food allergies in an unselected child population: An epidemiological survey from Finland. *Pediatr Allergy Immunol* 2011;22:e124-e132.
69. Pyrhonen K, Nayha S, Kaila M, Hiltunen L, Laara E. Occurrence of parent-reported food hypersensitivities and food allergies among children aged 1-4 yr. *Pediatr Allergy Immunol* 2009;20:328-338.
70. Pyziak K, Kamer B. Natural history of IgE-dependent FA diagnosed in children during the first three years of life. *Adv Med Sci* 2011;56:48-55.
71. Rance F, Grandmottet X, Grandjean H. Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. *Clin Exp Allergy* 2005;35:167-172.
72. Roberts G, Peckitt C, Northstone K, Strachan D, Lack G, Henderson J *et al.* Relationship between aeroallergen and food allergen sensitization in childhood. *Clin Exp Allergy* 2005;35:933-940.
73. Lack G, Fox D, Northstone K, Golding J. Factors Associated with the Development of Peanut Allergy in Childhood. *N Engl J Med* 2003;348:977-985.
74. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E *et al.* The prevalence of FA: A meta-analysis. *J Allergy Clin Immunol* 2007;120:638-646.
75. Ronchetti R, Jesenak M, Trubacova D, Pohanka V, Villa MP. Epidemiology of atopy patch tests with food and inhalant allergens in an unselected population of children. *Pediatr Allergy Immunol* 2008;19:599-604.
76. Sandin A, Annus T, Bjorksten B, Nilsson L, Riikjarv MA, van Hage-Hamsten M *et al.* Prevalence of self-reported FA and IgE antibodies to food allergens in Swedish and Estonian schoolchildren. *Eur J Clin Nutr* 2005;59:399-403.
77. Soost S, Leynaert B, Almqvist C, Edenharter G, Zuberbier T, Worm M. Risk factors of adverse reactions to food in German adults. *Clin Exp Allergy* 2009;39:1036-1044.
78. Roehr CC, Edenharter G, Reimann S, Ehlers I, Worm M, Zuberbier T *et al.* FA and non-allergic food hypersensitivity in children and adolescents. *Clin Exp Allergy* 2004;34:1534-1541.
79. Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S, Hantke T *et al.* Prevalence of adverse reactions to food in Germany - A population study. *Allergy* 2004;59:338-345.
80. Schnabel E, Sausenthaler S, Schaaf B, Schafer T, Lehmann I, Behrendt H *et al.* Prospective association between food sensitization and FA: Results of the LISA birth cohort study. *Clin Exp Allergy* 2010;40:450-457.
81. Schafer T, Bohler E, Ruhdorfer S, Weigl L, Wessner D, Heinrich J *et al.* Epidemiology of FA/food intolerance in adults: Associations with other manifestations of atopy. *Allergy* 2001;56:1172-1179.
82. Steinke M, Fiocchi A, Kirchlechner V, Ballmer-Weber B, Brockow K, Hischenhuber C *et al.* Perceived FA in children in 10 European nations: A randomised telephone survey. *Int Arch Allergy Immunol* 2007;143:290-295.
83. Venter C, Arshad SH, Grundy J, Pereira B, Bernie Clayton C,

Voigt K *et al.* Time trends in the prevalence of peanut allergy: Three cohorts of children from the same geographical location in the UK. *Allergy* 2010;65:103-108.

84. Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B *et al.* Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. *Allergy* 2008;63:354-359.
85. Dean T, Venter C, Pereira B, Arshad SH, Grundy J, Clayton CB *et al.* Patterns of sensitization to food and aeroallergens in the first 3 years of life. *J Allergy Clin Immunol* 2007;120:1166-1171.
86. Venter C, Pereira B, Grundy J, Clayton CB, Roberts G, Higgins B *et al.* Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life. *J Allergy Clin Immunol* 2006;117:1118-1124.
87. Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: A population-based study. *Pediatr Allergy Immunol* 2006;17:356-363.
88. Von Hertzen L, Makela MJ, Petays T, Jousilahti P, Kosunen TU, Laatikainen T *et al.* Growing disparities in atopy between the Finns and the Russians: A comparison of 2 generations. *J Allergy Clin Immunol* 2006;117:151-157.
89. Zuidmeer L, Goldhahn K, Rona RJ, Gislason D, Madsen C, Summers C *et al.* The prevalence of plant food allergies: A systematic review. *J Allergy Clin Immunol* 2008;121:1210-1218.e4.
90. Martens M, Schnoor HJ, Malling H-J, Poulsen LK. The clinical relevance of in vivo/in vitro tests for cereal and peanut sensitization in grass pollen allergic patients. *Clin Transl Allergy* 2011;1:15.
91. Wang J, Calatroni A, Visness CM, Sampson HA. Correlation of specific IgE to shrimp with cockroach and dust mite exposure and sensitization in an inner-city population. *J Allergy ClinImmunol* 2011;128:834-837.
92. Sidenius KE, Hallas TE, Poulsen LK, Mosbech H. Allergen cross-reactivity between house-dust mites and other invertebrates. *Allergy* 2001;56:723-733.
93. The EAACI Food Allergy and Anaphylaxis Public Declaration: http://www.eaaci.org/attachments/FoodAllergy &AnaphylaxisPublicDeclarationCombined.pdf. Last accessed 26 April 26 2014.
94. Papadopoulos NG, Agache I, Bavbek S, Bilo BM, Braido F, Cardona V *et al.* Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;2:21.

1.2

PREVALENCE OF COMMON FOOD ALLERGIES IN EUROPE

SYSTEMATIC REVIEW AND META-ANALYSIS

BI Nwaru[1, 2], L Hickstein[3], SS Panesar[2], G Roberts[4-6], A Muraro[7], A Sheikh[2, 8, 9] on behalf of The EAACI Food Allergy & Anaphylaxis Guidelines Group

EAACI Food Allergy & Anaphylaxis Guidelines Group: S Halken, K Hoffmann-Sommergruber, T Werfel, C Bindslev-Jensen, M Worm, K Beyer, A Dubois, P Eigenmann, R van Ree, L Poulsen, V Cardona, I Agache, N Papadopoulos, CA Akdis, G DuToit, M Fernandez Rivas, A Høst, E Knol, G Lack, MJ Marchisotto, B Niggemann, I Skypala, A Schoepfer, C Venter, B Vlieg–Boerstra, B Ballmer- Weber, C Nilsson

AFFILIATIONS

[1] School of Health Sciences, University of Tampere, Finland

[2] Allergy & Respiratory Research Group, Center for Population Health Sciences, The University of Edinburgh, UK

[3] Institute for Medical Informatics, Biometry and Epidemiology, University of Munich, Germany

[4] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[5] NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, UK

[6] Human Development and Health and Clinical Experimental Sciences Academic Units, Faculty of Medicine, University of Southampton, UK

[7] Department of Pediatrics, Center for Food Allergy Diagnosis and Treatment, Veneto Region, University of Padua, Italy

[8] Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Boston, MA, USA

[9] Department of Medicine, Harvard Medical School, Boston, MA, USA

Background: *Allergy to cow's milk, egg, wheat, soy, peanut, tree nut, fish, and shellfish constitute the majority of food allergy reactions, but reliable estimates of their prevalence are lacking. This systematic review aimed to provide up-to-date estimates of their prevalence in Europe.*

Methods: *Studies published in Europe from January 1, 2000 to September 30, 2012 were identified from searches of four electronic databases. Two independent reviewers appraised the studies and extracted the estimates of interest. Data were pooled using random-effects meta-analyses.*

Results: *Fifty studies were included in a narrative synthesis and 42 studies in the meta-analyses. Although there were significant heterogeneity between the studies, the overall pooled estimates for all age groups of self-reported lifetime prevalence of allergy to cow's milk was 6.0% (95% Confidence Interval: 5.7-6.4), egg 2.5% (2.3-2.7), wheat 3.6% (3.0-4.2), peanut 0.4% (0.3-0.6), tree nut 1.3% (1.2-1.5), fish 2.2% (1.8-2.5), and shellfish 1.3% (0.9-1.7). The prevalence of food-challenge defined cow's milk allergy was 0.6% (0.5-0.8), egg 0.2% (0.2-0.3), wheat 0.1% (0.01-0.2), soy 0.3% (0.1-0.4), peanut 0.2% (0.2-0.3), tree nut 0.5% (0.08-0.8), fish 0.1% (0.02-0.2), and shellfish 0.1% (0.06-0.3). Allergy to cow's milk and egg was more common among younger children, while peanut, tree nut, fish, and shellfish were more common among the older ones. There were insufficient data to compare the estimates of soy and wheat allergy between the age groups. Allergy to most foods, except soy and peanut, appeared to be more common in Northern Europe. The lifetime self-reported prevalence of allergy to common foods in Europe ranged from 0.1-6.0%. The heterogeneity between studies was high and participation rates varied across studies reaching as low as less than 20% in some studies.*

Conclusions*: The current study has provided the most comprehensive and up-to-date estimates so far of the eight most common food allergies across different age groups and regions in Europe. Standardizing the methods of assessment of food allergies and initiating strategies to increase participation will advance this evidence base.*

Originally published as: Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A on behalf of The EAACI Food Allergy & Anaphylaxis Guidelines Group. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014; DOI:10.1111/all.12423. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

The majority of allergic reactions to foods, particularly in children, are suggested to be caused primarily by eight foods, namely cow's milk, egg, wheat, soy, peanut, tree nut, fish, and shellfish (1), although there is no sufficient evidence to support this in Europe. Although it has been suggested that the prevalence of adverse reactions to these foods are increasing and constituting major public health problems, including increasing hospital utilization, increasing associated medical costs, and increased burden of care on immediate families (1-8), reliable estimates of their prevalence in Europe are lacking.

As part of the efforts of the European Academy of Allergy and Clinical Immunology (EAACI) to develop guidelines (*EAACI Guidelines for Food Allergy and Anaphylaxis*) for the management and prevention of food allergy and anaphylaxis, we undertook a systematic review to appraise the evidence base on the epidemiology of food allergy, its prevention, diagnosis and clinical management, and impact on quality of life, which will be used to inform the clinical recommendations. In our first report of the findings of this synthesis, we presented estimates of the prevalence, time-trends, and risk and prognostic factors for allergy to any food (Chapter 1.1) (9). In the present analysis, we present the estimates of the prevalence of the above-named eight most common food allergies in Europe.

Methods

Study protocol, search strategy, and study selection

The detailed methodological approach employed in this systematic review has been presented in our first report (9). Briefly, we developed a protocol in advance on the review processes, including the search strategies, inclusion and exclusion criteria, methods of analyses and syntheses, and choice of risk of bias tools for assessing study quality. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) at http://www.crd.york.ac.uk/prospero/ (registration number CRD42013003704) and has been published (10). We implemented a highly sensitive search strategy in four electronic databases (OVID MEDLINE, OVID EMBASE, CINAHL, and ISI Web of Science), which was devised on OVID MEDLINE and then adapted to the other databases. Experts active in the field commented the search strategy and the list of included studies. Additional references were located by searching the references cited in the identified studies. Unpublished work and research in progress were searched through discussion with experts in the field. We made no restrictions based on language; and literature in languages other than English were, where possible, translated.

In terms of study design, we included systematic reviews and meta-analyses, cohort studies, case-control studies, cross-sectional studies, and routine healthcare studies, but excluded review and discussion papers, non-research letters and editorials, case studies and case series, animal studies, and all randomized controlled trials. As our initial search (including studies published worldwide between January 1990 and September 2012) retrieved large quantities of articles, we restricted the studies to those published in Europe between January 1, 2000 and September 30, 2012. After initial screening of the retrieved studies by two independent reviewers, the abstracts and full text copies of potentially relevant studies were obtained and their eligibility for inclusion was independently assessed by two reviewers (BN and LH). Any discrepancies were resolved by consensus and, if necessary, a third reviewer (AS) arbitrated.

Outcomes

The food allergy outcomes assessed in this review included cow's milk, egg, wheat, soy, peanut, tree nut, fish, and shellfish. We included eligible studies that have assessed these outcomes based on self-report (i.e., participants or their parents reported that they have any of the outcomes or not), skin prick test (SPT) positivity, specific immunoglobulin E (IgE) positivity, open food challenge (OFC)/double blind placebo-controlled food challenge (DBPCFC)-positivity, OFC/DBPCFC-positivity or convincing clinical history (i.e., outcomes confirmed by a convincing clinical judgment by a physician without food challenge).

Assessment of risk of bias

We assessed the risk of bias in the studies by using an adapted and modified relevant version of the Critical Appraisal Skills Programme (CASP) quality assessment tool (http://www.casp-uk.net/). As we described in our previous report, each component of the studies (i.e., the appropriateness of the study design for the

research question, the risk of selection bias, exposure measurement, and outcome assessment) was graded and an overall grading was calculated from grading for the different study components (9). Two reviewers (BN and LH) independently assessed the risk of bias in the studies and any discrepancies were resolved by consensus and, if necessary, a third reviewer (AS) arbitrated.

Analysis

Using a customized data extraction form, we recalculated all the frequency estimates of food allergy occurrence if adequate data were provided by authors using minimal measured events rather than extrapolated estimates. If any discrepancies were observed between our recalculated estimates and those of the authors, we preferentially reported our recalculated estimates. If inadequate data were given to enable recalculation, we reported the estimates provided by the authors. Where needed and possible, we contacted authors of primary studies for clarifications. To adjudge the precision of the prevalence estimates presented in the studies, we extracted the 95% confidence intervals (95% CI) of the estimates from the studies and where we undertook the recalculation of the estimates, the 95% CI were computed by using the Wilson score method without continuity correction (11). All the different reports from the same primary study were reported together. We performed a random-effects meta-analysis for clinically and methodologically comparable studies (comparable particularly with regards to the type of endpoint measure [point or lifetime prevalence] and assessment method [self-report, SPT, IgE, FC] reported in the studies), excluding systematic reviews, to estimate the prevalence of each specific food allergy based on the different assessment methods.

The pooled estimates were stratified by age (≤ 1 year, 2-5 years, 6-17 years, ≥18 years) and geographical region of Europe (i.e., East, West, South, and North). A study with overlap between the age groups was included in an age group if the age distribution was skewed to that age group. For cohort studies that gave frequency estimates at different ages for the same individuals, we used the estimates for the highest age within each age strata in computing the pooled estimates. For studies reporting more than one tree nut, each tree nut was separately included in the pooled estimates. The heterogeneity of the estimates was computed both for the stratified analysis and for all the groups combined. Statistical analyses were undertaken using STATA 11 (Stata Corp, College Station, Tx).

Results

Study selection and characteristics

Our initial database searches identified 4053 articles and an additional 11 studies through hand searches and expert suggestions, giving a total of 4064 articles that were screened. After removal of duplicates and taken into account the pre-defined exclusions based on titles and abstracts, the full texts of 109 articles were examined in more detail. For the current report, of the 109 articles, 26 were excluded for not being population-based, 8 for not studying any of the eight specific food allergies of interest, and 10 excluded for being unable to be translated into English, leaving us with 65 papers (based on 50 primary studies) that were finally included in the narrative synthesis (12-80), and 42 studies included in at least one meta-analysis. Of the 50 primary studies reviewed, 27 were cross-sectional studies, 17 cohort studies, three systematic reviews, and three case-control studies. A majority of the studies (n = 37) were undertaken exclusively in children, usually those less than 18 years of age. The majority of the studies were from Northern and Western Europe.

Of the 50 primary studies, 42 examined cow's milk allergy, 44 egg allergy, 25 wheat allergy, 17 soy allergy, 36 peanut allergy, 26 tree nut allergy, 31 fish allergy, and 15 shellfish allergy (Table 1 and Tables E1 & E2). Of the 42 studies included in the meta-analysis, 35 were included for cow's milk allergy, 33 for egg allergy, 17 for wheat allergy, 11 for soy allergy, 29 for peanut allergy, 20 for tree nut allergy, 19 for fish allergy, and 9 for shellfish allergy. For each specific food allergy, all of the assessment methods (self-report, SPT sensitization, specific IgE sensitization, and food challenge) were employed to measure food allergy, although self-report was most commonly used. Some studies combined symptoms plus either SPT or IgE sensitization to measure food allergy, while few studies used food challenge or convincing clinical history (Table 1). Table 1 presents the characteristics of the studies included in the review. The participation rate across studies varied widely, ranging between as low as 17.3% to 99.5%, while in several studies the participation rate was not reported.

Table 1 Summary of the characteristics of studies in the review: studies published 1 January 2000 – 30 September 2012

Reference, country[1]	Study design	Number invited/ eligible participants	Participation rate N (%)	Age of subjects	Method of outcome assessment	Measure(s) of occurrence
Burney *et al.* 2010 (12); Woods *et al.* 2001 (13), Europe, USA, Australia, New Zealand	Cross-sectional study	Not indicated	4522	20-44 years old	Self-reported, sIgE	Point and life-time prevalence
Caffarelli *et al.* 2011 (14), Italy	Cross-sectional study	900	625 (69.4)	5-14 years old	Self-reported	Point and life-time prevalence
Chafen *et al.* 2010 (15), World-wide	Systematic review	1216 studies	72 studies included	All age groups	Self-reported, physician-diagnosis, SPT, sIgE, OFC, DBPCFC	Point, period, life-time prevalence; cumulative incidence, incidence rate
Du Toit *et al.* 2008 (16), UK and Israel	Cross-sectional study	10786	8826 (81.8)	4-18 years old	Self-reported, clinical history, OFC	Point prevalence
Dubakiene *et al.* 2012 (17), Lithuania	Cohort study	Not indicated	1558	6-12 months old	Self-reported, SPT, sIgE, DBPCFC	Point prevalence
Eggesbø *et al.* 2003, 2001a and 2001b (18-20), Norway	Cohort study	4973	3754 (75.5)	2.5 years old	Self-reported, physician diagnosis, SPT, sIgE, OFC, DBPCFC	Point prevalence, cumulative incidence
Eller *et al.* 2009 (21), Kjaer *et al.* 2008 (22), Johnke *et al.* 2006 (23), Denmark	Cohort study	1095	562 (51.3)	6 years old	Self-reported, SPT, sIgE, OFC, DBPCFC	Point prevalence, cumulative incidence
Falcaõ *et al.* 2004 (24), Portugal	Cross-sectional study	1565	659 (42.1)	>39 years old	Self-reported	Point prevalence
Fox *et al.* 2009 (26), UK	Case-control study	Not indicated	133 cases, 310 controls	< 4 years	SPT, sIgE, DBPCFC	Point prevalence
Frongia *et al.* 2005 (27), Italy	Cross-sectional study	Not indicated	2284	11-20 years old	Self-reported	Point prevalence
Gelincik *et al.* 2008 (28), Turkey	Cross-sectional study	17064	11816 (69.2)	≥ 18 years old	Self-reported, SPT, sIgE, DBPCFC	Point and life-time prevalence
Grundy *et al.* 2002 (29), UK	Cohort study	2858	1273 (44.5)	3-4 years old	Self-report, SPT, OFC	Point prevalence
Hourihane *et al.* 2007 (31), UK	Cross-sectional study	5072	1125 (22.2)	4-5 years old	SPT, sIgE, DBPCFC	Point prevalence
Høst *et al.* 2002 (30), Denmark	Cohort study	1758	1749 (99.5)	15 years old	SPT, sIgE, OFC, DBPCFC	Point prevalence
Isolauri *et al.* 2004 (32), Finland	Cross-sectional study	Not indicated	400	7, 27, 47, 67 years	Self-reported, sIgE	Lifetime prevalence and point prevalence
Johansson *et al.* 2005 (33), Sweden and Norway	Cross-sectional study	Not indicated	Sweden 1002; Norway 500	Adults	sIgE	Point prevalence
Julge *et al.* 2001 (34), Vasar *et al.* 2000 (35), Estonia	Cohort study	455	298 (65.5)	5 years	SPT, sIgE	Point prevalence
Krause *et al.* 2002 (37), Greenland	Cross-sectional study	1213	1 068 (88.1)	5-18 years old	sIgE	Point prevalence

Table 1 (continued)

Reference, country[1]	Study design	Number invited/ eligible participants	Participation rate N (%)	Age of subjects	Method of outcome assessment	Measure(s) of occurrence
Kristinsdottir *et al.* 2011 (38), Iceland	Cohort study	Not indicated	1341	1 year old	Self-reported, SPT, specific sIgE, DBPCFC	Point prevalence
Kucosmanoglu *et al.* 2008 (39), Turkey	Cross-sectional study	1415	1015 (71.7)	8-18 months	SPT	Point prevalence
Kurulaaratchy *et al.* 2005 (40), Arshad *et al.* 2001 (41), Tariq *et al.* 2000 (42), UK	Cohort study	1536	1456 (94.8)	4 years old	SPT	Point prevalence, cumulative incidence
Kvenshagen *et al.* 2009 (43), Norway	Cohort study	Not indicated	609	2 years old	Self-reported, SPT, sIgE, OFC, DBPCFC	Point prevalence
Majkowska-Wojciechowska *et al.* 2009 (44), Poland	Cross-sectional study	Not indicated	2148	7-10 years old	Self-reported	Life-time prevalence
Marklund *et al.* 2004 (45), Sweden	Cross-sectional study	2064	1488 (72.1)	13-21 years old	Self-reported	Point prevalence
Matricardi *et al.* 2007 (46), Germany	Cross-sectional study	7609	1314 (17.3)	2-10 years old	sIgE	Point prevalence
Mossakowska *et al.* 2008 (47) Poland	Cross-sectional study	Not indicated	301	>100 years old	Self-reported	Point prevalence
Nicolaou *et al.* 2010 (48), UK	Cohort study	1085	1029 (94.8)	8 years old	Self-reported, SPT, sIgE, OFC, DBPCFC	Point and lifetime prevalence
Niggemann *et al.* 2011 (49), Germany	Cross-sectional study	26787	13100 (48.9)	0-17 years old	sIgE	Point prevalence
Orhan *et al.* 2009 (50), Turkey	Cross-sectional study	3500	2739 (78.2)	6-9 years old	Self-reported, SPT, OFC, DBPCFC	Life-time and point prevalence
Östblom *et al.* 2008a, 2008b, 2008c (51-53) and Almqvist *et al.* 2005 (54), Sweden	Cohort study	Not indicated	4089	4-8 years old	Self-reported, sIgE	Point and period prevalence
Osterballe *et al.* 2009 (55), Denmark	Cross-sectional study	1094	843 (77.1)	Mean age 22 years	Self-reported, SPT, OFC, DBPCFC	Point prevalence
Osterballe *et al.* 2005 (56), Denmark	Cohort study	Not indicated	1834	Children and adults	Self-reported, physician diagnosis, SPT, sIgE, OFC, DBPCFC	Point prevalence
Penard-Morand *et al.* 2005 (57), France	Cross-sectional study	9615	7781 (80.9)	9-11 years old	Self-reported, SPT	Point prevalence
Pereira *et al.* 2005 (58), UK	Cross-sectional study	3144	1532 (48.7)	11 and 15 year old	Self-reported, physician diagnosis, SPT, OFC, DBPCFC	Point prevalence
Pyrhönen *et al.* 2011 and 2009 (59-60), Finland	Cohort study	5973	3899 (65.3)	0-4 years old	Self-reported, physician-diagnosis, SPT, sIgE, OFC	Life-time prevalence, cumulative incidence
Pyziak and Kamer 2011 (61), Poland	Cross-sectional study	Not indicated	83	6-17 years old	Self-reported, sIgE, SPT, OFC	Point prevalence
Rance *et al.* 2005 (62), France	Cross-sectional study	3500	2716 (77.6)	Mean age 8.9 years	Self-reported	Point and life-time prevalence

Table 1 (continued)

Reference, country[1]	Study design	Number invited/ eligible participants	Participation rate N (%)	Age of subjects	Method of outcome assessment	Measure(s) of occurrence
Roberts *et al.* 2005 (63) and Lack *et al.* 2003 (64), UK	Cohort study	13971	12090 (86.5)	0-7 years	Self-reported, SPT, DBPCFC	Point Prevalence
Rona *et al.* 2007 (65), World-wide	Systematic review	Not indicated	Number of studies included in review not indicated	All age groups	Self-reported, physician-diagnosis, SPT, sIgE, OFC, DBPCFC	Point, period, life-time prevalence, cumulative incidence, incidence rate
Ronchetti *et al.* 2008 (66), Italy	Cross-sectional study	Not indicated	380	9 and 13 years old	SPT	Point prevalence
Sandin *et al.* 2005 (67), Sweden and Estonia	Case-control study	All 985 Sweden 645 Estonia 340	All 770 (78.2) Sweden 483 (74.9) Estonia 287 (84.4)	10-11 years old	Self-report, sIgE	Point prevalence
Schnabel *et al.* 2010 (68), Germany	Cohort study	3097	1082 (34.9)	6 years old	Self-reported, sIgE	Point prevalence
Schäfer *et al.* 2001 (69), Germany	Nested case-control study	2539	1537 (60.5)	25-74	Self-reported, SPT	Point prevalence, lifetime prevalence
Soost *et al.* 2009 (70) and Zuberbier *et al.* 2004 (72), Roehr *et al.* 2004 (71), Germany	Cross-sectional study	13300	All: 4093 (30.8) Age 0-17 years: 739 Age 18-79 years: 3227	0-79 years old	Self-reported, physician diagnosis, SPT, sIgE, OFC, SBPCFC, DBPCFC	Point and life-time prevalence
Steinke *et al.* 2007 (73), Europe	Cross-sectional study	Not indicated	40426	< 18 years	Self-reported	Point prevalence
Venter *et al.* 2010 (74), UK	Cohort study	5283	3382 (64.0)	3-4 years old	Physician diagnosis, SPT, sIgE, OFC, DBPCFC	Point prevalence
Venter al 2008 (75); Dean *et al.* 2007 (76); Venter *et al.* 2006 (77), UK	Cohort study	1096	969 (88.4)	3 years old	Self-report, SPT, OFC, DBPCFC	Point and period prevalence, cumulative incidence
Venter *et al.* 2006 (78), UK	Cross-sectional study	1440	798 (55.4)	6 years old	Self-report, SPT, OFC, DBPCFC	Point prevalence
von Hertzen *et al.* 2006 (79), Finland and Russia	Cross-sectional study	Finland: children 546 mothers 546	Finland: Children 413 (75.6) Mothers 409 (74.9)	7-16 years children	SPT	Point prevalence
Zuidmeer *et al.* 2008 (80), World-wide	Systematic review	396 studies	33 studies included	All age groups	Self-reported, physician-diagnosis, SPT, sIgE, OFC, DBPCFC	Point, period, and life-time prevalence

[1]All studies were graded as at moderate overall risk of bias, except Caffarelli *et al.*(14) which was graded strong.
CI = confidence interval; DBPCFC = double blind placebo-controlled food challenge; OFC = oral food challenge; sIgE = specific immunoglobulin E; SPT = skin prick test; SR = self-reported

Assessment of risk of bias

We presented details of the risk of bias grading of the studies included in this systematic review in our first report (9). The overall grading indicates that almost all of the studies (n = 48) had a "moderate" grading, while only one study had "strong" grading.

Frequency of food allergy

The detailed results of the frequencies of the different food allergies are shown in Tables E1 & E2. Table E3 shows the summarized ranges of frequencies for each food allergy for the different age groups (< 1, 2-5, 6-17, ≥ 18 years) according to the different assessment methods used to measure food allergy. Estimates in Table E3 are the lifetime prevalence for self-reported food allergy and point prevalence for all assessment methods. The pooled prevalence estimates of the specific food allergies are shown in Figures 1-8 and Figures E2-E9. There was significant heterogeneity between the studies when pooled together regardless of the assessment method used.

Cow's milk allergy

The detailed estimates of the frequency of cow's milk allergy are presented in Table E1 and range of estimates in Table E3. Across all assessment methods and age groups, the prevalence of cow's milk allergy varied across studies, the greatest variation seen in point prevalence of self-reported cow's milk allergy. The range of point prevalence of food-challenged cow's milk allergy was the same for all age groups (0.0%-3.0%) (Table E3). The pooled age-stratified prevalence estimates of cow's milk allergy according to the different assessment methods are shown in Figure 1 and the region-stratified estimates are shown in Figure E2. The overall lifetime prevalence of self-reported cow's milk allergy was 6.0% (95% CI 5.7-6.4). The overall point prevalence of self-reported cow's milk allergy was 2.3% (95% CI 2.1-2.5); 0.3% (95% CI 0.03-0.6) for SPT positivity; 4.7 (95% CI 4.2-5.1) for specific-IgE positivity; 0.6% (95% CI 0.5-0.8) for FC positivity; and 1.6% (95% CI 1.2-1.9) for FC or history of cow's milk allergy. In most cases these estimates were usually higher in younger age groups than older ones (Figure 1). The region-stratified estimates show that in most cases, the estimates of cow's milk allergy according to each assessment method were higher in Northern Europe than in other regions (Figure E2).

Egg allergy

Frequency estimates of hen's egg allergy are shown in Table E1 and the range of estimates in Table E3. The ranges of the prevalence estimates of egg allergy were comparable across the age groups regardless of the assessment method used, but varied widely between studies (Table E3). The pooled age-stratified prevalence estimates of egg allergy according to the different assessment methods are shown in Figure 2 and the region-stratified estimates are shown in Figure E3. The overall lifetime prevalence of self-reported egg allergy was 2.5% (95% CI 2.3-2.7). The overall point prevalence of self-reported egg allergy was 1.5% (95% CI 1.3-1.6); 0.8% (95% CI 0.6-0.9) for SPT positivity; 3.6 (95% CI 3.2-4.0) for specific-IgE positivity; 0.2% (95% CI 0.2-0.3) for FC positivity; and 1.0% (95% CI 0.8-1.3) for FC or history of egg allergy. The estimates were usually higher in younger age groups than older ones (Figure 2), while the region-stratified estimates were highest in Northern Europe (Figure E3).

Wheat allergy

Frequency estimates of wheat allergy are shown in Table E1 and the range of estimates in Table E3. The ranges of the prevalence estimates of wheat allergy were also comparable across the age groups regardless of the assessment method used, but varied between studies (Table E3). The overall pooled estimate of wheat allergy was 3.6% (95% CI 3.0-4.2) for lifetime self-reported prevalence; 1.5% (95% CI 1.3-1.8) for point self-reported prevalence; 0.7% (95% CI 0.4-1.0) for SPT positivity; 3.9 (95% CI 3.4-4.4) for specific-IgE positivity; 0.1% (95% CI 0.01-0.2) for food challenge positivity; and 0.3% (95% CI 0.02-0.6) for food challenge or history of wheat allergy. Although in most cases, the estimates appeared higher in older age groups than younger ones, the data were insufficient to compare the between age groups as in many cases only one study was available for a particular age group (Figure 3). The region-stratified estimates were higher in Northern Europe for lifetime and point self-reported prevalence, but higher in Southern Europe for point prevalence of SPT positivity and in Western Europe for specific-IgE positivity, FC positivity and FC or history of wheat allergy (Figure E4).

Soy allergy

Frequency estimates of soy allergy are shown in Table E1 and the range of estimates in Table E3. For each assessment method, the ranges of the prevalence

estimates of soy allergy were comparable across the age groups and between studies, although some notable variations between studies were seen for specific-IgE positivity (Table E3). Only one study each was eligible for pooling for lifetime self-reported prevalence and SPT positivity, and no study for FC or history of soy allergy, hence no pooled estimates are presented for these assessment methods. The overall pooled point prevalence of self-reported soy allergy was 1.5% (95% CI 1.2-1.8); 3.2% (95% CI 2.7-3.6) for specific-IgE positivity; and 0.3% (95% CI 0.1-0.4) for FC positivity. Although estimates appeared higher in younger children than the older age groups, there were insufficient data to compare the pooled estimates between age groups as in most cases only one study was available for a particular age group (Figure 4). The region-stratified estimates showed that all studies on point self-reported prevalence of soy allergy were undertaken only in Northern Europe, while others were done only in Northern and Western Europe. The point prevalence of specific-IgE positivity and FC positivity were higher in Western than Northern Europe (Figure E5).

Peanut allergy

Frequency estimates of peanut allergy are shown in Table E2 and the range of estimates in Table E3. For each assessment method, the ranges of prevalence estimates of peanut allergy were comparable across age groups, but there were variations between studies particularly with regards to specific-IgE positivity (Table E3). The overall lifetime prevalence of self-reported peanut allergy was 0.4% (95% CI 0.3-0.6); 1.7% (95% CI 1.5-1.8) for self-reported point prevalence; 1.7% (95% CI 1.6-1.9) for SPT positivity; 8.6% (95% CI 8.2-9.0) for specific-IgE positivity; 0.2% (95% CI for 0.2-0.3) for FC positivity; and 1.6% (95% CI 1.2-1.9) for FC or history of peanut allergy. In most cases the estimates were higher in older age groups than in younger children (Figure 5), while the region-stratified estimates were mostly higher in Western Europe than in other regions (Figure E6).

Tree nut allergy

Frequency estimates of tree nut allergy are shown in Table E2 and the range of estimates in Table E3. Generally, the ranges of prevalence estimates for each assessment method of tree nut allergy were comparable across age groups, except for SPT positivity where the estimates appeared much higher in the older age groups. There were no studies on specific-IgE assessment of tree nut allergy among children 17 years and younger. Variations between studies were particularly seen with regards to specific-IgE positivity, and SPT positivity (Table E3). Only one study was eligible for pooling with regards to assessment of tree nut allergy based on specific-IgE positivity, hence no pooled estimates were presented for specific-IgE positivity. The overall lifetime prevalence of self-reported tree nut allergy was 1.3% (95% CI 1.2-1.5); 1.8% (95% CI 1.6-2.0) for point self-reported prevalence; 0.6% (95% CI 0.5-0.7) for SPT positivity; 0.5% (95% CI for 0.08-0.8) for FC positivity; and 0.1% (95% CI 0.1-0.2) for FC or history of tree nut allergy. The estimates were higher in older age groups than in younger children (Figure 6), while the region-stratified estimates were mostly higher in Northern Europe than in other regions (Figure E7).

Fish allergy

Frequency estimates of fish allergy are shown in Table E2 and the range of estimates in Table E3. The ranges of prevalence estimates for each assessment method of fish allergy were comparable across age groups and wide variations were seen between studies based on lifetime and point self-reported prevalence of fish allergy (Table E3). The overall lifetime prevalence of self-reported fish allergy was 2.2% (95% CI 1.8-2.5); 0.6% (95% CI 0.5-0.7) for point self-reported prevalence; 0.6% (95% CI 0.5-0.8) for SPT positivity; 0.7% (95% CI for 0.4-0.9) for specific-IgE positivity; 0.1% (95% CI 0.02-0.2) for FC positivity; and 0.1% (95% CI 0.01-0.2) for FC or history of fish allergy. The estimates were higher in younger age groups with regards to lifetime self-reported prevalence and specific-IgE positivity, but higher in older age groups based on other assessment methods (Figure 7). The region-stratified estimates were highest in Northern Europe (Figure E8).

Shellfish allergy

Frequency estimates of shellfish allergy are shown in Table E2 and the range of estimates in Table E3. There were no studies on lifetime self-reported prevalence of shellfish allergy among children ≤ 5 years, on specific-IgE positivity among children 17 years and younger, and no studies altogether on FC or history among all age groups. The ranges of prevalence estimates for each assessment method of shellfish allergy were comparable across age groups and wide variations were

seen between studies based on point prevalence of self-reported shellfish allergy (Table E3). In pooling, there were no eligible studies on SPT positivity, specific-IgE positivity, and FC or history; hence pooled estimates are not presented for these assessment methods. The overall lifetime prevalence of self-reported shellfish allergy was 1.3% (95% CI 0.9-1.7); 0.7% (95% CI 0.6-0.8) for point self-reported prevalence; and 0.1% (95% CI 0.06-0.3) for FC positivity. The estimates were higher in older age groups than in younger age groups (Figure 8). All studies on lifetime self-reported prevalence of shellfish allergy were undertaken in Western Europe, while studies on point prevalence of self-reported shellfish allergy and FC positivity were undertaken only in Western and Northern Europe. While the pooled estimates for self-reported point prevalence of shellfish allergy was higher in Northern Europe, the estimates were comparable between the two regions with regards to FC positivity (Figure E9).

Discussion

Statement of main findings

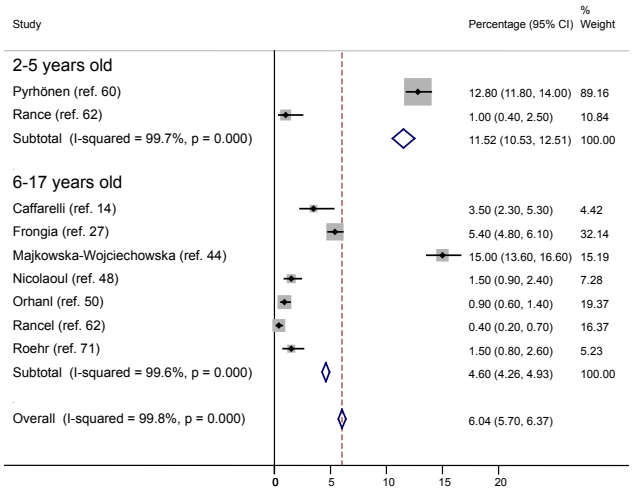
This synthesis of studies provides the most comprehensive and up-to-date estimates of the frequency of the eight most common specific food allergies across different age groups and geographical regions in Europe. Overall, most studies were graded as at "moderate" risk of bias, taking into account appropriateness of the study design, potential for selection bias, and exposure and outcome assessments methods used. Most of the studies were undertaken among children, usually those less than 18 years old. Only a few studies were done in Eastern and Southern Europe compared to studies from Western and Northern Europe.

The overall pooled lifetime self-reported prevalence was highest for cow's milk allergy (6.0%) and lowest for soy allergy (0.3%). The point prevalence of self-reported was also highest for cow's milk allergy (2.3%) but lowest for fish allergy (0.6%). Based on objectively verified FC, the prevalence was also highest for cow's milk allergy (0.6%) and lowest for wheat and shellfish allergies, both each having 0.1% prevalence. Generally, the prevalence of cow's milk allergy and egg allergy were higher in younger age groups than older age groups, while the prevalence of peanut allergy, tree nut allergy, fish allergy, and shellfish allergy were higher in the older age groups than the younger age groups. There were insufficient data to compare the estimates of soy and wheat allergy between the age groups as in most cases only one study was available for particular age group. The prevalence of cow's milk allergy, egg allergy, wheat allergy, tree nut allergy, fish allergy, and shellfish allergy were in general higher in Northern Europe than other regions, while the prevalence of soy allergy and peanut allergy were higher in Western Europe than in other regions.

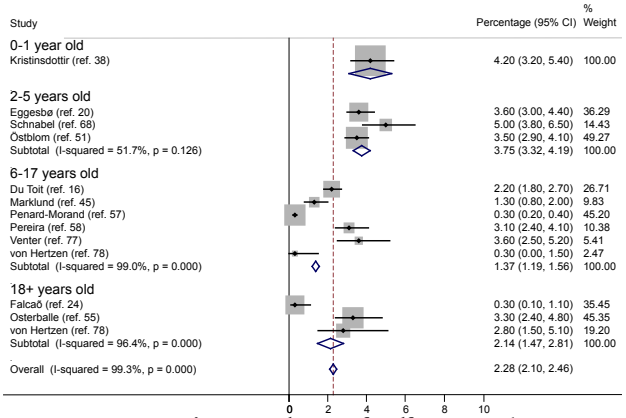
Strengths and limitations

In addition to the rigorous steps undertaken to produce the current synthesis, other strengths of the review include a comprehensive literature search that covered the major electronic databases, although we cannot rule out the possibility that our search terms might have missed some relevant articles; no language restriction; and systematic and painstaking screening and appraisal of the primary studies included. We however limited the period of the review to studies published only in Europe between 2000 and 2012 due to the large quantity of studies found at the initial search; this will limit the generalizability of findings beyond the period in focus and outside Europe. We observed significant heterogeneity between the studies, which might indicate important differences between studies in terms of study design and methods used to measure food allergy, particularly FC and SPT methodologies. There were also wide variations in participation rates across studies, ranging between 17.3% to 99.5%, while in several studies, neither the participation rates were reported nor were there adequate information provided to allow for recalculation, thus indicating potential selection bias in several of the studies. These methodological limitations will influence the estimates of the frequency of food allergies reported from this pooled analysis, most likely the pooled estimates are underestimates of the actual frequencies. We therefore recommend that caution should be exercised in interpreting these results. Unexpectedly, the point prevalence estimates of peanut and tree nut allergies were greater than their lifetime prevalence estimates. Although one reason for this discrepancy is that the estimates of lifetime and point prevalence came from different studies, a more plausible explanation is that this underscores the need for consistent study designs and reporting of results in future studies.

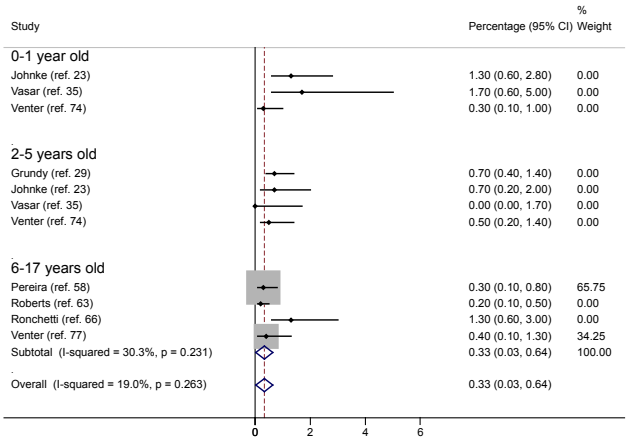
To our knowledge, this is the first study providing



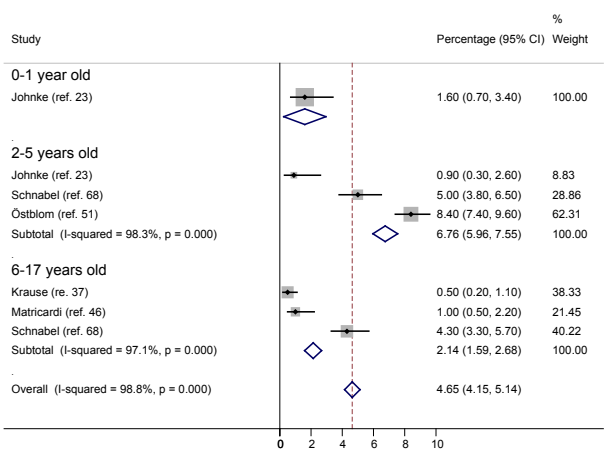
PANEL I: Lifetime prevalence of self-reported CMA



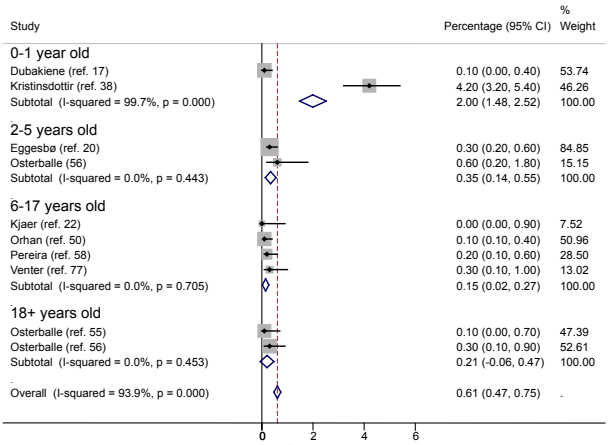
PANEL II: Point prevalence of self-reported CMA



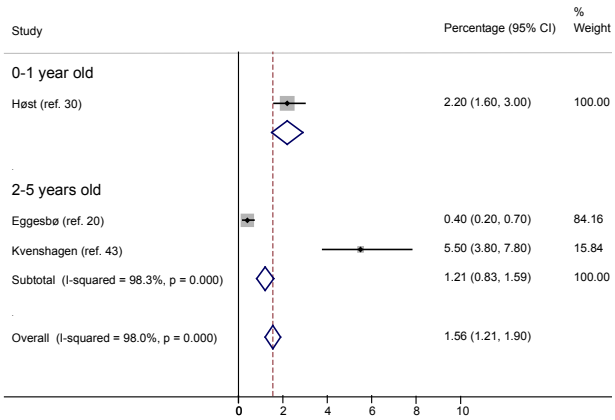
PANEL III: Point prevalence of SPT positive CMA



PANEL IV: Point prevalence of IgE positive CMA

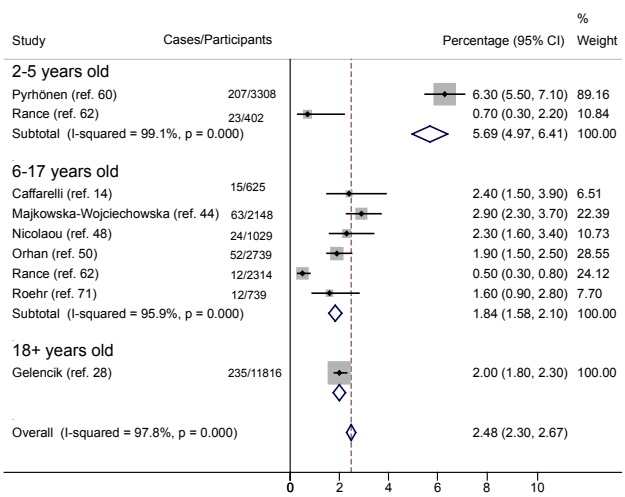


PANEL V: Point prevalence of FC positive CMA

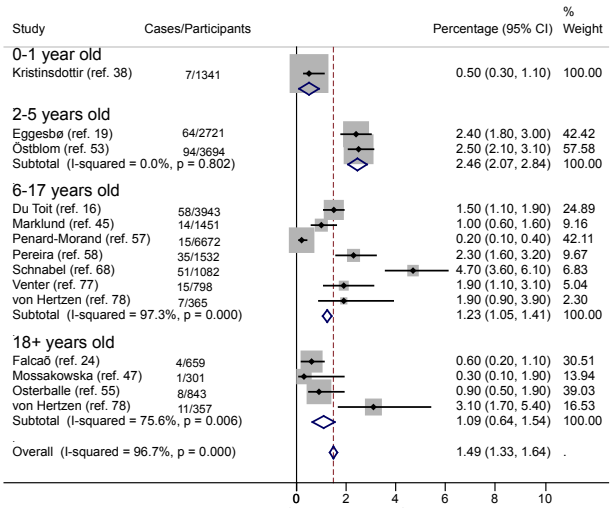


PANEL VI: Point prevalence of FC or history of CMA

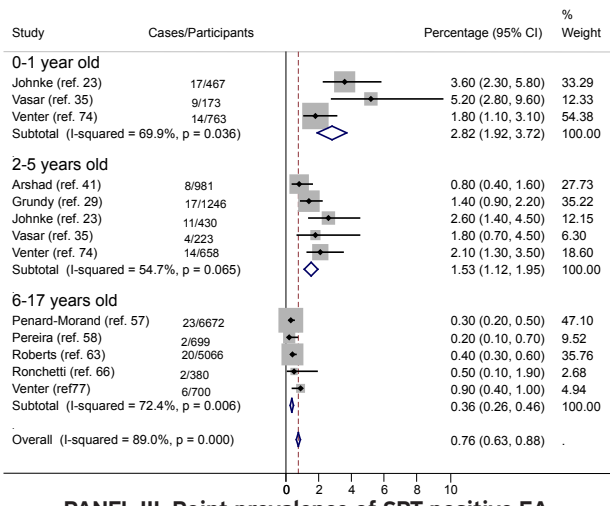
Figure 1 Age-stratified pooled prevalence of cow's milk allergy (CMA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size



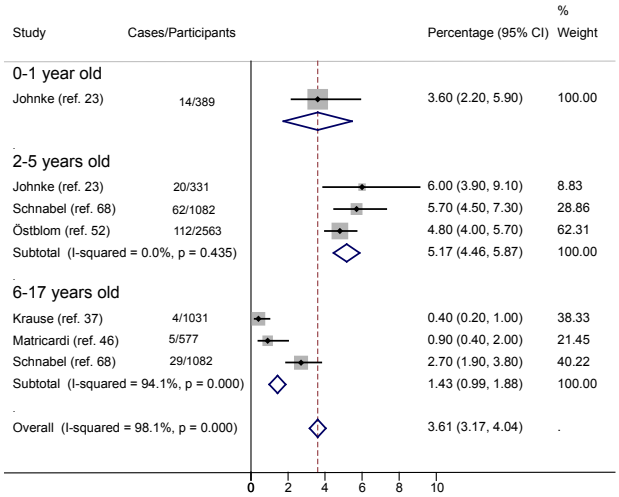
PANEL I: Lifetime prevalence of self-reported EA



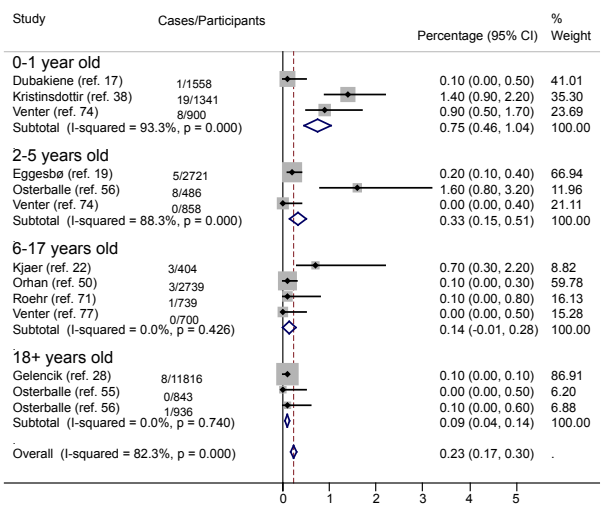
PANEL II: Point prevalence of self-reported EA



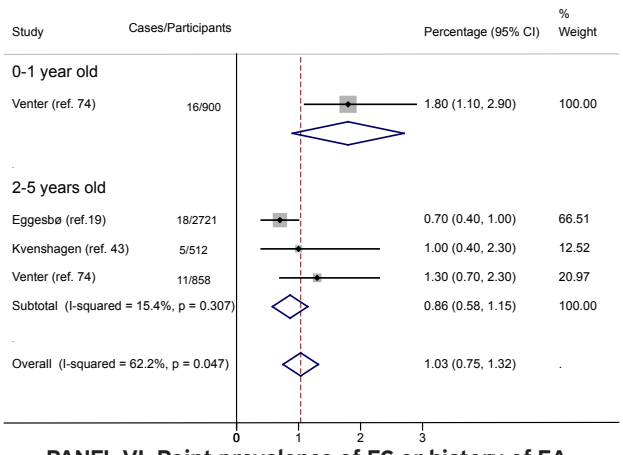
PANEL III: Point prevalence of SPT positive EA



PANEL IV: Point prevalence of IgE positive EA

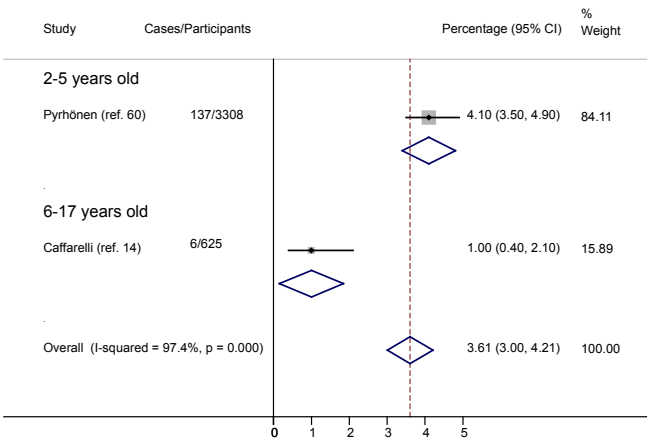


PANEL V: Point prevalence of FC positive EA

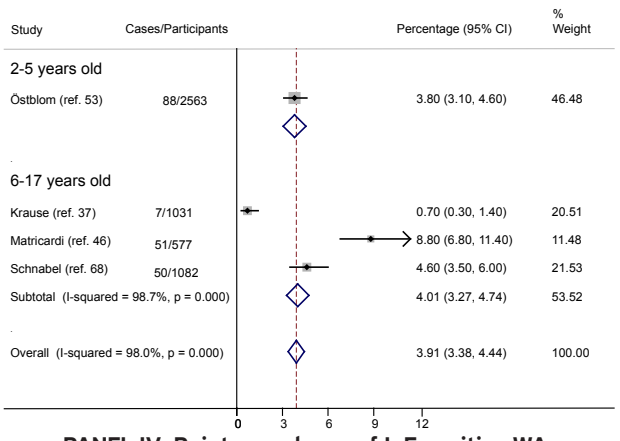


PANEL VI: Point prevalence of FC or history of EA

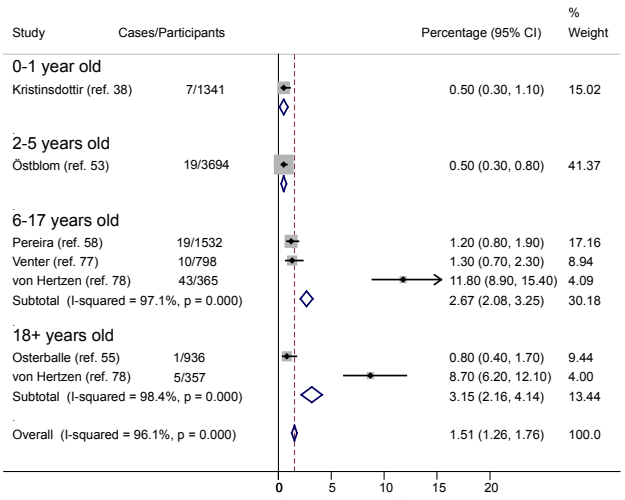
Figure 2 Age-stratified pooled prevalence of egg allergy (EA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size



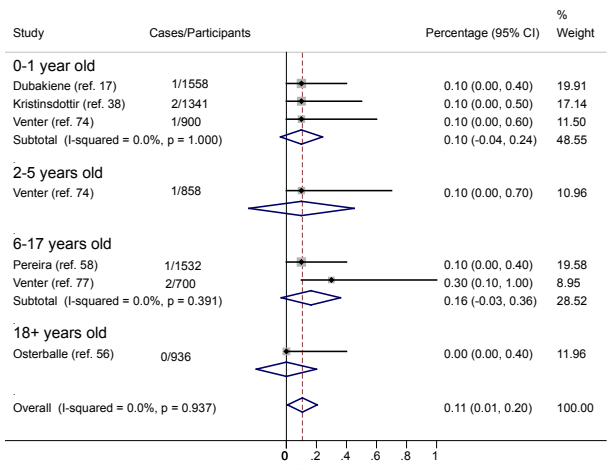
PANEL I: Lifetime prevalence of self-reported WA



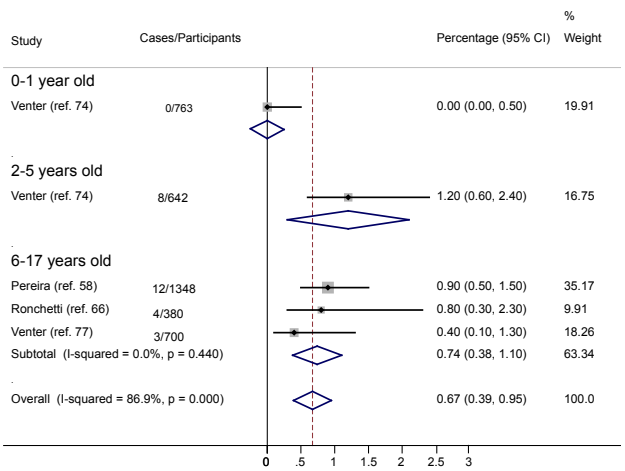
PANEL IV: Point prevalence of IgE positive WA



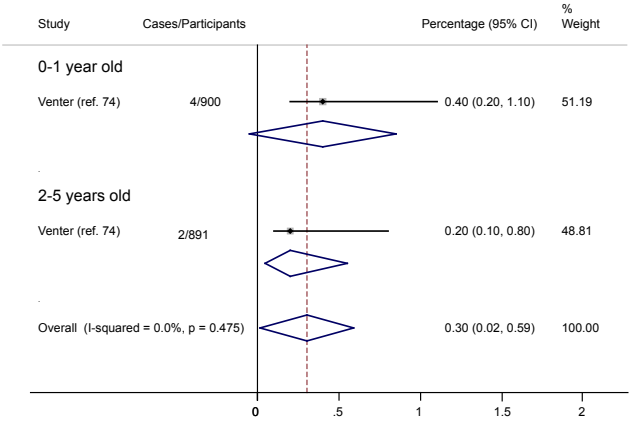
PANEL II: Point prevalence of self-reported WA



PANEL V: Point prevalence of FC positive WA

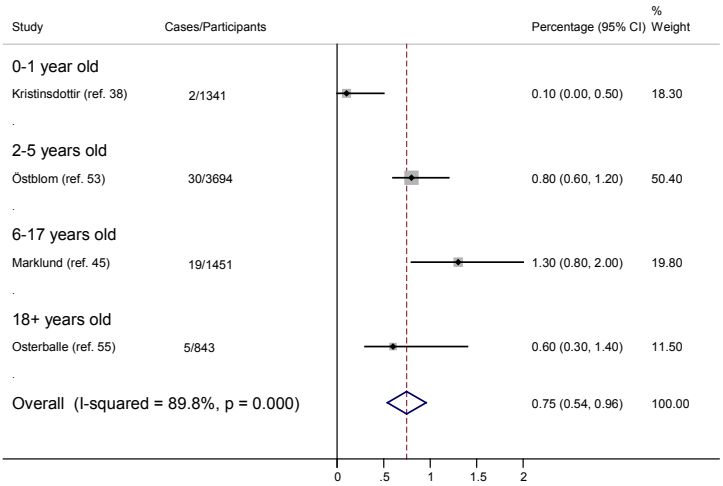


PANEL III: Point prevalence of SPT positive WA

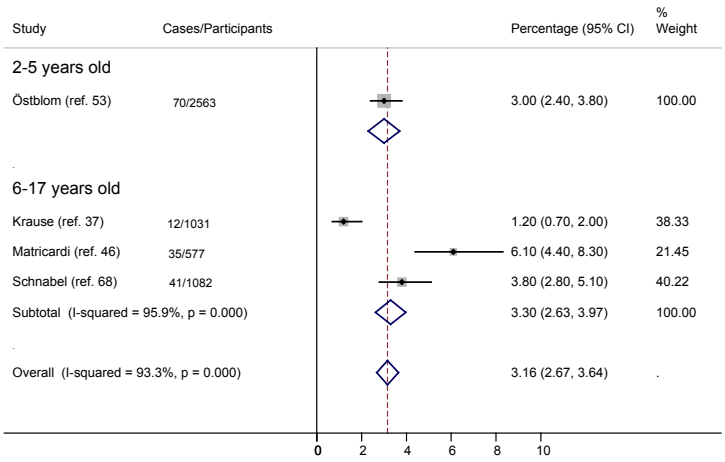


PANEL VI: Point prevalence of FC or history of WA

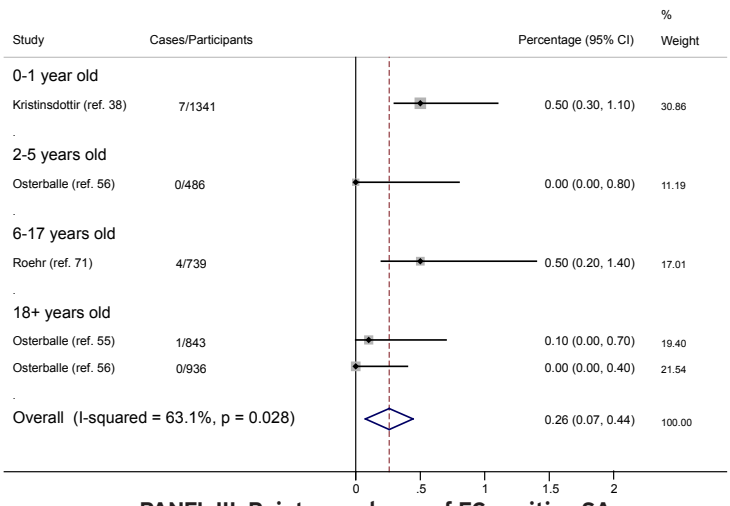
Figure 3 Age-stratified pooled prevalence of wheat allergy (WA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size



PANEL I: Point prevalence of self-reported SA

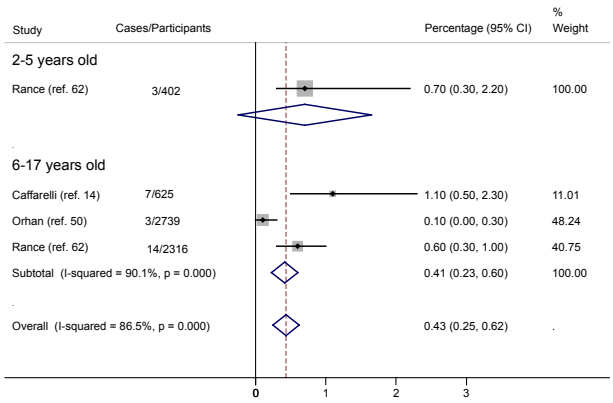


PANEL II: Point prevalence of IgE positive SA

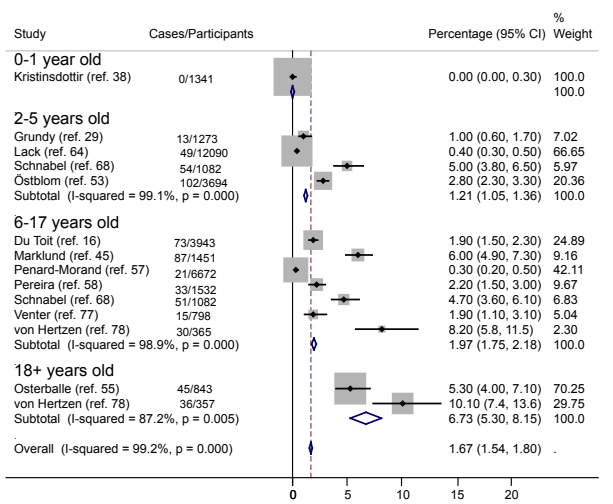


PANEL III: Point prevalence of FC positive SA

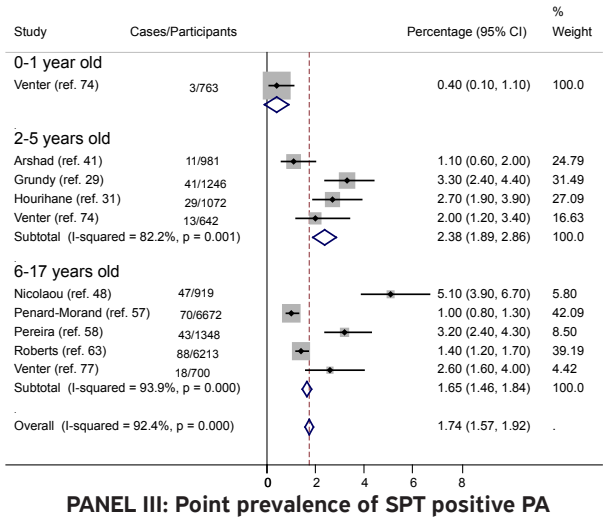
Figure 4 Age-stratified pooled prevalence of soy allergy (SA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size



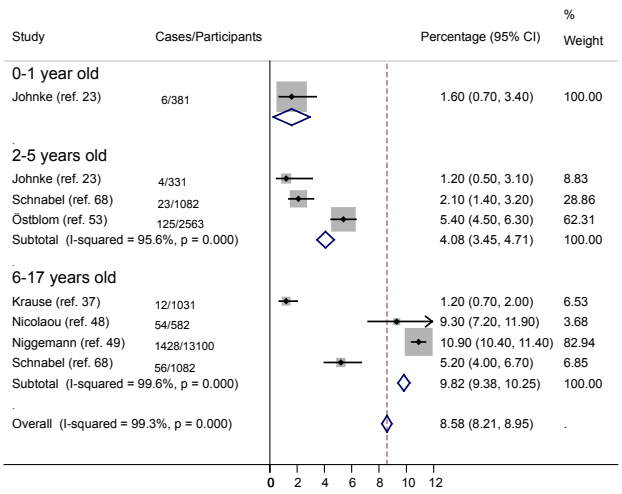
PANEL I: Lifetime prevalence of self-reported PA



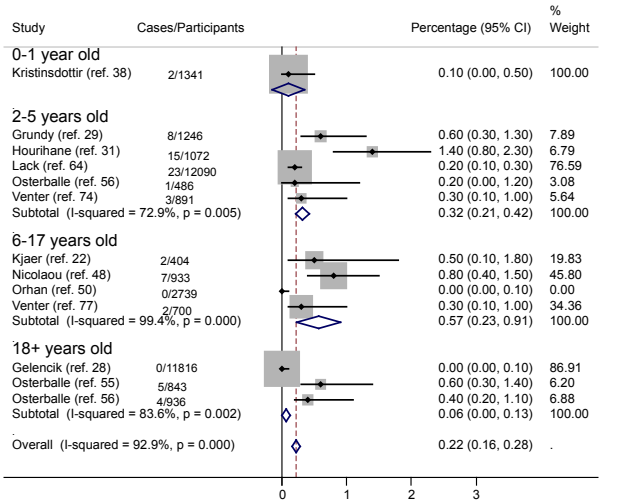
PANEL II: Point prevalence of self-reported PA



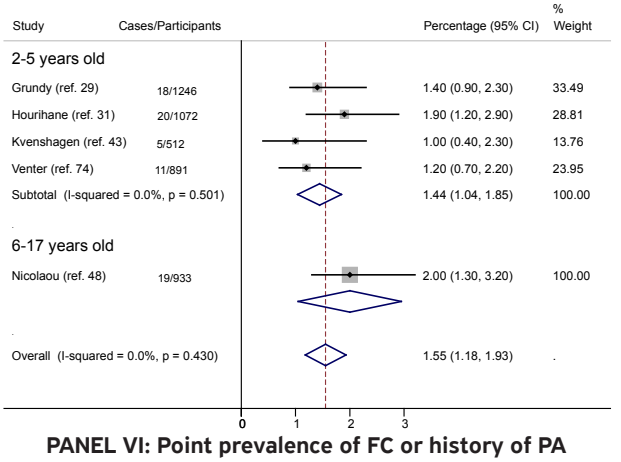
PANEL III: Point prevalence of SPT positive PA



PANEL IV: Point prevalence of IgE positive PA

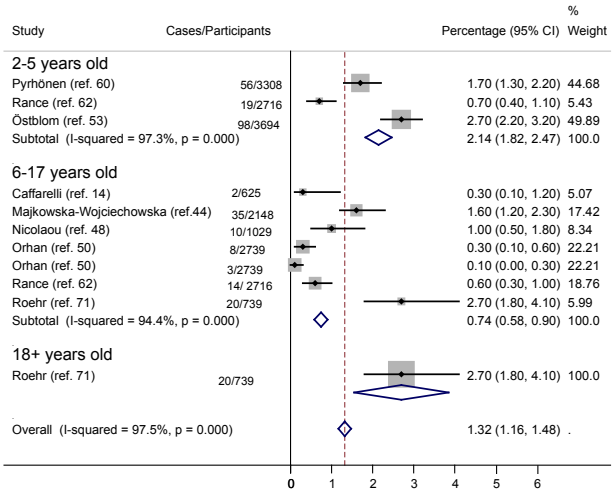


PANEL V: Point prevalence of FC positive PA

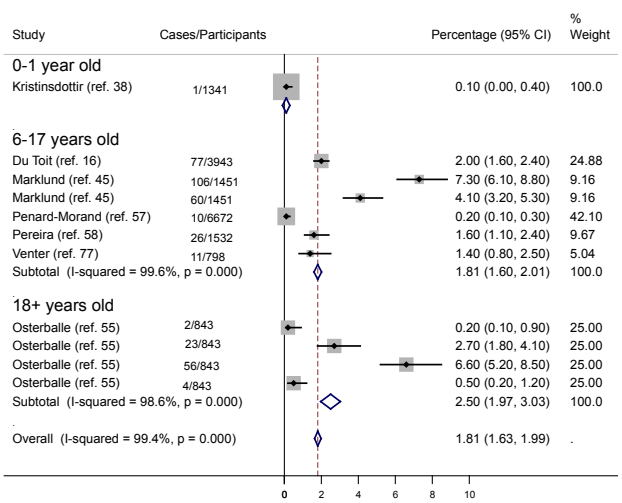


PANEL VI: Point prevalence of FC or history of PA

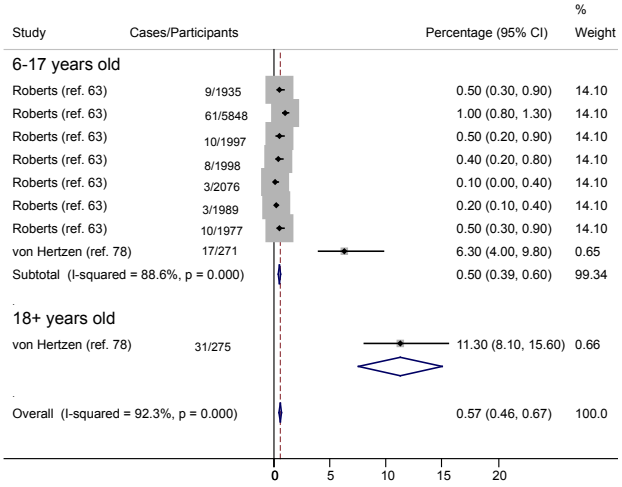
Figure 5 Age-stratified pooled prevalence of peanut allergy (PA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size



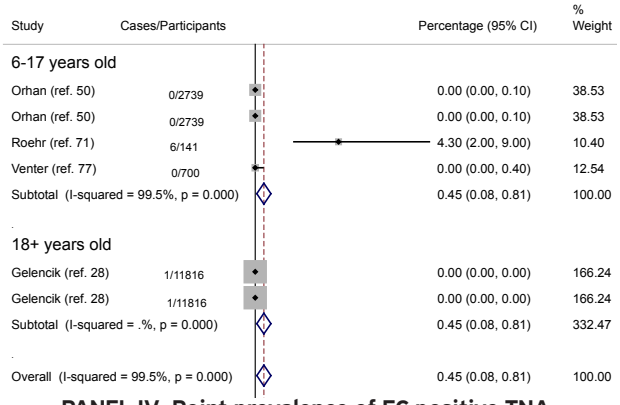
PANEL I: Lifetime prevalence of self-reported TNA



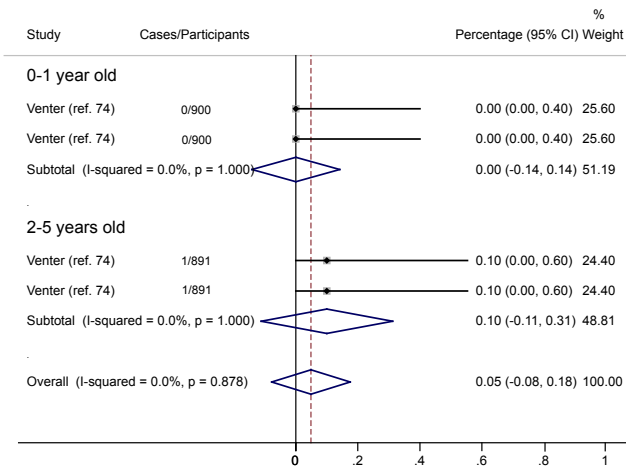
PANEL II: Point prevalence of self-reported TNA



PANEL III: Point prevalence of SPT positive TNA

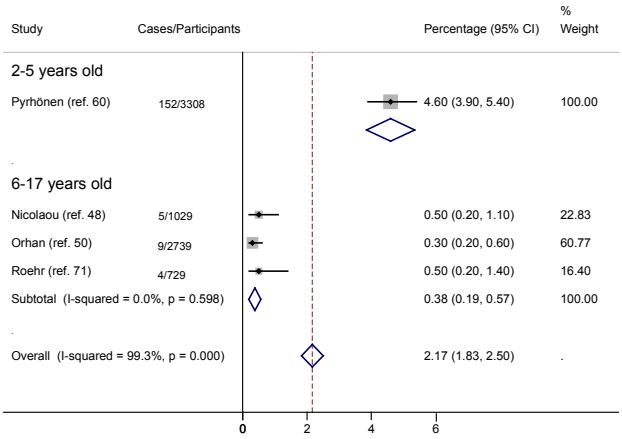


PANEL IV: Point prevalence of FC positive TNA

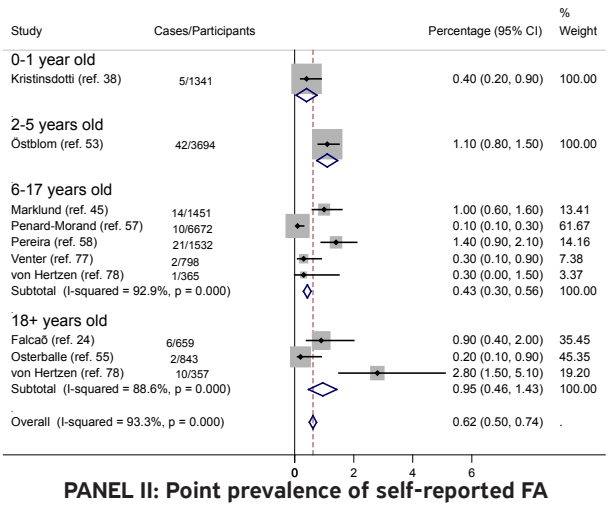


PANEL V: Point prevalence of FC or history of TNA

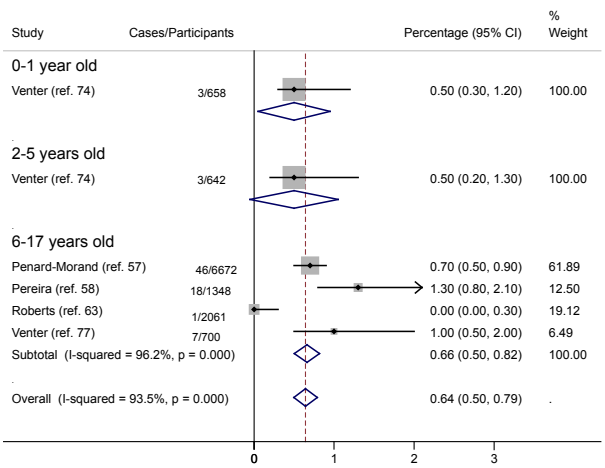
Figure 6 Age-stratified pooled prevalence of tree nut allergy (TNA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size



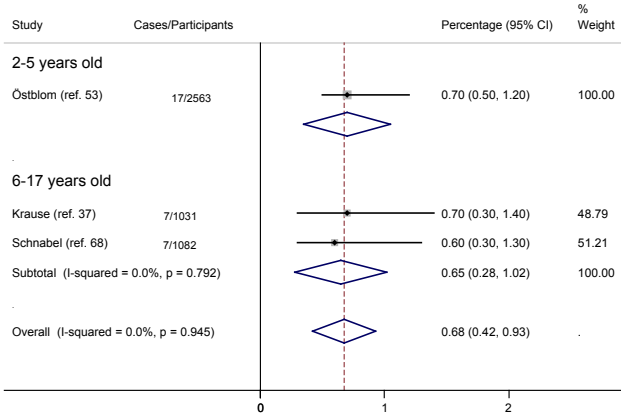
PANEL I: Lifetime prevalence of self-reported FA



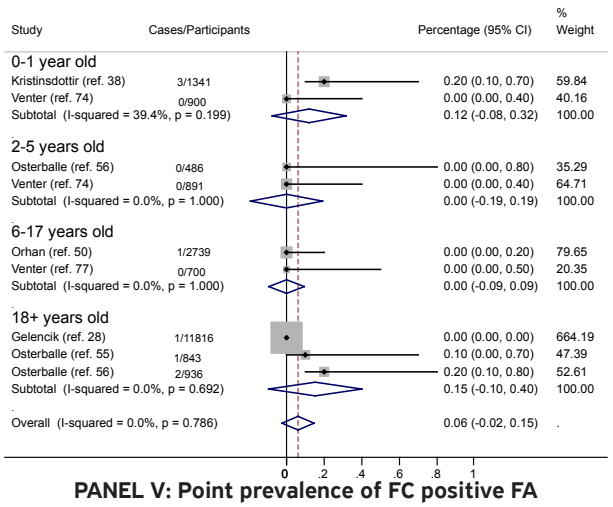
PANEL II: Point prevalence of self-reported FA



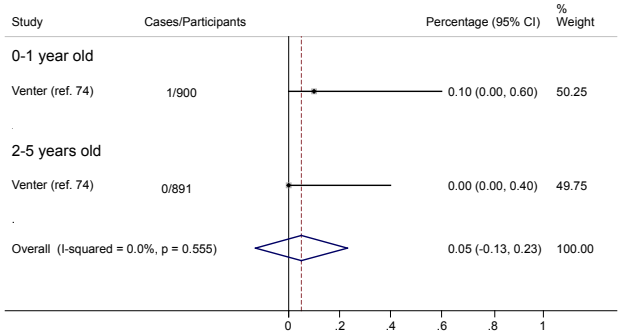
PANEL III: Point prevalence of SPT positive FA



PANEL IV: Point prevalence of IgE positive FA

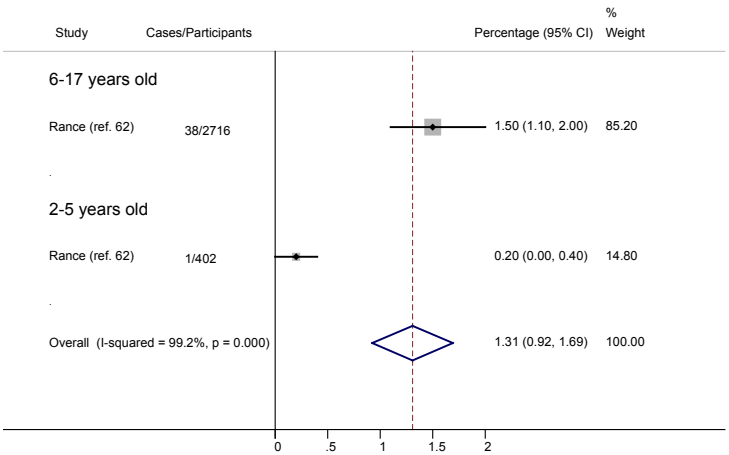


PANEL V: Point prevalence of FC positive FA

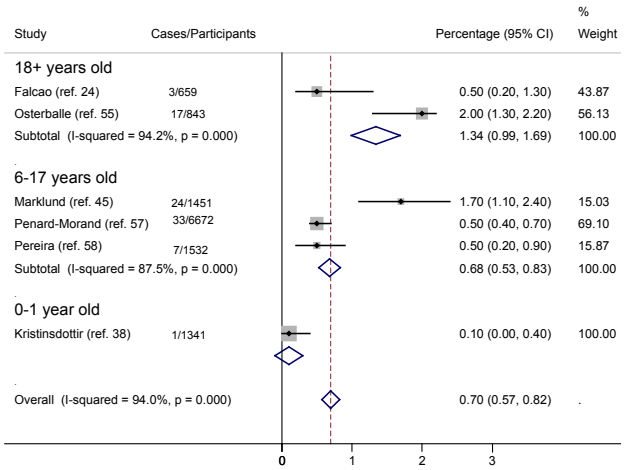


PANEL VI: Point prevalence of FC or history of FA

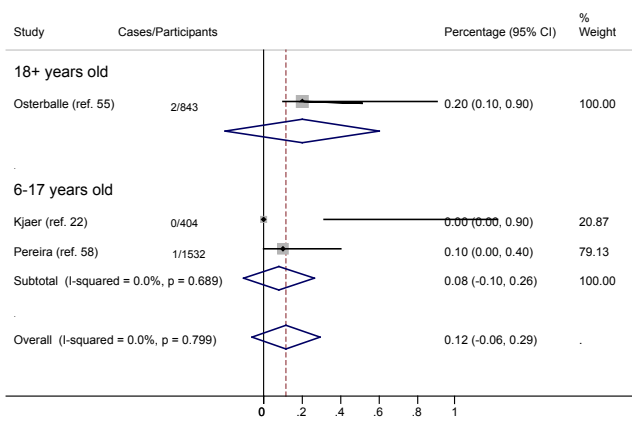
Figure 7 Age-stratified pooled prevalence of fish allergy (FA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size



PANEL I: Lifetime prevalence of self-reported SFA



PANEL II: Point prevalence of self-reported SFA



PANEL III: Point prevalence of FC positive SFA

Figure 8 Age-stratified pooled prevalence of shellfish allergy (SFA) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI and boxes represent study size

comprehensive estimates of the prevalence of the most common specific food allergies across the different geographical regions of Europe and well-defined age groups. The observed regional differences in the estimates of the different food allergies may indicate the importance of spatial distributions of the diseases; hence, spatial distributions of food allergies should be considered in future studies. The observed regional differences may also reflect the variations and non-standardized methods applied in the assessment of food allergies across the different European settings. Very few studies were undertaken in Eastern and Southern Europe, possibly a true reflection of fewer studies done in these settings in this evidence base or that most studies are published in local journals and not indexed in the databases included in our search. Clearly more studies are required from these regions in order to establish the putative frequency of food allergies.

A further strength of this study is that we were able to analyze all possible methods that have been used to measure food allergy, including self-report, SPT, specific IgE sensitization, FC, and the various combination of these measures, particularly FC or convincing clinical history. However, because of the wide variations in the definition of food allergies based on each of these methods, particularly, the cut-off points used to define IgE or SPT sensitization to food allergens across the studies, comparison of estimates across studies is challenging. As indicated in our previous report (Chapter 1.1) (9), we were interested in estimating the frequency of IgE-mediated and non-IgE-mediated phenotypes of food allergy, but this was not feasible as most studies failed to make clear the different phenotypes of food allergy studied. The methodological grading of most of the studies was moderate, and as we also noted earlier (9), there is an opportunity to improve the methodological quality of studies across all regions. In particular, more systematic application of established standard methods for assessment of food allergy across populations would improve the measurement of food allergies and allow for better comparison between studies.

Comparison of our findings with previous studies

Only three previous systematic reviews (15, 65, 80) have examined the prevalence of food allergies, however, comparison of our findings is primarily made with regards to two of these studies (65, 80) as the third study (15) presented estimates already given in one of the studies (65). Rona and colleagues (65) presented range of estimates that are to great extent comparable to the ranges of estimates we have reported in this study. It was not however clear if the self-reported estimates in that study were lifetime prevalence or point prevalence. In the study by Zuidmeer *et al.* (80), the pooled self-reported prevalence of wheat allergy among adults was 0.4% and 2.1% for point prevalence of specific IgE sensitization, although it was not also clear if the self-reported estimates were lifetime or point prevalence. The point prevalence of self-reported wheat allergy in the current study among adults was 1.5%, whereas we did not find any eligible studies for pooling among adults based on specific IgE sensitization to wheat. Among children, Zuidmeer and colleagues presented pooled self-reported prevalence of tree nut allergy of 0.5%, soy allergy of 0.3%, and SPT positivity to wheat of 0.4%. In our study, the corresponding point prevalence of self-reported tree nut allergy among children was up to 1.8%, up to 4.2% for soy allergy, and 3.9% SPT positivity to wheat, much greater estimates than the estimates given by Zuidmeer and colleagues (80). Similar to our observation, the prevalence of tree nuts compared to other allergies was higher among adults than in children in the study by Zuidmeer and colleagues (80), possibly indicating difference in timing of introduction of these foods. Some of the discrepancies between our estimates and those of the previous reviews could be explained by the fact that the previous reviews included studies from all parts of the world whereas our study was limited only to Europe. In addition, the previous reviews included studies from 1990 whereas the earliest studies in our review were those published in 2000.

Conclusions

The current study has provided so far the most comprehensive and up-to-date estimates of the eight most common food allergies across different age groups and regions in Europe. Overall, at least 1 in 20 children are believed by parents to have had one or more food allergy in their lifetime. Dairy products are the most commonly implicated foods by parents than other foods. There was up to 10-fold difference between self-reported and challenge-verified prevalence of food allergy, with these being most

marked for wheat, tree nut, egg, shellfish, and least for tree nut. This discrepancy, particularly for milk, soy, and wheat, may be due in part to non-IgE-mediated food allergy. The prevalence of food allergy varied by age groups and European regions. Further studies will improve this evidence base by employing standardized methodology for the assessment of food allergies across populations and initiating strategies that will increase participation rates across studies.

Funding

EAACI

Contributorship

AS, AM and GR conceived this review. It was undertaken by BN and LH, with the support of SSP. BN, LH, and AS led the drafting of the manuscript and all authors critically commented on drafts of the manuscript.

Conflicts of interest

None known

References

1. Allen JK, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. *Immunol Allergy Clin N Am* 2012; 32:35-50.
2. Prescott S, Allen KJ. FA: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol* 2011;22:155-160.
3. Lack G. Update on risk factors for FA *J Allergy Clin Immunol* 2012;129:1187-1197.
4. Sicherer SH. Epidemiology of FA. *J Allergy Clin Immunol* 2011;127:594-602.
5. Masilamani M, Commins S, Shreffler W. Determinants of food allergy. *Immunol Allergy Clin N Am* 2012;32:11-33.
6. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M *et al.* ICON: food allergy. *J Allergy Clin Immunol* 2012;129:906-20.
7. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004;34:520-6.
8. Worth A, Regent L, Levy M, Ledford C, East M, Sheikh A. Living with severe allergy: an Anaphylaxis Campaign national survey of young people. *Clin Transl Allergy* 2013;22:2.
9. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V *et al.* The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014;69: 62-65.
10. Nwaru BI, Panesar SS, Hickstein L, Rader T, Werfel T, Muraro A *et al.* The epidemiology of food allergy in Europe: protocol for a systematic review. *Clin Transl Allergy* 2013;3:13.
11. Newcombe RG. Two-sided confidence intervals for the single proportion: Comparison of seven methods. *Stat Med* 1998;17:857-872.
12. Burney P, Summers C, Chinn S, Hooper R, Van Ree R, Lidholm J. Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: A EuroPrevall analysis. *Allergy* 2010;65:1182-1188.
13. Woods RK, Abramson M, Bailey M, Walters EH. International prevalences of reported food allergies and intolerances. Comparisons arising from the European community respiratory health survey (ECRHS) 1991-1994. *Eur J Clin Nutr* 2001;55:298-304.
14. Caffarelli C, Coscia A, Ridolo E, Povesi Dascola C, Gelmett C, Raggi V *et al.* Parents' estimate of food allergy prevalence and management in Italian school-aged children. *Pediatr Int* 2011;53:505-510.
15. Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al.* Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;303:1848-56.
16. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR *et al.* Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-991.
17. Dubakiene R, Rudzeviciene O, Butiene I, Sezaite I, Petronyte M, Vaicekauskaite D *et al.* Studies on early allergic sensitization in the Lithuanian birth cohort. *The Scientific World Journal* 2012;909524.
18. Eggesbø M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol* 2003;112:420-426.
19. Eggesbø M, Botten G, Halvorsen R, Magnus P. The prevalence of allergy to egg: a population-based study in young children. *Allergy* 2001;56:403-411.
20. Eggesbø M, Botten G, Halvorsen R, Magnus P. The prevalence of CMA/CMPI in young children: The validity of parentally perceived reactions in a population-based study. *Allergy* 2001;56:393-402.
21. Eller E, Kjaer HF, Høst A, Andersen KE, Bindslev-Jensen C. Food Allergy and food sensitization in early childhood: Results from the DARC cohort. *Allergy* 2009;64:1023-1029.
22. Kjaer HF, Eller E, Høst A, Andersen KE, Bindslev-Jensen C. The prevalence of allergic diseases in an unselected group of 6-year-old children. The DARC birth cohort study. *Pediatr Allergy Immunol* 2008;19:737-745.
23. Jøhnke H, Norberg LA, Vach W, Høst A, Andersen KE. Patterns of sensitization in infants and its relation to atopic dermatitis. *Pediatr Allergy Immunol* 2006;17:591-600.
24. Falcão H, Lunet N, Lopes C, Barros H. Food hypersensitivity in Portuguese adults. *Eur J Clin Nutr* 2004;58:1621-1625.
25. Flokstra-de Blok BMJ, Doriene van Ginkel C, Roerdink EM, Kroeze MAJM, Stel AA, van der Meulen G N *et al.* Extremely low prevalence of epinephrine autoinjectors in high-risk

food-allergic adolescents in Dutch high schools. *Pediatr Allergy Immunol* 2011;22:374-377.

26. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy *J Allergy Clin Immunol* 2009;123:417-423.
27. Frongia O, Bellomo AR, Di Giorgio G, Fiumalbi C, Frizza J, Maresca C *et al.* Food allergies and intolerance in infants and children. Intolleranze e allergie alimentari nella prima infanzia. *Medico e Bambino* 2005;24:533-538.
28. Gelincik A, Büyükoztürk S, Gül H, Işik E, Işsever H, Ozşeker F *et al.* Confirmed prevalence of food allergy and non-allergic food hypersensitivity in a Mediterranean population *Clin Exp Allergy* 2008;38:1333-1341.
29. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;110:784-789.
30. Høst A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol* 2002;13:23-28.
31. Hourihane JO, Aiken R, Briggs R, Gudgeon LA, Grimshaw KEC, DunnGalvin A *et al.* The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry. *J Allergy Clin* 2007;119:1197-1202.
32. Isolauri E, Huurre A, Salminen S, Impivaara O. The allergy epidemic extends beyond the past few decades. *Clin Exp Allergy* 2004;34:1007-1010.
33. Johansson SGO, Nopp A, Florvaag E, Lundahl J, Söderstrom T, Guttormsen AB *et al.* High prevalence of IgE antibodies among blood donors in Sweden and Norway. *Allergy* 2005;60:1312-1315.
34. Julge K, Vasar M, Björkstén B. Development of allergy and IgE antibodies during the first five years of life in Estonian children. *Clin Exp Allergy* 2001;31:1854-1861.
35. Vasar M, Julge K, Björkstén B. Development of atopic sensitization and allergic diseases in early childhood. *Acta Paediatri* 2000;89:523-527.
36. Kotz D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. *J Allergy Clin Immunol* 2011;127:623-630, e621.
37. Krause TG, Koch A, Poulsen LK, Kristensen B, Olsen OR, Melbye M. Atopic sensitization among children in an Arctic environment. *Clin Exp Allergy* 2002;32:367-372.
38. Kristinsdóttir H, Clausen M, Ragnarsdóttir HS, Halldórsdóttir IH, McBride D, Beyer K *et al.* [Prevalence of FA in Icelandic infants during first year of life]. [Icelandic] Algengi faeduofnaemis hja islenskum bornum a fyrsta ari. *Laeknabladid* 2011;97:11-18.
39. Kucukosmanoglu E, Yazi D, Yesil O, Akkoc T, Gezer M, Bakirci N *et al.* Prevalence of egg sensitization in Turkish infants based on skin prick test. *Allergologia Et Immunopathologia* 2008;36:141-144.
40. Kurukulaaratchy RJ, Matthews S, Arshad SH. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. *Allergy* 2005;60:1280-1286.
41. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 2001;108:E33.
42. Tariq SM, Matthews SM, Hakim EA, Arshad SH. Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. *Pediatr Allergy Immunol* 2000;11:162-167.
43. Kvenshagen B, Halvorsen R, Jacobsen M. Is there an increased frequency of food allergy in children delivered by caesarean section compared to those delivered vaginally? *Acta Pædiatr* 2009;98:324-327.
44. Majkowska-Wojciechowska B, Wardzyńska A, Luczyńska M, Kowalski MK, Makowska J, Kowalski ML. Food hypersensitivity in the population of school children in Lodz - Results of the "EuroPrevall" surveys. *Alergia Astma Immunologia* 2009;14:35-44.
45. Marklund B, Ahlstedt S, Nordström G. Health-related quality of life among adolescents with allergy-like conditions: with emphasis on food hypersensitivity. *Health Qual Life Outcomes* 2004;2:65.
46. Matricardi PM, Bockelbrink A, Beyer K, Keil T, Niggemann B, Grüber C *et al.* Primary versus secondary immunoglobulin e sensitization to soy and wheat in the Multi-Centre Allergy Study cohort. *Clin Exp Allergy* 2008;38:493-500.
47. Mossakowska M, Pawlinska-Chmara R, Broczek KM. Asthma, allergy, and respiratory symptoms in centenarians living in Poland. *J Physiol Pharmacol* 2008;Suppl 6:483-489.
48. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G *et al.* Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125:191-197.
49. Niggemann B, Schmitz R, Schlaud M, The high prevalence of peanut sensitization in childhood is due to cross-reactivity to pollen. *Allergy* 2011;66:980-981.
50. Orhan F, Karakas T, Cakir M, Aksoy A, Baki A, Gedik Y. Prevalence of immunoglobulin E-mediated food allergy in 6-9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. *Clin Exp Allergy* 2009;39:1027-1035.
51. Ostblom E, Lilja G, Ahlstedt S, van Hage M, Wickman M. Patterns of quantitative food-specific IgE-antibodies and reported food hypersensitivity in 4-year-old children. *Allergy* 2008;63:418-424.
52. Ostblom E, Lilja G, Pershagen G, Van Hage M, Wickman M. Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life. *Clin Exp Allergy* 2008;38:1325-1332.
53. Ostblom E, Wickman M, van Hage M, Lilja G. Reported symptoms of food hypersensitivity and sensitization

to common foods in 4-year-old children. *Acta Paediatr* 2008;97:85-90.

54. Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin Exp Allergy* 2005;35:612-618.
55. Osterballe M, Mortz CG, Hansen TK, Andersen KE, Bindslev-Jensen C. The prevalence of food hypersensitivity in young adults. *Pediatr Allergy Immunol* 2009;20:686-692.
56. Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005;16:567-573.
57. Pénard-Morand C, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Charpin D *et al.* Prevalence of FA and its relationship to asthma and allergic rhinitis in schoolchildren. *Allergy* 2005;60:1165-1171.
58. Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. *J Allergy Clin Immunol* 2005;116:884-892.
59. Pyrhönen K, Hiltunen L, Kaila M, Näyhä S, Läärä E. Heredity of food allergies in an unselected child population: An epidemiological survey from Finland. *Pediatr Allergy Immunol* 2011;22:e124-e132.
60. Pyrhonen K, Näyhä S, Kaila M, Hiltunen L, Läärä E. Occurrence of parent-reported food hypersensitivities and food allergies among children aged 1-4 yr. *Pediatr Allergy Immunol* 2009;20:328-338.
61. Pyziak K, Kamer B. Natural history of IgE-dependent food allergy diagnosed in children during the first three years of life. *Adv Med Sci* 2011;56:48-55.
62. Rancé F, Grandmottet X, Grandjean H. Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. *Clin Exp Allergy* 2005;35:167-172.
63. Roberts G, Peckitt C, Northstone K, Strachan D, Lack G, Henderson J *et al.* Relationship between aeroallergen and food allergen sensitization in childhood. *Clin Exp Allergy* 2005;35:933-940.
64. Lack G, Fox D, Northstone K, Golding J. Factors Associated with the Development of Peanut Allergy in Childhood. *N Engl J Med* 2003;348:977-985.
65. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E *et al.* The prevalence of food allergy: A meta-analysis. *J Allergy Clin Immunol* 2007;120:638-646.
66. Ronchetti R, Jesenak M, Trubacova D, Pohanka V, Villa MP. Epidemiology of atopy patch tests with food and inhalant allergens in an unselected population of children. *Pediatr Allergy Immunol* 2008;19:599-604.
67. Sandin A, Annus T, Björkstén B, Nilsson L, Riikjärv MA, van Hage-Hamsten M *et al.* Prevalence of self-reported food allergy and IgE antibodies to food allergens in Swedish and Estonian schoolchildren. *Eur J Clin Nutr* 2005;59:399-403.
68. Schnabel E, Sausenthaler S, Schaaf B, Schäfer T, Lehmann I, Behrendt H *et al.* Prospective association between food sensitization and food allergy: Results of the LISA birth cohort study. *Clin Exp Allergy* 2010;40:450-457.
69. Schäfer T, Böhler E, Ruhdorfer S, Weigl L, Wessner D, Heinrich J *et al.* Epidemiology of food allergy/food intolerance in adults: Associations with other manifestations of atopy. *Allergy* 2001;56:1172-1179.
70. Soost S, Leynaert B, Almqvist C, Edenharter G, Zuberbier T, Worm M. Risk factors of adverse reactions to food in German adults. *Clin Exp Allergy* 2009;39:1036-1044.
71. Roehr CC, Edenharter G, Reimann S, Ehlers I, Worm M, Zuberbier T *et al.* Food allergy and non-allergic food hypersensitivity in children and adolescents. *Clin Exp Allergy* 2004;34:1534-1541.
72. Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S, Hantke T *et al.* Prevalence of adverse reactions to food in Germany - A population study. *Allergy* 2004;59:338-345.
73. Steinke M, Fiocchi A, Kirchlechner V, Ballmer-Weber B, Brockow K, Hischenhuber C *et al.* Perceived food allergy in children in 10 european nations: A randomised telephone survey. *Int Arch Allergy Immunol* 2007;143:290-295.
74. Venter C, Hasan Arshad S, Grundy J, Pereira B, Bernie Clayton C, Voigt K *et al.* Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy* 2010;65:103–108.
75. Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B *et al.* Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. *Allergy* 2008;63:354-359.
76. Dean T, Venter C, Pereira B, Arshad SH, Grundy J, Clayton CB *et al.* Patterns of sensitization to food and aeroallergens in the first 3 years of life. *J Allergy Clin Immunol* 2007;120:1166-1171.
77. Venter C, Pereira B, Grundy J, Clayton CB, Roberts G, Higgins B *et al.* Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life. *J Allergy Clin Immunol* 2006;117:1118-1124.
78. Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: A population-based study. *Pediatr Allergy Immunol* 2006;17:356-363.
79. Von Hertzen L, Mäkelä MJ, Petäys T, Jousilahti P, Kosunen TU, Laatikainen T *et al.* Growing disparities in atopy between the Finns and the Russians: A comparison of 2 generations. *J Allergy Clin Immunol* 2006;117:151-157.
80. Zuidmeer L, Goldhahn K, Rona RJ, Gislason D, Madsen C, Summers C *et al.* The prevalence of plant food allergies: A systematic review. *J Allergy Clin Immunol* 2008;121:1210-1218.e1214.

1.3

THE DIAGNOSIS OF FOOD ALLERGY

SYSTEMATIC REVIEW AND META-ANALYSIS

K Soares-Weiser[1], Y Takwoingi[2], SS Panesar[3], A Muraro[4], T Werfel[5], K Hoffmann-Sommergruber[6], G Roberts[7-9], S Halken[10], L Poulsen[11], R Van Ree[12], BJ Vlieg–Boerstra[13], A Sheikh[3, 14] on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group

On behalf of the EAACI Food Allergy and Anaphylaxis Group: CA Akdis, R Alvarez, K Beyer, C Bindslev-Jensen, V Cardona, P Demoly, A Dubois, P Eigenmann, M Fernandez Rivas, A Høst, G Lack, MJ Marchisotto, B Niggeman, C Nilsson, N Papadopoulos, I Skypala, M Worm

AFFILIATIONS

[1] Enhance Reviews Ltd, UK

[2] Public Health, Epidemiology and Biostatistics, School of Health and Population Sciences, University of Birmingham, UK

[3] Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, UK

[4] Department of Pediatrics, Center for Food Allergy Diagnosis and Treatment, Veneto Region, University of Padua, Italy

[5] Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany

[6] Department of Pathophysiology and Allergy Research, Medical University of Vienna, Austria

[7] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[8] NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, UK

[9] Human Development and Health and Clinical and Experimental Sciences Academic Units, Faculty of Medicine, University of Southampton, Southampton, UK

[10] Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[11] Laboratory of Medical Allergology, Allergy Clinic, Copenhagen University Hospital, Hellerup, Denmark

[12] Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, The Netherlands

[13] Emma Children's Hospital, Academic Medical Center, Department of Pediatric Respiratory Medicine and Allergy, Amsterdam, The Netherlands

[14] Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston, USA

Background: *We investigated the accuracy of tests used to diagnose food allergy.*

Methods: *Skin prick tests (SPT), specific-IgE (sIgE), component-resolved diagnosis (CRD) and the atopy patch test (APT) were compared with the reference standard of double-blind, placebo-controlled food challenge. Seven databases were searched and international experts were contacted. Two reviewers independently identified studies, extracted data and used QUADAS-2 to assess risk of bias. Where possible, meta-analysis was undertaken.*

Results: *24 (2,831 participants) studies were included. For cows' milk allergy, the pooled sensitivities were 53% (95% CI 33-72), 88% (95% CI 76-94) and 87% (95% CI 75-94), and specificities were 88% (95% CI 76-95), 68% (95% CI 56-77) and 48% (95% CI 36-59) for APT, SPT, sIgE, respectively. For egg, pooled sensitivities were 92% (95% CI 80-97) and 93% (95% CI 82-98), and specificities were 58% (95% CI 49-67) and 49% (40% to 58%) for skin prick tests and specific-IgE. For wheat, pooled sensitivities were 73% (95% CI 56-85) and 83% (95% CI 69-92), and specificities were 73% (95% CI 48-89) and 43% (95% CI 20% to 69%) for SPT and sIgE. For soy, pooled sensitivities were 55% (95% CI 33-75) and 83% (95% CI 64-93), and specificities were 68% (95% CI 52-80) and 38% (95% CI 24-54) for SPT and sIgE. For peanut, pooled sensitivities were 95% (95% CI 88-98) and 96% (95% CI 92-98), and specificities were 61% (95% CI 47-74), and 59% (95% CI 45-72) for SPT and sIgE.*

Conclusions: *The evidence base is limited and weak, and is therefore difficult to interpret. Overall, SPT and sIgE appear sensitive though not specific for diagnosing IgE-mediated food allergy*

Originally published as: Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Halken S, Poulsen L, van Ree R, Vlieg-Boerstra BJ & Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group. The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy* 2014;69:76–86. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

'Food allergy' refers to the subgroup of food hypersensitivity reactions (1) in which immunologic mechanisms have been implicated, whether IgE-mediated and/or non-IgE-mediated (2). The first and most important step in the diagnosis of food allergy is a full dietary history and this should be supplemented with a clinical examination.

The double-blind, placebo-controlled food challenge (DBPCFC) is usually considered the 'gold standard' diagnostic test (3). DBPCFC is, however, time-consuming, resource-intensive, and may induce anaphylaxis, hence there is a need to try and find safer and cheaper alternatives (3).

The most common additional tests are the skin prick test (SPT)(4), serum food-specific-IgE (specific-IgE) (5) and, to a lesser extent, component specific-IgE (6) and atopy patch testing (APT)(7). Specific-IgE and SPT indicate the presence of IgE sensitization to a specific food. Sensitization is, however, not always associated with a clinical reaction to that food (8). Non-IgE-mediated immunological reactions to food result from activation of other immunologic pathways (e.g. T-cell mediated) and manifestations include atopic eczema/dermatitis, food protein-induced enterocolitis, or proctocolitis (8). APT may be positive in some of these non-IgE mediated conditions (8).

The literature on diagnosis of food allergy currently lacks clear consensus regarding the accuracy and safety of different diagnostic approaches. This systematic review is one of seven inter-linked evidence syntheses that were undertaken in order to provide a state-of-the-art synopsis of the current evidence base. They will be used to inform the formulation of clinical recommendations in the *EAACI Guidelines for Food Allergy and Anaphylaxis*. This systematic review assessed the diagnostic accuracy of tests aimed at supporting the clinical diagnosis of food allergy.

Methods

A protocol for the systematic review was developed prospectively (9) and registered with the International Prospective Register of Systematic Reviews (PROSPERO) at http://www.crd.york.ac.uk/prospero/, registration number CRD42013003707.

Search strategy

Articles were retrieved using a highly sensitive search strategy implemented in the following databases: Cochrane Library including Cochrane Database of Systematic Reviews (CDSR); Database of Reviews of Effectiveness (DARE); CENTRAL (Trials); Methods Studies; Health Technology Assessments (HTA); Economic Evaluations Database (EED); MEDLINE (OVID); Embase (OVID); CINAHL (Ebscohost); ISI Web of Science (Thomson Web of Knowledge); TRIP Database (web www.tripdatabase.com); and Clinicaltrials.gov (NIH web).

The search strategies were supplemented by contacting an international panel of experts for potential studies. There were no language restrictions, and where possible, non-English language papers were translated.

Inclusion and exclusion criteria

Prospective or retrospective, cross-sectional or case control studies that evaluated APT, SPT, specific-IgEs, and component specific-IgE in children or adults presenting with suspected food allergy caused by cow's milk, hen's egg, wheat, soy, peanut, tree nut, fish, or shellfish were included. The reference standard was DBPCFC used in at least 50% of the participants (Figure 1). Studies in which participants were selected based on having a positive food allergy test result (index test or reference standard) or for which no 2x2 data could be extracted were excluded.

Study selection and data extraction

Two reviewers (SSP, KSW) independently checked titles and abstracts identified by the search, followed by review of the full text for assessment of eligibility. Both reviewers also extracted data using a customized form, and assessed risk of bias using the QUADAS-2 tool (10). Any discrepancies were resolved by consensus and, where necessary, a senior reviewer (AS) was consulted. We collected study characteristics and recorded the number of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) for constructing a 2x2 table for each study. In cases where 2x2 data were not available, where possible we derived them from reported summary statistics such as sensitivity, specificity, and/or likelihood ratios.

Data analysis, synthesis and reporting

For each test, diagnostic accuracy was assessed

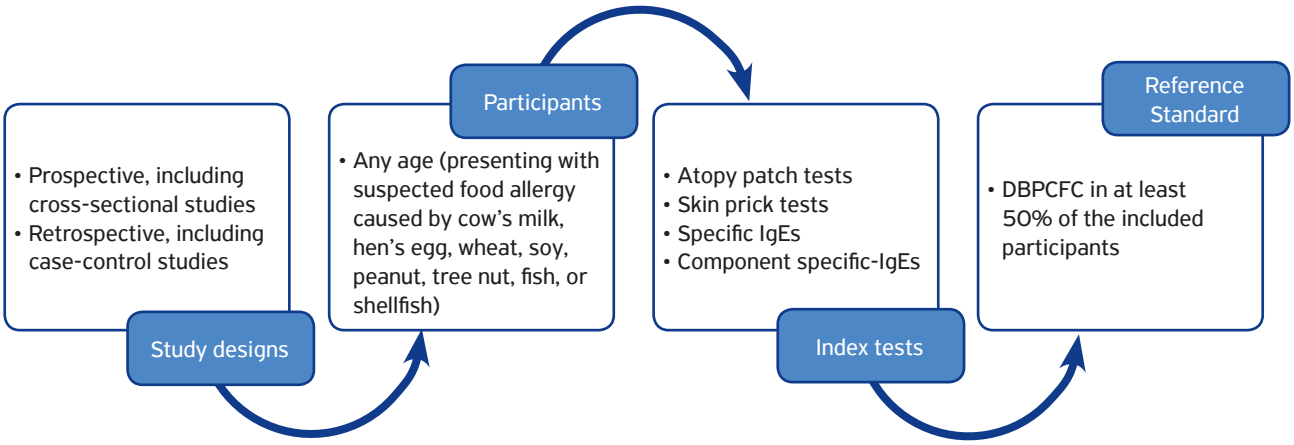


Figure 1 Study designs, participants, index tests, and reference standard eligible for this review

according to target food. Preliminary exploratory analyses were conducted for each test by plotting pairs of sensitivity and specificity from each study on forest plots and in receiver operating characteristic (ROC) space (11). Hierarchical summary ROC (HSROC) models (12, 13) were used to summarize the accuracy of each test, and to compare the accuracy of two or more tests. Where studies used a common or similar cut-off, we used parameter estimates from the models to compute summary sensitivities and specificities with 95% confidence regions. Analyses were performed in Review Manager 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012), and SAS software (version 9.2; SAS Institute, Cary, NC).

Results

Study selection

We identified 6,260 studies (excluding duplicates) and 312 were eligible for full-text review. Twenty-four studies (33 references) (7, 45) with a total of 2,831 participants were included in the quantitative analyses. Figure E1 in the online supplement shows the PRISMA flowchart for the study screening and selection process.

Characteristics of included studies

Table 1 summarizes the characteristics and methodological quality of the 24 included studies. Of the 24 studies, 17 were conducted in Europe. Twenty-two studies were cohort studies and 2 were case-control studies. The majority (n=21) included infants or children under 18 years of age. At the study entry all participants in six studies had atopic eczema/dermatitis. Eight studies reported data on more than one target food. Most studies were judged to be at high or unclear risk of bias in all domains except flow and timing. Applicability concerns were judged as high mainly in the index test domain because in 18 studies, there was prior testing with SPT and/or specific-IgE when a diagnosis of food allergy was suspected. Further details are available in the online supplement.

Main findings

Table 2 shows summary results for each target food where meta-analysis was possible.

Cow's milk: Figure E2 shows the pairs of sensitivity and specificity from each study, including the cut-offs used, for APT (3 studies), SPT (6 studies), and specific-IgE (6 studies). The summary sensitivity and specificity of APT were 53% (95% CI 33% to 72%) and 88% (76% to 95%). For SPT and specific-IgE, the summary sensitivities were 88% (76% to 94%) and 87% (75% to 94%), and specificities were 68% (56% to 77%) and 48% (36% to 59%), respectively. Although there was some between-study heterogeneity, the summary estimates suggest that specific IgE detects on average the same number of cases per 100 people with cow's milk allergy as SPT, but gives on average 20 additional false positive diagnoses for every 100 people without the allergy ($p<0.01$).

Table 1 Summary of the characteristics of studies in the review: studies published 1 January 2000 – 30 September 2012

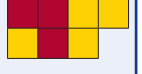
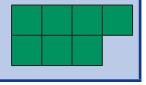
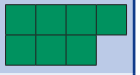
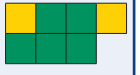
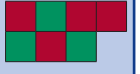
First author, year (reference)	Study design	Sample size	Foods evaluated	Population	Index test(s) (definition of a positive result)	Reference standard (participants)	QUADAS-2 domains*
Alessandri, 2012 (43)	Cohort	68	Hen's egg	Children suspected of HE allergy based on reported history of reactions and positive SPT or SIgE to HE white extracts.	Fresh and commercial SPT (recorded as wheal areas and expressed in mm^2); SIgE ImmunoCAP (optimal cut off points); Detection of Gal d 1, Gal d 2, Gal d 3 and Gal d 5 (ISAC 103 microarray test)	DBPCFC (n=68)	
Ando, 2008 (40)	Cohort	108	Hen's egg	Children suspected of egg allergy	SIgE ImmunoCAP (≥ 0.35 kUA/L and optimal cut off points)	DBPCFC (n=108)	
Ayuso, 2012 (24, 27)	Cohort	37	Shrimp	Children and adults reporting immediate allergic reactions following shrimp ingestion	Fresh SPT (not reported); SIgE ImmunoCAP (≥ 0.35 kUA/LIMB SDS-Page	DBPCFC (n=31) OFC (n=21)	
Breuer, 2004 (42)	Cohort	64	Cow's milk, hen's egg, wheat, soybean	Children withmoderate to severe AD	SIgE CAP RAST FEIA (≥0.35 kU/l); APT (erythema with an infiltration)	106 DBPCFC (n=64)	
Caffarelli, 1995 (38)	Case control	33	Hen's egg	Children who as infants had food allergy	Commercial SPT (wheal diameter ≥ 3 mm); SIgE RAST (a score of ++, range 0-4)	DBPCFC (n= 33)	
Daul, 1988 (36)	Cohort	30	Shrimp	Adults with symptoms within 1 hour of ingestion	Commercial SPT (wheal diameter ≥ 3 mm); SIgERAST (>3% label bound)	DBPCFC (n=30)	
Dieguez, 2009 (39)	Cohort	157	Hen's egg	Children with allergy to egg	Commercial yolks and whites SPT (wheal diameter ≥ 3 mm); SIgE FEIA (≥ 0.35 kUA/L)	159 DBPCFC (n=159)	
Eigenmann, 1998 (31)	Case control	Not reported	Cow's milk, hen's egg, wheat, soybean, peanut	Children with AD suspected of IgE-mediated allergies to egg, milk, peanut, soybean, and/or wheat	Commercial SPT (mean diameter / surface area of wheal: 4 mm / 16 mm^2 for egg, 5 mm / 29 mm^2 for milk, 6 mm / 40 mm^2 for peanut, 3 mm / 9 mm^2 for soy, and 3 mm / 7 mm^2 for wheat)	DBPCFC (not clear whether participants received same reference standard)	
Flinterman, 2006 (29)	Cohort	27	Peanut	Children with peanut sensitization	Commercial SPT (not reported, we assumed wheal diameter ≥ 3 mm) SIgE CAP system FEIA (≥ 0.35 IUA/mL)	DBPCFC (n=27)	
Flinterman, 2008 (32)	Cohort	26	Tree nuts	Children with tree nut sensitivity	SIgE CAP- FEIA (≥ 0.35 kU/L) IMB SDS-Page	DBPCFC (n=26)	
Glaumann, 2012 (25)	Cohort	43	Peanut	Children with suspected peanut allergy	SIgE ImmnunoCAP (≥0.1kUA/l) CD-Sens	DBPCFC (n=38)	
Isolauri, 1996 (15)	Cohort	183	Cow's milk	Children with AD not suspected of cow's milk allergy	APT (significant erythema, or erythema with edema or eczema); Commercial SPT (≥ 1/2 the histamine reactions size)	DBPCFC (n=118) or OFC (n=65)	
Keskin, 2005 (16)	Cohort	37	Cow's milk	Children with suspected cow's milk allergy	APT (erythema with infiltration and papulation); Commercial SPT (wheal diameter ≥ 3mm); SIgE ImmunoCAP (≥0.7kU/L)	DBPCFC (n=31)	

Table 1 (Continued)

First author, year (reference)	Study design	Sample size	Foods evaluated	Population	Index test(s) (definition of a positive result)	Reference standard (participants)	QUADAS-2 domains*
Masthoff, 2012 (26)	Cohort	172	Tree nuts	Children with history suggestive of tree nut allergy	Commercial SPT (wheal diameter ≥ 3 mm); SIgE ImmunoCap (≥ 0.35 kUA/l)	DBPCFC (n= 172)	
Mehl, 2006 (8, 14, 22, 34)	Cohort	437	Cow's milk, hen's egg, wheat, soybean	Children with suspected food allergy	APT (erythema with infiltration or papules); Fresh SPT (wheal diameter ≥ 3 mm); SIgE FEIA and ImmunoCap (≥0.35 kU/L)	DBPCFC (n=437)	
Ortolani, 2000 (21, 30)	Cohort	86	Tree nuts	Children and adults with history of symptoms after tree nut ingestion	Fresh & commercial SPT (wheal diameter ≥3 mm); SIg ECAP-FEIA (≥ 0.7 kU/L)	DBPCFC (n=86) OFC (n=11)	
Rancé, 2002 (19)	Cohort	363	Peanut	Children with suspected food allergy	Commercial SPT (wheal diameter ≥ 3 mm); SIgE CAP-FEIA (> 0.35 kUA/l)	DBPCFC (n=363)	
Roehr, 2001 (17, 28, 33, 35)	Cohort	98	Cow's milk, hen's egg, wheat, soybean	Children with AD	ATP (erythema with infiltration); Fresh SPT (wheal diameter ≥ 3 mm); SIgE CAP-FEIA (> 0.35 kU/L)	DBPCFC (n= 98)	
Sampson, 1984 (20, 45)	Cohort	40	Cow's milk, hen's egg, wheat, soybean, peanut, shellfish/ fish, pork, chicken	Children with AD	Commercial SPT (wheal diameter ≥ 3 mm with erythema); SIgE RAST (>0.5% of radioactivity)	DBPCFCs (n=40) OFC (n=83)	
Sampson, 1997 (37)	Cohort	196	Cow's milk, hen's egg, wheat, soybean, peanut, shellfish/fish	Children with AD	Commercial SPT (wheal diameter ≥ 3 mm); SIgE CAP-FEIA (≥0.35 kUA/l)	DBPCFC (n=149)	
Sampson, 2001 (18)	Cohort	100	Cow's milk, hen's egg, wheat, soybean, peanut, shellfish/fish	Children	Commercial SPT (wheal diameter ≥ 3 mm); SIgE CAP-FEIA (> 0.35 kUA/L)	DBPCFC (n=100)	
Scibilia, 2006 (41)	Cohort	27	Wheat	Children and adults with suspected wheat allergy	Commercial SPT (wheal diameter ≥ 3 mm); SIgE CAP-FEIA (≥ 0.35 kUA/L)	DBPCFC (n=27)	
van den Berg, 2012 (44)	Cohort	396	Cow's milk, hen's egg, peanut, tree nuts	Children with suspected food allergy	SIgE (> 0.35 kU/l)	DBPCFC (n=396)	
van Nieuwaal, 2010 (23)	Cohort	103	Peanut	Children with suspected peanut allergy	SIgE CAP- FEIA (≥10.4, 24.8, and 26.5 kU/L)	DBPCFC (n=103)	

* Risk of Bias 1 2 3 4; Applicability 1 2 3

AD, atopic/eczema dermatitis; APT, atopy patch test; CAP-FEIA, fluorenzyme immunoassay; CAP-RAST, Immunocap-radioallergosorbictest; DBPCFC, double-blind placebo-controlled food challenge; IMB, immunoblotting; OFC, open food challenge;RAST, radioallergosorbic test; SIgE, serum food-specific-IgE; SPT, skinprick test. QUADAS-2 domains: 1- Patient Selection, 2- Index Test, 3- Reference Standard, and 4- Flow and timing (flow of patients through the study and timing of the index tests and reference standard). Risk of bias is assessed for each domain of the QUADAS-2 tool but concerns about applicability is only assessed for 3 of the 4 domains (the flow and timing domain is not assessed). Applicability:concerns regarding applicability of a study to the review question.

Low risk of bias or low applicability concern (green); Unclear risk of bias or unclear applicability concern (yellow); High risk of bias or high applicability concern (red)

Table 2 Summary estimates of the accuracy of atopy patch test (APT), skin prick test (SPT), and specific-IgE for each target food

Test (cut-off)	Studies	Participants	Cases	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
COW'S MILK: FIVE PROSPECTIVE COHORTS (8, 15, 16, 20, 44), TWO RETROSPECTIVE COHORTS (37, 42), ONE RETROSPECTIVE CASE CONTROL STUDY (30)							
APT	3	495	254	52.8 (32.6, 72.1)	88.1 (75.5, 94.7)	4.43 (2.61, 7.51)	0.54 (0.37, 0.77)
SPT (≥3mm)	5	587	284	87.9 (75.6, 94.4)	67.5 (56.0, 77.2)	2.70 (2.09, 3.50)	0.18 (0.10, 0.34)
Specific-IgE (mixed cut-offs)	6	831	390	87.3 (75.2, 93.9)	47.7 (36.4, 59.2)	1.67 (1.44, 1.93)	0.27 (0.16, 0.45)
Ratio[1]				1.0 (0.93, 1.06), P=0.9	0.71 (0.60, 0.83), P<0.01		
HEN'S EGG: THREE PROSPECTIVE COHORTS (8, 20, 4), ONE RETROSPECTIVE COHORT (37), ONE PROSPECTIVE CASE-CONTROL STUDY (38), ONE RETROSPECTIVE CASE-CONTROL STUDY (31)							
SPT (mixed cut-offs)	5	448	287	92.4 (79.9, 97.4)	58.1 (49.1, 66.6)	2.30 (1.77, 2.74)	0.13 (0.05, 0.36)
Specific-IgE (mixed cut-offs)	5	572	346	93.4 (82.1, 97.8)	49.2 (40.2, 58.1)	1.84 (1.52, 2.21)	0.13 (0.05, 0.38)
Ratio				1.01 (0.70, 0.96), P=0.7	0.85 (0.68, 1.05), P=0.1		
WHEAT: THREE PROSPECTIVE COHORTS (8, 20, 41), TWO RETROSPECTIVE COHORTS (36, 41), ONE RETROSPECTIVE CASE-CONTROL STUDY (31)							
SPT (≥3mm)	5	350	114	72.6 (55.7, 84.8)	73.3 (47.9, 89.1)	2.72 (1.32, 5.60)	0.37 (0.23, 0.60)
Specific-IgE (mixed cut-offs)	4	408	102	83.2 (69.0, 91.7)	42.7 (19.8, 69.1)	1.45 (0.95, 2.22)	0.39 (0.20, 0.77)
Ratio				1.15 (0.97, 1.36), P=0.1	0.58 (0.40, 0.85), P<0.01		
SOY: TWO PROSPECTIVE COHORTS (8, 20), ONE RETROSPECTIVE COHORT (37), ONE RETROSPECTIVE CASE-CONTROL STUDY (31)							
SPT (≥3mm)	4	366	94	55.0 (33.2, 75.0)	68.0 (52.4, 80.3)	1.71 (1.29, 2.27)	0.66 (0.47, 0.94)
Specific-IgE (mixed cut-offs)	3	404	74	82.9 (63.8, 93.0)	38.0 (24.2, 54.0)	1.34 (1.13, 1.58)	0.45 (0.24, 0.83)
Ratio				1.51 (1.10, 2.07), P=0.01	0.56 (0.43, 0.72), P<0.01		
PEANUT: FIVE PROSPECTIVE COHORTS (19, 20, 23, 29, 44), ONE RETROSPECTIVE COHORT (37), ONE RETROSPECTIVE CASE-CONTROL STUDY (31)							
SPT (≥3mm)	5	499	245	94.7 (87.9, 97.8)	61.0 (46.6, 73.6)	2.43 (1.69, 3.48)	0.09 (0.04, 0.21)
Specific-IgE (mixed cut-offs)	5	817	452	96.3 (91.6, 98.4)	59.3 (45.4, 72.0)	2.37 (1.69, 3.32)	0.06 (0.03, 0.15)
Ratio				1.02 (0.97, 1.06), P=0.5	0.97 (0.84, 1.12), P=0.7		

[1] Ratio of the summary sensitivity of specific-IgE to that of SPT, and ratio of the summary specificity of specific-IgE to that of SPT. P-values were obtained from Wald tests.

Where studies reported multiple cut-offs, only results for the lowest cut-off was chosen for inclusion in the meta-analysis so that the same population was included only once for each test. Where assumptions were made regarding the use of mixed cut-offs, e.g., SPT data from studies which used cut-offs between ≥3mm and ≥4mm, and specific-IgE data from studies which used cut-offs between >0.35 kU/L or not reported, these cut-offs were considered clinically similar enough to be included in the meta-analysis of each test in order to produce summary estimates. Data for APT are shown for cow's milk only because at least three studies reported this test. Meta-analysis was not performed for tree nuts, fish and shellfish due to the limited number of studies and substantial variation in specificity.

Hen's egg: Figure E3 shows the pairs of sensitivity and specificity from each study for APT (1 study), SPT (5 studies), and specific-IgE (5 studies) at the different cut-offs reported. The sensitivity and specificity of APT in the single study were 41% (32% to 50%) and 88% (77% to 95%). For SPT and specific-IgE, the summary sensitivities were 92% (80% to 97%) and 93% (82% to 98%), and specificities were 58% (49% to 67%) and 49% (40% to 58%), respectively. No significant differences in sensitivity and/or specificity were observed when SPT was compared to specific-IgE (Table 2).

Wheat: Figure E4 shows the pairs of sensitivity and specificity from each study for APT (1 study), SPT (5 studies), and specific-IgE (5 studies) at the different cut-offs reported. The sensitivity of APT was 26% (16% to 40%) and specificity was 89% (82% to 94%) in the single study. For SPT and specific-IgE, the summary sensitivities were 73% (56% to 85%) and 83% (69% to 92%), and specificities were 73% (48% to 89%) and 43% (20% to 69%), respectively. There was a significant difference in specificity (P<0.01) with SPT having a higher specificity than specific-IgE (Table 2). The results suggest that specific-IgE detects on average 11 more cases out of every 100 people with wheat allergy than SPT, but gives on average 31 additional false positive diagnoses for every 100 people without the allergy.

Soy: Figure E5 shows the sensitivities and specificities for studies that evaluated APT (1 study), SPT (4 studies), and specific-IgE (3 studies) at the different cut-offs reported. The single study of APT reported a sensitivity of 24% (12% to 41%) and specificity of 86% (79% to 91%). For SPT and specific-IgE, the summary sensitivities were 73% (56% to 85%) and 83% (69% to 92%), and specificities were 73% (48% to 89%) and 43% (20% to 69%), respectively. Significant differences in sensitivity and specificity were observed with specific-IgE having a higher sensitivity than SPT (P=0.01) but lower specificity (P< 0.01) (Table 2). The summary estimates suggest that specific-IgE detects on average 28 more cases out of every 100 people with soy allergy than SPT, but gives on average 30 additional false positive diagnoses for every 100 people without the allergy.

Peanut: The individual study estimates of sensitivity and specificity of SPT (5 studies) and specific-IgE (6 studies) are shown in Figure E6 for the different cut-offs reported. The summary sensitivities of SPT and specific-IgE were very similar (Table 2) – 95% (88% to 98%) and 96% (92% to 98%), respectively – with no significant difference between them (P=0.5). Similarly, there was no significant difference (P=0.7) between the specificities of SPT (61% [47% to 74%]) and specific-IgE (59% [45% to 72%]).

Tree nuts: Hazelnut was assessed in three prospective cohorts (26, 30, 44). At the ≥3mm cut-off, one study (30) reported SPT sensitivities of 88% and 90%, and specificities of 28% and 6% for hazelnut allergy using natural and commercial extracts, respectively (Figure E7). For specific-IgEs, sensitivities were 75% to 99% and specificities were 17% to 77%, depending on the cut-off.

Fish: One prospective cohort (20) and one retrospective cohort (37) showed sensitivities of 91% and 100%, but the same specificity of 57% for SPT at a cut-off of ≥3mm (Figure E8). For specific-IgEs, sensitivities were 67% to 94%, and specificities were 65% to 88% at different cut-offs.

Shellfish: Shrimp allergy was evaluated in two prospective cohorts (27, 36) (Figure E9). For SPT, sensitivities were 100% for both studies, and the specificities were 32% and 50%. For specific-IgE, one study (27), gave a sensitivity of 100% (80% to 100%) and specificity of 45% (23% to 68%) at a cut-off of >0.35 KU/L.

Component specific-IgE

Single studies evaluated the accuracy of component specific-IgEs for hen's egg, peanut, tree nuts, and shellfish.

One study (43) including 68 children evaluated the accuracy of component specific-IgEs (Gal d1, 2, 3, 5) in boiled and raw eggs. The study reported cut-offs varying from 0 to 0.41 KUa/L (ISAC). The sensitivity estimates were 20% to 84% and specificities 84% to 100%.

Another study (25) including 43 children evaluated the accuracy of component specific-IgEs (Ara h2) in peanut allergy. The study reported a threshold of 16% for basophil allergen CD-sens (derived from the basophil allergen concentration). The sensitivity was 100%, and specificity of 77%.

One study (32) including 26 children evaluated the accuracy of component specific-IgEs (Cor a1, 2, 8; rCor a1, Pru p3, Bet v1) in hazelnut allergy. The study reported a cut-off of 0.35 kU/L (CAP FEIA system).

The sensitivities were 25% to 100%, and specificities 22% to 94%. An additional case control study (46) reported the percentage of people positive for rCor a1, 8; rBet v1, 2 (component specific-IgEs), but did not report enough information to calculate sensitivity or specificity.

One study (27) including 37 adults evaluated the accuracy of component specific-IgE (rPen a 1) for shrimp allergy. The estimated sensitivity was 100%, and the specificity was 80%.

Investigation of heterogeneity and sensitivity analyses

Due to the limited number of studies available for each meta-analysis, we were unable to use meta-regression to explore potential sources of heterogeneity in test performance as planned.

Discussion

We included 24 studies that evaluated the accuracy of APT, SPT, specific-IgEs, and component specific-IgEs at different cut-offs.

Our systematic review suggests that SPT and specific-IgE have good sensitivity, but poor specificity with wide variation in estimates for each of the food allergies investigated. The limited evidence available for APT suggested poor sensitivity, but good specificity. The strength of evidence on the relative accuracy of SPT and specific-IgE was weak; we relied on indirect comparisons of the two tests which may be prone to bias due to differences in population characteristics and study design. Very few studies have compared the tests head-to-head in the same population, and direct or indirect comparisons of accuracy between the other tests were not possible.

Our inclusion criteria were similar to those used in a recent RAND report (47). The main differences, however, were that we limited the inclusion criteria to studies in which at least 50% of participants received a DBPCFC to minimise verification bias, and we did not exclude studies based on language of publication. We also contacted senior researchers in the field in order to locate additional studies for inclusion in the review.

The strengths of this review include the use of internationally-recommended methods for study identification, methodological quality assessment, and meta-analysis. The main limitation was the poor reporting of primary accuracy studies. In particular, inclusion and exclusion criteria were not clearly defined, and there was lack of information on test cut-offs and details of how the tests were applied. Regarding population, the index tests evaluated in the included studies were previously used to select participants in 75% of the studies included in the quantitative analyses. A third of the studies were performed in a specific population; in eight studies all participants had atopic dermatitis, and in three all participants had asthma. These population issues impact on the generalisability of our findings. Furthermore, protocols for the index tests are likely to differ between countries, thus limiting applicability. Lastly, although DBPCFC is generally accepted as the reference standard for diagnosing food allergy, it is not widely used (48) and accounts for the exclusion of 30% of the potentially relevant studies.

Implications for patient care

This review has identified relevant evidence for different tests available for a range of foods most commonly implicated in suspected food allergy, and highlighted both the volume and strength of evidence available to guide clinical decision-making.

Direct comparisons are difficult because of the limited body of evidence in which these tests have been compared in the same population. That said, overall, this body of work indicates that SPT and specific-IgE (and probably also component specific-IgE) offer high sensitivity in relation to a range of allergens implicated in immediate IgE-mediated food allergy. There was, however, greater variation in the specificity of these tests, with specific-IgE tending to a higher rate of false positives.

Local decisions about which tests to employ and the order in which these are undertaken need to be guided by the above considerations, the comparability of the populations being cared for to those enrolled in studies (i.e. mainly high-risk populations being seen in specialist care settings), and the relative availability, safety, and costs of tests.

Implications for research

Most of the evidence in this review was derived from small studies, with a high or unclear risk of bias. Future studies should be prospective with consecutive recruitment, adequate sample sizes, and should be

representative of the population in which the tests will be used in practice (49). Head-to-head comparisons of specific-IgE, SPT, and component tests are needed to determine the relative accuracy of the tests. Test accuracy is only one aspect of the assessment of a test (50), and the balance between benefit and harm should also be assessed, ideally within a randomized controlled trial (51, 52).

Conclusions

SPT and specific-IgEs are sensitive, but not specific for diagnosis of food allergy, although test performance may differ between foods. However, the findings should be viewed with caution due to the limited evidence base and the paucity of good quality studies.

Acknowledgements

We would like to acknowledge the support of the EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing this systematic review. We would also like to thank the EAACI Executive Committee for their helpful comments and suggestions.

Funding

EAACI

Contributorship

AS, AM, SSP, and GR conceived this review. It was undertaken by KS-W and YT, with the support of SSP. KS-W, YT, AS, and GR drafted the manuscript and all authors including TW, KH-S, SH, LP, RvR, and BV-B critically commented on drafts of the manuscript.

Conflicts of interest

None known

References

1. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T *et al.* A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813-824.
2. Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al.* Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;303:1848-1856.
3. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW *et al.* Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;130:1260-1274.
4. Du Toit G, Santos A, Roberts G, Fox AT, Smith P, Lack G. The diagnosis of IgE-mediated food allergy in childhood. *Pediatr Allergy Immunol* 2009;20:309-319.
5. Stiefel G, Roberts G. How to use serum-specific IgE measurements in diagnosing and monitoring food allergy. *Arch Dis Child Educ Pract Ed* 2012;97:29-36(quiz 34).
6. Borres MP, Ebisawa M, Eigenmann PA. Use of allergen components begins a new era in pediatric allergology. *Pediatr Allergy Immunol* 2011;22:454-461.
7. Mehl A, Rolinck-Werninghaus C, Staden U, Verstege A, Wahn U, Beyer K *et al.* The atopy patch test in the diagnostic workup of suspected food-related symptoms in children *J Allergy Clin Immunol* 2006;118:923-929.
8. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M *et al.* ICON: food allergy. *J Allergy Clin Immunol* 2012;129:906-920.
9. Soares-Weiser K, Panesar SS, Rader T, Takwoingi Y, Werfel T, Muraro A, Hoffman-Sommergruber K, Roberts G, Sheikh A; EAACI Food Allergy and Anaphylaxis Group. The diagnosis of food allergy: a protocol for a systematic review. *Clin Transl Allergy* 2013;3:18
10. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529-536.
11. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors), *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.* The Cochrane Collaboration, 2010. Available from: http://srdta.cochrane.org/.
12. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001;20:2865-2884.
13. Macaskill P. Empirical Bayes estimates generated in a hierarchical summary ROC analysis agreed closely with those of a full Bayesian analysis. *J Clin Epidemiol* 2004;57:925-932.
14. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K *et al.* The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35:268-273.
15. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996;97:9-15.
16. Keskin O, Tuncer A, Adalioglu G, Sekerel BE, Sackesen C, Kalayci O. Evaluation of the utility of atopy patch testing, skin prick testing, and total and specific IgE assays in the diagnosis of cow's milk allergy. *Ann Allergy Asthma Immunol* 2005;94:553-560.
17. Roehr CC, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch tests, together with

determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;107:548-553.

18. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-896.
19. Rance F, Abbal M, Lauwers-Cances V. Improved screening for peanut allergy by the combined use of skin prick tests and specific IgE assays. *J Allergy Clin Immunol* 2002;109: 1027-1033.
20. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challanges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984;74:26-33.
21. Ballmer-Weber BK, Vieths S, Bucher C, Luttkopf D, Wuthrich B. Hazelnut allergy. Validation of diagnostic procedures on the basis of double-blind placebo-controlled food challenges. [German]Haselnulssallergie. Validierung der diagnostischen verfahren anhand der doppelblinden, plazebokontrollierten nahrungsmittel provokation. *Allergologie* 2000;23:285-291.
22. Ahrens B, Lopes De Oliveira LC, Schulz G, Borres MP, Niggemann B, Wahn U *et al.* The role of hens egg-specific IgE, IgG and IgG4 in the diagnostic procedure of hens egg allergy. *Allergy* 2010;65:1554-1557.
23. van Nieuwaal NHG, Lasfar W, Meijer Y, Kentie PA, Flinterman AE, Pasmans SGAM *et al.* Utility of peanut-specific IgE levels in predicting the outcome of double-blind, placebo-controlled food challenges. *J Allergy Clin Immunol* 2010; 125:1391-1392.
24. Gamez C, Sanchez-Garcia S, Ibanez MD, Lopez R, Aguado E, Lopez E *et al.* Tropomyosin IgE-positive results are a good predictor of shrimp allergy *Allergy* 2011;66:1375-1383.
25. Glaumann S, Nopp A, Johansson SGO, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. *Allergy* 2012;67:242-247.
26. Masthoff LJ, Pasmans SG, Van Hoffen E, Knol MJ, Bruijnzeel-Koomen CA, Flinterman AE *et al.* Diagnostic value of hazelnut allergy tests including rCor a 1 spiking in double-blind challenged children. *Allergy* 2012;67:521-527.
27. Ayuso R, Sanchez-Garcia S, Pascal M, Lin J, Grishina G, Fu Z *et al.* Is epitope recognition of shrimp allergens useful to predict clinical reactivity. *Clin Exp Allergy* 2012;42:293-304.
28. Niggemann B, Reibel S, Wahn U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000;55:281-285.
29. Flinterman AE, Pasmans SG, Hoekstra MO, Meijer Y, van Hoffen E, Knol EF *et al.* Determination of no-observed-adverse-effect levels and eliciting doses in a representative group of peanut-sensitized children. *J Allergy Clin Immunol* 2006;117:448-454.
30. Ortolani C, Ballmer-Weber BK, Hansen KS, Ispano M, Wuthrich B, Bindslev-Jensen C *et al.* Hazelnut allergy: A double-blind, placebo-controlled food challenge multicenter study. *J Allergy Clin Immunol* 2000;105:577-581.
31. Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatric Allergy and Immunology* 1998;9:186-191.
32. Flinterman AE, Akkerdaas JH, den Hartog Jager CF, Rigby NM, Fernandez-Rivas M, Hoekstra MO *et al.* Lipid transfer protein-linked hazelnut allergy in children from a non-Mediterranean birch-endemic area. *J Allergy Clin Immunol* 2008;121:423-428.e422.
33. Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo- controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 1999; 29:91-96.
34. Verstege A, Mehl A, Rolinck-Werninghaus C, Staden U, Nocon M, Beyer K *et al.* The predictive value of the skin prick test weal size for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35:1220-1226.
35. Niggemann B, Reibel S, Roehr CC, Felger D, Ziegert M, Sommerfeld C *et al.* Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;108:1053-1058.
36. Daul CB, Morgan JE, Hughes J, Lehrer SB. Provocation-challenge studies in shrimp-sensitive individuals. *J Allergy Clin Immunol* 1988;81:1180-1186.
37. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997; 100:444-451.
38. Caffarelli C, Cavagni G, Giordano S, Stapane I, Rossi C. Relationship between oral challenges with previously uningested egg and egg-specific IgE antibodies and skin prick tests in infants with food allergy. *J Allergy Clin Immunol* 1995;95:1215-1220.
39. Dieguez MC, Cerecedo I, Muriel A, Zamora J, Abraira V, Camacho E *et al.* Utility of diagnostic tests in the follow-up of egg-allergic children. *Clin Exp Allergy* 2009;39:1575-1584.
40. Ando H, Moverare R, Kondo Y, Tsuge I, Tanaka A, Borres MP *et al.* Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol* 2008;122:583-588.
41. Scibilia J, Pastorello EA, Zisa G, Ottolenghi A, Bindslev-Jensen C, Pravettoni V *et al.* Wheat allergy: a double-blind, placebo-controlled study in adults. *J Allergy Clin Immunol* 2006;117:433-439.
42. Breuer K, Heratizadeh A, Wulf A, Baumann U, Constien A, Tetau D *et al.* Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004;34:817-824.
43. Alessandri C, Zennaro D, Scala E, Ferrara R, Bernardi ML,

Santoro M *et al.* Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation. *Clin Exp Allergy* 2012;42:441-450.

44. van den Berg ME, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Kerkhof M, van der Heide S, Koppelman GH *et al.* Parental eczema increases the risk of double-blind, placebo-controlled reactions to milk but not to egg, peanut or hazelnut. *Int Arch Allergy Immunol* 2012;158:77-83.
45. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 1983;71:473-480.
46. Jarlot S, Morisset M, Hosotte M, Kanny G. Predictive value of skin test and specific IgE to hazelnut. *Allergy: J Allergy Clin Immunol* 2011;66:390-391.
47. Schneider Chafen JJ, Newberry S, Riedl M, Bravata DM, Maglione MA, Suttorp M *et al. Prevalence, natural history, diagnosis, and treatment of food allergy: a systematic review of the evidence.* Santa Monica, CA: RAND Corporation, 2010. Available from: http://www.rand.org/pubs/working_papers/ WR757-1
48. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. *J Allergy Clin Immunol* 2004;114:1164-1168.
49. Linnet K, Bossuyt PM, Moons KG, Reitsma JB. Quantifying the accuracy of a diagnostic test or marker. *Clin Chem* 2012;58:1292-1301.
50. Lijmer JG, Leeflang M, Bossuyt PM. Proposals for a phased evaluation of medical tests. *Med Decis Making* 2009;29:E13-E21.
51. Lord SJ, Irwig L, Bossuyt PM. Using the principles of randomized controlled trial design to guide test evaluation. *Med Decis Making* 2009;29:E1-E12.
52. Lord SJ, Irwig L, Simes RJ. When is measuring sensitivity and specificity sufficient to evaluate a diagnostic test, and when do we need randomized trials? *Ann Intern Med* 2006;144:850-855.

1.4

ACUTE AND LONG-TERM MANAGEMENT OF FOOD ALLERGY

SYSTEMATIC REVIEW

D de Silva[1], M Geromi[1], SS Panesar[2], A Muraro[3], T Werfel[4], K Hoffmann-Sommergruber[5], G Roberts[6-8], V Cardona[9], AEJ Dubois[10], S Halken[11], A Host[11], LK Poulsen[12], R Van Ree[13], BJ Vlieg–Boerstra[14], I Agache[15], A Sheikh[2, 16] on behalf of the EAACI Food Allergy and Anaphylaxis Group

EAACI Food Allergy and Anaphylaxis Group: CA Akdis, R Alvarez, K Beyer, C Bindslev-Jensen, P Demoly, P Eigenmann, M Fernandez Rivas, G Lack, MJ Marchisotto, B Niggeman, C Nilsson, N Papadopoulos, I Skypala, M Worm.

AFFILIATIONS

[1] The Evidence Centre, UK

[2] Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, UK

[3] Department of Pediatrics, Center for Food Allergy Diagnosis and Treatment, Veneto Region, University of Padua, Italy

[4] Hanover Medical School, Hanover, Germany

[5] Department of Pathophysiology and Allergy Research, Medical University of Vienna, Austria

[6] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[7] NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, UK

[8] Human Development and Health and Clinical and Experimental Sciences Academic Units, Faculty of Medicine, University of Southampton, UK

[9] Hospital Valld'Hebron, 5 Barcelona, Spain

[10] Department of Paediatrics, Division of Paediatric Pulmonology and Paediatric Allergy, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[11] Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[12] Laboratory of Medical Allergology, Allergy Clinic, Copenhagen University Hospital, Hellerup, Denmark

[13] Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, The Netherlands

[14] Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, Department of Pediatric Respiratory Medicine and Allergy, University of Amsterdam, The Netherlands

[15] Transylvania University, Brasov, Romania

[16] Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston, USA

Background: *Allergic reactions to food can have serious consequences. This systematic review summarizes evidence about the immediate management of reactions and longer-term approaches to minimize adverse impacts.*

Methods: *Seven bibliographic databases were searched from their inception to September 30, 2012 for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after and interrupted time series studies. Experts were consulted for additional studies. There were no language or geographic restrictions. Two reviewers critically appraised the studies using the appropriate tools. Data were not suitable for meta-analysis due to heterogeneity so were narratively synthesized.*

Results: *Eighty-four studies were included, but two-thirds were at high risk for potential bias. There was little evidence about acute management for non-life-threatening reactions. H1-antihistamines may be of benefit, but this evidence was in part derived from studies on those with cross-reactive birch pollen allergy. Regarding long-term management, avoiding the allergenic food or substituting an alternative was commonly recommended, but, apart from for infants with cow's milk allergy, there was little high-quality research on this management approach. To reduce symptoms in children with cow's milk allergy, there was evidence to recommend alternatives such as extensively hydrolyzed formula. Supplements such as probiotics have not proven helpful, but allergen-specific immunotherapy may be disease modifying and therefore warrants further exploration.*

Conclusions: *Food allergy can be debilitating and affects a significant number of people. However, the evidence base about acute and longer-term management is weak and needs to be strengthened as a matter of priority.*

Originally published as: de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Cardona V, Dubois AEJ, Halken S, Host A, Poulsen LK, Van Ree R, Vlieg-Boerstra BJ, Agache I, Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Group. Acute and long-term management of food allergy: systematic review. *Allergy* 2014;69:159–167. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

Food allergy affects many millions of people and is responsible for substantial morbidity, impaired quality of life and costs to the individual, family and society (1). In some cases, it may prove fatal (2). Allergy may develop to almost any food, but is triggered most commonly by cow's milk, hen's eggs, wheat, soy, peanuts, tree nuts, fish and seafood (3, 4). There are two main approaches to managing food allergy: those targeting immediate symptoms and those aiming to support longer-term management. This review summarizes research about strategies for the acute and long-term management of children and adults with IgE- and non-IgE-mediated food allergy.

This systematic review is one of seven inter-linked syntheses undertaken to provide a state-of-the-art synopsis of the evidence base in relation to the epidemiology, prevention, diagnosis, management, and impact on quality of life, which will be used to inform clinical recommendations in the *EAACI Guidelines for Food Allergy and Anaphylaxis*. The aims of the review were to examine what pharmacological and non-pharmacological interventions have been researched to (i) manage immediate non-life threatening symptoms of food allergy (i.e. acute treatment) and (ii) manage long-term symptoms and promote desensitization/tolerance (i.e. longer-term management).

Methods

Protocol and registration

The review was registered with the International Prospective Register of Systematic Reviews. The protocol has been published previously (5) so only brief details about the methodology are provided here.

Search strategy

The following databases were searched: Cochrane Library; MEDLINE, Embase, CINAHL, ISI Web of Science, TRIP Database and Clinicaltrials.gov. Experts in the field were contacted for additional studies. Further details are included in the review protocol (6) (Data E1).

Inclusion and exclusion criteria

Studies of children or adults diagnosed with food allergy or reporting that they had food allergy were included. This included allergy where food was the primary sensitizer and pollen-associated food allergy if there was a direct diagnosis of food allergy. Studies of interventions for life-threatening manifestations were excluded because they were the focus of another review in this series (7).

Systematic reviews and meta-analyses, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies and interrupted time series studies published up until September 30, 2012 were eligible. No language restrictions were applied and, where possible, relevant studies in languages other than English were translated.

Study selection

The titles and abstracts of articles were checked by two independent reviewers and categorized as included, not included and unsure (DdS and MG). Full text copies of potentially relevant studies were obtained and their eligibility for inclusion was independently assessed by two reviewers (DdS and MG). Any discrepancies were resolved by consensus or discussion with a third reviewer (AS).

Risk of bias assessment

Risk of bias was independently carried out by two reviewers (DdS and MG) using adapted versions of the Critical Appraisal Skills Programme (CASP) tool (http://www.casp-uk.net/) and the Cochrane Effective Practice and Organization of care Group (EPOC) Risk of Bias tools. An overall grading of high, medium or low quality was assigned to each study.

Analysis, synthesis and reporting

A customized data extraction form was used to abstract data from each study, this process being independently undertaken by two reviewers (DdS and MG). Discrepancies were resolved by discussion. Three experts in the field checked all of the data extraction for accuracy and relevance (AS, RvR, TW). Meta-analysis was not appropriate because the studies were heterogeneous in focus, design, target populations and interventions. Findings were synthesized narratively by grouping studies according to topic, design, quality and outcomes. The narrative synthesis was checked by a group of methodologists and subject experts to ensure accuracy and relevance.

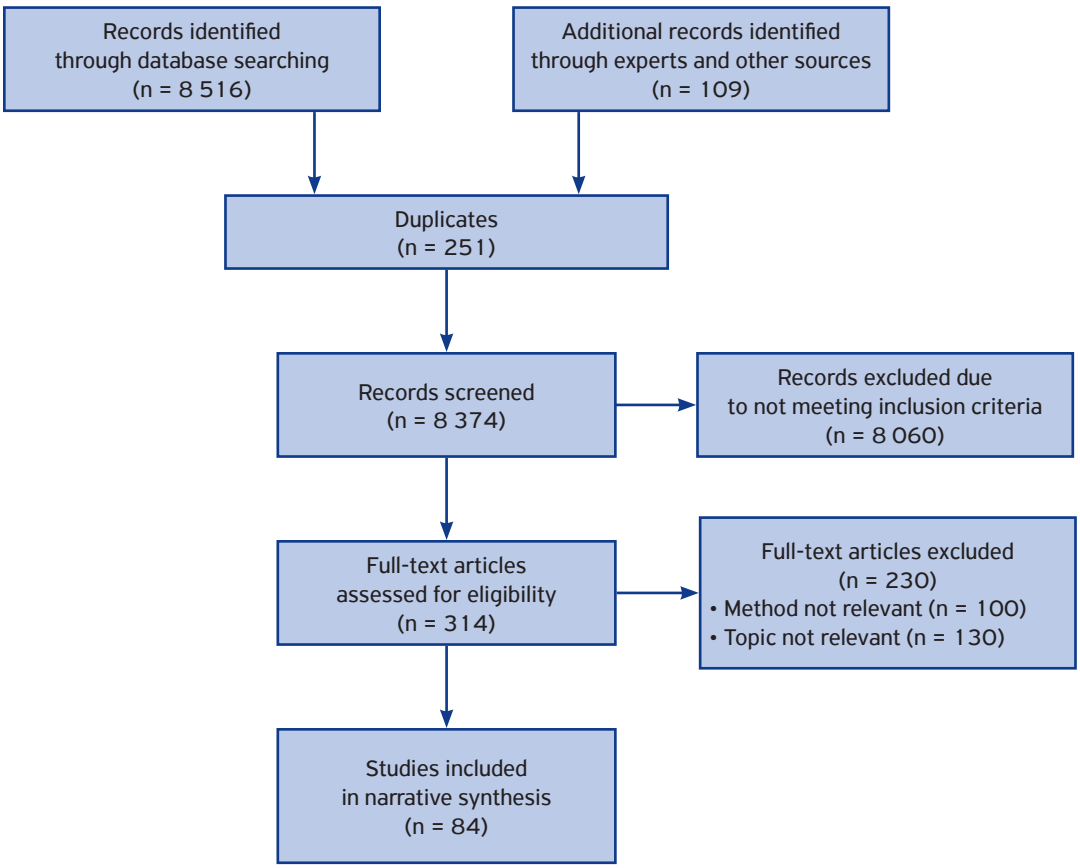


Figure 1 PRISMA flow diagram for selection of studies

Results

Study selection and characteristics

Figure 1 shows the PRISMA flowchart. Eighty-four studies were included, comprising 12 systematic reviews (15%), 54 randomized controlled trials (64%) and 18 non-randomized comparative or controlled cross-over studies (21%). Based on the risk of bias assessment, nine of the studies were deemed to be of high quality (11%), 20 were of moderate quality (24%) and 55 were of low quality (65%), often due to small sample sizes. Further details about each study are available in the online supplement (Tables E1, E2, E3, E4).

Managing acute reactions

Table 1 lists the key findings.

People with food allergy are often advised to completely avoid allergenic foods, but this may not always be possible. Pharmacological treatments are available to help people manage the symptoms when they are exposed to food allergens. The most common class of drugs assessed for this purpose is H1-antihistamines, taken as required when symptoms occur.

Three randomized trials and two non-randomized comparisons, all with methodological issues, suggested that H1-antihistamines may have some benefit, particularly in combination with other drugs (8-12). Some of the literature about H1-antihistamines focused on treating those with a primary birch pollen allergy and cross-reactive symptoms with biological related foods (pollen-food syndrome), while other studies included people with a diverse range of disease manifestations. The safety profile of H1-antihistamines in people with food allergy was not well reported.

Other medications have been used in people with food allergy, but we failed to identify any studies investigating these medicines that fulfilled the inclusion criteria.

Table 1 Summary of key findings

Intervention	Studies	% High quality	Overall findings
STRATEGIES TO TREAT ACUTE SYMPTOMS			
Antihistamines	5	0%	Three randomized trials and two non-randomized comparisons found that antihistamines may reduce immediate symptoms or severity in children and adults (8-12).
LONG-TERM MANAGEMENT STRATEGIES			
Antihistamines	1	0%	One trial found prophylactic antihistamines improved symptoms (22).
Mast cell stabilizers	9	0%	Four randomized trials and two non-randomized comparisons found that prophylactic mast cell stabilizers reduced symptoms or severity in children, adults or both (13-18). Three randomized trials found no benefits. Side effects were noted (19-21).
Other pharmacological treatments	2	0%	One trial of calf thymus acid lysate derivative found improved skin lesions (23). One trial of a herbal treatment found no improvement in symptoms (24).
Dietary elimination	4	0%	One trial and one non-randomized comparison found that dietary elimination worked well for children allergic to cows' milk or eggs, (41, 42) but a systematic review and a non-randomized comparison suggested no benefits for spices or fruit allergies in children (43, 44). No relevant studies were identified in adults.
Dietary substitution: cows' milk formula substitutes	17	12%	One trial and one non-randomized comparison found extensively hydrolyzed formulas to be well tolerated (25, 26). A systematic review and three randomized trials found that amino acid-based formulas were well tolerated and may reduce symptoms among infants with cows' milk allergy (27-30). A systematic review and a randomized controlled trial concluded that soy milk is nutritionally adequate and well tolerated, (31, 32) but a randomized trial concluded that soy may be less well tolerated than extensively hydrolyzed whey formula (33). Two randomized controlled trials found that rice hydrolyzate formula was well tolerated, (34, 35) but one randomized trial found no benefits (36). One randomized trial found that almond milk was well tolerated (37). Another randomized trial found that chicken-based formula was better tolerated than soy-based formula (38). A systematic review concluded that donkey or mare's milk was as allergenic as cows' milk, (31) but a randomized trial suggested that donkey's milk was better tolerated than goat's milk (39). A non-random comparison found that meat-based formulas were well tolerated and reduced symptoms in infants with other food allergies (40).
Probiotic supplements	11	27%	One systematic review, three randomized trials and one non-randomized comparison found that probiotic supplements may reduce symptoms and support long-term tolerance in infants with cows' milk allergy or other allergies (45-49). Five randomized trials found no benefits in infants and one trial found no benefits in young adults (50-55).
Subcutaneous immunotherapy	9	11%	Five randomized trials and four other studies found improved tolerability in children and adults (56-63). One trial found no benefits (64).
Sublingual immunotherapy	5	0%	Four trials found that sublingual immunotherapy was associated with improved tolerability for those with peanut and fruit allergies (65-68). One trial found no benefit (69).
Oral immunotherapy	18	22%	Two systematic reviews, nine randomized trials and four non-randomized comparisons found that oral immunotherapy was associated with improved tolerability for children and adults with various food allergies (70-83). One randomized trial found no benefit (84). Two systematic reviews found mixed evidence and concluded that oral immunotherapy should not be routine treatment (85, 86).

Longer-term management

Pharmacological treatment

Pharmacological strategies for long-term management involve taking ongoing treatment to prevent symptoms from reappearing or worsening (as well as potentially treating existing manifestations).

There were mixed findings about mast cell stabilizers used prophylactically for food allergy symptoms. Four randomized trials and two non-randomized comparisons found that mast cell stabilizers reduced symptoms or severity in children, adults or both (13-18). Three randomized trials found no benefits (19-21). Side-effects were noted, but were usually not severe.

There was insufficient evidence upon which to base recommendations about other pharmacological treatments. One randomized trial found that H1-antihistamines could have a prophylactic effect (22) and one trial of calf thymus acid lysate derivative found improvement in skin lesions (23). A trial of a herbal treatment was not effective (24).

Dietary interventions

More research was available about dietary interventions. For instance, a number of studies investigated alternatives to cow's milk formula for infants with cow's milk allergy. Here the evidence base was moderate. Although in common use, cow's milk hydrolyzates were not rigorously compared to standard cow's milk formula alone. Instead, extensively hydrolyzed cow's milk formulas were often used as a comparator in studies of other alternatives such as soy or amino acid-based formulas.

There was some evidence to suggest that extensively hydrolyzed cow's milk formula and amino acid-based formula may be useful long-term management strategies for infants with cow's milk allergy of which extensively hydrolysed formulas are the first choice. For example, one randomized trial and one non-randomized comparison found that extensively hydrolyzed cow's milk formulas were well tolerated (25, 26). One systematic review and three randomized trials found that amino acid-based formulas were well tolerated and may reduce symptoms among infants with cow's milk allergy (27-30). The research suggested that amino acid-based formulas may be as effective, or more effective, than extensively hydrolyzed whey formula.

Another systematic review and a randomized controlled trial concluded that soy milk was nutritionally adequate and well tolerated in children allergic to cow's milk (31, 32), but a randomized trial found that soy may be less well tolerated than extensively hydrolyzed whey formula, especially among infants younger than six months (33). Two randomized controlled trials suggested that rice hydrolyzate formula was well tolerated among infants with cow's milk allergy and may even reduce the duration of allergy (34, 35). However, another randomized trial found no improvements (36).

There was less evidence about other alternatives to cow's milk. One randomized trial found that almond milk was well tolerated (37). Another randomized trial found that chicken-based formula was better tolerated than soy-based formula (38). A systematic review concluded that donkey or mare's milk were as allergenic as cow's milk (31), but a randomized trial suggested that donkey's milk was better tolerated than goat's milk and reduced symptoms in infants with cow's milk allergy (39).

Our review identified no high-quality studies about other alternatives such as camel's milk or oat milk.

In infants with allergies to food other than cow's milk, a non-random comparison found that meat-based formulas were well tolerated and reduced symptoms (40).

Another key strategy in the long-term management of food allergy involved eliminating the offending food from the diet. Apart from the studies above about eliminating cow's milk for infants, this intervention has received relatively little research attention, perhaps because it is deemed 'common sense' that avoidance will reduce symptoms. One randomized trial and one non-randomized comparison found that eliminating the foods that children were allergic to from the diet was associated with remission of symptoms and reduced reactions to allergens over time (41, 42). This worked well for children allergic to cow's milk or hen's eggs. However a review and a non-randomized comparison suggested dietary elimination may be more difficult for spices (43) or fruit allergies (44). No relevant studies were identified solely focusing on adults.

Dietary supplements

Evidence about the effectiveness of using probiotic supplements as a way to minimize food allergy was mixed. A systematic review, three randomized controlled trials and one non-randomized comparison

found that probiotic supplements may reduce symptoms and support long-term tolerance in infants with cow's milk allergy or other allergies (45-49). However, five randomized trials found no benefits in infants and one trial found no benefits in young adults (50-55). Some of the studies found that probiotics were more effective in IgE-mediated food allergy.

The review identified no studies meeting the inclusion criteria that focused on prebiotics or other supplements for the long-term management of food allergy.

Allergen-specific immunotherapy

The greatest amount of research focused on different forms of immunotherapy, either with food extracts or cross-reactive pollen extract. Studies generally found that subcutaneous immunotherapy with food extract was associated with improved tolerance and reduced symptoms in children and adults with various food allergies (56, 57). The same was true with cross-reactive pollen extract, (58-61) and other extracts (62). However, the amount of food tolerated remained small and side effects were common. One randomized trial found no benefit (63).

Another option is sublingual immunotherapy, where allergen extracts are placed under the tongue to promote desensitization. Four randomized trials found that sublingual immunotherapy with food extracts was associated with improved tolerance and reduced symptoms for those with peanut, hazelnut and peach allergies (64-67). The treatment was generally well tolerated, with few suffering adverse reactions. One randomized trial with cross-reactive pollen extract found no benefit (68).

Two systematic reviews, nine randomized trials and four non-randomized comparisons found that oral immunotherapy (or specific oral tolerance induction; SOTI) was associated with improved tolerance and reduced symptoms for children and adults with various food allergies (69-82). Around half of participants suffered side effects, though these were not usually severe. One randomized trial found no benefit (83). One systematic review of oral immunotherapy found mixed evidence and suggested that this should not be recommended as routine treatment (84).

Immunotherapy is currently only a research intervention, but may be promising therapeutically. As with all of other interventions considered in this review, however, the evidence base was overall of low quality. Another issue is that most immunotherapy studies did not explore what happens once the relatively short-term treatment phase ceases. Whereas most studies of dietary interventions and probiotic supplements have focused on children, the majority of research into injection immunotherapy for food allergy has targeted adults. Studies of oral ingestion have included both children and adults.

There were no high-quality studies identified about other long-term management strategies such as educational or behavioral interventions. Nor did any studies about cost-effectiveness meet the inclusion criteria.

Discussion

Statement of principal findings

This is one of the most comprehensive systematic reviews about the management of food allergy ever undertaken. There was a substantial body of experimental evidence uncovered. However, much of it comprises small-scale, relatively low-grade studies. Nonetheless, there was some evidence that H1-antihistamines can be effective in improving acute cutaneous manifestations of food allergy.

Regarding longer-term management, avoiding or substituting food was a common approach. There was evidence that cow's milk substitutes can be particularly beneficial for cow's milk allergy. There was no evidence to recommend probiotic supplements to improve outcomes in children or adults with food allergy.

A large quantity of research has been undertaken about different forms of immunotherapy. Although immunotherapy is not currently used in routine practice, the preliminary data were encouraging and further study is warranted. It is important to balance the benefits with the risks of immunotherapy, and further investigation is required to explore any sub-groups that may benefit most. It is uncertain whether any gains in tolerance will continue while on treatment or when treatment ceases. Where studies did examine this, tolerance tended to persist only for a few months after immunotherapy ceased.

Strengths and limitations

This review included the most up-to-date research about both the acute and long-term management of food allergy, with studies from Europe, North America, Asia and Australasia. It was conducted using stringent

international standards and drew on a substantially greater evidence base than previous reviews on this subject (85, 86).

However, the studies included were heterogeneous, meaning that meta-analysis was not possible. The inclusion criteria meant that studies about educational, behavioral and psychological interventions were omitted as these tended to be investigated using uncontrolled before-and-after designs or lower quality methods. Safety was assessed only in some studies. Further trials using standardized measures of side effects are required to assess the risks associated with different treatments. Furthermore, the review was unable to quantify overall treatment effects, draw conclusions about the comparative effectiveness of different management approaches or the population sub-groups that may benefit most.

Conclusions

Food allergy is complex because the best management strategy is likely to depend on exactly what the person is allergic to, the ways this manifests, the types of treatments they have tried in the past and their responses to those treatments.

There is weak evidence to recommend H1-antihistamines to alleviate immediate, non-life threatening symptoms in children and adults with food allergy. There is also weak evidence to recommend mast cell stabilizer drugs for the prophylactic treatment of symptoms in some children or adults with food allergy.

There is moderate evidence to recommend alternatives to cow's milk formula for infants with cow's milk allergy. Extensively hydrolyzed whey formula and amino acid-based formula have been found to have benefits, with less evidence for soy and rice hydrolyzate. There is no evidence for other foods or for how foods should be re-introduced to the diet.

There is more encouraging evidence to support further exploration of immunotherapy, although the quality of the evidence base is questionable and the treatment is often associated with adverse effects. Further research could usefully explore whether the benefits of treatment continue after the intervention is stopped, as this is an area where there are limited data.

Overall, the review suggests that there is an urgent need to better understand how to support the millions of people who suffer from food allergy.

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing this systematic review. We would also like to thank the EAACI Executive Committee for their suggestions.

Funding

EAACI

Contributorship

AS, AM, DdS and GR conceived this review. The review was undertaken by DdS, MG and colleagues at The Evidence Centre. DdS led the drafting of the manuscript and all authors commented on drafts of the manuscript and agreed the final version. This review was undertaken as part of a series managed by SSP and overseen by AS.

Conflicts of interest

None known

References

1. Vickery BP, Burks W. Oral immunotherapy for food allergy. *Cur Opin Pediatr* 2010;22:765–770.
2. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol* 2007;119:1016–1018.
3. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010;125:S116-125.
4. Lack G. Food allergy. *N Engl J Med* 2008;359:1252–1260.
5. de Silva D, Panesar SS, Thusu S, Rader T, Werfel T, Muraro A *et al.* The acute and long-term management of food allergy: protocol for a rapid systematic review. *Clin Transl Allergy* 2013;3:12.
6. de Silva D, Panesar SS, Thusu S, Rader T, Werfel T, Muraro A *et al.* The acute and long-term management of food allergy: protocol for a rapid systematic review. *CRD Register* 2013: CRD42013003708. Available online at http://www.metaxis.com/prospero/full_doc.asp?RecordID=3708.
7. Dhami S, Panesar SS, Rader T, Muraro A, Roberts G, Worm M *et al.* The acute and long-term management of anaphylaxis: protocol for a systematic review. *Clin Transl Allergy* 2013;3:14.
8. Lin RY, Curry A, Pesola GR, Knight RJ, Lee H-S, Bakalchuk L *et al.* Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med* 2000;36:462–468.
9. Pacor ML, Peroli P, Favari F, Lunardi C. Controlled study of oxatomide versus disodium chromoglycate for treating

adverse reactions to food. *Drugs Exp Clin Res* 1992;18: 119–123.

10. Ciprandi G, Scordamaglia A, Ruffoni S, Pizzorno G, Ferrini O, Canonica GW. Terfenadine (single or associated) treatment of adverse reactions to foods. *Allergol Immunopathol* 1987;15:201–203.
11. Ciprandi G, Scordamaglia A, Bagnasco M, Canonica GW. Pharmacologic treatment of adverse reactions to foods: comparison of different protocols *Ann Allergy* 1987;58: 341–343.
12. Bindslev-Jensen C, Vibits A, Stahl Skov P, Weeke B. Oral allergy syndrome: the effect of astemizole. *Allergy* 1991;46: 610–613.
13. Businco L, Benincori N, Nini G, Businco E, Cantani A, De Angelis M. Double-blind crossover trial with oral sodium cromoglycate in children with atopic dermatitis due to food allergy. *Ann Allergy* 1986;57:433–438.
14. Zur E, Kaczmarski M *et al.* The effectiveness of oral sodium cromoglycate in the treatment of food allergy in children. *Przeglad Pediatryczny* 2002;32:300–307.
15. Gerrard JW. Oral cromoglycate: its value in the treatment of adverse reactions to foods. *Ann Allergy* 1979;42:135–138.
16. Spira C, André C. Food allergy. Results of a multicenter study. *Allerg Immunol* 1988;20:147–151.
17. Ortolani C, Pastorello E, Zanussi C. Prophylaxis of adverse reactions to foods. A double-blind study of oral sodium cromoglycate for the prophylaxis of adverse reactions to foods and additives. *Ann Allergy* 1983;50:105–109.
18. Ellul-Micallef R. Effect of oral sodium cromoglycate and ketotifen in fish-induced bronchial asthma. *Thorax* 1983; 38:527–530.
19. Dannaeus A, Foucard T, Johansson SG. The effect of orally administered sodium cromoglycate on symptoms of food allergy. *Clin Allergy* 1977;7:109–115.
20. Daugbjerg PS, Bach-Mortensen N, Osterballe O. Oral sodium cromoglycate treatment of atopic dermatitis related to food allergy. *Allergy* 1984;39:535–541.
21. Burks AW, Sampson HA. Double-blind placebo-controlled trial of oral cromolyn in children with atopic dermatitis and documented food hypersensitivity. *J Allergy Clin Immunol* 1988;81:417–423.
22. Boner AL, Richelli C, Antolini I, Vibelli C, Andri L. The efficacy of ketotifen in a controlled double-blind food challenge study in patients with food allergy. *Ann Allergy* 1986;57:61–64.
23. Cavagni G, Piscopo E, Rigoli E, Iuliano P, Bertolini P, Cazzola P. Food allergy in children: an attempt to improve the effects of the elimination diet with an immunomodulating agent (thymomodulin). A double-blind clinical trial. *Immunopharmacol Immunotoxicol* 1989;11:131–142.
24. Wang J, Patil SP, Yang N, Ko J, Lee J, Noone S *et al.* Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, double-blinded, placebo-controlled, dose escalation, phase 1 study. *Ann Allergy Asthma Immunol* 2010;105:75–84.
25. Niggemann B, von Berg A, Bollrath C, Berdel D, Schauer U, Rieger C *et al.* Safety and efficacy of a new extensively hydrolyzed formula for infants with cow's milk protein allergy. *Pediatr Allergy Immunol* 2008:19:348–354.
26. Halken S, Høst A, Hansen LG, Osterballe O. Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation. *Pediatr Allergy Immunol* 1993;4:53–59.
27. Hill DJ, Murch SH, Rafferty K, Wallis P, Green CJ. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. *Clin Exp Allergy* 2007;37:808–822.
28. Niggemann B, Binder C, Dupont C, Hadji S, Arvola T, Isolauri E. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol* 2001;12:78–82.
29. Isolauri E, Sütas Y, Mäkinen-Kiljunen S, Oja SS, Isosomppi R, Turjanmaa K. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. *J Pediatr* 1995;127:550–557.
30. McLeish CM, MacDonald A, Booth IW. Comparison of an elemental with a hydrolysed whey formula in intolerance to cows' milk. *Arch Dis Child* 1995;73:211–215.
31. Muraro MA, Giampietro PG, Galli E. Soy formulas and nonbovine milk. *Ann Allergy Asthma Immunol* 2002;89: 97–101.
32. Galli E, Chini L, Paone F, Moschese V, Knafelz D, Panel P *et al.* Clinical comparison of different replacement milk formulas in children with allergies to cow's milk proteins. 24-month follow-up study. *Minerva Pediatr* 1996;48:71–77.
33. Klemola T, Vanto T, Juntunen-Backman K, Kalimo K, Korpela R, Varjonen E. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr* 2002;140:219–224.
34. Reche M, Pascual C, Fiandor A, Polanco I, Rivero-Urgell M, Chifre R *et al.* The effect of a partially hydrolysed formula based on rice protein in the treatment of infants with cow's milk protein allergy. *Pediatr Allergy Immunol* 2010;21: 577–585.
35. Terracciano L, Bouygue GR, Sarratud T, Veglia F, Martelli A, Fiocchi A. Impact of dietary regimen on the duration of cow's milk allergy: a random allocation study. *Clin Exp Allergy* 2010;40:637–642.
36. Savino F, Castagno E, Monti G, Serraino P, Peltran A, Oggero R *et al.* Z-score of weight for age of infants with atopic dermatitis and cow's milk allergy fed with a rice-hydrolysate formula during the first two years of life. *Acta Paediatr Suppl* 2005;94:115–119.
37. Salpietro CD, Gangemi S, Briuglia S, Meo A, Merlino MV, Muscolino G *et al.* The almond milk: a new approach to the management of cow-milk allergy/intolerance in infants. *Minerva Pediatr* 2005;57:173–180.

38. Jirapinyo P, Densupsoontorn N, Wongarn R, Thamonsiri N. Comparisons of a chicken-based formula with soy-based formula in infants with cow milk allergy. *Asia Pac J Clin Nutr* 2007;16:711–715.
39. Vita D, Passalacqua G, Di Pasquale G, Caminiti L, Crisafulli G, Rulli I, Pajno GB. Ass's milk in children with atopic dermatitis and cow's milk allergy: crossover comparison with goat's milk. *Pediatr Allergy Immunol* 2007;18:594-598.
40. Cantani A. A home-made meat-based formula for feeding atopic babies: a study in 51 children. *Eur Rev Med Pharmacol Sci* 2006;10:61–68.
41. Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998;9:13–19.
42. Agata H, Kondo N, Fukutomi O, Shinoda S, Orii T. Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferative responses to food Allergens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J Allergy Clin Immunol* 1993;91:668–679.
43. Chen JL, Bahna SL. Spice allergy. *Ann Allergy Asthma Immunol* 2011;107:191–199.
44. Alonso A, Seoane MA, Irañeta SG, Scavini LM, Rodríguez SM. A citrus fruit-exclusion diet in sensitive patients and its influence on specific antibodies. *J Investig Allergol Clin Immunol* 1994;4:146–148.
45. Szajewska H, Mrokowicz JZ. Probiotics in the treatment and prevention of food allergy - Systematic review. *Pediatria Wspolczesna* 2002;4:79–83.
46. Cukrowska B, Rosiak I, Klewicka E, Motyl I, Schwarzer M, Libudzisz Z *et al.* Probiotic lactobacillus casei and lactobacillus paracasei strains in treatment of food allergy in children. *Pol. Przeglad Pediatryczny* 2010:21–25.
47. Berni Canani R, Nocerino R, Terrin G, Coruzzo A, Cosenza L, Leone L *et al.* Effect of Lactobacillus GG on tolerance acquisition in infants with cow's milk allergy: a randomized trial. *J Allergy Clin Immunol* 2012;129:580–582.
48. Kirjavainen PV, Salminen SJ, Isolauri E. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. *J Pediatr Gastroenterol Nutr* 2003;36:223–227.
49. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997; 99:179–185.
50. Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T *et al.* Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy* 2005;60:494–500.
51. Hol J, van Leer EH, Elink Schuurman BE, de Ruiter LF, Samsom JN, Hop W *et al.* The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. *J Allergy Clin Immunol* 2008;121:1448–1454.
52. Brouwer ML, Wolt-Plompen SA, Dubois AE, van der Heide S, Jansen DF, Hoijer MA *et al.* No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clin Exp Allergy* 2006;36:899–906.
53. Sistek D, Kelly R, Wickens K, Stanley T, Fitzharris P, Crane J. Is the effect of probiotics on atopic dermatitis confined to food sensitized children? *Clin Exp Allergy* 2006;36:629–633.
54. Flinterman AE, Knol EF, van Ieperen-van Dijk AG, Timmerman HM, Knulst AC, Bruijnzeel-Koomen CA *et al.* Probiotics have a different immunomodulatory potential in vitro versus ex vivo upon oral administration in children with food allergy. *Int Arch Allergy Immunol* 2007;143:237–244.
55. Helin T, Haahtela S, Haahtela T. No effect of oral treatment with an intestinal bacterial strain, Lactobacillus rhamnosus (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. *Allergy* 2002;57:243–246.
56. Miller JB. A double-blind study of food extract injection therapy: a preliminary report. *Ann Allergy* 1977;38:185–191.
57. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992;90:256–262.
58. Bolhaar ST, Tiemessen MM, Zuidmeer L, van Leeuwen A, Hoffmann-Sommergruber K, Bruijnzeel-Koomen CA *et al.* Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. *Clin Exp Allergy* 2004;34:761–769.
59. Mauro M, Russello M, Incorvaia C, Gazzola G, Frati F, Moingeon P *et al.* Birch-apple syndrome treated with birch pollen immunotherapy. *Int Arch Allergy Immunol* 2011;156: 416–422.
60. Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy* 1998;28:1368–1373.
61. Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. *Allergy* 2004;59: 1272–1276.
62. King WP, Fadal RG, Ward WA, Trevino RJ, Pierce WB, Stewart JA *et al.* Provocation-neutralization: a two-part study. Part II. Subcutaneous neutralization therapy: a multi-center study. *Otolaryngol Head Neck Surg* 1988;99:272–277.
63. van Hoffen E, Peeters KA, van Neerven RJ, van der Tas CW, Zuidmeer L, van Ieperen-van Dijk AG *et al.* Effect of birch pollen-specific immunotherapy on birch pollen-related hazelnut allergy. *J Allergy Clin Immunol* 2011;127:100–101.
64. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W *et al.* Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011;127:640–646.e1.
65. Enrique E, Pineda F, Malek T, Bartra J, Basagaña M, Tella R *et al.* Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005;116:1073–1079.
66. Fernández-Rivas M, GarridoFernández S, Nadal JA, Díaz

de Durana MD, García BE, González-Mancebo E *et al.* Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. *Allergy* 2009;64:876–883.

67. García BE, González-Mancebo E, Barber D, Martín S, Tabar AI, Díaz de Durana AM *et al.* Sublingual immunotherapy in peach allergy: monitoring molecular sensitizations and reactivity to apple fruit and Platanus pollen. *J Investig Allergol Clin Immunol* 2010;20:514–520.
68. Hansen KS, Khinchi MS, Skov PS, Bindslev-Jensen C, Poulsen LK, Malling HJ. Food allergy to apple and specific immunotherapy with birch pollen. *Mol Nutr Food Res* 2004;48:441–448.
69. Calvani M, Giorgio V, MiceliSopo S. Specific oral tolerance induction for food. A systematic review. *Eur Ann Allergy Clin Immunol* 2010;42:11–19.
70. Lee JH, Noh G, Noh J, Lee S, Choi WS, Kim HS *et al.* Clinical characteristics of oral tolerance induction of IgE-mediated and non-IgE-mediated food allergy using interferon gamma. *Allergy Asthma Proc* 2010;31:e39–e47.
71. Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Pasquale T *et al.* Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003;17:459–465.
72. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology* 1998;45:52–58.
73. Martorell A, De la Hoz B, Ibáñez MD, Bone J, Terrados MS, Michavila A *et al.* Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy* 2011;41:1297–1304.
74. Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R *et al.* Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Eur Ann Allergy Clin Immunol* 2007;39:12–19.
75. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S *et al.* The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2012;129:448–455.
76. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG *et al.* A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008;122:1154–1160.
77. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M *et al.* Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol* 2010;105:376–381.
78. Caminiti L, Passalacqua G, Barberi S, Vita D, Barberio G, De Luca R *et al.* A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. *Allergy Asthma Proc* 2009;30:443–448.
79. Kim JS, Nowak-Węgrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol* 2011;128:125–131.e2.
80. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW *et al.* Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012;367:233-243.
81. Nurmatov U, Venderbosch I, Devereux G, Simons FE, Sheikh A. allergen-specific oral immunotherapy for peanut allergy. *Cochrane Database Syst Rev* 2012;9:CD009014.
82. Kopac P, Rudin M, Gentinetta T, Gerber R, PichlerCh, Hausmann O *et al.* Continuous apple consumption induces oral tolerance in birch-pollen-associated apple allergy. *Allergy* 2012;67:280–285.
83. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007;62:1261–1269.
84. Fisher HR, du Toit G, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?: a meta-analysis of published RCTs. *Arch Dis Child* 2011;96:259–264.
85. Schneider Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al.* Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010; 303:1848–1856.
86. Schneider Chafen JJ, Newberry S, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al.* Prevalence, Natural History, Diagnosis, and Treatment of Food Allergy. A Systematic Review of the Evidence. Santa Monica, RAND, 2010.

1.5

DIAGNOSIS AND MANAGEMENT OF FOOD ALLERGY

EAACI GUIDELINES

A Muraro[1*], T Werfel[2*], K Hoffmann-Sommergruber[3*], G Roberts [4-6], K Beyer[7], C Bindslev-Jensen[8], V Cardona[9], A Dubois[10], G duToit[11, 12], P Eigenmann[13], M Fernandez Rivas[14], S Halken[15], L Hickstein[16], A Høst[15], E Knol[17], G Lack[11, 12], MJ Marchisotto[17], B Niggemann[7], BI Nwaru[18], NG Papadopoulos[19, 20], LK Poulsen[21], AF Santos[11, 22, 23], I Skypala[24], A Schoepfer[25], R Van Ree[26], C Venter[4], M Worm[7], B Vlieg–Boerstra[27], NW de Jong[28], S Panesar[29], D de Silva[30], K Soares-Weiser[31], A Sheikh[29, 32], BK Ballmer-Weber[33], C Nilsson C[34], CA Akdis[35], on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group

AFFILIATIONS

[1] The Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region. Department of Mother and Child Health - University of Padua. Padua, Italy

[2] Department of Dermatology and Allergy, Hannover Medical University, Hannover, Germany

[3] Department of Pathophysiology and Allergy Research, Medical University of Vienna, Vienna, Austria

[4] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK

[5] Clinical and Experimental Sciences and Human Development and Health Academic Units, University of Southampton Faculty of Medicine, Southampton, UK

[6] NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[7] Division of Paediatric Pneumology and Immunology, Charité University Hospital, Berlin, Germany

[8] Department of Dermatology and Allergy Centre, Odense University Hospital

[9] Allergy Section, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[10] University of Groningen, University Medical Center Groningen, Department of Pediatric Pulmonology and Pediatric Allergy, and GRIAC Research Institute, Groningen, the Netherlands

[11] MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK

[12] Department of Paediatric Allergy, Guy's and St Thomas' NHS Foundation Trust, London, UK

[13] Department of Child and Adolescent, University Hospitals of Geneva, Geneva, Switzerland

[14] Hospital Clinico San Carlos, Allergy Dept. Madrid, Spain

[15] Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[16] Department of (Paediatric) Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

[17] Food Allergy and Anaphylaxis Research and Education- FARE

[18] University of Tampere, Tampere, Finland

[19] Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

[20] Center for Pediatrics and Child Health Institute of Human Development The University of Manchester

[21] Allergy Clinic Copenhagen University Hospital at Gentofte, Copenhagen Denmark

[22] Department of Pediatric Allergy, Division of Asthma, Allergy & Lung Biology, King's College, London

[23] Immunoallergology Department, Coimbra University Hospital, Coimbra, Portugal

[24] Department of Rehabilitation and Therapies, Royal Brompton and Harefield NHS Foundation Trust

[25] Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

[26] Academic Medical Center, University of Amsterdam, The Netherlands

[27] Emma Children's Hospital, Academic Medical Center, University of Amsterdam, The Netherlands

[28] Dept. of Internal Medicine, Section Allergology, ErasmusMC, Rotterdam, the Netherlands

[29] Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Scotland, UK

[30] The Evidence Centre, 126 London, UK

[31] Enhance Reviews Ltd, Wantage, UK

[32] Evidence-Based Health Care Ltd, Edinburgh, UK

[33] Allergy Unit, Department of Dermatology, University Hospital Zürich

[34] Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet and Sachs' Children's Hospital, Stockholm, Sweden

[35] Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Christine Kühne–Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

** Joint first author*

EXPERT PANEL

A Assa'ad[1], AM Staiano[2], A Moneret Voutren[3], S Bahna[4], W Burks[5], C Sackesen[6], C Agostoni[7], G Wong[8], G Pajno[9], M Gustavo[10], H Sampson[11], M Groetch[12], M Ebisawa[13], N Pham-Thi[14], R Troncone[15], O Rudzeviciene[16], S Sicherer[11], S Jones[17], A Nowak-Wegrzyn[11], K Allen[18]

[1] Cincinnati Children's Hospital Medical Center, USA

[2] Department of Pediatrics, University of Naples "Federico II," Naples, Italy

[3] Lorraine-Nancy University, Allergy vigilance Network, France.

[4] Louisiana State University Health Sciences Center, Shreveport, Louisiana, USA

[5] Department of Pediatrics, University of North Carolina, Chapel Hill, NC, USA

[6] Department of Pediatric Allergy, Hacettepe University School of Medicine, Ankara, Turkey.

[7] Department of Pediatrics, San Paolo Hospital, University of Milan, Italy.

[8] Chinese University of Hong Kong, Hong Kong, China

[9] Department of Pediatrics- Allergy Unit, University of Messina, Italy

[10] Departamento de Alergología e Inmunología Clínica, Hospital Universitario Austral, Argentina

[11] Division of Allergy and Immunology, Department of Pediatrics, Elliot and Roslyn Jaffe Food Allergy Institute, Kravis Children's Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[12] Icahn School of Medicine at Mount Sinai, New York, USA

[13] Japanese Society of Allergology (JSA) and World Allergy Organization (WAO), Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara National Hospital, Sagamihara, Kanagawa, Japan.

[14] Necker Sick Children's Hospital, Faculté Paris 5, CNRS Paris

[15] European Laboratory for the Investigation of Food Induced Diseases, University of Naples, Federico II, Naples, Italy

[16] Clinic of Children's Diseases, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

[17] Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, Ark, USA

[18] Murdoch Childrens Research Institute, University of Melbourne and Royal Children's Hospital, Melbourne Australia

Food allergy can result in considerable morbidity, impact negatively on quality of life and prove costly in terms of medical care. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Food Allergy and Anaphylaxis Guidelines Group, building on previous EAACI position papers on adverse reaction to foods and three recent systematic reviews on the epidemiology, diagnosis and management of food allergy and provide evidence-based recommendations for the diagnosis and management of food allergy. While the primary audience is allergists, this document is relevant for all other healthcare professionals including primary care physicians, and paediatric and adult specialists, dieticians, pharmacists and paramedics. Our current understanding of the manifestations of food allergy, the role of diagnostic tests and the effective management of patients of all ages with food allergy is presented. The acute management of non-life threatening reactions is covered in these guidelines, but for guidance on the emergency management of anaphylaxis, readers are referred to the related EAACI anaphylaxis guidelines.

Originally published as: Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, Cardona V, Dubois A, duToit G, Eigenmann P, Fernandez Rivas M, Halken S, Hickstein L, Høst A, Knol E, Lack G, Marchisotto MJ, Niggemann B, Nwaru BI, Papadopoulos NG, Poulsen LK, Santos AF, Skypala I, Schoepfer A, van Ree R, Venter C, Worm M, Vlieg–Boerstra B, de Jong NW, Panesar SS, de Silva D, Soares-Weiser K, Sheikh A, Ballmer-Weber BK, Nilsson C, Akdis CA, on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. Allergy 2014; DOI: 10.1111/all.12429. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

Food allergy has been defined as adverse reactions to food in which "immunologic mechanisms have been demonstrated" (1, 2); this term therefore encompasses both immunoglobulin E (IgE)-mediated and non-IgE-mediated food allergies (Tables 1, 2). Food allergy can result in considerable morbidity and in some instances results in life-threatening anaphylaxis. These guidelines aim to provide evidence-based recommendations for the diagnosis and management of patients of any age with suspected or confirmed food allergy. Development of the guidelines has been based on three systematic reviews of the epidemiology (Chapters 1.1, 1.2), diagnosis (Chapter 1.3) and management (Chapter 1.4) of food allergy with weaker forms of evidence being used where there were insufficient data from more robust studies or where high level evidence is practically or ethically unobtainable. These guidelines build on the previous EAACI position paper on adverse reaction to foods (3) and are complementary to the other current food allergy guidelines, including the United States (US) National Institute of Allergy and Infectious Diseases (NIAID) guidelines (4). Distinctive features include a European focus and the placing of particular emphasis on the practical issues associated with diagnosis and long-term management of food allergy.

Table 1 Key Terms (2)

Term	Definition
Allergen	Any substance stimulating the production of immunoglobulin IgE or a cellular immune response; usually a protein.
Atopic eczema/ dermatitis	Chronic inflammatory skin disease characterized by typical age related lesions with pruritus and personal or family history of atopic disease.
Co-factors	Patient related external circumstances that are associated with more severe allergic reactions. They are also known as augmentation factors.
Eosinophilic esophagitis	A chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.
Food	Any substance, whether processed, semi-processed or raw, which is intended for human consumption, and includes drink, chewing gum and any substance which has been used in the manufacture, preparation or treatment of "food" but does not include cosmetics or tobacco or substances used only as drugs (Codex Alimentarius).
Food allergy	An adverse reaction to food mediated by an immunological mechanism, involving specific IgE (IgE mediated), cell–mediated mechanisms (non IgE mediated) or both IgE and cell mediated mechanisms (mixed IgE and non IgE mediated).
Food desensitization	Induction of short-term tolerance that may disappear after withdrawal of the treatment.
Oral tolerance	A state of local and systemic immune unresponsiveness induced by oral administration of innocuous antigens / allergens.
Oligo-allergenic diet	An empirical elimination diet with minimal content of major food allergens for the given population.
Oral tolerance induction	A state of local and systemic permanent immune unresponsiveness induced by following oral administration consumption of innocuous antigens such as food proteins; does not disappear after withdrawal of the antigens.
Prebiotic	Non-digestible substances that provide a beneficial physiological effect for the host by selectively stimulating the favourable growth or activity of a limited number of indigenous bacteria.
Probiotic	Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.
Sensitization	Presence of specific IgE to an allergen.
Symbiotics	A mixture of probiotics and prebiotics.

Table 2 Food-induced allergic disorders (classified based on the underlying immunopathology)

Disorder	Clinical features	Typical age group	Prognosis
IgE MEDIATED			
Pollen food allergy syndrome	Pruritus, mild edema confined to oral cavity	Onset after pollen allergy established (adult > young child)	May be persistent and may vary by season
Urticaria/angioedema	Triggered by ingestion or direct contact	Children > adults	Depends on food
Rhinoconjunctivitis/ asthma	Accompanies food-induced allergic reaction but rarely isolated symptoms May be triggered by inhalation of aerosolized food protein	Infant/child > adult, except for occupational disease	Depends on food
Gastrointestinal symptoms	Symptoms such as nausea, emesis, abdominal pain and diarrhea triggered by food ingestion	Any age	Depends on food
Anaphylaxis	Rapid progressive, multisystem reaction	Any age	Depends on food
Food-dependent, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion is followed temporally by exercise	Onset in late childhood/ adulthood	Presumed persistent
MIXED IgE AND CELL MEDIATED			
Atopic eczema/ dermatitis	Associated with food in 30%-40% of children with moderate/severe eczema	Infant > child > adult	Usually resolves
Eosinophilic gastrointestinal disorders	Symptoms vary depending on the site of the intestinal tract involved and degree of eosinophilic inflammation	Any age	Likely persistent
CELL MEDIATED			
Dietary protein-induced proctitis/proctocolitis	Mucus-laden, bloody stools in infants	Infancy	Usually resolves
Food protein-induced enterocolitis syndrome	Chronic exposure: emesis, diarrhea, poor growth, lethargy Re-exposure after restriction: emesis, diarrhea, hypotension a couple of hour after ingestion	Infancy	Usually resolves

Modified from Sicherer and Sampson (16)

Methods

These guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (5, 6). This is a structured approach for the production of guidelines designed to ensure appropriate representation of the full range of stakeholders, a careful search and appraisal of the relevant literature and a systematic approach to the formulation and presentation of recommendations. In order to ensure that the risk of bias is minimized at each step of the process, interim consensus meetings were organised. An overview of the approach is provided below.

Clarifying the scope and purpose of the guidelines

The scope of these EAACI guidelines is multi-faceted providing statements that assist clinicians in the management of food allergy in daily practice; harmonizing the approach to this disease among stakeholders across Europe; and advocating for further research.

Ensuring appropriate stakeholder involvement

Participants and experts in the Food Allergy Diagnosis and Management Taskforce represented a range of 12 European countries and disciplinary and clinical backgrounds (gastroenterologists A Schoepfer, A Staiano, R Troncone; primary care A Sheikh; dietitians C Venter, I Skypa BJ Vlieg-Boerstra, M Groetch) and patient groups (MJ Marchisotto -FARE).

Systematic reviews of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration into three key questions that were then pursued through two formal systematic reviews of the evidence (7-9) (see Box 1).

Formulating recommendations

We graded the strength and consistency of key findings from these systematic reviews to formulate evidence-linked recommendations for care (10) (Box 2). This involved formulation of clear recommendations and the strength of evidence underpinning each recommendation. Experts identified barriers and facilitators to the implementation of each recommendation and included advice how to implement and listed audit criteria that may facilitate organizational compliance.

Box 1 Key questions addressed in the supporting systematic reviews: diagnosis and management (7-9)

- What is the epidemiology (i.e. frequency, risk factors and outcomes) of food allergy in Europe and how does this vary by time, place and person?
- What is the diagnostic accuracy of tests aimed at supporting the clinical diagnosis of food allergy?
- What is the effectiveness of pharmacological and non-pharmacological interventions for the management of acute, non-life-threatening food allergic reactions?
- What is the effectiveness of pharmacological and non-pharmacological interventions for the longer-term management of food allergy?

Peer review and public comment

A draft of these guidelines was externally peer-reviewed by invited experts from a range of organizations, countries and professional backgrounds.

Additionally, the draft guidelines were made available on the EAACI website for a 3 week period (June 2013) to allow all stakeholders to comment. All feedback was considered by the Food Allergy Diagnosis and Management Taskforce and, where appropriate, revisions were made.

Identification of evidence gaps

The process of developing these guidelines has identified a number of evidence gaps and it is planned to formally prioritize these in the future. We plan to draft outline research briefs that funders can use to commission research on these questions.

Editorial independence and managing conflict of interests

The production of these guidelines was funded and supported by EAACI. The funders did not have any influence on the guidelines production process, its contents or on the decision to publish. Taskforce members' conflicts of interest were taken into account by the Taskforce chair as recommendations were formulated.

Updating the guidelines

We plan to update these guidelines in 2017 unless there are important advances before then.

Epidemiology

To estimate the incidence and prevalence, time-trends, and potential risk and prognostic factors for food allergy in Europe, we conducted a systematic review of recent (i.e. 2000-2012) European studies (7) (Chapters 1.1, 1.2). One hundred and nine articles were assessed for eligibility and 75 (comprising of 56 primary studies) were included in a narrative synthesis and 30 studies in a meta-analysis. Most of the studies were graded as at moderate risk of bias.

A summary of the key findings is presented in Table 3. The point prevalence of self-reported food allergy was approximately six times higher than the point prevalence of challenge proven food allergy. The prevalence of food allergy was generally higher in

Box 2 Assigning levels of evidence and recommendations according to new grading system (11,12)

LEVEL OF EVIDENCE FOR ESTABLISHING DIAGNOSTIC TEST ACCURACY	
Level I	A systematic review of level II studies
Level II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
Level III-1*	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
Level III-2*	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
Level III-3*	Diagnostic case-control study
Level IV	Study of diagnostic yield (no reference standard)
Level V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
LEVEL OF EVIDENCE FOR ASSESSING EFFECTIVENESS OF INTERVENTIONS	
Level I	Systematic reviews, meta-analysis, randomized control trials
Level II	Two groups, non-randomized studies (e.g. cohort, case-control)
Level III	One-group non-randomized (e.g. before and after, pre-test and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case-series)
Level V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
GRADES OF RECOMMENDATION	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level

* For consistency with the anaphylaxis guidelines (Chapter 4.3), level III-1 to level III-3 for establishing diagnostic test accuracy are summarised as level III in this document.

children than in adults. While the prevalence of primary food allergy appeared to be stable over time, the prevalence of secondary food allergy caused by cross-reactions of food allergens with inhalant allergens appears to be increasing. There were no consistent risk or prognostic factors for the development or resolution of food allergy. However, sex, age, country of residence, familial atopic history, and the presence of other allergic diseases may play an important role in its etiology.

Few studies employed double-blind, placebo-controlled food challenge (DBPCFC) in a population-based sample; further studies are therefore required to establish the actual prevalence of objectively-confirmed food allergy in the general population. Further studies are also needed to investigate the long-term prognosis of food allergy.

Table 3 Summary of the pooled prevalence of food allergy (FA) in Europe, by age and region: studies published 1 January 2000 – 30 September 2012[1]

	Self-reported food allergy		Sensitization to at least one food allergen (point prevalence)		Symptoms + sensitization to at least one food allergen (point prevalence)		Convincing clinical history or positive food challenge[2] (point prevalence)	Positive open food challenge or DBPCFC[2] (point prevalence)
	(life time prevalence)	(point prevalence)	positive specific-IgE	positive skin prick test	symptoms + positive specific-IgE	symptoms + positive skin prick		
All	17.3 (17.0-17.6)	5.9 (5.7-6.1)	10.7 (9.4-10.8)	3.0 (2.7-3.3)	2.7 (1.7-3.7)	1.5 (1.3-1.7)	2.6 (2.1-3.1)	0.9 (0.8-1.1)
AGE								
Children (0-17 years)	17.4 (16.9-18.0)	6.9 (6.6-7.2)	12.2 (11.4-13.1)	3.0 (2.7-3.3)	3.6 (2.8-4.4)	1.5 (1.3-1.7)	2.6 (2.1-3.1)	1.0 (0.8-1.2)
Adults (≥ 18 years)	17.2 (16.0-17.6)	5.1 (4.8-5.3)	4.1 (3.2-5.1)	—[6]	2.2 (0.8-3.7)	—[6]	—[6]	0.9 (0.8-1.0)
REGION[3]								
Western Europe	23.8 (22.9-24.7)	3.3 (3.1-3.5)	11.7 (9.8-13.6)	1.8 (1.5-2.1)	2.6 (1.3-3.8)	1.4 (1.1-1.7)	—[6]	3.1 (2.6-3.7)
Eastern Europe	41.6 (39.5-43.7)	3.3 (1.2-5.4)	—[6]	—[6]	—[6]	—[6]	—[6]	—[6]
Southern Europe[4]	8.6 (8.2-9.0)	3.5 (2.5-4.5)	—[6]	4.2 (2.2-6.3)	—[6]	1.8 (1.3-2.3)	—[6]	0.2 (0.1-0.3)
Northern Europe	30.3 (28.7-31.9)	14.5 (13.9-15.2)	9.8 (9.0-10.5)	5.4 (4.6-6.1)	3.0 (2.1-3.9)	1.6 (0.9-2.3)	2.6 (2.1-3.1)	1.1 (0.9-1.3)
Europe[5]	19.2 (18.6-19.8)	5.0 (4.6-5.5)	—[6]	—[6]	—[6]	—[6]	—[6]	—[6]

Figures are percentages (95% CI).

[1] The pooled prevalence of FA was based on random-effects meta-analysis for 30 clinically and methodologically comparable studies.

[2] Where a study reported estimates for both open food challenges and DBPCFC, the DBPCFC estimates were always used; otherwise open food challenges estimates were used if DBPCFC was not done in the study.

[3] European region were classified based on the United Nations classification (http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe accessed on December 28, 2012).

[4] We further added studies from Turkey into Southern Europe.

[5] For studies that included several European countries and gave overall estimate for all the countries and in which it was not possible to calculate the frequency for each country studied.

[6] No study undertaken for this group for this particular outcome.

Box 3 EAACI Recommendation on the diagnosis of food allergy

Recommendations	Evidence level	Grade	Key reference
A - PATIENT'S CLINICAL HISTORY			
Detailed clinical history is essential for the diagnosis of food allergy.	IV	D	Expert Opinion
When taking a clinical history eliciting allergens, timing and chronicity, symptoms, severity and signs, reproducibility, known risk (co) factors, family history, co-existing medical problems including other allergic diseases should be addressed.	V	D	Expert Opinion
The use of structured questions on symptoms, foods and other background information is recommended.	V	D	Expert Opinion
B - DETERMINATION OF SENSITIZATION TO FOOD			
Where available, standardized tests and procedures should be used.	IV	D	Expert Opinion
IgE sensitization does not always predict clinical relevant food allergy, so specific allergy testing should be directed by case history.	IV	C	(9)
Either SPT or sIgE can be the test of choice for sensitization depending on local availability and absolute and relative contraindications to SPT.	IV	C	(9)
Evidence of IgE sensitization to common food and appropriate aeroallergens can support a diagnosis of food allergy in conjunction with clinical history and/or food challenge.	I-III*	A-C	(9)
In the presence of a suggestive history, a negative SPT or sIgE needs to be interpreted with caution particularly as these are expected in non-IgE mediated food allergy.	IV	C	(9)
Where SPT and sIgE tests are inconclusive, CRD (if available) may provide additional diagnostic information.	I – IV*	A – C*	(9, 28-30)
If clinical history with SPT and/or sIgE results is not highly predictive (see Figure 1), an OFC is required.	IV	D	Expert Opinion
Determination of total IgE is particularly useful in patients with severe eczema; a very high total IgE level suggests that positive specific IgE results should be interpreted with care as they may represent asymptomatic sensitization.	IV	D	Expert Opinion
C - ELIMINATION DIETS FOR DIAGNOSTIC PURPOSES			
Determining which foods to be avoided should be based on the allergy-focused diet history, clinical history and allergy testing (SPTs and/or sIgE).	V	D	Expert Opinion
For each individually avoided food, the results of the diagnostic elimination diet should be carefully monitored and evaluated over 2-4 weeks of avoidance.	V	D	Expert Opinion
Where the elimination diet leads to a significant relief of symptoms, it should be continued until the provocation test is performed.	V	D	Expert Opinion
Where the elimination diet does not lead to a significant relief of symptoms, food allergy to the eliminated foods is highly unlikely.	V	D	Expert Opinion

Box 3 (continued)

Recommendations	Evidence level	Grade	Key reference
D - ORAL FOOD CHALLENGE (OFC)			
The OFC (particularly the double-blind placebo-controlled food challenge) is the gold standard investigation for the objective diagnosis of IgE-and non-IgE mediated food allergy.	IV	D	Expert Opinion
OFC's should be used to demonstrate allergy or tolerance and in so doing facilitate safe dietary expansion or appropriate allergen avoidance.	IV	D	Expert Opinion
The DBPCFC should be performed when symptoms are subjective, with delayed or atypical symptoms, where patients and/or care givers are anxious, and considered in all research settings.	IV	D	(24, 26)
A negative DBPCFC should end with an open or cumulative ingestion of the food based on a normal age appropriate portion to confirm oral tolerance.	IV	D	Expert Opinion
OFC must be performed in a specialist setting with emergency support immediately available; where there is a moderate to high risk of a severe reaction, intensive care support must be immediately available.	IV	D	Expert Opinion
E - DIAGNOSIS OF EOE			
Every patient with EoE should be referred to an allergist/immunologist for workup.	IV	D	(47)
EoE is diagnosed by an upper endoscopy with 2-4 biopsies from both the proximal and distal esophageal biopsies. Biopsies should be performed when the patient has been treated for at least 6 weeks with double dose proton pump inhibitors to rule out esophageal eosinophilia caused by gastro-esophageal reflux disease (GERD) and to exclude proton-pump inhibitor responsive esophageal eosinophilia.	IV	D	(47, 48)
The clinical utility of measuring serum food-specific IgE and skin prick test results to generate a successful elimination diet needs further investigation. Future studies should clearly document a clinical and histologic benefit from dietary interventions guided by results from serum-IgE levels, skin prick testing or atopy patch testing.	IV	D	(47)
F - UNCONVENTIONAL TESTS, INCLUDING SPECIFIC IgG TESTING			
There are no unconventional tests which can be recommended as an alternative or complementary diagnostic tool in the work up of suspected food allergy, and their use should be discouraged.	III	C	(54)

*Range of levels of evidence and grades are due to range of different foods tested

Diagnosis

Patient's clinical history and examination

The clinical presentation of food allergy involves a large spectrum of symptoms ranging from skin (urticaria, angioedema, atopic eczema/dermatitis), gastrointestinal (i.e. vomiting, colic, abdominal pain, diarrhoea, constipation), respiratory (rhinorrhea, sneezing, cough, dyspnea) to circulatory (cardiovascular collapse). Attention should be paid to the fact, that reactions can be triggered by food ingestion, inhalation and skin contact. A careful dietary history is fundamental to the diagnosis of food allergy (see Appendix I-A and I-B). It can establish the likelihood of the diagnosis, suggest whether an IgE- or non-IgE mechanism is involved and identify the potential food triggers. A small amount of literature indicates that the predictive value of the clinical history for immediate symptoms, either alone or in combination with skin prick tests (SPT) or serum specific-IgE (sIgE) blood tests, ranges from 50-00% (13-15). The clinical evaluation should include a thorough examination of nutritional status and growth, especially in children, as well as associated atopic diseases such as atopic eczema/dermatitis, allergic rhinitis and asthma.

Recommendations Box 3-A

Diagnostic tests for food allergy

In vivo SPT and sIgE for food allergens are the first line tests to assess IgE sensitization. However, like the patient history, these tests cannot always accurately diagnose food allergy. Elimination diet for diagnostic purposes and oral food challenges are still required both for IgE and non-IgE mediated food allergy in order to define the clinical relevance of the initial investigations. For some clinical manifestations such as food-induced enteropathies, endoscopy and biopsy are often required to establish the diagnosis. The diagnostic workup of food allergy is summarized in Figure 1.

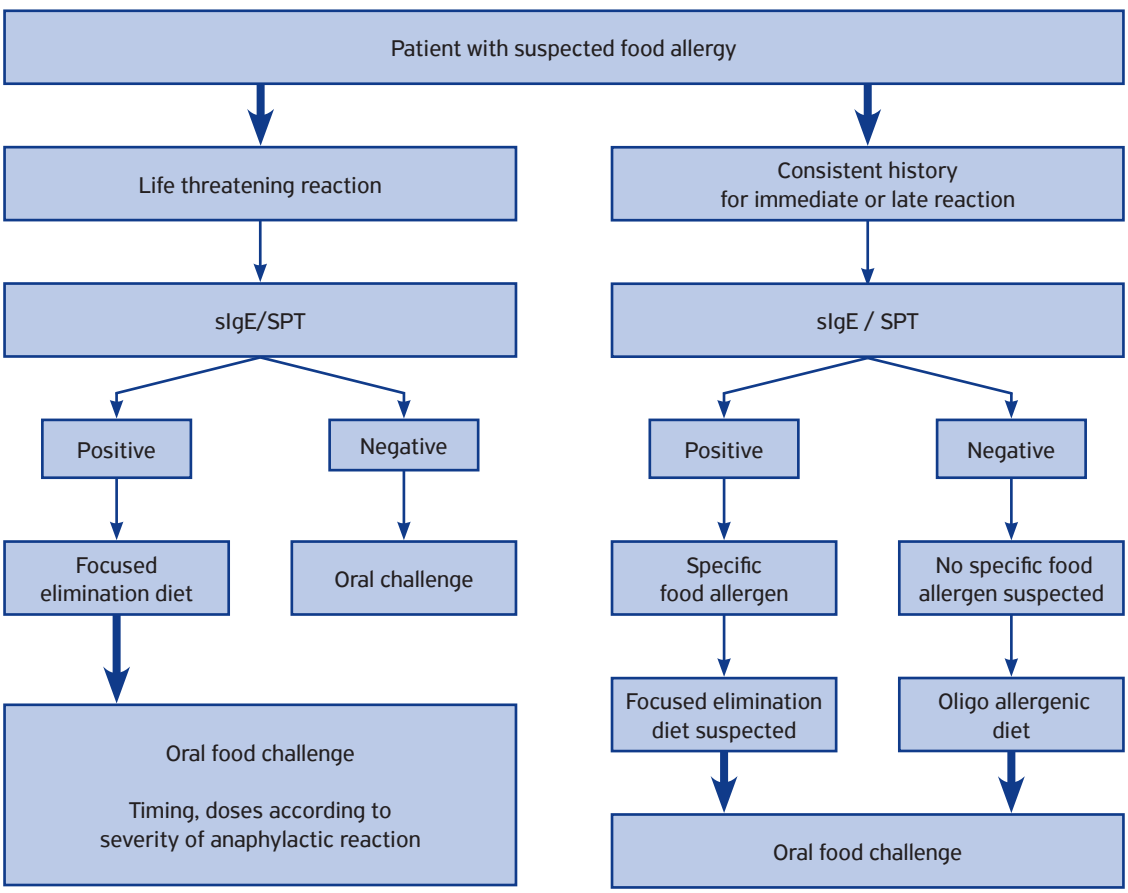


Figure 1 Algorithm for the diagnosis of food allergy

Specific IgE: In-vitro and skin tests

The determination of sensitization to suspected food allergens includes the assessment of co- and cross-sensitization to related food or aeroallergens. To avoid identifying food allergens where sensitization is seen without clinical relevance, only food and aeroallergens related to the clinical presentation, age, geographic location and ethnic dietary habits of the patient should be investigated.

Specific IgE and SPT are scientifically valid tests although not all are standardized. Currently single recombinant protein solutions for SPT are not approved in the EU. However, in some countries purified natural date profilin and Pru p 3 are available for SPT. Determination of total IgE levels can be helpful in the interpretation of results as very high IgE levels can be associated with multiple positive SPTs or sIgE results that are not clinically relevant.

SPT can be undertaken in patients of any age although reactivity that may be lower in infants and possibly the elderly (17). The choice of tests should be guided by the detailed clinical history. The use of good quality food allergen extracts, characterized by demonstration of clinical efficacy and the presence of relevant allergens is strongly recommended when available. Due to a possible under-representation of minor allergens or instability of the allergenic proteins false negative reactions can occur. Whenever these types of extracts are not available and/or minor- or instable allergens are relevant for the sensitization (i.e. most fruits and vegetables), fresh foods should be used. Only trained healthcare professionals, able to interpret results and manage possible adverse reactions, should perform SPTs. These tests are performed on the forearm or upper back. Negative (saline 0.9%) and positive (histamine 10mg/ml) controls are required and the maximum wheal diameter is reported with an arbitrary positive cut-off diameter ≥ 3mm after 15 minutes (18, 19). There are numerous variables to be considered when performing and interpreting SPT including lancet type, recording of wheal diameter, timing, age, sex, and site of testing (18, 20). In addition, it should be considered that European parameters may differ from North American ones. For food allergy, intradermal skin testing is not recommended because of its low specificity, high potential for irritant reactions and risk for systemic reactions, except in particular situations, e.g. alpha-gal allergy (21).

In our systematic review (Chapter 1.3) we found reasonable sensitivity (70-100%), although less for most plant food allergies, but moderate specificity (40-70%) both for sIgE and SPT using the DBPCFC as the reference test (9). Sensitivity and specificity of serum IgE testing and SPT varied depending on the food being tested and due to the heterogeneity of studies with respect to inclusion criteria for patients, their geographic background, and their age and ethnicity, as well as recruitment processes. High quality performance of these tests is observed for allergens such as peanut, egg, milk, hazelnut, fish and shrimp, but less so for soy and wheat (9). For other plant-derived (carrot, celery, kiwi, lupine, maize and melon) or animal-derived foods (chicken and pork) only single studies were included in the recent systematic analysis.

sIgE and SPT tests are good to confirm or rule out involvement of IgE in (self-) reported food hypersensitivity. Interpretation is improved when presenting features and the magnitude of results are taken into account (Appendix I-C). However, they are often unable to differentiate between clinical relevant allergy and tolerance and oral challenges are therefore required.

Atopy patch test

Due to the lack of standardized test substances and the lack of studies showing advantages of Atopy Patch Test (APT) over SPT or sIgE, APTs are not recommended for routine diagnosis of food allergy (22, 23).

Elimination diet

An elimination diet for diagnostic purposes consists of the avoidance of the food(s) suspected of triggering allergic reactions based on the clinical history, allergy-focused diet history and adjunct allergy testing such as SPT and sIgE. The duration of the avoidance should be no longer than necessary to achieve a significant relief of symptoms, usually two to four weeks for IgE mediated symptoms and longer for non-IgE ones (e.g. up to six weeks for EoE). The diet should be thoroughly monitored and results evaluated to establish or refute the diagnosis to prevent unnecessary food restrictions. If the effect of the avoidance is limited, the diet needs to be carefully re-evaluated in case potential food allergens have been overlooked. Co-factors may also be implicated. For cow's milk allergy, extensively hydrolysed formula may not be effective in achieving remission, and an amino acid based formula may be required. When a properly performed elimination diet

does not ameliorate the symptoms, food allergy to the eliminated foods is highly unlikely. The avoidance phase should be followed by a planned reintroduction of the eliminated food(s). Where there is no risk of a severe reaction, reintroduction may occur at home. A reported clinical reaction should be confirmed by OFC under medical supervision.

Recommendations Box 3-B & 3-C

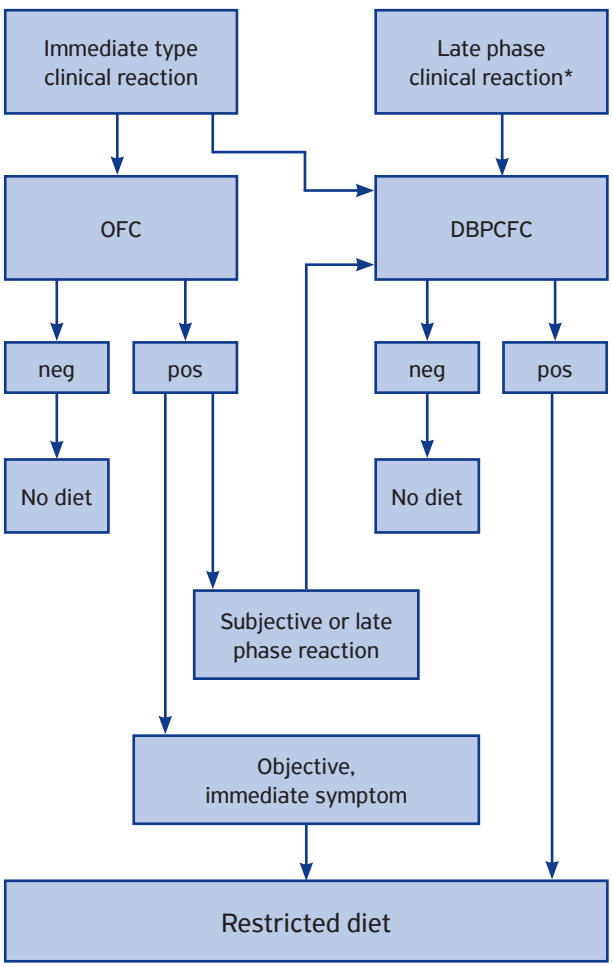
Oral food challenges

Oral food challenges (OFCs) are usually required to confirm the diagnosis of food allergy, to monitor food allergy or to prove oral tolerance to a given food (Table 4). There are guidelines, including one from the EAACI (24, 25) and a recent PRACTALL consensus (26), that describe procedures of OFCs in detail. These recommendations deal with the many variables involved in designing a patient specific challenge. These include patient selection, safety criteria, type and quantity of the food allergen to be administered, timings between doses, outcome criteria, observation periods and recipes to be used. Some of the key recommendations are summarized in Table 5.

Table 4 Indications for oral challenge tests

Indication	Rationale
Demonstrate allergy	Uncertain diagnostic outcome despite use of detailed clinical history and IgE sensitisation testing.
	Suspected food allergy reaction for which the cause is uncertain despite allergy testing (e.g. composite meal eaten).
	Determine threshold dose of causative allergen.
Demonstrate tolerance	When allergy tests suggest tolerance but food has never been eaten and patients and/or parents too cautious to introduce at home.
	Non clinically relevant cross-reactivity suspected, e.g. a patient with a low positive IgE result to hazelnut but high positive birch pollen sensitization.
	When the diet is restricted due to a suspicion that one or more foods is resulting in delayed allergic symptoms (e.g. eczema).
	Allergy suspected to have been outgrown.
Monitor therapy for food allergy	To monitor response to immunomodulatory treatment in research setting.

Oral food challenges can be performed in an open or blinded manner. Blinded challenges can be single- or double-blinded. In many cases an open OFC with an objective unequivocal reaction is sufficient for the diagnosis of food allergy. The double-blind, placebo-controlled food challenge (DBPCFC) is considered the gold standard diagnostic test for the diagnosis of food allergy. However, a negative open challenge of a regular age appropriate serving or the negative outcome of the administration of a cumulative dose of the previous challenge on another day (27) is required for confirming the result of a negative DBPCFC (Figure 2). DBPCFC is time-consuming and resource-intensive to undertake. A negative OFC may be useful as a first step in ruling out food allergy. In patients with atopic eczema, subjective



* Atopic dermatitis, gastrointestinal symptoms

Figure 2 Algorithm for Oral Food Challenge

Table 5 Variables associated with oral food challenges

VARIABLE	
Design	May be open (cumulative or incremental) or blinded (single or double blinded). Design selected according to the indication and purpose for which the challenge is being performed.
Form of challenge food	The challenge food should closely replicate the usual edible form of the food or form of the food implicated in allergic reaction. Food processing can significantly influence allergenicity of the food (e.g. baked versus raw egg). For OFC's performed to diagnose the pollen food syndrome, fresh fruit and vegetables should be used, as the responsible proteins are commonly heat labile.
Choice of food matrix	Strictly avoid use of allergenic ingredients for individual patient. Minimise number of ingredients used. Provide adequate allergen protein in a manageable portion size. For placebo foods, sensory qualities should closely replicate those of active challenge food.
DOSES	
Number of doses	In most cases half-logarithmic (9) dose increments are indicated. If a negative outcome is anticipated, and there are no safety concerns, a single cumulative dose is appropriate.
Initial dose	In clinical settings, 3mg of food protein seems adequate for most common food allergens such as cow's milk, hen's egg, peanuts and tree nuts. Lower doses are used for threshold studies in research setting or for patients at high risk of a severe reaction.
Top dose	Equivalent to an 'age appropriate' portion, 3g of food protein seems adequate for the most common food allergens such as cow's milk, hen's egg, peanuts and tree nuts.
Time intervals between doses	15-30 minutes, but may be adjusted to the patient's history.
Total challenge duration	Usually completed within 8 hours (immediate symptoms) and 1-4 weeks (delayed symptoms).

or suspected psychological symptoms the DBPCFC is superior to an OFC. The food should be blinded for taste, smell, texture and appearance (consistency, colour and shape). The placebo and the active food should be sensory indistinguishable from each other.

In order to avoid severe reactions, patients receive the food in titrated doses often with half-logarithmic (9) dose increments, at set intervals. For many foods such as cow's milk, hen's egg, peanut or tree nuts dose ranges from 3mg to 3g of food protein seem sufficient in clinical practice (see Appendix I-D).

Food allergy challenges are usually stopped if objective clinical reactions are observed or the last dose is consumed without clinical symptoms. Immediate reactions usually appear within two hours after the last food intake, atopic eczema may worsen several hours or days following an oral challenge. Urticaria and/or angioedema are the most common objective signs seen, gastrointestinal, respiratory or cardiovascular system involvement are also common.

To optimize safety, vital signs should be closely monitored during OFC and equipment and appropriately trained staff should be in place to deal with allergic reactions – including anaphylaxis.

For patients with non-IgE mediated reactions challenges tailored on the individual modalities of reactions should be designed.

Recommendations Box 3-D

Promising novel diagnostic approaches

In molecular or component-resolved diagnostic tests (CRD), sIgE antibodies are measured against individual allergenic molecules from foods with the potential to improve the specificity of serum IgE testing and the specificity for selected food. This can be performed in either single test formats or in a microarray, testing a range of purified allergens simultaneously. For peanut allergy, determination of sIgE for the major allergen, Ara h 2, showed sensitivity of 100% and specificity of 70-80% in two recent studies (28, 29). The determination of omega-5-gliadin proved to be of high

diagnostic relevance in exercise induced food allergy to wheat in a number of recent case reports and cohort studies (30) as well as the determination of rGly m 4 for allergy to soy milk in birch sensitized patients (31). For certain fruits (i.e. apple, peach, kiwi and melon), vegetables (i.e. carrot and celery), tree nuts and peanut, soy, fish and shrimp, CRD are also available and provide better insight into sensitization patterns (29). The technique of CRD is promising and broadly studied, and some important clinical results are summarized in Appendix I-E. Evidence from well-designed randomized controlled studies on the diagnostic test accuracy of CRD is still required to properly assess its diagnostic value (see Box 3B).

Basophil activation tests (BAT) have been applied in the diagnosis of cow's milk, egg and peanut allergy (28, 32, 33) as well as in the diagnosis of pollen-food syndromes in small clinical studies (34, 35). BAT has shown higher specificity and negative predictive value than SPT and sIgE, without losing sensitivity or positive predictive value. However, BAT requires a specialized laboratory setting and large clinical studies on its diagnostic performance are lacking. Thus the use of this promising test is still limited to research purposes on food allergy.

Another promising research area is the determination of IgE antibodies against overlapping synthetic linear peptides of food allergens, as it has been performed for milk (36-38), peanut (39, 40), egg (41) and shrimp (42, 43).

Recommendations Box 3-B

Diagnostic workup of gastrointestinal non-IgE mediated symptoms

Infants in the first year of life may present with gastrointestinal food related clinical manifestations such food protein induced enterocolitis syndrome (FPIES), proctocolitis and enteropathy (44). Usually patients have negative food specific IgE testing (see Table 2). The diagnosis is based on symptoms, clinical history, elimination diet for up to three weeks and specifically designed OFCs (45). Endoscopy with biopsies might be helpful in confirming bowel inflammation. Currently there is scarce evidence that APT is helpful in diagnosing this form of food allergy (46).

Eosinophilic esophagitis (EoE) is defined as a chronic, immune/antigen-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. All age groups can be affected and the current estimated prevalence is around 1 in 24,000 adults (47). Adult patients mostly present with dysphagia, less frequently with retrosternal pain and food bolus impaction, whereas the symptom presentation in children is much more variable and includes failure to thrive, vomiting, regurgitation, thoracic and abdominal pain. EoE is diagnosed by an upper endoscopy and biopsies (48). Biopsies should be performed when the patient has been treated for at least six weeks with double the standard dose proton pump inhibitors to rule out esophageal eosinophilia caused by gastro-esophageal reflux disease (GERD) and to exclude proton-pump inhibitor responsive esophageal eosinophilia. Other disorders associated with esophageal eosinophilia such as Crohn's disease, celiac disease, achalasia, or eosinophilic gastroenteritis should be ruled out. Approximately 15–43% EoE patients are diagnosed with food allergies and sensitization rate to aeroallergens is up to 80%. A close collaboration between gastroenterologists and allergists is essential to optimize management of patients with EoE (47).

Recommendations Box 3-E

Unconventional tests including specific IgG testing

A number of expensive diagnostic alternative approaches are sometimes promoted to physicians and often used by complementary and alternative medicine practitioners in cases of suspected food allergy. Examples are bioresonance, kinesiology, iridology, hair analysis, cytotoxic test, and IgG and IgG4 determination. These tests are not currently validated and cannot be recommended in diagnosing food allergy (49-53). For example, IgG-measurements cannot be correlated with any clinical symptoms or disease. Food specific IgG4 levels indicate that the atopic individual has been repeatedly exposed to high doses of food components, which are recognized as foreign proteins by the immune system. Therefore, EAACI gave a clear recommendation not to use these tests (54).

Recommendations Box 3-F

Recommendations, gaps and research needs in diagnosis of food allergy are summarized in Box 3 and 4, respectively.

Management of food allergy

The clinical management of food allergy includes short-term interventions to manage acute reactions and long-term strategies to minimize the risk of further reactions. The latter aim is primarily achieved through dietary modification, education and behavioral approaches to avoid allergens and pharmacological and non-pharmacological management strategies for further reactions. There is growing interest in the effectiveness of potential immuno-modulatory treatment approaches, including sublingual and oral immunotherapy to induce tolerance (55).

Management of acute reactions

Most foods contain proteins which may be allergenic and cause food allergy and, in some cases, anaphylaxis. Recently severe reactions have been attributed to carbohydrate components (e.g. alpha gal (21)). Assessment of the risk of severe reactions is crucial in successfully managing patients with food allergy. The risks vary in different patient subgroups; for example patients with previous anaphylaxis or severe asthma have a higher risk than other patients; known cofactors include non-steroidal anti-inflammatory drugs (NSAID), exercise, infections, and mastocytosis. For detailed guidance on the emergency management of anaphylaxis, readers are referred to the EAACI anaphylaxis guidelines (Chapter 4.3) (76).

In our systematic review (Chapter 1.4) we found weak evidence to support the benefits of H1 antihistamines for children and adults with acute non-life threatening symptoms from food allergy in three randomised trials and two non-randomised comparisons (8). Importantly, there is no evidence for efficacy of antihistamines in the treatment of more severe symptoms. The prophylactic administration of antihistamines can mask early symptoms of anaphylaxis and lead to delayed treatment of dangerous reactions with adrenaline (epinephrine).

Recommendations Box 4-A

Long-term management strategies

Elimination diet and dietary interventions

Dietary avoidance is the key intervention in the management of food allergy resulting in complete or almost complete resolution of symptoms. Little research has been published about dietary eliminations due to the difficultly to perform RCTs in subjects for ethical issues. The findings from the few studies available (57-60) are mixed, and all had a high risk of potential bias. The lack of evidence does not mean that elimination diets are not effective, just that any recommendations made about elimination diets may need to rely on expert opinion and experience rather than a high quality research base.

Dietary restrictions should eliminate the culprit food allergen(s) and be tailored to the individual's specific allergic and nutritional needs. This will cover a wide spectrum of issues such as the nutritional needs of food allergic infants who are currently being introduced to solid foods, which are very different, form the nutritional needs of adults with primary or secondary fruit and vegetable allergies. Extensive and long-term avoidance should be carefully monitored as it can result in nutritional compromises and impair quality of life. Ideally the patient should receive proper counselling by a dietician with specific competence in food allergy. This is particularly important in infants and children. In addition, it is crucial to take into account that individual tolerance levels to the allergenic food may differ and change overtime, especially in children, and may affect the stringency of avoidance advice. In breast-fed infants suffering symptoms due to maternal intake of food allergens, the mother should eliminate the foods in question and following a dietetic review, receive a calcium supplement following a dietetic review if cow's milk, cow's milk substitutes and derivatives are eliminated.

Education is the key pillar of an effective long-term elimination diet. Patients, their families, close relatives and caregivers should be aware of risk situations, and should be instructed in reading labels and how to avoid the relevant food allergens both in and outside the home (e.g. at restaurants). They should know that European Union (EU) directives ask for the declaration of allergenic ingredients in foods and be informed about precautionary labelled foods. They should also be provided with information on possible substitute products for most food allergens.

Patients should be re-evaluated at regular intervals to assess whether they have developed tolerance to avoid inappropriate or unnecessarily lengthy dietary elimination. This is discussed below.

Box 4 EAACI recommendation on the management of food allergy

Recommendations	Evidence level	Grade	Key reference
A - ACUTE MANAGEMENT			
The patient at risk of severe reactions should be properly and timely identified	IV	D	Expert Opinion
There is evidence to support the benefits of antihistamines for children and adults with acute non-life threatening symptoms from food allergy.	III	C	(8)
The prophylactic application of antihistamines is not recommended.	V	D	Expert Opinion
Mast cell stabilisers are not recommended for the prophylactic treatment of food allergy.	III	C	(8)
B - LONG-TERM MANAGEMENT STRATEGIES			
B1 - ELIMINATION DIET			
A sufficient elimination diet should be based on a formal allergy diagnosis identifying the food allergen(s) responsible of the patient's symptoms/ reactions. The indications should be re-evaluated at appropriate intervals.	IV	D	(57, 58, 60)
Appropriate dietary avoidance is the key treatment in the management of food allergy.	IV	D	Expert Opinion
Patients with food allergy who are on long term elimination diets should have access to appropriate dietetic counseling, ideally by a dietitian with competencies in food allergy, and regular monitoring of growth (in children).	IV	D	Expert Opinion
Extensively hydrolysed cow's milk formulas with documented hypoallergenicity can be recommended as first choice for the treatment of cow's milk allergy, especially in infants and young children. Amino acid formulas can also be recommended especially for the subgroup of patients with more severe symptoms.	I	A	(61, 63, 65, 89)
Soy formulas should not be recommended before 6 months of age and at any age in the presence of gastrointestinal symptoms. From 6-12 months it can be considered on a case-by-case basis.	I	B	(8)
Currently, probiotic supplements cannot be recommended for the management of food allergy.	I	D	(8, 75)
B2 - EDUCATION AND RISK ASSESSMENT			
Patients and caregivers need to be informed about the foods that should be avoided and practical advice given on avoidance measures, how to recognize a further reaction and the self-management of these reactions.	V	D	Expert opinion
The diagnosis of food allergy should, with permission, be communicated to all relevant caregivers.	V	D	Expert opinion
Patients/carers should be encouraged to join an appropriate patient support organization.	V	D	Expert opinion
All patients with food allergy require a management plan with appropriate education for the patient, caregiver including school.	V	D	Expert opinion
Education should cover allergen avoidance, symptom recognition and indication for specific treatment and administration of specific mediation.	V	D	Expert opinion
Absolute indications with adrenaline auto-injector include previous anaphylaxis to any food, food allergy associated with persistent or severe asthma and exercise-induced, food-dependent anaphylaxis	IV	D	Expert opinion, refer to the anaphylaxis guidelines chapter

Box 4 (continued)

Recommendations	Evidence level	Grade	Key reference
Relative indications for adrenaline auto-injector with food allergy include (1) food allergies that are likely to be persistent; (2) mild-to-moderate allergic reaction to peanut and/or tree nut (3) mild-to-moderate reaction to very small amounts of food and (4) specific high risk groups, e.g. adolescents, young adult males, poor access to medical care.	IV-V*	C-D*	Expert opinion, refer to the anaphylaxis guidelines chapter
Adrenaline should be immediately administered for cardiovascular symptoms and / or respiratory symptoms such as altered voice, stridor or bronchospasm that are thought to be induced by food allergy.	IV	C	Refer to the anaphylaxis guidelines chapter
Short acting beta agonists should be included in the management plan for all patients with co-existing asthma and should be administered for bronchospasm after adrenaline has been administered.	V	D	Expert opinion, refer to the anaphylaxis guidelines chapter
Patient held glucocorticosteroids may be given with reactions to possibly prevent late phase respiratory symptoms (self administered if travelling far from medical care, otherwise in emergency center).	V	D	Expert opinion, refer to the anaphylaxis guidelines chapter
Any patient who has received adrenaline should be reviewed in an emergency department.	IV	D	Expert opinion, refer to the anaphylaxis guidelines chapter
B3 - SPECIFIC IMMUNOTHERAPY			
Food allergen-specific immunotherapy for primary food allergy is a promising immune-modulatory treatment approach (I), but it is associated with risk of adverse reactions, including anaphylaxis (I); it is therefore not currently recommended for routine clinical use.	III	C	(8)
For patients with respiratory or other allergy symptoms to inhalant allergens that may also cause cross reactive food allergy, specific immunotherapy is only recommended for the treatment of the respiratory symptoms, not for cross-reactive food allergy.	IV	D	Expert opinion
B4 - ANTI-IGE			
The use of anti-IgE alone or in combination with specific immunotherapy is currently not recommended for the treatment of food allergy although it represents a promising treatment modality.	IV	D	(8)
B5 - CHALLENGES AT REGULAR INTERVALS TO ASSESS ACHIEVEMENTS OF TOLERANCE			
OFC should be performed at regularly at intervals, as appropriate for the specific food and patient's history, in order to assess achievement of tolerance.	V	D	Expert opinion
Specific IgE testing (in vitro and skin prick test) has limited value in guiding adequately the timing of oral food challenges for development of tolerance.	V	D	Expert opinion
B6 - COFACTORS			
In food allergy reactions, the potential augmenting role of cofactors (e.g. exercise, NSAID, omeprazole, alcohol intake) should be assessed in a structured history.	III-IV**	D	Expert opinion
In allergic reactions occurring after exercise, NSAID or alcohol intake, an underlying allergy to foods consumed in the previous hours should be assessed (especially gliadin sensitization or LTP in southern Europe).	IV	D	(30, 77, 78)

* Range of levels of evidence and grades are due to range of indications.
** Range of levels of evidence and grades are due to range of different cofactors.

Cow's milk substitutes

In children with cow's milk allergy, several substitutes are available. In infants and young children these products are especially necessary to ensure a diet that is adequate for growth and development. In infants younger than six months, such formulas have to fulfil the general requirements for full nutrition until the introduction of complementary foods. In addition, these substitutes may also be required in older children to ensure a satisfactory calorie intake. There is some moderate level evidence about some alternatives to cow's milk. However, most of the research is of low quality and there are a relatively small number of studies about each type of alternative formula. There is some evidence to suggest that extensively hydrolyzed formula, amino acid-based formula and soy-based formula, may all be useful long-term management strategies. Extensively hydrolysed cow's milk formulas are the first choice as an alternative to cow's milk. However, amino acid-based formulas are the only completely non-allergenic formula and they can be effective in patients not responding to extensively hydrolysed formulas and in subgroups of children. These include infants with severe growth faltering (61-63) those with, cow's milk protein allergy with severe symptoms and non-IgE mediated syndromes such as food protein induced enterocolitis and enteropathies, eosinophilic gastroenteropathies. Soy formulas may be useful provided that nutritional evaluation regarding the phytate and phyto-oestrogens content is considered, they cannot be recommended before 6 months of age. Rice hydrolyzed formulas have been recently introduced to the market in some European countries and further research is needed to compare these formulas with extensively hydrolyzed formula and soy formulas. The substitutes for cow's milk should fulfil the criteria for documented hypoallergenicity and for nutritional adequacy (64, 65). To achieve these requirements, the formula should be investigated in consecutive patients with both IgE and non-IgE mediated cow's milk protein allergy (66). Some extensively hydrolyzed formulas have been investigated and fulfill these criteria (62, 67-69). In addition, attention should be paid to taste and price as reimbursement policies for these types of formulas differ across the EU.

Based on several reports partially hydrolysed cow's milk based formulas are not regarded as safe for patients with cow's milk allergy (70, 71). There is less evidence regarding other mammalian milk. Goat and sheep's milk are very similar to the proteins in cow's milk, and therefore should not be recommended for patients with cow's milk allergy (72). Camel, donkey or mare's milk have been shown to be less cross-reactive than goat's milk, although evidence for recommendations is lacking as well as for chicken-based formula (73) or meat-based formula (74). In summary, it is recommended that the choice of an appropriate cow's milk substitute should be assessed carefully balancing the following factors; age, type of food allergy (IgE / non IgE) coexistence of gastrointestinal symptoms, history of life threatening reactions and nutritional requirements as well as cost effectiveness.

Probiotics and prebiotics

Probiotics have been investigated as another option for management of patients with food allergy, particularly cow's milk allergy, either added to formulas or given as a supplement. Evidence that probiotic supplements have preventative or therapeutic activity for food allergy is lacking (8) and further research is needed to make recommendations in this area (75).

Recommendations Box 4-B1

Pharmacological treatment

Studies on the prophylaxis of food allergy with mast cell stabilizers have led to different clinical results (Chapter 1.4) (8). Four randomized trials and two non-randomized comparisons found that mast cell stabilizers reduced symptoms of food allergy but three randomized trials found no benefits. Overall, the evidence is not sufficient to recommend mast cell stabilisers for the prophylactic treatment of food allergy.

Education and risk assessment

Education and training are a fundamental part of managing food allergies and should be combined with a risk assessment of those patients at risk of severe reactions (76). A personalised management plan, including an emergency plan, should be issued as part of the overall educational package offered to patients (family and caregivers; see also anaphylaxis guidelines). The plan should be personalised to take into account the many variables that may influence the identification and treatment of allergic reactions: age of the patient, literacy of patient and family, type and range of food allergy, concomitant disease, geographic location and access to medical support. Training should cover patient-specific avoidance strategies at home and in the wider environment, interpretation

of warning signals, when and how to treat reactions including use of self-injectable adrenaline if appropriate (3). All professionals, including family doctors, school nurses, dieticians, school teachers and nursery staff, should be trained. There is some evidence that a multi-disciplinary clinical approach (8) and the provision of educational printed and online materials for food allergy (10) improve knowledge, correct use of adrenaline auto-injectors and reduce reactions (see anaphylaxis guidelines).

Recommendations Box 4-B2

Co-factors

Several augmentation factors are known to increase the severity of some food allergic reactions. Sometimes these factors are even obligatory to elicit symptoms of food allergy. Among the best characterised factors are physical exercise and NSAID, others include alcohol, fever and acute infection. One example is wheat-dependent, exercise-induced anaphylaxis due to omega-5-gliadin sensitization (30); other allergens such as lipid transfer proteins (LTP) seem to be relevant in certain geographic areas (77, 78). Potential co-factors should be assessed in any case of food allergy.

Recommendations Box 4-B6

Immunomodulation

Specific immunotherapy of food allergy

For the treatment of food allergy, specific immunotherapy with food allergens using the subcutaneous, oral or sublingual route have been assessed (8) (chapter 1.4). Most controlled studies have been performed with peanuts, hazelnut, hen's egg or cow's milk. For pollen-associated food allergy, immunotherapy has been performed with, subcutaneous or sublingual pollen allergens and the oral or sublingual food allergen.

Two low quality controlled crossover studies suggest that subcutaneous immunotherapy with food allergens is effective. For pollen-associated food allergy, three very low quality RCTs (79, 80) and two non-randomized studies showed conflicting efficacy for the injection treatment with pollen allergen.

Four randomized trials found that sublingual immunotherapy (SLIT) with food allergens was associated with improved tolerance and reduced symptoms for those with peanut, hazelnut and peach allergies (81, 82). One trial with birch pollen allergen found no benefit in subjects with apple allergy (83).

For oral immunotherapy two systematic reviews, eight randomized trials and three non-randomized comparisons found that oral immunotherapy with food allergens was associated with improved tolerance and reduced symptoms for children and adults with various food allergies (8). However, around 90% of participants have side effects although these were usually not severe. Oral immunotherapy was more efficacious for desensitization to cow's milk than SLIT but was accompanied by more systemic side effects in one study (84). One randomized trial found no benefit (85). The two systematic reviews found mixed evidence and suggested that oral immunotherapy should not currently be recommended as routine treatment (86, 87). In light of its potential benefit, it should be performed only in highly specialized centres, with expert staff and adequate equipment, and in accordance with clinical protocols approved by local ethics committees.

The evidence from these studies supports the need for further exploration of immunotherapy with food allergens (8), although especially in subcutaneous and oral immunotherapy the treatment seems to be associated with significant adverse effects. In regard to pollen-associated food allergy there is conflicting evidence on efficacy of subcutaneous and sublingual immunotherapy with pollen allergens; these therapeutic interventions should only be used for the pollen allergy symptoms.

Recommendations Box 4-B3

Anti-IgE treatment

Omalizumab is a humanized monoclonal anti-IgE antibody, which is licensed for the treatment of allergic asthma. The impact of omalizumab and another anti-IgE antibody (TNX-901) on food allergy have been investigated (8) (chapter 1.4). Increased thresholds of tolerance to food allergens were found in a subgroup of participants. Studies suggest that the clinical benefits of omalizumab are achieved after just a few doses of omalizumab. Moreover, it has been demonstrated that more rapid up-dosing and higher doses of milk protein could be administered when omalizumab was used as an adjunct therapy (88).

Recommendations Box 4-B4

Challenges at regular intervals to assess development of tolerance

As tolerance can be acquired spontaneously for some food allergens, particularly in children, or can develop with pollen sensitization. There is therefore a need to regularly re-evaluate patients to prevent inappropriate or unnecessarily lengthy dietary eliminations that may impair the quality of life, affect normal growth, and incur unnecessary healthcare costs. Repeated IgE testing can be helpful to determine if sensitization is decreasing (common in egg and milk allergy) and help to identify associated allergies (e.g. peanut, associated with tree nut, sesame (20)).

Currently, OFC are the only tests that can predict with adequate certainty the achievement of tolerance although it has been shown that low food allergen specific IgE levels at diagnosis and a decrease over time both correlate with clinical tolerance. It is therefore recommended that OFC should be performed at regular intervals in order to avoid unnecessary dietary restrictions. The eliciting food may influence this process as, for example, in cow's milk and hen's egg allergy the majority of children will become tolerant within a few years while most patients with peanut or tree nut allergy remain allergic throughout their life. In cow's milk or hen's egg allergy intervals for re-evaluation might be every 6-12 months while for peanut and tree nut allergy OFC every two years in the absence of an accidental reaction would be more appropriate.

Recommendations Box 4-B5

Management of eosinophilic esophagitis

Symptomatic EoE patients should be treated not only for quality of life reasons but also to reduce the risk for the occurrence of the potentially dangerous food bolus impactions. Untreated eosinophil-predominant inflammation leads to esophageal remodeling with narrowing of the esophageal caliper and a loss of function. Treatment modalities include drugs, diets, and esophageal dilation. Swallowed topical corticosteroids (budesonide or fluticasone) and diets have shown to reduce symptoms and eosinophilic infiltration. The following diet types are available: amino-acid based formula diet (often necessitates a feeding tube), targeted elimination diet (according to allergy workup) and empiric elimination diet. Esophageal dilation of strictures can increase esophageal diameter and improve symptoms, however, it does not influence the underlying inflammation. The long-term treatment strategies are not yet defined. Close collaboration between allergists/immunologists and gastroenterologists is advised (47).

Recommendations, gaps and research needs in the management of food allergy are summarized in Box 4 and 6 respectively.

Conclusions and future perspectives

Food allergy appears to be an increasing burden, which needs to be properly addressed in a structured diagnostic and management approach. The overall body of evidence indicates that patients' clinical history, through the use of structured questions on symptoms, food and background information, should guide the allergy testing as IgE sensitization does not always equate with clinically relevant food allergy. SPT and sIgE (and probably CRD) offer high sensitivity in relation to a range of allergens implicated in IgE mediated food allergy. Direct comparisons among the tests are difficult given the limited body of evidence in which these tests have been compared in the same population. There is greater variation in the specificity of these tests, since they indicate sensitization that may not be of clinical relevance, with specific IgE tending to have a higher rate of false positive results. There is limited evidence for the value of APT in diagnosis. The comparability of the local population and the relative availability, safety and costs of the tests will influence local protocols for diagnostic evaluation.

An elimination diet based on an allergy focused clinical history and allergy testing should be followed until a significant relief of symptoms is achieved. Careful consideration should be given to the nutritional completeness of patients' diet. Given the limitation of other tests, OFC (ideally DBPCFC) are still the gold standard in IgE and non-IgE mediated food allergy in order to establish a firm diagnosis, determine threshold reactivity, assess tolerance and the response to immunomodulation. Facilities for OFC are lacking and reimbursement policies vary across national European countries. Efforts should be provided to adequate diagnostic facilities and capabilities to all food allergic patients in Europe.

Box 5 Gaps and research needs in the diagnosis of food allergy

Gaps in the evidence	Plan to address	Priority
A - PATIENT'S CLINICAL HISTORY		
Lack of studies comparing the accuracy of predictions made using standardised expertly compiled allergy-focused dietary history questionnaires to that obtained following all stages of the food allergy diagnostic pathway including double-blind, placebo-controlled oral food challenge.	Clinical studies.	1
More studies modelling the use of history and tests to predict the diagnosis of different types of food allergy in both, children and adults.	Development of mathematical models.	1
B - DETERMINATION OF SENSITIZATION		
Lack of well-designed studies to assess diagnostic utility of different tests and how these compare.	There is an urgent need for well-designed clinical studies on both routine diagnosis including CRD and novel approaches including BAT and linear IgE epitope mapping.	1
C - ELIMINATION DIETS FOR DIAGNOSTIC PURPOSES		
Best approach to elimination diets.	Need for studies on the procedure of avoidance diets during the diagnostic phase.	2
D - ORAL CHALLENGE TESTS		
Lack of standardized protocols for open and blinded challenges in adults and children.	Need for more studies to harmonize protocols for open and blinded challenges in relation to age.	2
Comparison between open versus blinded challenges.	More studies needed to investigate the bias between open versus blinded challenges.	2
Comparison of different challenge protocols – open versus blinded in different age groups and in children with different allergic disease.	More clinical studies.	2
Lack of evidence addressing the utility of different challenge protocols in different clinical setting.	More research needed in secondary and tertiary criteria level centres.	3
Scarce evidence in validation of diagnostic criteria; subjective versus objective criteria during the challenges.	More research needed in interpretation of symptoms between and within individuals.	2
Lack of validated age-appropriate OFC recipes (active and placebo).	More studies on validation of recipes.	2
E - UNCONVENTIONAL TESTS INCLUDING SPECIFIC IgG TESTING		
Lack of knowledge among the public of the ineffectiveness of these tests.	Need of properly designed information and education programmes on allergy diagnostic tests for health professionals and the public. Need to facilitate access to qualified allergy services.	2
Lack of understanding of the costs related to misdiagnosis.	Socio-economic evaluation of misdiagnosis of food allergy.	2

Box 6 Gaps and research needs in the management of food allergy

Gaps in the evidence	Plan to address	Priority
A - ACUTE MANAGEMENT		
Biomarkers for identifying patients at risk of severe reactions.	More research in biomarkers identification.	1
Lack of effective prophylactic drugs in the management of food allergy.	More research for the development of prophylactic drugs.	2
B- LONG-TERM MANAGEMENT		
B1-ELIMINATION DIET		
The long term effect of dietary avoidance on nutrition and quality of life.	High quality prospective studies of infants and young children focused on efficacy, growth and quality of life. High quality prospective studies of adults focused on efficacy, nutritional status and quality of life.	2
The possible effect of using modified food allergens (e.g. baked milk and egg) to improve and accelerate tolerance.	High quality prospective randomised controlled trials of infants and young children and adults with documented food allergy.	1
Indications for the use of amino acid formulas versus extensively hydrolysed formulas.	Large cohort studies of children with cow's milk allergy comparing the cost effectiveness of these two types of formulas at different ages and with different clinical symptoms.	2
Long term nutritional value of rice and soy formulas.	High quality prospective randomised controlled trials of infants and young children with documented food allergy.	2
The effect of supplementation with different probiotic strains for management of food allergy.	High quality prospective randomised controlled trials of infants, young children and adults with documented food allergy.	2
B2 - EDUCATION AND RISK ASSESSMENT		
A multidisciplinary approach (e.g. physician, clinical nurse specialist, dietician with simulation training) should be taken to allow patients to achieve competence in managing their food allergy.	Randomized controlled studies looking at the how different facets of education impact on patients' competency.	2
The optimal approach to educating patients and their caregivers.	Randomised controlled studies comparing the impact of different educational approaches to patients' competency.	2
B3 - SPECIFIC IMMUNOTHERAPY		
What are the effectiveness, risks, cost-effectiveness and long-term benefits and risks of food allergen specific immunotherapy for primary food?	Large multicentre trials for different allergens and route of specific immunotherapy with foods.	1
Long term outcomes needs to be determined.	Clinical trials applying longer observation periods.	1
What are the effectiveness, risks and cost-effectiveness of allergen specific immunotherapy to pollens in those with pollen associated food allergy?	Prospective clinical studies.	2

Box 6 (continued)

Gaps in the evidence	Plan to address	Priority
What is the efficacy of immunotherapy for pollen allergy in preventing the development of pollen associated food allergy?	Prospective clinical studies.	2
B4 - ANTI-IgE THERAPY		
Identification of subsets of patients that would benefit the most from omalizumab.	Large multi-centre trials are however needed to confirm the above findings.	2
Does the use of biologicals (e.g. anti-IgE) - in the context of food allergen-specific immunotherapy for primary food allergy - enhance the effectiveness of treatment and /or reduce the risks of severe adverse reactions?	Prospective clinical studies.	1
B5 - CHALLENGES AT REGULAR INTERVALS TO ASSESS ACHIEVEMENTS OF TOLERANCE		
No evidence of the best intervals for repeating challenges. Lack of tests valuable in assess the development of tolerance.	Large cohort studies complemented by evaluation of biomarkers for development of tolerance.	2
B6 - CO-FACTORS		
Controlled data to assess epidemiology of co-factors for allergic reactions.	Controlled studies.	2
Mechanisms involved in the amplifying role of cofactors.	Pathophysiological studies in animal models and humans.	2
Lack of relevant data for infections, menstrual cycle and stress as potential cofactors.	Observational studies.	3

The optimal management of food allergy consists of a multi-disciplinary and multi-faceted approach, which encompasses treatment of acute episodes of the disease, identification of patients at risk of severe reactions and long-term management strategies in order to minimize recurrences of reactions and improve quality of life.

Although there are several management strategies available, evidence of effectiveness is very limited in this context. The data on pharmacologic treatment is limited with only H1-antihistamines considered to alleviating acute symptoms but only non-life threatening ones. Dietary avoidance of properly identified culprit food(s) is the cornerstone of management. There is some evidence to recommend extensively hydrolyzed formulas with documented hypoallergenicity or amino acids formulas as alternatives to cow's milk formula. However, few extensively hydrolyzed formulas have been investigated for hypoallergenicity in properly designed studies, particularly in children with newly documented cow's milk protein allergy. There is currently no evidence for recommending probiotics and prebiotics with the aim to induce tolerance, although there might be new findings in this field in the near future. Patients at risk of anaphylaxis should have access to self-injectable adrenaline for treating future severe reactions. Facilitated access to allergy consultations, counseling by dietitians with competencies in food allergy, psychological interventions as well as coordination among the several healthcare professionals dealing with the various clinical manifestations of the disease should all be ideally put in place for the effective treatment of these patients.

More proactive treatment for food allergy is urgently needed to address the associated health risk and

social burden. Findings suggest that immunotherapy for food allergy through several routes (subcutaneous, sublingual, oral, epicutaneous) may help to increase tolerance with accidental exposure although the expected improvement may be small. Oral immunotherapy may be useful for IgE mediated food allergy but is associated with a significant risk of local and systemic reactions. Overall, specific immunotherapy is not yet suitable for use in routine clinical care and should be performed in specialized clinical settings under supervision by an allergist with expertise in the field. As a long term strategy, further research is required into whether immunotherapy could be offered in daily clinical practice.

Education is a key feature in the management of food allergy and should be heavily promoted to patients, families and caregivers as well as to health professionals. Developing and validating educational tools will further the establishment of vertical and horizontal networks between Centres of Excellence, allergy specialists and primary care practitioners. Implementation at the community level should be in partnership with the patient organizations (see community guidelines chapter, chapter 5.1). Adequate reimbursement from national health systems and insurance bodies for diagnostic procedures and the management strategies, including education, should be available.

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing these guidelines. We would like to thank Catherine Crowley and Lara Fioravanzo for their administrative help in preparing the guidelines. We would also like to thank our EAACI members and the EAACI Executive Committee for their helpful comments and suggestions.

Authors' contribution

Antonella Muraro, Chair of the EAACI Food Allergy and Anaphylaxis Guidelines Initiative, has steered and coordinated the publication. Thomas Werfel, Karin Hoffman-Sommergruber and Graham Roberts facilitated and edited these guidelines. Susanne Halken, Berber Vlieg Boestra, Kirsten Beyer, Carsten Bindslev-Jensen, George du Toit and Margitta Worm contributed to the subsections discussion. Karla Soares-Weiser, Debra de Silva, Bridget Nwaru and Sukhmeet Panesar undertook the supporting systematic reviews under the supervision of Aziz Sheikh. All authors participated in the discussion of the systematic review, the evidence table, recommendations, gaps and specific sections and approved the final version.

Conflicts of interest

Antonella Muraro has provided scientific advice for Meda. Graham Roberts has provided scientific advice for Danone and ALK-Abelló; Thomas Werfel has provided scientific advice for Meda and Novartis. Caroline Nilsson, Susanne Halken have provided scientific advice for ALK-Abelló. Barbara Ballmer-Weber has provided scientific advice for Thermo Fisher Scientific. Thermo Fisher and ALK-Abelló have provided consumables for his research activities. Tony DuBois has provided scientific advice for ALK-Abelló and received funding from ALK-Abelló to support his research activities. Margitta Worm has provided scientific advice for ALK-Abelló, Meda, Novartis and Stallergenes. Montserrat Fernández Rivas has provided scientific advice to GSK and has received funding from the European Union, the Spanish Ministry of Science and ALK-Abelló. Carsten Bindslev-Jensen has received funding from Thermo Fisher, HAL, Stallergens and Anergis, ALK, Novartis, MSD, Schering-Plough for his research activities. Victoria Cardona has provided scientific advice for ALK-Abelló. Philippe Eigenmann has provided scientific advice for Danone, Novartis, ALK-Abelló, DBV technologies and Stallergenes; he has received funding for research activities from LETI, Nestlé and Thermo Fisher. Carina Venter has produced educational material for Danone, Mead Johnson and Nestlé and has received research funding from Thermo Fischer, Danone and Mead Johnson. Berber Vlieg-Boerstra has received research funding from Danone/Nutricia, Yakult and Mead Johnson. Debra de Silva, Sukhmeet Panesar and Aziz Sheikh have received funding for coordinating guidelines production, and generating the systematic reviews from EAACI. Aziz Sheikh has provided scientific advice to ALK-Abelló, Meda, Lincoln Medical, Thermo Fisher, Pfizer and Stallergenes; he is on the Anaphylaxis Campaign UK's Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee and the BSACI's Standard of Care Committee. Lars Poulsen has provided scientific advice to Nvozymes and has received funding for research from ALK-Abelló, Anergis, Biomay,

Stallergenes. Kirsten Beyer has received funding for research activities from the European Union, German Research Foundation, Berliner Sparkasse, BEA-Stiftung, Food Allergy & Anaphylaxis Network, Food Allergy Initiative, Danone, Thermo Fisher, DST Diagnostische Systeme & Technologien GmbH, Allergopharma. Gideon Lack, George du Toit and Bodo Niggemann have no conflict of interests. Karin Hoffmann-Sommergruber has received honoraria from Thermo Fisher and Milupa.

References

1. Sackeyfio A, Senthinathan A, Kandaswamy P, Barry PW, Shaw B, Baker M, Guideline Development Group. Diagnosis and assessment of food allergy in children and young people: summary of NICE guidance. *BMJ* 2011;342:d747.
2. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF *et al.* Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-836.
3. Bruijnzeel-Koomen C, Ortolani C, Aas K, Bindslev-Jensen C, Bjorksten B, Moneret-Vautrin D *et al.* Adverse reactions to food. European Academy of Allergology and Clinical Immunology Subcommittee. *Allergy* 1995;50:623-635.
4. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA *et al.* Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010; 126:S1-58.
5. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care* 2003;12:18-23.
6. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care *Prev Med* 2010;51: 421-424.
7. Nwaru BI, Panesar S, Hickstein L, Rader T, Werfel T, Muraro A *et al.* Epidemiology of food allergy in Europe. *Clin Transl Allergy* 2013;3:13.
8. de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K *et al.* Acute and long-term management of food allergy: systematic review. *Allergy* 2014;69:159-167.
9. Soares-Weiser K, Panesar SS, Rader T, Werfel T, Muraro A, Hoffmann-Sommergruber K *et al.* Diagnosis of Food Allergy: a systematic review. *Clin Transl Allergy* 2013;3:18.
10. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A *et al.* Going from evidence to recommendations. *BMJ* 2008;336:1049-1051.
11. Harbour R, J M. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323:334-336.
12. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 2009;9:34.
13. Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis *Clin Exp Allergy* 1999; 29:91-96.
14. Breuer K, Heratizadeh A, Wulf A, Baumann U, Constien A, Tetau D *et al.* Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004;34:817-824.
15. Sampson HA. Food allergy--accurately identifying clinical reactivity. *Allergy* 2005;60 Suppl 79:19-24.
16. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010;125:S116-125.
17. Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S *et al.* GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy* 2009;64:1498-1506.
18. Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. *Allergy* 1993;48:48-82.
19. Konstantinou GN, Bousquet PJ, Zuberbier T, Papadopoulos NG. The longest wheal diameter is the optimal measurement for the evaluation of skin prick tests. *Int Arch Allergy Immunol* 2010;151:343-345.
20. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG *et al.* Practical guide to skin prick tests in allergy to aeroallergens. *Allergy* 2012;67:18-24.
21. Commins SP, Platts-Mills TA. Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,3-galactose (alpha-gal). *Curr Allergy Asthma Rep* 2013;13: 72-77.
22. Turjanmaa K, Darsow U, Niggemann B, Rance F, Vanto T, Werfel T. EAACI/GA2LEN position paper: present status of the atopy patch test. *Allergy* 2006;61:1377-1384.
23. Mehl A, Rolinck-Werninghaus C, Staden U, Verstege A, Wahn U, Beyer K *et al.* The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *J Allergy Clin Immunol* 2006;118:923-929.
24. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J *et al.* Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology *Allergy* 2004;59:690-697.
25. Werfel T, Ballmer-Weber B, Eigenmann PA, Niggemann B, Rance F, Turjanmaa K *et al.* Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA2LEN. *Allergy* 2007;62:723-728.
26. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW *et al.* Standardizing double-blind, placebo-controlled oral food challenges: American Academy

of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;130:1260-1274.

27. Niggemann B, Lange L, Finger A, Ziegert M, Muller V, Beyer K. Accurate oral food challenge requires a cumulative dose on a subsequent day. *J Allergy Clin Immunol* 2012;130:261-263.
28. Glaumann S, Nopp A, Johansson SG, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. *Allergy* 2012;67:242-247.
29. Eller E, Bindslev-Jensen C. Clinical value of component-resolved diagnostics in peanut-allergic patients. *Allergy* 2013;68:190-194.
30. Morita E, Matsuo H, Chinuki Y, Takahashi H, Dahlstrom J, Tanaka A. Food-dependent exercise-induced anaphylaxis -importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis. *Allergol Int* 2009;58:493-498.
31. Berneder M, Bublin M, Hoffmann-Sommergruber K, Hawranek T, Lang R. Allergen chip diagnosis for soy-allergic patients: Gly m 4 as a marker for severe food-allergic reactions to soy. *Int Arch Allergy Immunol* 2013;161:229-233.
32. Sato S, Tachimoto H, Shukuya A, Kurosaka N, Yanagida N, Utsunomiya T *et al.* Basophil activation marker CD203c is useful in the diagnosis of hen's egg and cow's milk allergies in children. *Int Arch Allergy Immunol* 2010;152 Suppl 1:54-61.
33. Rubio A, Vivinus-Nebot M, Bourrier T, Saggio B, Albertini M, Bernard A. Benefit of the basophil activation test in deciding when to reintroduce cow's milk in allergic children. *Allergy* 2011;66:92-100.
34. Erdmann SM, Heussen N, Moll-Slodowy S, Merk HF, Sachs B. CD63 expression on basophils as a tool for the diagnosis of pollen-associated food allergy: sensitivity and specificity. *Clin Exp Allergy* 2003;33:607-614.
35. Ebo DG, Hagendorens MM, Bridts CH, Schuerwegh AJ, De Clerck LS, Stevens WJ. Flow cytometric analysis of in vitro activated basophils, specific IgE and skin tests in the diagnosis of pollen-associated food allergy. *Cytometry B Clin Cytom* 2005;64:28-33.
36. Jarvinen KM, Chatchatee P, Bardina L, Beyer K, Sampson HA. IgE and IgG binding epitopes on alpha-lactalbumin and beta-lactoglobulin in cow's milk allergy. *Int Arch Allergy Immunol* 2001;126:111-118.
37. Jarvinen KM, Beyer K, Vila L, Chatchatee P, Busse PJ, Sampson HA. B-cell epitopes as a screening instrument for persistent cow's milk allergy. *J Allergy Clin Immunol* 2002; 110:293-297.
38. Cerecedo I, Zamora J, Shreffler WG, Lin J, Bardina L, Dieguez MC *et al.* Mapping of the IgE and IgG4 sequential epitopes of milk allergens with a peptide microarray-based immunoassay. *J Allergy Clin Immunol* 2008;122:589-594.
39. Beyer K, Ellman-Grunther L, Jarvinen KM, Wood RA, Hourihane J, Sampson HA. Measurement of peptide-specific IgE as an additional tool in identifying patients with clinical reactivity to peanuts. *J Allergy Clin Immunol* 2003; 112:202-207.
40. Lin J, Bruni FM, Fu Z, Maloney J, Bardina L, Boner AL *et al.* A bioinformatics approach to identify patients with symptomatic peanut allergy using peptide microarray immunoassay. *J Allergy Clin Immunol* 2012;129:1321-1328.e5.
41. Jarvinen KM, Beyer K, Vila L, Bardina L, Mishoe M, Sampson HA. Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. *Allergy* 2007;62:758-765.
42. Ayuso R, Sanchez-Garcia S, Lin J, Fu Z, Ibanez MD, Carrillo T *et al.* Greater epitope recognition of shrimp allergens by children than by adults suggests that shrimp sensitization decreases with age. *J Allergy Clin Immunol* 2010;125: 1286-1293 e1283.
43. Ayuso R, Sanchez-Garcia S, Pascal M, Lin J, Grishina G, Fu Z *et al.* Is epitope recognition of shrimp allergens useful to predict clinical reactivity? *Clin Exp Allergy* 2012;42:293-304.
44. Leonard SA, Nowak-Wegrzyn A. Manifestations, diagnosis, and management of food protein-induced enterocolitis syndrome. *Pediatr Ann* 2013;42:135-140.
45. Nowak-Wegrzyn A. Chapter 16: Food Protein-Induced Enterocolitis and Enteropathies. In: Metcalfe DD, Sampson HA, RA Simon, editors. *Food Allergy 4th ed.* Blackwell Publishing, 2008.
46. Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome *Pediatr Allergy Immunol* 2006;17: 351-355.
47. Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I *et al.* Pediatric and adult eosinophilic esophagitis: similarities and differences *Allergy* 2012;67:477-490.
48. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J* 2013;108:679-692; quiz 693.
49. Benson TE, Arkins JA. Cytotoxic testing for food allergy: evaluation of reproducibility and correlation. *J Allergy Clin Immunol* 1976;58:471-476.
50. Ernst E. Iridology: A systematic review. *Forsch Komplementarmed* 1999;6:7-9.
51. Garrow JS. Kinesiology and food allergy *BMJ* 1988;296: 1573-1574.
52. Niggemann B, Gruber C. Unproven diagnostic procedures in IgE-mediated allergic diseases. *Allergy* 2004;59:806-808.
53. Sethi TJ, Lessof MH, Kemeny DM, Lambourn E, Tobin S, Bradley A. How reliable are commercial allergy tests?

Lancet 1987;1:92-94.

54. Stapel SO, Asero R, Ballmer-Weber BK, Knol EF, Strobel S, Vieths S *et al.* Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. *Allergy* 2008;63:793-796.
55. Lack G. Clinical practice. Food allergy. *N Engl J Med* 2008; 359:1252-1260.
56. Shreffler WG, Beyer K, Chu TH, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes *J Allergy Clin Immunol* 2004;113:776-782.
57. Agata H, Kondo N, Fukutomi O, Shinoda S, Orii T. Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J Allergy Clin Immunol* 1993;91:668-679.
58. Alonso A, Seoane MA, Iraneta SG, Scavini LM, Rodriguez SM. A citrus fruit-exclusion diet in sensitive patients and its influence on specific antibodies. *J Investig Allergol Clin Immunol* 1994;4:146-148.
59. Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998;9:13-19.
60. Chen JL, Bahna SL. Spice allergy. *Ann Allergy Asthma Immunol* 2011;107:191-199; quiz 199, 265.
61. Hill DJ, Murch SH, Rafferty K, Wallis P, Green CJ. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. *Clin Exp Allergy* 2007;37:808-822.
62. Niggemann B, von Berg A, Bollrath C, Berdel D, Schauer U, Rieger C *et al.* Safety and efficacy of a new extensively hydrolyzed formula for infants with cow's milk protein allergy. *Pediatr Allergy Immunol* 2008;19:348-354.
63. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S *et al.* Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:221-229.
64. EEC – European Communities Commission amending Directive 91/321/EEC,1996.
65. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R *et al.* Dietary prevention of allergic diseases in infants and small children. Part III: Critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004;15:291-307.
66. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R *et al.* Dietary prevention of allergic diseases in infants and small children. Part I: immunologic background and criteria for hypoallergenicity. *Pediatr Allergy Immunol* 2004;15:103-111.
67. Halken S, Host A, Hansen LG, Osterballe O. Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation. *Pediatr Allergy Immunol* 1993;4:53-59.
68. Host A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol* 1994;5:1-36.
69. Giampietro PG, Kjellman NI, Oldaeus G, Wouters-Wesseling W, Businco L. Hypoallergenicity of an extensively hydrolyzed whey formula. *Pediatr Allergy Immunol* 2001;12:83-86.
70. Ragno V, Giampietro PG, Bruno G, Businco L. Allergenicity of milk protein hydrolysate formulae in children with cow's milk allergy. *Eur J Pediatr* 1993;152:760-762.
71. Ellis MH, Short JA, Heiner DC. Anaphylaxis after ingestion of a recently introduced hydrolyzed whey protein formula. *J Pediatr* 1991;118:74-77.
72. Vita D, Passalacqua G, Di Pasquale G, Caminiti L, Crisafulli G, Rulli I *et al.* Ass's milk in children with atopic dermatitis and cow's milk allergy: crossover comparison with goat's milk. *Pediatr Allergy Immunol* 2007;18:594-598.
73. Jirapinyo P, Densupsoontorn N, Wongarn R, Thamonsiri N. Comparisons of a chicken-based formula with soy-based formula in infants with cow milk allergy. *Asia Pac J Clin Nutr* 2007;16:711-715.
74. Galli E, Chini L, Paone F, Moschese V, Knafelz D, Panel P *et al.* [Clinical comparison of different replacement milk formulas in children with allergies to cow's milk proteins. 24-month follow-up study]. *Minerva pediatrica* 1996;48:71-77.
75. Hol J, van Leer EH, Elink Schuurman BE, de Ruiter LF, Samsom JN, Hop W *et al.* The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. *J Allergy Clin Immunol* 2008 121:1448-1454.
76. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernandez-Rivas M *et al.* Anaphylaxis: Guidelines from the European Academy of Allergology and Clinical Immunology. *Allergy;* in press.
77. Cardona V, Luengo O, Garriga T, Labrador-Horrillo M, Sala-Cunill A, Izquierdo A *et al.* Co-factor-enhanced food allergy. *Allergy* 2012;67:1316-1318.
78. Romano A, Scala E, Rumi G, Gaeta F, Caruso C, Alonzi C *et al.* Lipid transfer proteins: the most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2012;42:1643-1653.
79. Miller JB. A double-blind study of food extract injection therapy: a preliminary report. *Annals of allergy* 1977;38: 185-191.
80. King WP, Rubin WA, Fadal RG, Ward WA, Trevino RJ, Pierce WB *et al.* Provocation-neutralization: a two-part study. Part I. The intracutaneous provocative food test: a multi-center comparison study. *Otolaryngol Head Neck Surg* 1988;99: 263-271.
81. Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, Diaz de Durana MD, Garcia BE, Gonzalez-Mancebo E *et al.* Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach

extract. *Allergy* 2009;64:876-883.

82. Garcia BE, Gonzalez-Mancebo E, Barber D, Martin S, Tabar AI, Diaz de Durana AM *et al.* Sublingual immunotherapy in peach allergy: monitoring molecular sensitizations and reactivity to apple fruit and Platanus pollen. *J Investig Allergol Clin Immunol* 2010;20:514-520.
83. Kinaciyan T, Jahn-Schmid B, Radakovics A, Zwolfer B, Schreiber C, Francis JN *et al.* Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. *J Allergy Clin Immunol* 2007;119:937-943.
84. Keet CA, Wood RA, Matsui EC. Limitations of reliance on specific IgE for epidemiologic surveillance of food allergy. *J Allergy Clin Immunol* 2012;130:1207-1209 e10.
85. Fisher HR, du Toit G, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?: a meta-analysis of published RCTs. *Arch Dis Child* 2011;96:259-264.
86. Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al.* Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;303:1848-1856.
87. Calvani M, Giorgio V, Miceli Sopo S. Specific oral tolerance induction for food. A systematic review. *Eur Ann Allergy Clin Immunol* 2010;42:11-19.
88. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol* 2011;127:1622-1624.
89. Niggemann B, Binder C, Dupont C, Hadji S, Arvola T, Isolauri E. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol* 2001;12:78-82.
90. Fagan TJ. Letter: Nomogram for Bayes theorem. *N Engl J Med* 1975;293:257.
91. Stiefel G, Roberts G. How to use serum-specific IgE measurements in diagnosing and monitoring food allergy. *Arch Dis Child Educ Pract Ed* 2012;97:29-36; quiz 34.
92. Alessandri C, Zennaro D, Scala E, Ferrara R, Bernardi ML, Santoro M *et al.* Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation. *Clin Exp Allergy* 2012;42:441-450.
93. Jarlot S, Morisset M, Hosotte M, G K. Predictive value of skin test and specific IgE to hazelnut. *Allergy* 2011;66:390-391.
94. Masthoff LJ, Pasmans SG, van Hoffen E, Knol MJ, Bruijnzeel-Koomen CA, Flinterman AE *et al.* Diagnostic value of hazelnut allergy tests including rCor a 1 spiking in double-blind challenged children. *Allergy* 2012;67:521-527.
95. Ballmer-Weber BK, Wuthrich B, Wangorsch A, Fotisch K, Altmann F, Vieths S. Carrot allergy: double-blinded, placebo-controlled food challenge and identification of allergens. *J Allergy Clin Immunol* 2001;108:301-307.
96. Ballmer-Weber BK, Vieths S, Luttkopf D, Heuschmann P, Wuthrich B. Celery allergy confirmed by double-blind, placebo-controlled food challenge: a clinical study in 32 subjects with a history of adverse reactions to celery root. *J Allergy Clin Immunol* 2000;106:373-378.
97. Reindl J, Anliker MD, Karamloo F, Vieths S, Wuthrich B. Allergy caused by ingestion of zucchini (Cucurbita pepo): characterization of allergens and cross-reactivity to pollen and other foods. *J Allergy Clin Immunol* 2000;106:379-385.

APPENDICES:

I. Tools to support implementation:

a. Key questions for patient's clinical history
b. Key observations
c. Interpreting allergy tests
d. Oral challenges: recommended doses
e. Component resolved IgE studies

II. Barriers and facilitators to implementation, audit criteria and resource implications of recommendations

Appendix I: Tools to support Implementation

A: Key Questions in the patients´ history of possible food allergy

Table I-A Questions

Description of food-induced allergic symptoms	What were the exact symptoms and their timing? How were the symptoms treated? What was the timing of the resolution of symptoms?
Eliciting food allergen	Which food induced the reaction? Is the allergen typical for age and country?
Timing of the reaction post exposure	How long after exposure did the reaction develop?
Reproducibility	Is the reaction reproducible?
Food processing	Does the reaction happen with processed and/or raw food?
Route of allergen exposure	What was the route of exposure to the food?
Amount of allergen	How much of the food allergen did the patient have before reacting?
Concomitant diseases	Does the patient have other medical conditions, including atopic diseases?
Co-factors	Did the patient exercise or take any alcohol or drugs before or after eating the index food?
Co- and cross-reactivity	Are related allergens eaten and tolerated? Is there cross-reactivity between inhalant allergens and food allergens? Is the patient allergic to latex?
Other foods	Is the patient able to eat ... (name specific foods)?
Dietary intake	Is the presence of a food allergy compromising dietary intake?
History of previous elimination diets	Did the patient follow elimination diets previously? Was it helpful?

B: Key Observations

Table I-B Key observations

• Milk and egg allergy are common in early childhood but comparatively rare in adulthood. Shellfish and plant food allergies are more common in adulthood. • An understanding of common regional allergens will guide subsequent allergy testing.
• Symptoms indicate possible underlying immunological mechanisms, namely IgE or non-IgE-mediated. • If the symptoms are not typical of an immune-mediated reaction then a differential diagnosis must be considered. • Confusing diagnostic scenarios in immediate-type reactions include: perioral erythema and irritation provoked by contact with skin irritants (e.g. raw tomato, citrus and berries), scromboid fish reactions, and chronic urticaria (for which food allergy is a rare cause). • In some children,food allergy may masquerade as a food aversion or refusal, but this may also be behavioural, due to oral tactile aversions, or odour sensitivity. • A history of severe allergic reactions determines a different risk assessment and a more stringent management plan.

- IgE-mediated allergic reactions usually occur within 30 minutes of the ingestion and mostly within 2 hours.
- Non-IgE mediated immune reactions are typically more delayed in onset.
- Non-immune mediated reactions can be of both immediate and delayed onset.

- Allergic reactions to a specific food should be consistent and develop every time the patient is exposed to that food.
- In children, peanut reactions typically present after the first known exposure, whereas other foods such as wheat, milk and fish, may present after multiple exposures.
- However adults may have eaten peanuts and tree nuts for many years before developing an allergy.

- Clinical reactivity may be influenced by processing of the food, e.g. egg allergic children commonly tolerate baked-egg protein whilst reacting to loosely cooked egg. In adults, soy may be tolerated in some forms but soy milk may provoke reactions in those with pollen-food syndrome.
- Patients with pollen-food syndrome usually tolerate cross reacting foods when eaten cooked but develop symptoms when eaten raw.

- In breast-fed infants, food allergens may be transmitted via human milk in small amounts (ng/ml)".
- Allergic reactions may occur after exposure to airborne allergen, typically fish and milk.
- A proportion of patients will react after skin contact or inhalation.

- Different patients react to different doses of the food allergen.
- The dose of allergen eaten is also important to establish tolerance, e.g. if a child has had a food regularly in very small amounts may not mean she/he would tolerate the food if she/he ate a larger amount.

- The majority of children with food allergy will have eczema, and at least 25% will go on to develop additional food allergies.
- Food allergic infants are at risk for the development of asthma; and asthma is a risk factor for more severe-food induced allergic reactions in all age groups.
- Adults with food allergy will often be sensitised or allergic to pollen, and therefore more likely to develop pollen-food syndrome. More than 50% of those with birch pollen allergy will report symptoms to plant foods due to cross-reactions.

- Asthma, medication use (esp. ACEI, β-blockers, acetyl salicylate), alcohol intake and/or exercise are factors, which may increase the severity of allergic reactions.

- Allergy to just one food is increasingly uncommon. The patient with peanut allergy is commonly sensitized to one or more tree nuts and or sesame.
- People with pollen-food syndrome often report reactions to many different fruits, nuts and vegetables.
- Some latex allergens are homologous to certain food allergens such as kiwi, avocado and chestnuts.

- Ask specifically about common allergenic foods, including foods causing co- and cross-reactivity with the index food.
- Ask whether foods which might contain the suspected allergen are tolerated, e.g. is multi-grain bread tolerated if soy is suspected.
- Ask if a child is able to consume age-appropriate quantities of specific foods, e.g. a 5 year old should be able to consume a whole egg/full glass of milk before being labelled as truly tolerant to the food.

- In the absence of dietetic supervision, all children with food allergy are at a greatly increased risk for nutritional compromise.
- Adults, who are avoiding major food groups such as milk or wheat, will also have a compromised nutritional intake.

- Elimination diets without decrease of symptoms should be stopped.

C: Interpreting allergy tests

The performance of allergy tests for the diagnosis of food allergy should ideally be validated against the gold standard investigation (i.e. the DBPCFC). There are studies, in different clinical scenarios and geographic settings that assess the diagnostic ability of allergy tests (SPT and/or sIgE) as compared to the DBPCFC. These analyses allow for the generation of 2x2 tables and *sensitivity* and *specificity* values.

Sensitivity refers to the proportion of patients with a condition who test positive. For the diagnosis of food allergy, sensitivity of SPT and sIgE is variable and allergen specific, for example for peanut it is modestly high at around >80%. *Specificity* refers to the proportion of persons without the condition who test negative; for food allergy the specificity of the SPT and peanut-IgE is lower than the sensitivity, for example 30% to 50% for peanut. A highly sensitive test is good at ruling out a diagnosis when the test is negative. A specific test is good at confirming a diagnosis when the test is positive.

The size of the test value (SPT and or sIgE) that is to be considered 'positive' dramatically alters the sensitivity/specificity of an investigation. Whilst it is useful to consider extreme values (both positive and negative) – as these carry better sensitivity or specificity – most patients seen in routine referral clinical settings will not present with test results at the extremes. Therefore, many patients have equivocal diagnostic outcome (history depending) that can only be resolved through performing an OFC.

As it is difficult to use sensitivity and specificity at the level of the individual, use is frequently made of positive and negative predictive values. The positive predictive value (PPV) is the probability that a patient has food allergy if the test is positive; the negative predictive value (NPV) is probability that the patient does not have food allergy if the test is negative. However, these predictive values are dependent on the population prevalence, the food allergen in question, background history, age, sex, geographic location, ethnicity, and concomitant allergies (e.g. eczema). It is therefore not easily possible to apply predictive values across different population and in different settings.

Given the above challenges, use is increasingly being made of likelihood ratios (LR) which offer a different diagnostic approach that is more practicable at the level of the individual patient. The use of LR's reflects the natural thought process that is undertaken by clinicians in routine medical diagnostic practice. So a determination is made of the pre-test probability of food allergy being present prior to the test (SPT and or sIgE); with the allergy test result known, a post-test probability can then be determined by combining these two values and a decision regarding management can then be made. For the diagnosis of food allergy this is crucial to decide whether or not the patient should undergo an OFC.

The pre-test probability is determined through combining the likely risk determined through clinical history, data on the local prevalence of the disease, personal clinical experience and published reports. The use of the LR places an emphasis on obtaining a robust clinical history as well as an understanding of the disease in a local setting.

A LR reflects how many times more likely a given test result is seen in a patient who is allergic to that food compared with a patient who is tolerant. The further the LR is above 1 the stronger the evidence for the presence of the disease. A LR ≥10 is highly suggestive of food allergy.

The LR of the test – given only two allergy outcomes – can be calculated directly from sensitivity and specificity (LR = sensitivity/(1 – specificity)]. The post-test probability is determined by this mathematical calculation or by using a simple statistically derived nomogram (Figure 1-C1), which can simplify this calculation to percentages rather than odds.

The use of a LR has the advantage of giving us the ability to interpret allergy tests within the subject's clinical context, as different patients in diverse clinical settings, but with the same test result, have different likelihoods of having food allergy.

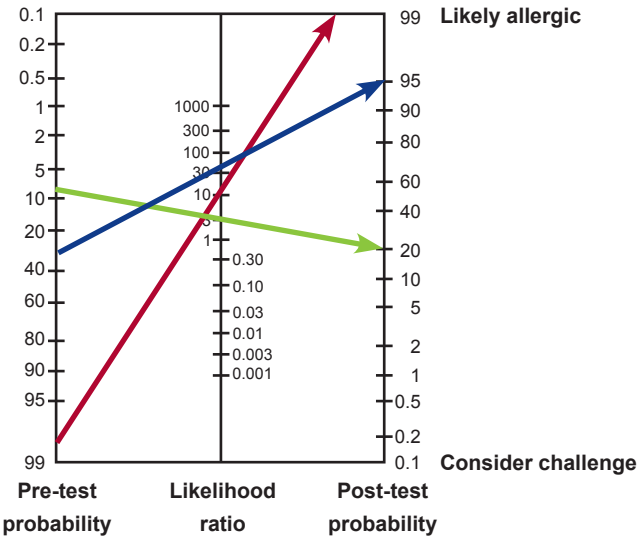


Figure I-C 1 Using likelihood ratios (LR) to diagnose allergy

Figure adapted from: Fagan TJ. (90)

The three arrows are examples of clinical situations described in the Table I-C below (Red arrow refers to scenario A, green to B and blue to C).

		Likelihood of clinical allergy from specific IgE (kU/L) or SPT (mm) results		
		Low (<0.35 or <3)	**Intermediate** (0.35 to <15 or 3 to < 8)	**High** (≥ 15 or ≥ 8)
Likelihood of clinical allergy from history	**High** e.g. Urticaria and wheeze on 2 exposures	Possible allergy	Probable allergy	Allergy
	Intermediate e.g. Urticaria on a single exposure	Possible allergy	Possible allergy	Probable allergy
	Low e.g. Non-IgE mediated symptoms	No allergy	Possible allergy	Possible allergy

Figure I-C 2 Using likelihood ratios (LR) to diagnose allergy

Children and adolescents in the possible allergy box require an OFC for a definitive diagnosis. Specific IgE and SPT values are specific for peanuts. Values associated with a high likelihood of clinical allergy are lower for egg, milk,and fish. Modified from Stiefel and Roberts (91).

Table I-C1 Clinical examples that relate to the diagnosis of peanut allergy

Scenario	History	Pre-test probability	Test results	Management
A	5 year old, British, male. 3 previous allergic reactions soon after peanut butter ingestion	At least 98% chance as guided by history	SPT 8mm, LR approx. 17.3 (in UK)	Strictly avoid peanut. Institute comprehensive education and emergency plan
B	8 year old, French female. No allergy concerns. Sibling peanut allergic. No known peanut exposure.	Epidemiological risk 7%	No SPT obtained. Peanut sIgE 2KU/L, LR approx. 2.6	Post test probability 20%, consider OFC or component testing if available
C	4 year old, British child, with egg allergy and early-onset moderate eczema. Never eaten peanut	Epidemiologic risk of 30%	SPT 3mm, LR 40.3 in UK	Likely allergy as post test probability 95%

Values will differ by geographic location and should best be determined in the clinical setting where they are applied. For example, hazelnut values will perform differently in parts of Europe where birch pollen allergy is commonplace; this will also differ with the age of the patient. The action to be taken with each post test LR will differ between clinics and is influenced by local practice, the family's preference, and the clinical scenario faced.

D: Oral Challenges: recommended doses

Table I-D Recommended incremental dosages for DBPCFC with milk, egg, peanut, wheat or soy

Food protein (mg)	3mg	10 mg	30 mg	100 mg	300 mg	1000 mg	3000 mg
Pasteurized cow's milk with 3.3% protein content	90.9 mg ≈ 0.1 ml	303.0 mg ≈ 0.3 ml	909.0 mg ≈ 0.9 ml	3,030.3 mg ≈ 3.0 ml	9,090.9 mg ≈ 9.1 ml	30,303.0 mg ≈ 30.3 ml	90,909.1 mg ≈ 90.9 ml
Skim milk powder with 36% protein content	8.3 mg	27.8 mg	83.3 mg	277.8 mg	833.3 mg	2,777.8 mg	8,333.3 mg
Pasteurized whisked hen's egg with 12.8% protein content	23.4 mg	78.1 mg	234.4 mg	781.3 mg	2,343.8 mg	7,812.5 mg	23,437.5 mg
Hen's egg powder with 47% protein content	6.4 mg	21.3 mg	63.8 mg	212.8 mg	638.3 mg	2,127.7 mg	6,383.0 mg
Peanut butter with 24% protein content	12.5 mg	41.7 mg	125.0 mg	416.7 mg	1,250.0 mg	4,166.7 mg	12,500.0 mg
Peanut flour with 50% protein content	6.0 mg	20.0 mg	60.0 mg	200.0 mg	600.0 mg	2,000.0 mg	6,000.0 mg
Gluten powder with 80% protein content	3.8 mg	12.5 mg	37.5 mg	125.0 mg	375.0 mg	1,250.0 mg	3,750.0 mg
Soy drink with 3.3% protein content	90.9 mg ≈ 0.1 ml	303.0 mg ≈ 0.3 ml	909.0 mg ≈ 0.9 ml	3,030.3 mg ≈ 3.0 ml	9,090.9 mg ≈ 9.1 ml	30,303.0 mg ≈ 30.3 ml	90,909.1 mg ≈ 90.9 ml
Soy powder with 50% protein content	6.0 mg	20.0 mg	60.0 mg	200.0 mg	600.0 mg	2,000.0 mg	6,000.0 mg

E: Component resolved IgE studies included in the systematic review

Target food	Component specific IgE	Reference
Hen's egg	Gal d 1, Gal d 2, Gal d 3, Gal d 5	(93)
Shrimp	Pen a 1	(44)
Peanut	Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9	(29)
Hazelnut	Cor a 1, Bet v 1, Bet v 2, Cor a 8	(94)
Hazelnut	Cor a 9 and Cor a 14	(95)
Carrot	Bet v 1, Bet v 2, Bet v 6	(96)
Celery	Bet v 1, Bet v 2	(97)
Courgette	Bet v 1, Bet v 2	(98)

Appendix II: Diagnosis - barriers and facilitators to implementation, audit criteria and resource implications of recommendations

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
PATIENT'S CLINICAL HISTORY					
Detailed clinical history is essential for the diagnosis of food allergy. When taking a clinical history eliciting allergens, timing and chronicity, symptoms, severity and signs, reproducibility, known risk (co)factors, family history, co-existing medical problems including other allergic diseases should be addressed. The use of structured questions on symptoms, foods and other background information is recommended	IV	C	Lack of standardized questionnaire Training of health professionals	Development of standardized questionnaire Training of health professionals	% of patients where diagnosis excluded on the basis of clinical history
DETERMINATION OF SENSITIZATION					
IgE sensitization does not always result in clinical relevant food allergy, therefore, specific allergy testing should be directed by case history.	IV	C	Health professionals attitudes Poor access to allergy consultation Lack of public information	Specific education of healthcare professionals Improved access to allergy consultation Improved information to the public	% of patients properly diagnosed with food allergy
SPT and/or sIgE can be the test of choice depending on local availability and absolute and relative contraindications to SPT.	IV	C	Lack of facilities and poor access to allergy consultation	Improvement of access to allergy testing Improvement of access to allergy training of primary care physicians	Increase in allergy testing Increase of facilities for allergy testing
IgE sensitization to common food allergens is determined by SPT and serum IgE tests and is used as a support to the diagnosis of food allergy by clinical history and/or food challenge. These tests are highly sensitive (75-100%). However, specificity of these tests is moderate (40-70%) and does not replace clinical history and food challenges.	I-III*	A-C*	Health professionals attitudes Poor access to allergy consultation Lack of public information	Specific education of healthcare professionals Improved access to allergy consultation Improved information to the public	% of patients properly diagnosed with food allergy
Where available, standardized tests and procedures should be used	IV	C			
In the presence of a suggestive history, a negative SPT or sIgE needs to be interpreted with caution particularly as these are expected in non-IgE mediated food allergy	IV	C			
In case SPT and sIgE tests are inconclusive CRD (if available) provides additional information.	I – IV*	A – C*	Lack of facilities Difficulty in interpreting Costs	Increase in availability of CRD testing Training of healthcare professionals Reimbursement policies	% of patients properly diagnosed with CRD testing

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
If clinical history with SPT and/or sIgE is not *highly predictive*, a provocation test is required.	IV	C	Health professionals attitudes Poor access to allergy consultation Lack of public information	Specific education of healthcare professionals Improved access to allergy consultation Improved information to the public	% of patients properly diagnosed with food allergy
Determination of total IgE is particularly useful in patients with severe eczema who often show very high total IgE levels which indicates that positive specific IgE results should be interpreted with care.	IV	C			
BAT and determination of sIgE to linear epitopes are promising techniques, which should be further studied.	V	D	Cost	Reduction of costs Research projects	Large cohort trials in patients with food allergy
ELIMINATION DIETS FOR DIAGNOSTIC PURPOSES					
The determination of the foods to be avoided should be based on the allergy-focused diet history, clinical history and adjunct allergy testing, i.e. SPTs and/or sIgE determination.	V	D	Health professionals attitudes Poor access to allergy consultation Lack of public information	Specific education of healthcare professionals Improved access to allergy consultation Improved information to the public	% of patients properly diagnosed with food allergy
For all of the individually avoided foods the results of the diagnostic elimination diet should be carefully monitored and evaluated for 2-4 weeks of avoidance.	V	D	Lack of consultation with dieticians with competence in food allergy	Training of dieticians in food allergy	Increase in % of dieticians with competence in food allergy
In case the elimination diet leads to a significant relief of symptoms, it should be continued until the provocation test is performed.	V	D	Health professionals attitudes Poor access to allergy consultation Lack of public information	Specific education of healthcare professionals Improved access to allergy consultation Improved information to the public	% of patients properly diagnosed with food allergy
If no significant reduction of symptoms is obtained by elimination diet, the respective food allergy is highly unlikely. After the exclusion of confounding factors foods should be reintroduced into the diet after 2-4 weeks.	V	D			
ORAL CHALLENGE TESTS					
The oral food challenge (particularly the double-blind placebo-controlled food challenge) is the gold standard investigation for the objective diagnosis of IgE-and non-IgE mediated food allergy.	IV	D	Health professionals attitudes Poor access to allergy consultation and lack of allergy services Lack of public information Reimbursement policies	Specific education of healthcare professionals Improved access to allergy consultation Improved information to the public Proper reimbursement from national health systems and Insurance bodies	National guidelines for food allergy. Increase in number of OFC performed Development of policies within the context of the public health approach.

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
There are many OFC designs available: standardized procedures should be used in order to achieve a safe and objective challenge outcome that is patient/ research specific. OFC's should be performed in patients who have an equivocal diagnosis of food allergy.	IV	D	Lack of information among healthcare professionals Lack of training	Diffusion of proper information Training of health professional	% of patients properly diagnosed with food allergy
OFC's should be used to demonstrate allergy or tolerance and in so doing facilitate safe dietary expansion or appropriate allergen avoidance.	IV	D			
The OFC may be performed as an open, single or double-blinded challenge; variables such as clinical history, food allergen, patient criteria (age, concomitant food and other allergic disease, anxiety…), and research criteria should guide the selection of the OFC.	IV	D			
The OFC, in additional to establishing a firm diagnosis can be used to determine threshold reactivity, response to OIT, spontaneous resolution of food allergy and the exclusion of food allergy.	IV	D			
The DBPCFC should be performed in the following settings: when symptoms are subjective, with delayed or atypical symptoms, where patients and/or caregivers are anxious, and considered in all research settings.	IV	D			
A negative DBPCFC should end with an open or cumulative ingestion of the food to confirm oral tolerance.	IV	D			
OFC are not without risk, and must be performed in a specialist setting with emergency support immediately available. In patients with a moderate to high risk of a severe reaction, intensive care support must be immediately available.	IV	D			
UNCONVENTIONAL TESTS (INCLUDING SPECIFIC IgG TESTING)					
There are no unconventional approaches which can be recommended as alternative or complementary diagnostic tools in the work up of suspected food allergy, and their use should be discouraged.	III	C	Miss information among the public Poor access to allergy consultation	Patient Organisations Counteraction of "myths"	Reduction in % of patients undertaking unconventional testing

*Range of levels of evidence and grades are due to range of different foods tested

APPENDIX II: Management – barriers and facilitators to implementation, audit criteria and resource implications of recommendations.

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
ACUTE MANAGEMENT					
The patient at risk of severe reactions should be properly and timely identified.	IV	D	Lack of epidemiological data of inter and intra individual risk factors Lack of biomarkers for risk of severe reactions	Improved knowledge of mechanisms underlying severity an allergic reaction Identification of biomarkers to support clinical evaluation	Surveillance epidemiological studies of acute episodes Large multi-centred trials evaluating biomarkers in patients with severe reactions
ANTIHISTAMINES AND MAST CELL STABILIZERS					
There is evidence to support the benefits of antihistamines for children and adults with acute non-life threatening symptoms from food allergy.	III	C	Health professional attitude Lack of public information	Education	Reduction of % of patients with anaphylaxis using antihistamines
The prophylactic application of antihistamines is not recommended	V	D	Health professional attitude	Specific education of health professionals	Reduction of % of patients with anaphylaxis using antihistamines
Mast cell stabilisers are not recommended for the prophylactic treatment of food allergy.	III	C	Health professional attitude	Specific education of health professional	Reduction of % of patients with anaphylaxis using antihistamines
ELIMINATION DIET					
A sufficient elimination diet should be based on a proper allergy diagnosis identifying the food allergen(s) responsible of the patient's symptoms /reactions. The indications should be re-evaluated at appropriate intervals.	IV	D	Lack of proper allergy diagnosis Lack of compliance	Access to allergy services Counselling with proper attractive menus, patients and family	Increase in allergy services
Appropriate avoidance diets are the key treatment in the management of food allergy.	IV	D	Costs of alternative foods Difficulty in finding alternative foods Monotonous diet and difficulty in finding a pleasant replacement	Pleasant food options Psychological counselling	Availability of special food for allergic consumer on the market Increase in quality of life in patients who receive psychological counselling
Patients with food allergy who are on long term elimination diets should have access to appropriate nutritional counseling, ideally by a dietitian with competencies in food allergy, and regular monitoring of growth.	IV	C	Lack of appropriately trained dietitian with competencies in food allergy	Education of food allergy among dietitian's training	% of patients with dietary compromises while on an elimination diet

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
Extensively hydrolysed cow's milk formulas with documented hypoallergenicity can be recommended as first choice for the treatment of cow's milk allergy, especially in infants and young children. Amino acid formulas can be recommended as well especially for a subgroup of patients with more severe symptoms.	I	A	Cost of the alternative formulas	Reduction of the costs Improvement in reimbursement polices	% of children with cow's milk allergy who receive first choice formulas Reduction of cost Availability of reimbursement of formulas for special needs
Soy formulas should not be recommended before 6 months of age and at any age in the presence of gastrointestinal symptoms. From 6-12 months it can be considered on a case-by-case basis.	I	B	Health professional attitudes Costs in developing countries	Education Reduction of the costs Improvement in reimbursement polices	Reduction of cost Availability of reimbursement of formulas for special needs
Currently, probiotic supplements cannot be recommended for the management of food allergy	I	D	Public and health professionals attitudes Lack of evidence based benefit in large cohort studies	Awareness of the results of currently available studies	Large cohort studies to provide evidence based conclusions
EDUCATION AND RISK ASSESSMENT					
Patients and caregivers need to be informed about the foods that should be avoided, and practical advice given on avoidance measures, how to recognize a further reaction and the self-management of these reactions.	V	D	Lack of awareness among health professionals	Allergy nurses and dieticians with competencies in food allergies patient organisations	Availability of tools designed for education on food allergy
Patients/carers should be encouraged to join an appropriate patient support organization.	V	D	Lack of relevant patient organisations Denial of having a disease requiring external support.	Establishment of patients' organisations where needed Distribution of information of the activities of patient organisations at allergic clinics	% of patients joining patients organisations. Presence of a food allergy patient organisation in each European country Increase in meetings organised by patient organisation on food allergy
All patients with food allergy require a management plan with appropriate education for the patient, caregiver including school.	V	D	Lack of standardized management plans	Standardized training courses to educate patients caregivers and schools Reimbursement policies for training courses	% of patients attending training courses Availability of reimbursement policies for training % of patients attending the ED % of patients hospitalized because of severe allergic reactions % of patients who die because of a further severe allergic reaction

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
Education should cover allergen avoidance, symptom recognition and indication for specific treatment and administration of specific medication.	V	D	Lack of knowledge and skills among parents, schools and professionals in recognizing symptoms Lack of allergy services	Written plans Educational courses Training courses	National and international policies for education within the context of a public health approach
Absolute indications with adrenaline auto-injector include previous anaphylaxis to any food, persistent or severe asthma, exercise induced food dependent anaphylaxis, and mastocytosis.	IV	C	Scarce knowledge among health professionals about proper management of severe allergic reactions Costs of self injectable devices Reimbursement policies	Development of tools for the management of severe reactions (i.e. on-line training courses, leaflets) to facilitate education of health professionals.	% of patients suffering from severe reactions prescribed with AAI % of patients with anaphylaxis who present to the ED having already used AAI Reduction of costs of AAI Improvement of reimbursement policies
Relative indications for adrenaline auto-injector with food allergy include (1) food allergies that are likely to be persistent; (2) mild-to-moderate allergic reaction to peanut and/or tree nut (3) mild-to-moderate reaction to very small amounts of food and (4) specific high risk groups, e.g. adolescents, young adult males, poor access to medical care.	IV-V*	C-D*	Scarce knowledge among health professionals about proper management of severe allergic reactions Costs of self injectable devices Reimbursement policies	Development of tools for the management of severe reactions (i.e. on-line training courses, leaflets) to facilitate education of health professionals.	% of patients suffering from severe reactions prescribed with AAI % of patients with anaphylaxis who present to the ED having already used AAI Reduction of costs of AAI Improvement of reimbursement policies
Adrenaline should be immediately administered for cardiovascular symptoms and/or respiratory symptoms such as altered voice, stridor or bronchospasm that is thought to be induced by food allergy.	IV	C	Scarce knowledge among health professionals about proper management of severe allergic reactions	Development of tools for the management of severe reactions (i.e. on-line training courses, leaflets) to facilitate education of health professionals. Written plans	Reduction of deaths due to anaphylaxis Surveillance epidemiological programmes
Short acting beta agonists should be included in the management plan for all patients with co-existing asthma and should be administered for bronchospasm after adrenaline has been administered.	V	D	Scarce knowledge among health professionals about proper management of severe allergic reactions	Development of tools for the management of severe reactions (i.e. on-line training courses, leaflets) to facilitate education of health professionals. Written plans	Reduction of deaths due to anaphylaxis Surveillance epidemiological programmes

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
Patient held glucocorticosteroids may be given with reactions to possibly prevent late phase respiratory symptoms.	V	D	Often used as first line treatment Lack of evidence to support intended use	Emphasis on adrenaline as first line treatment Education of healthcare staff Clear protocols in emergency department may prevent biphasic reactions	Compare outcomes of anaphylaxis in patients who received adrenaline treatment with and without glucocorticocosteroids
Any patient who has received adrenaline should be reviewed in an emergency department.	III	C	Lack of proper information from the patient	Education	% of patients presenting at ED after having been administered self-injectable adrenaline
SPECIFIC IMMUNOTHERAPY					
Food allergen-specific immunotherapy for primary food allergy is a promising immune-modulatory treatment approach (I), but it is associated with risk of adverse reactions, including anaphylaxis (I); it is therefore not at present recommended for routine clinical use.	III	C	Lack of established requirements for centres performing food allergen specific immunotherapy Lack of proper information among the patients	Identification of criteria for centres of excellence Increase in qualified allergy centres	Increase in large multi-centre trials for food allergen immunotherapy Increase in % of patients recruited for proper food allergen immunomodulatory treatment
Immunotherapy in patients with respiratory symptoms /allergy to inhalant allergens that may also cause cross reactive food allergy, specific immunotherapy is recommended for the treatment for the respiratory symptoms but currently not for the primary treatment of cross-reactive food allergy.	IV	D	Lack of established requirements for centres performing food allergen specific immunotherapy Lack of proper information among the patients	Identification of criteria for centres of excellence Increase in qualified allergy centres	Increase in large multi-centre trials for food allergen immunotherapy Increase in % of patients recruited for proper food allergen immunomodulatory treatment
ANTI-IgE					
The use of anti-IgE alone or in combination with specific immunotherapy is currently not recommended for the treatment of food allergy even though it represents a promising modality.	IV	D	Health professionals' attitude Lack of proper information among the patients	Identification of criteria for centres of excellence Increase in qualified allergy centres	Increase in large multi-centre trials for anti-IgE immunotherapy
CHALLENGES AT REGULAR INTERVALS TO ASSESS ACHIEVEMENTS OF TOLERANCE					
OFC should be performed at regularly intervals appropriate for the specific food and patients history in order to assess achievement of tolerance.	V	D	A lack of allergy services Reimbursement polices	Access to allergy services Proper reimbursement from National Health systems and Insurance bodies	Increase in number of OFC Increase in allergy services National and EU polices on OFC reimbursement
Specific IgE tests (in vitro and skin-prick-test) are currently of little value in guiding adequately the timing of oral food challenges for development of tolerance.	V	D	Knowledge among health professionals	Education of health professionals	Survey of ongoing management of patients with food allergy

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
COFACTORS					
In food allergic reactions, the potential augmenting role of co-factors, i.e. such as exercise, NSAID, omeprazol or alcohol intake, should be assessed in a structured history.	III-IV**	D	Lack of standardized questionnaires	Development of properly designed questionnaires	Large surveillance programmes on incidence and prevalence of co-factors % of co-factors identified in patients suffering for severe reactions
In allergic reactions occurring after exercise, NSAID or alcohol intake, underlying food allergy to foods consumed in the previous hours should be assessed (especially gliadin sensitization or LTP in southern Europe).	IV	D	Lack of standardized questionnaires	Development of properly designed questionnaires	Large surveillance programmes on incidence and prevalence of co-factors % of co-factors identified in patients suffering for severe reactions

*Range of levels of evidence and grades are due to range of indications.
**Range of levels of evidence and grades are due to range of different cofactors.

SECTION 2

PRIMARY PREVENTION OF FOOD ALLERGY

2.1

PRIMARY PREVENTION OF FOOD ALLERGY IN CHILDREN AND ADULTS

SYSTEMATIC REVIEW

D de Silva[1], M Geromi[1], S Halken[2], A Host[2], SS Panesar[3], A Muraro[4], T Werfel[5], K Hoffmann-Sommergruber[6], G Roberts[7-9], V Cardona[10], AEJ Dubois[11], LK Poulsen[12], R van Ree[13], B Vlieg–Boerstra[14], I Agache[15], K Grimshaw[9], L O'Mahony[16], C Venter[17], S. H. Arshad[7-9], A Sheikh[3, 18], on behalf of the EAACI Food Allergy and Anaphylaxis Group

EAACI Food Allergy and Anaphylaxis Group: CA Akdis, R Alvarez, K Beyer, C Bindslev Jensen, P Demoly, P Eigenmann, M Fernandez Rivas, G Lack, MJ Marchisotto, B Niggeman, C Nilsson, N Papadopoulos, I Skypala, M Worm.

AFFILIATIONS

[1] The Evidence Centre, London, UK

[2] Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[3] Allergy and Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, UK

[4] Department of Pediatrics, Center for Food Allergy Diagnosis and Treatment, Veneto Region, University of Padua, Italy

[5] Hanover Medical School, Hanover, Germany

[6] Department of Pathophysiology and Allergy Research, Medical University of Vienna, Austria

[7] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[8] NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[9] Human Development and Health and Clinical and Experimental Sciences Academic Units, Faculty of Medicine, University of Southampton, UK

[10] Hospital Valld'Hebron, Barcelona, Spain

[11] Department of Paediatrics, Division of Paediatric Pulmonology and Paediatric Allergy, University Medical, Centre Groningen, University of Groningen, Groningen, The Netherlands

[12] Laboratory of Medical Allergology, Allergy Clinic, Copenhagen University Hospital, Gentofte, Hellerup, Denmark

[13] Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, The Netherlands

[14] Emma Children's Hospital, Academic Medical Center, Department of Pediatric Respiratory Medicine and Allergy, Amsterdam, The Netherlands

[15] Transylvania University, Brasov, Romania

[16] Swiss Institute of Allergy and Asthma Research, University of Zurich, Davos, Switzerland

[17] School of Health Sciences and Social Work, University of Portsmouth, Portsmouth, UK

[18] Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston, USA

***Background**: Food allergies can have serious physical, social and financial consequences. This systematic review examined ways to prevent the development of food allergy in children and adults.*

***Methods**: Seven bibliographic databases were searched from their inception to September 30, 2012 for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series and cohort studies. Experts were consulted for additional studies. There were no language or geographic restrictions. Two reviewers appraised the studies using appropriate tools. Data were not suitable for meta-analysis due to heterogeneity so were narratively synthesized.*

***Results**: Seventy-four studies were included; one third of which were of high quality. There was no good evidence to recommend that pregnant or breastfeeding women should change their diet or take supplements to prevent allergies in infants at high or normal risk. There were mixed findings about the preventive benefits of breastfeeding for infants at high or normal risk, but there was evidence to recommend avoiding cow's milk and substituting with extensively or partially hydrolyzed whey or casein formulas for infants at high risk for the first four months. Soy milk and delaying the introduction of solid foods beyond four months did not have preventive benefits in those at high or normal risk. There was very little evidence about strategies for preventing food allergy in older children or adults.*

***Conclusions**: There is much to learn about preventing food allergy and this is a priority given the high societal and healthcare costs involved.*

Originally published as: de Silva D, Geromi M, Halken S, Host A, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Cardona V, Dubois AEJ, Poulsen LK, Van Ree R, Vlieg-Boerstra B, Agache I, Grimshaw K, O'Mahony L, Venter C, Arshad SH and Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group. Primary prevention of food allergy in children and adults: systematic review. *Allergy* 2014;69:581–589.
© 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

People with food allergies suffer symptoms that affect both their health and lifestyle so there is considerable interest in ways to reduce the risk of developing a food allergy. The causes of food allergy are likely related to both genetic factors and environmental exposure (1, 2). Genetic factors are not modifiable so strategies to prevent food allergy have focused on limiting early exposure to potential allergens antenatally or during breastfeeding, by changing what mothers eat in the hope that this will limit allergen exposure to their babies or boost protective mechanisms (3, 4). Prevention strategies may also directly target the infant formula and foods that babies and children consume (5). This review summarizes evidence about the most effective ways to prevent food allergy in children and adults.

This systematic review is one of seven inter-linked syntheses undertaken to provide a state-of-the-art synopsis of the evidence base in relation to the epidemiology, prevention, diagnosis, management, and impact on quality of life. This will be used to inform clinical recommendations in the European Academy of Allergy and Clinical Immunology (EAACI) Guidelines for Food Allergy and Anaphylaxis.

Methods

Protocol and registration

The review was registered with the International Prospective Register of Systematic Reviews. The protocol has been published previously (6) so only brief details about the methodology are provided here.

Search strategy

The following databases were searched: Cochrane Library; Medline, Embase, CINAHL, ISI Web of Science, TRIP Database and Clinicaltrials.gov. Experts in the field were contacted for additional studies. Further details are included in the review protocol (6).

Inclusion and exclusion criteria

This review focused solely on studies that were primarily concerned with preventing sensitization to food(s) and/or the development of food allergy. Studies seeking to prevent potential manifestations of food allergy such as atopic eczema/dermatitis or asthma, but not including an explicit diagnosis of sensitization to food or food allergy, were not included.

Systematic reviews and meta-analyses, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series studies and prospective cohort studies published up until September 30, 2012 were eligible. No language restrictions were applied and, where possible, relevant studies in languages other than English were translated.

Study selection

The titles and abstracts of articles were checked by two independent reviewers and categorized as included, not included and unsure (DdS and MG). Full text copies of potentially relevant studies were obtained and their eligibility for inclusion was independently assessed by two reviewers (DdS and MG). Any discrepancies were resolved by consensus or discussion with other reviewers (SH and AS).

Risk of bias assessment

Risk of bias was independently carried out by two reviewers (DdS and MG) using adapted versions of the Critical Appraisal Skills Programme (CASP) tool and the Cochrane Effective Practice and Organisation of Care Group (EPOC) Risk of Bias tools. An overall grading of high, medium or low quality was assigned to each study.

Analysis, synthesis and reporting

Two reviewers independently used a customized data extraction form to obtain data from each study (DdS and MG). Discrepancies were resolved by discussion. Experts in the field checked all of the data extraction for accuracy and relevance (SH and AH). Meta-analysis was not appropriate because the studies were heterogeneous in focus, design, target populations and interventions. Findings were synthesized narratively by grouping studies according to intervention and target population. These syntheses were checked by a group of methodologists and experts to ensure accuracy and relevance.

Results

Study selection and characteristics

Figure 1 shows the PRISMA flowchart. Seventy-four studies were included, comprising 15 systematic

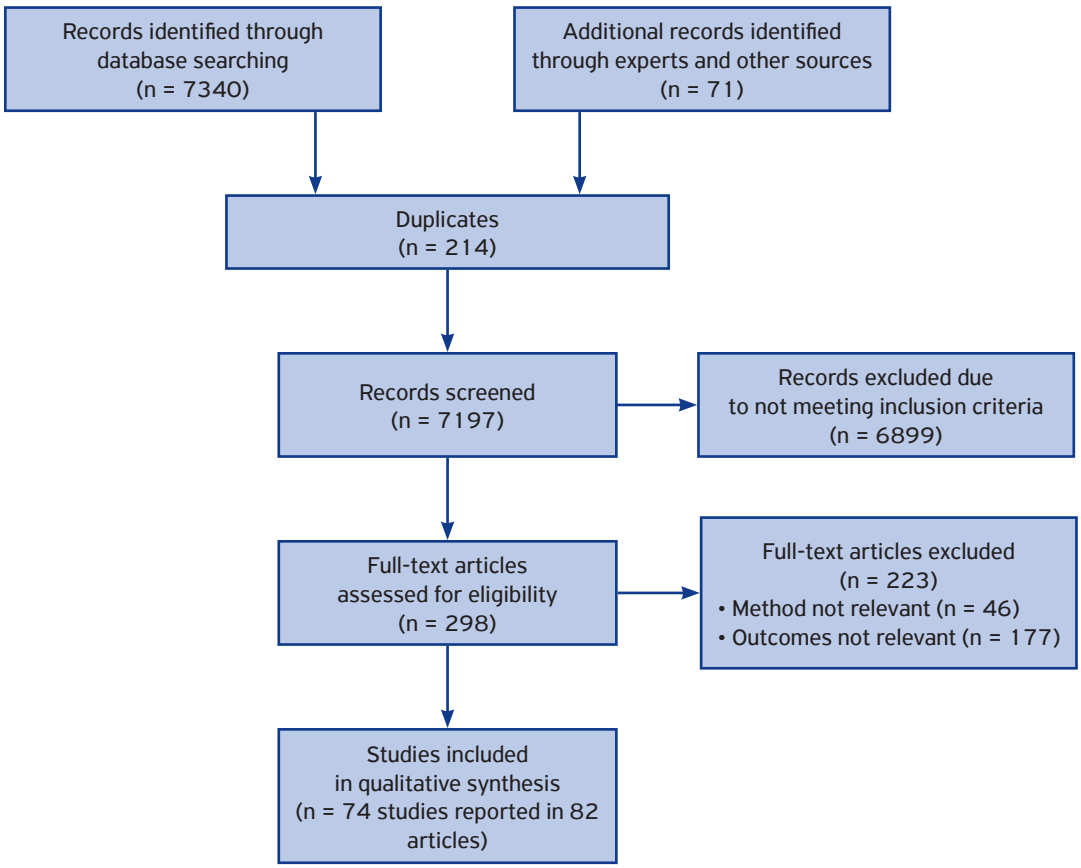


Figure 1 PRISMA flow diagram for selection of studies

reviews (20%), 32 randomized controlled trials (43%), nine non-randomized comparative studies (12%) and 19 cohort studies (25%). Based on the risk of bias assessment, 25 of the studies were deemed to be of high quality (34%), 19 were of moderate quality (26%) and 30 were of low quality (40%), often due to small sample sizes or non-randomized designs. Further details about each study are available in the online supplement.

Most studies focused on preventing the development of food allergy from an early age (i.e. in unborn children and infants). Many studies focused on babies at high risk due to having a family history of allergy or atopy. Throughout the review, the term 'at high risk' is used as an abbreviation to mean that infants had an increased risk of developing food allergy or atopy due to a familial history of allergic disease

Table 1 summarizes the key findings.

Prevention strategies in pregnant women

High-risk families

Unborn children may be sensitized to the foods their mothers' consume (7, 8). Investigations have therefore been undertaken to establish whether avoiding particularly allergenic foods during pregnancy has an impact on the development of food allergy in their offspring, but the answer remains unclear. A systematic review (9) and two randomized controlled trials found no benefit from restricting common food allergens among pregnant women (10, 11).

Supplements to modulate the developing immune system are another approach that has received interest. Fish oil supplements may be worthy of further investigation because two randomized controlled trials suggested trends towards reduced sensitization to egg (12, 13), although there was no beneficial impact demonstrated on the development of food allergy (14).

Table 1 Summary of key evidence about prevention strategies

Strategies	Studies (% high quality)	Findings about preventive effects in those at high risk	Findings for normal risk or unselected populations
ANTENATAL STRATEGIES			
Maternal diet	5 (20%)	One systematic review (9) and two randomised trials (10, 11) found **no benefit.**	One study with results from two cohort studies found that different aspects of maternal diet may be associated with an **increased risk** of food allergy. High maternal celery and citrus fruit intake increased sensitization to food in infants (16, 17).
Maternal fish oil supplements	2 (50%)	Two randomised trials suggested a **preventive effect** against egg sensitization (12, 13).	
Maternal probiotic supplements	1 (100%)	One randomised trial found a **benefit** for sensitization, but was inconclusive overall (15).	
STRATEGIES TARGETING BREASTFEEDING MOTHERS			
Diet when breastfeeding	2 (0%)	Two non-randomised comparisons found **no evidence** of a protective effect for food allergy (20, 21).	
Probiotics when breastfeeding	1 (100%)	One randomised trial found **no protective effect** (22).	
Fish oil when breastfeeding	3 (67%)		One systematic review (23) and two randomised trials found **no good evidence of a benefit** (24, 25).
STRATEGIES TARGETING INFANTS			
Breastfeeding	11 (9%)	One systematic review found that most studies of breastfeeding in those at high risk identified a protective **benefit** (1). Two cohort studies suggested no benefit and that exclusively breastfeeding may even increase the risk of food allergy (28, 29).	One systematic review (1) and three cohort studies found that breastfeeding was associated with a **reduced risk** of sensitization or food allergy (58-60), three cohort studies suggested an increased risk (61-63) and three cohorts found no association (64-66).
Alternatives to cows' milk formula	18 (44%)	Two systematic reviews and four randomised trials found a **benefit** from extensively hydrolysed whey or casein formula, (1, 30-33) though one study found no benefit (34). Two systematic reviews two randomised trials and two non-randomised comparisons found a **benefit** from partially hydrolysed formula compared to cows' milk formula (36-41). One randomised trial and one non-randomised study found no effect (34, 35). One systematic review (36) and two randomised trials found no benefit from soy-based formula (43, 44).	
Infant prebiotic supplements	2 (50%)		One systematic review found **insufficient evidence** (67) and one trial found no benefits (68).
Infant probiotic supplements	7 (86%)	Four trials found **no evidence of a benefit** (45-48).	Two systematic reviews (69, 70) and one trial (71) found **no evidence of a benefit**.

Table 1 (continued)

Strategies	Studies (% high quality)	Findings about preventive effects in those at high risk	Findings for normal risk or unselected populations
Other supplements	2 (0%)		One trial and one cohort study found **no evidence** to recommend other supplements (72, 73).
Age at introduction of solid foods	7 (14%)	Two cohort studies found **no benefit** from delaying the introduction of solid foods longer than four months (49, 50).	One systematic review (17) and two cohort studies found **no benefit** of delaying the introduction of solid foods longer than four months (17, 75). Two cohort studies found **reduced food allergy** when solids were introduced earlier than four months (64, 76).
Exposure to food allergens	6 (33%)	One randomised trial found **no benefit** from withholding cows' milk or foods made with cow's milk during the first four months of infancy (51).	One systematic review and one trial found that exposure to cows' milk protein the first days of life **did not alter the risk**, (66, 78) but one trial and one cohort suggested an increased risk of cows' milk allergy (66, 78). One cohort study found that consumption of fish during infancy may protect against food allergy or sensitization (80).
Multifaceted strategies combining changes to environment and diet	9 (33%)	Two randomised trials, two non-randomised comparisons and one cohort study found a **benefit** from combining dietary and environmental strategies (53-57). Two systematic reviews found **insufficient evidence** to make firm recommendations about preventive strategies (83, 84).	
STRATEGIES FOR OLDER CHILDREN AND ADULTS			
Vaccinations	1 (100%)		One systematic review found that BCG vaccinations had **no protective effect** against food allergy (80).
Supplements	2 (50%)		One review found **no benefit** from fish oil supplements (81). One cohort study found that taking vitamins before age five may **protect** against food allergy (82).

There was insufficient evidence about probiotics, with just one inconclusive trial identified about this (15).

Normal-risk families

In unselected populations, one study with results from two cohort studies suggested that what women eat during pregnancy may impact on food sensitization in infants. High maternal celery and citrus fruit intake increased infant sensitization to food (16, 17) but these studies have not been replicated and did not focus on allergy development so there is no strong evidence to recommend changes to the diet of pregnant women to prevent food allergy in infants.

Prevention strategies for breastfeeding mothers

High-risk families

It has been hypothesized that mothers may inadvertently sensitize their children to certain foods through breast milk (18, 19), but there is little evidence that changing what mothers consume when breastfeeding prevents food allergy in infants. Two non-randomized comparisons found that maternal dietary changes while breastfeeding may not prevent food allergies in high-risk infants (20, 21), and one

trial of probiotics found no benefit (22).

Normal-risk families

One systematic review (23) and two randomized controlled trials (24, 25) found no differences in most infant allergy outcomes from fish oil supplements taken by unselected populations of breastfeeding women.

Prevention during infancy

High-risk families

More research has been published about preventive strategies targeting infants. Although breastfeeding is widely promoted and has many other benefits (26, 27), there is insufficient evidence to draw conclusions about its impact on preventing food allergies in high-risk infants. One systematic review identified many studies suggesting a benefit from exclusive and non-exclusive breastfeeding (1); in contrast, however, two cohort studies suggested that extended exclusive breastfeeding may increase the likelihood of sensitization or food allergy in infants at high risk (28, 29).

There is more positive evidence about the benefits of alternatives to cow's milk formula for babies at high risk. Two systematic reviews and three randomized trials suggested that extensively hydrolyzed whey or casein formula may have a protective effect (1, 30-33) although the evidence was conflicting (34).

Partially hydrolyzed infant formula also appears to have a protective effect. Although a small number of studies failed to find any benefit (35), two systematic reviews, two randomized controlled trials and two non-randomized comparisons found that partially hydrolyzed formula may protect against food allergy compared with standard cow's milk formula (36-41). There appeared to be little difference between whey- or casein-based formulations or between partially or extensively hydrolyzed formulas.

There was no evidence to support soy-based formulas. One systematic review (42) and two randomized trials (43, 44) found that soy-based formulas may not protect against food allergies compared to cow's milk formula or other alternatives.

It is also unlikely that probiotic supplements confer preventive benefits during infancy. Four randomized controlled trials found no benefit for preventing food allergy or sensitization (45-48).

Another strategy is to delay the introduction of solid foods. Infants may not need, or may not be physiologically ready to eat, solid foods until after the age of four to six months, but two cohort studies found that delaying the introduction of solid foods longer than four months did not seem to confer any protective benefits (49, 50). Another cohort study found that avoiding cow's milk or foods containing cow's milk for four months had no impact (51).

Although the quality of evidence is low, there is some evidence from six studies to suggest that combining dietary with environmental modifications during infancy may be useful (52-57). Further research in this area is needed because there are few data about specific food allergy outcomes and it is difficult to differentiate cause and effect relationships.

Normal-risk families

The evidence about preventive strategies for infants in unselected populations or those at normal risk is also mixed. One systematic review (1) and three cohort studies found that breastfeeding was associated with a reduced risk of food allergy or sensitization in childhood (58-60), three cohort studies suggested an increased risk (61-63) and three cohort studies found no association in unselected populations (64-66).

There is no evidence to support prebiotics or probiotics to prevent food allergy in unselected or mixed-risk populations. One systematic review (67) found insufficient evidence and one trial found no benefits from prebiotics (68). Two systematic reviews (69, 70) and one randomized trial (71) found no benefit from probiotics in unselected or mixed populations. One randomized trial (72) and one cohort study found no evidence to recommend other supplements (73).

One systematic review (74) and two cohort studies found that introducing solid foods after four months did not protect against food allergy in unselected populations (17, 75). Two cohort studies found reduced food allergy when solids were introduced earlier than four months (64, 76).

Studies have investigated whether exposure to cow's milk proteins in the first three days of life may protect against sensitization to foods. Two randomized controlled trials found that early exposure to cow's milk protein did not alter the risk of food allergy (77, 78), but two cohort studies suggested an increased risk of cow's milk allergy if children in unselected populations were fed cow's milk protein early (28, 66).

There is little other evidence about avoiding potential

food allergens, although one cohort study found that consuming fish during infancy may protect against food allergy or sensitization (79).

Prevention during childhood and adulthood

Very little has been published about strategies to prevent food allergy development in children and adults, and all available studies are in unselected populations. One systematic review found that BCG vaccinations for children had no protective effect against food allergy (80) and another systematic review found no protective benefit from fish oil supplements for children and adults (81). A cohort study found that taking vitamins before age five may protect against food allergy, but the quality of this type of evidence is low (82).

Discussion

Statement of principal findings

This comprehensive and rigorously undertaken review indicates that there is much still to learn about how to prevent the development of food allergy. Overall, the evidence is not strong enough to recommend changing the diet or supplements of pregnant or breastfeeding women at normal or high risk. While breastfeeding may have many other benefits, the evidence in relation to the prevention of food allergy is not strong. This to a large extent reflects the ethical challenges of randomizing infants to a non-breastfeeding arm. There is more evidence about the benefits of alternatives to cow's milk formula for babies at high risk. Extensively hydrolyzed whey or casein formula and partially hydrolyzed formula may have a protective effect, but it appears that soy formula does not protect against food allergies. Probiotics do not seem to be protective in infants at high or normal risk, and neither does delaying the introduction of solid foods until later than the recommended minimum weaning age. Combining dietary with environmental modifications during infancy may be the best way forward for infants at high risk.

Strengths and limitations

This review included the most up to date research about preventing food allergy, with studies from Europe, North America, Asia and Australasia. It was conducted using stringent international standards and drew on a substantially greater evidence base than previous reviews (83, 84).

However, the studies included were heterogeneous, and as a result it was not appropriate to quantitatively synthesize this evidence. The inclusion criteria meant that studies about manifestations of food allergy such as atopic eczema, dermatitis and asthma were not included unless food allergy or sensitization was also studied as an outcome. Furthermore, due to the mixed findings and small evidence base, we were unable to draw conclusions about the comparative benefits and risks of different prevention approaches, or to quantify potential effects.

There are also limitations with the studies themselves. To date, the focus of research has largely been on preventing IgE-mediated food allergy rather than non-IgE-mediated food allergy. Many studies are small, short-term and focus on the surrogate measure of food sensitization rather than food allergy. Sensitization may be a normal, harmless and transitory phenomenon which does not necessarily correlate with allergic disease.

Another issue is the extent to which research provides meaningful information for clinical practice. For example, many infants and young children grow out of their food allergy, especially those who are allergic to cow's milk protein during the first three to five years of life. To provide useful information, studies should include follow-ups from birth at regular intervals during the first years of life, as well as when the children have symptoms suggestive of food allergy. This would help to avoid claims that an intervention makes a difference when any change is merely a function of the natural course of the condition's progression.

Conclusions

Finding ways to prevent the development of food allergy would significantly reduce morbidity and costs of managing this disorder (85). The evidence suggests that some interventions are unlikely to be useful, such as changing the diet or supplements of pregnant or breastfeeding women. However, other strategies appear more promising. There is evidence to support alternatives to cow's milk formula for babies at high risk, although changes to infant diet such as delaying the introduction of solid foods are unlikely to protect against food allergy. Combining environmental with dietary changes is feasible, but there is much work to be done to identify the most effective strategies.

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing this systematic review. We would also like to thank the EAACI Executive Committee for their suggestions.

Funding

EAACI

Contributorship

AS, AM, DdS and GR conceived this review. The review was undertaken by DdS, MG and colleagues at The Evidence Centre. DdS led the drafting of the manuscript and all authors commented on drafts of the manuscript and agreed the final version. SH provided detailed feedback at each stage. This review was undertaken as part of a series managed by SSP and overseen by AS.

Conflicts of interest

K. Grimshaw has received payment for attending and presenting at conferences hosted by Nutricia Ltd. L. O'Mahony has been a consultant to Alimentary Health Ltd. C. Venter has produced educational material for Danone, Mead Johnson and Nestle´ and has received research funding from Thermofischer, Danone and Mead Johnson. The other authors of the paper declare no conflict of interest.

References

1. van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LA *et al.* Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 2003;58:833-843.
2. Muraro A, Dreborg S, Halken S, Høst A, Niggemann B, Aalberse R *et al.* Dietary prevention of allergic diseases in infants and small children. Part II. Evaluation of methods in allergy prevention studies and sensitization markers. Definitions and diagnostic criteria of allergic diseases. *Pediatr Allergy Immunol* 2004;15:196-205.
3. Agostoni C, Decsi T, Fewtrell M, Goulet O, Kolacek S, Koletzko B *et al.* Medical Position Paper. Complementary Feeding: A Commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol and Nutr* 2008;46:99-110.
4. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy ClinImmunol* 2009;123:417-423.
5. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121:183-191.
6. de Silva D, Panesar SS, Thusu S, Rader T, Halken S, Muraro A *et al.* Preventing food allergy: protocol for a rapid systematic review. *Clin Transl Allergy* 2013;3:10.
7. Kemp AS, Ponsonby AL, Dwyer T, Cochrane JA, Pezic A, Jones G. Maternal antenatal peanut consumption and peanut and rye sensitization in the offspring at adolescence. *Clin Exp Allergy* 2011;41:224-231.
8. Chatzi L, Torrent M, Romieu I, Garcia-Esteban R, Ferrer C, Vioque J *et al.* Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax* 2008;63:507-513.
9. Kramer MS, Kakuma R. Maternal dietary allergen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2012;9:CD000133.
10. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SG, Oman H. Effects of maternal diet during late pregnancy and lactation on the development of IgE and egg- and milk-specific IgE and IgG antibodies in infants. *Clin Exp Allergy* 1991;21:195-202.
11. Fälth-Magnusson K, Kjellman NI. Allergy prevention by maternal elimination diet during late pregnancy - a 5 year follow-up of a randomized study. *J Allergy Clin Immunology* 1992;89:709-713.
12. Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddle R, Gibson RA *et al.* Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. *BMJ* 2012; 344: e184.
13. Denburg JA, Hatfield HM, Cyr MM, Hayes L, Holt PG, Sehmi R *et al.* Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. *Pediatric Research* 2005; 57: 276-281.
14. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG *et al.* Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high-risk of atopy: a randomized, controlled trial. *J Allergy ClinImmunol* 2003;112:1178-1184.
15. Huurre A, Laitinen K, Rautava S, Korkeamäki M, Isolauri E. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: a double-blind placebo-controlled study. *Clin Exp Allergy* 2008;38: 1342-1348.
16. Sausenthaler S, Koletzko S, Schaaf B, Lehmann I, Borte M, Herbarth O *et al.* Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clinical Nutrition* 2007;85:530-537.

17. Sausenthaler S, Heinrich J, Koletzko S. Early diet and the risk of allergy: What can we learn from the prospective birth cohort studies GINIplus and LISAplus? *Am J Clinical Nutrition* 2011;94:2012S-2017S.
18. Gamboni SE, Allen KJ, Nixon RL. Infant feeding and the development of food allergies and atopic eczema: An update. *Australas J Dermatol* 2013;54:85-89.
19. Szajewska H. Early nutritional strategies for preventing allergic disease. *Isr Med Assoc J* 2012;14:58-62.
20. Lovegrove JA, Hampton SM, Morgan JB. The immunological and long-term atopic outcome of infants born to women following a milk-free diet during late pregnancy and lactation: a pilot study. *Br J Nutr* 1994;71:223-238.
21. Hattevig G, Kjellman B, Sigurs N, Björkstén B, Kjellman NI. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989;19:27-32.
22. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001; 357:1076-1079.
23. Klemens CM, Berman DR, Mozurkewich EL. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: a systematic review. *BJOG* 2011;118:916-925.
24. Manley BJ, Makrides M, Collins CT, McPhee AJ, Gibson RA, Ryan P *et al.* High-dose docosahexaenoic acid supplementation of preterm infants: respiratory and allergy outcomes. *Pediatrics* 2011;128:e71-e77.
25. Furuhjelm C, Warstedt K, Fagerås M, Fälth-Magnusson K, Larsson J, Fredriksson M *et al.* Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. *Ped Allergy Immunol* 2011;22:505-514.
26. Robinson S, Fall C. Infant nutrition and later health: a review of current evidence. *Nutrients* 2012;4:859-874.
27. Faucher MA. An updated scientific review of the benefits of breastfeeding with additional resources for use in everyday practice. *J Midwifery Womens Health* 2012;57:422-423.
28. Saarinen KM, Juntunen-Backman K, Järvenpää A-L, Kultunen P, Lope L, Renlund M *et al.* Supplementary feeding in maternity hospitals and the risk of cows' milk allergy: A prospective study of 6209 infants. *J Allergy Clin Immunol* 1999;104:457-461.
29. Wetzig H, Schulz R, Diez U, Herbarth O, Viehweg B, Borte M. Associations between duration of breast-feeding sensitization to hens' eggs and eczema infantum in one and two year old children at high-risk of atopy. *Int J Hygiene Env Health* 2000;203:17-21.
30. Hays T, Wood RA. A systematic review of the role of hydrolyzed infant formulas in allergy prevention. *Arch Pediatr Adolesc Med* 2005;159:810-816.
31. Halken S, Hansen KS, Jacobsen HP, Estmann A, Faelling AE, Hansen LG *et al.* Comparison of a partially hydrolyzed infant formula with two extensively hydrolyzed formulas for allergy prevention: a prospective randomized study. *Pediatric Allergy Immun* 2000;11:149-161.
32. Halken S, Høst A, Hansen LG, Østerballe O. Preventive effect of feeding high-risk infants a casein hydrolysate formula or an ultrafiltrated whey hydrolysate formula. A prospective, randomized, comparative clinical study. *Pediatr Allergy Immunol* 1993:4:173–181.
33. Oldaeus G, Anjou K, Björkstén B, Moran JR, Kjellman NI. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. *Arch Dis Child* 1997;77:4-10.
34. Mallet E, Henocq A. Long-term prevention of allergic diseases by using protein hydrolysate formula in at-risk infants. *J Pediatrics* 1992;121(5 Pt 2):S95-S100.
35. de Seta L. Siani P, Cirillo G, Di Gruttola M, Cimaduomo L, Coletta S. The prevention of allergic diseases with a hypoallergenic formula: a follow-up at 24 months. The preliminary results. *Pediatr Med Chir* 1994;16:251-254.
36. Osborn DA, Sinn JKH. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;(4):CD003664.
37. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed whey formula for the prevention of allergic diseases. *Current Med Res Opin* 2010;26:423-437.
38. von Berg A, Filipiak-Pittroff B, Krämer U, Link E, Bollrath C, Brockow I *et al.* Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). *J Allergy Clin Immunology* 2008;121:1442-1447.
39. Vandenplas Y, Hauser B, Van den Borre C, Clybouw C, Mahler T, Hachimi-Idrissi S *et al.* The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. *Eur J Pediatrics* 1995;154:488-494.
40. Chirico G, Gasparoni A, Ciardelli L, De Amici M, Colombo A, Rondini G. Immunogenicity and antigenicity of a partially hydrolyzed cow's milk infant formula. *Allergy* 1997;52: 82-88.
41. D'Agata A, Betta P, Sciacca P, Morano C, Praticò G, Curreri R *et al.* Role of dietary prevention in newborns at risk for atopy. Results of a follow-up study. *Pediatr Med Chir* 1996;18:469-472.
42. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;(4):CD003741.
43. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB *et al.* Effect of a partially hydrolyzed whey infant formula at weaningon risk of allergic disease in high-risk children: A randomized controlled trial. *J Allergy Clin Immunology* 2011;128:360-365.
44. Kjellman NI, Johansson SG. Soy versus cow's milk in infants with a biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years

of age. *Clin Allergy* 1979;9:347-358.

45. Morisset M, Aubert-Jacquin C, Soulaines P, Moneret-Vautrin DA, Dupont C. A non-hydrolyzed fermented milk formula reduces digestive and respiratory events in infants at high-risk of allergy. *Eur J Clin Nutrition* 2011;65:175-183.
46. Kukkonen AK, Savilahti EM, Juntunen-Backman K, Korpela R, Poussa T, Tuure T *et al.* Ovalbumin-specific immunoglobulins A and Glevelsatage 2 years are associated with the occurrence of atopic disorders. *Clin Exp Allergy* 2011;41:1414-1421.
47. Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpela R, Poussa T, Tuure T *et al.* Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol* 2009; 123: 335-341.
48. Marschan E, Kuitunen M, Kukkonen K, Poussa T, Sarnesto A, Haahtela T *et al.* Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. *Clinical Exp Allergy* 2008;38:611-618.
49. Kajosaari M. Atopy prevention in childhood: the role of diet. Prospective 5-year follow-up of high-risk infants with six months exclusive breastfeeding and solid food elimination. *Ped Aller Immun* 1994;5(6 Suppl):26-28.
50. Poysa L, Korppi M, Remes K, Juntunen-Backman K. Atopy in childhood and diet in infancy. A nine-year follow-up study. I. Clinical manifestations. *Allergy Proc* 1991;12:107-111.
51. Merrett TG, Burr ML, Butland BK, Merrett J, Miskelly FG, Vaughan-Williams E. Infant feeding and allergy: 12-month prospective study of 500 babies born into allergic families. *Annals of Allergy* 1988; 61(6 Part II):13-20.
52. Halmerbauer G, Gartner C, Schier M, Arshad H, Dean T, Koller DY *et al.* Study on the prevention of allergy in Children in Europe (SPACE): allergic sensitization in children at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2002;13(Suppl 15):47-54.
53. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007;119:307-313.
54. Halken S, Host A, Hansen LG, Osterballe O. Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. A prospective study of 159 "high-risk" infants. *Allergy* 1992;47:545-553.
55. Bardare M, Vaccari A, Allievi E, Brunelli L, Coco F, de Gaspari GC *et al.* Influence of dietary manipulation on incidence of atopic disease in infants at risk. *Ann Allergy* 1993;71: 366-371.
56. Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years' follow-up. *Acta Paediatr Suppl* 1996;414:1-21.
57. Bruno G, Milita O, Ferrara M, Nisini R, Cantani A, Businco L. Prevention of atopic diseases in high-risk babies (long-term follow-up). *Allergy Proceedings* 1993;14:181-186.
58. Kull I, Melen E, Alm J, Hallberg J, Svartengren M, van Hage M *et al.* Breast-feeding in relation to asthma lung function and sensitization in young school children. *J Allergy Clin Immun* 2010;125:1013-1019.
59. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 year sold. *Lancet* 1995;346:1065-1069.
60. Matheson MC, Erbas B, Balasuriya A, Jenkins MA, Wharton CL, Tang ML *et al.* Breast-feeding and atopic disease: a cohort study from childhood to middle age. *J Allergy Clin Immun* 2007;120:1051-1057.
61. Saarinen KM, Savilahti E. Infant feeding patterns affect the subsequent immunological features in cow's milk allergy. *Clin Exp Allergy* 2000;30:400-406.
62. Pesonen MM, Kallio JT, Ranki A, Siimes MA. Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years. *Clin Exp Allergy* 2006;36:1011-1018.
63. Mihrshahi S, Ampon R, Webb K, Almqvist C, Kemp AS, Hector D *et al.* The association between infant feeding practices and subsequent atopy among children with a family history of asthma. *Clin Exp Allergy* 2007;37:671-679.
64. Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B *et al.* Factors associated with maternal dietary intake, feeding and weaning practices and the development of food hypersensitivity in the infant. *Pediatr Allergy Immunol* 2009;20:320-327.
65. Kramer MS, Matush L, Bogdanovich N, Aboud F, Mazer B, Fombonne E *et al.* Health and development outcomes in 6.5-y-old children breastfed exclusively for 3 or 6 mo. *Am J Clin Nutr* 2009;90:1070-1074.
66. Høst A, Husby S, Osterballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. Incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. *Acta Paediatr Scand* 1988;77:663-670.
67. Osborn DA, Sinn JKH. Prebiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev* 2009;(4):CD006474.
68. Grüber C, van Stuijvenberg M, Mosca F, Moro G, Chirico G, Braegger CP *et al.* Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. *J Allergy Clin Immunol* 2010;126:791-797.
69. Tang LJ, Chen J, Shen Y. Meta-analysis of probiotics preventing allergic diseases in infants. *Zhonghua ErKe ZaZhi* 2012;50:504-509.
70. Osborn DA, Sinn JKH. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev* 2007;(4):CD006475.

71. Prescott SL, Wiltschut J, Taylor A, Westcott L, Jung W, Currie H *et al.* Early markers of allergic disease in a primary prevention study using probiotics: 2.5-Year follow-up phase. *Allergy* 2008;63:1481-1490.

72. Zachariassen G, Faerk J, Esberg BH, Fenger-Gron J, Mortensen S, Christesen HT *et al.* Allergic diseases among very preterm infants according to nutrition after hospital discharge. *Ped Allergy Immunology* 2011;515-520.

73. Kull I, Bergstrom A, Melén E, Lilja G, van Hage M, Pershagen G, Wickman M. Early-life supplementation of vitamins A and D in water-soluble form or in peanut oil and allergic diseases during childhood. *J Allergy ClinImmunol* 2006; 118:1299-1304.

74. Tarini BA, Carroll AE, Sox CM, Christakis DA. Systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease. *Arch Ped Adol Med* 2006;160:502-507.

75. Schoetzau A, Filipiak-Pittroff B, Franke K, Koletzko S, Von Berg A, Gruebl A *et al.* Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. *Pediatr Allergy Immunol* 2002;13:234-242.

76. Joseph CL, Ownby DR, Haversustad SL, Woodcroft KJ, Wegienka G, MacKechnie H *et al.* Early complementary feeding and risk of food sensitization in a birth cohort. *J Allergy Clin Immunology* 2011;127:1203-1210.

77. de Jong MH, Scharp-Van Der Linden VT, Aalberse R, Heymans HS, Brunekreef B. The effect of brief neonatal exposure to cows' milk on atopic symptoms up to age 5. *Arch Dis Child* 2002;86:365-369.

78. Lindfors A, Danielsson TL, Enocksson E, Johansson SG, Westin S. Allergic symptoms up to 4-6 years of age in children given cow milk neonatally. A prospective study. *Allergy* 1992;47:207-211.

79. Kull I, Bergström A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy* 2006;61:1009-1015.

80. Arnoldussen D, Linehan LM, Sheikh A. BCG vaccination and allergy: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2011;127:246-253.

81. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. *Allergy* 2009;64:840-848.

82. Marmsjo K, Rosenlund H, Kull I, Håkansson N, Wickman M, Pershagen G *et al.* Use of multivitamin supplements in relation to allergic disease in 8-y-old children. *Am J Clin Nutrition* 2009;90:1693-1698.

83. Schneider Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al.* Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;303:1848-1856.

84. Schneider Chafen JJ, Newberry S, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al. Prevalence, Natural History, Diagnosis, and Treatment of Food Allergy. A Systematic Review of the Evidence.* Santa Monica, RAND, 2010.

85. Papadopoulos NG, Agache I, Bavbek S, Bilo BM, Braido F, Cardona V *et al.* Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;2:21.

2.2

PRIMARY PREVENTION OF FOOD ALLERGY IN CHILDREN AND ADULTS

EAACI GUIDELINES

A Muraro[1*], S Halken[2*], SH Arshad[3-5], K Beyer[6], AEJ Dubois[7], G Du Toit[8], PA Eigenmann[9], KEC Grimshaw[3], A Hoest[2], G Lack[8], L O'Mahony[10], NG Papadopoulos[11], SS Panesar[12], S Prescott[13], G Roberts[3-5], D de Silva[12], C Venter[4, 14], V Verhasselt[15], AC Akdis[16], A Sheikh[17, 18], on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group

AFFILIATIONS

[1] The Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region. Department of Mother and Child Health - University of Padua. Padua, Italy

[2] Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[3] Clinical and Experimental Sciences Academic Unit, University of Southampton Faculty of Medicine, Southampton, United Kingdom

[4] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, United Kingdom

[5] NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom

[6] Clinic for Pediatric Pneumology & Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany

[7] Department of Pediatric Pulmonology and Paediatric Allergy, University of Groningen, University Medical Centre Groningen, and GRIAC Research Institute, Groningen, the Netherlands.

[8] Department of Paediatric Allergy, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, Division of Asthma, Allergy and Lung Biology, King's College London and Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

[9] Department of Child and Adolescent, Allergy Unit, University Hospitals of Geneva, Switzerland

[10] Swiss Institute of Allergy and Asthma Research, University of Zurich, Switzerland

[11] Institute of Human Development, University of Manchester, UK and Allergy Department, 2nd Pediatric Clinic, University of Athens, Greece

[12] Evidence-Based Health Care Ltd, Edinburgh

[13] University of Western Australia

[14] School of Health Sciences and Social Work, University of Portsmouth, Portsmouth, United Kingdom

[15] Université de Nice Sophia-Antipolis EA 6302 "Tolérance Immunitaire", Hôpital de l'Archet, Nice, France

[16] Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[17] Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Scotland, UK

[18] Division of General Internal Medicine and Primary Care Brigham and Women's Hospital/Harvard Medical School Boston, USA

** Joint first author*

EXPERT PANEL

A Custovic[1], PG Holt[2], S Lau[3], U Nurmatov[4], H Szajewska[5], A von Berg[6], M Wickmann[7]

[1] University of Manchester, Manchester, UK
[2] University of Western Australia, Perth, Australia
[3] Charité University, Berlin, Germany
[4] University of Edinburgh, Edinburgh, UK
[5] Medical University of Warsaw, Warsaw, Poland
[6] Research Institute, Wesel, Germany
[7] Karolinska Institutet, Stockholm, Sweden

Food allergy can have significant effects on morbidity and quality of life and can be costly in terms of medical visits and treatments. There is therefore considerable interest in generating efficient approaches that may reduce the risk of developing food allergy. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Prevention and is part of the EAACI Guidelines for Food Allergy and Anaphylaxis. It aims to provide evidence-based recommendations for primary prevention of food allergy. A wide range of antenatal, perinatal, neonatal and childhood strategies were identified and their effectiveness assessed and synthesized in a systematic review.

Based on this evidence families can be provided with evidence-based advice about preventing food allergy, particularly for infants at high-risk for development of allergic disease. The advice for all mothers includes a normal diet without restrictions during pregnancy and lactation. For all infants exclusive breastfeeding is recommended for at least the first 4-6 months of life. If breastfeeding is insufficient or not possible, infants at high-risk can be recommended a hypoallergenic formula with a documented preventive effect for the first 4 months. There is no need to avoid introducing complementary foods beyond four months, and currently the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after four months once weaning has commenced, irrespective of atopic heredity. There is no evidence to support the use of prebiotics or probiotics for food allergy prevention.

Originally published as: Muraro A, Halken S, Arshad SH, Beyer K, Dubois AEJ, Du Toit G, Eigenmann PA, Grimshaw KEC, Hoest A, Lack G, O'Mahony L, Papadopoulos NG, Panesar S, Prescott S, Roberts G, De Silva D, Venter C, Verhasselt V, Akdis AC, Sheikh A on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group. EAACI Food Allergy and Anaphylaxis Guidelines. Primary prevention of food allergy. *Allergy* 2014;69:590–601. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

Food allergy can have a significant effect on people's morbidity and quality of life, and can be costly in terms of medical visits and treatments (Box 1). Given the morbidity resulting from food allergy, there is considerable scientific, professional and lay interest in approaches that may reduce the risk of developing food allergy. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Prevention and is part of the *EAACI Guidelines for Food Allergy and Anaphylaxis*. These guidelines aim to provide evidence-based recommendations for the primary prevention of food allergy. The primary audience is allergists throughout Europe, but these guidelines are also likely to be of relevance to all other healthcare professionals (e.g. doctors, nurses and pharmacists) in hospitals' primary care and other ambulatory settings.

The causes of food allergy are likely to reflect an interaction between genetic factors and environmental exposure. Genetic factors are currently not modifiable, so strategies to prevent food allergy have tended to focus on early likely exposures to the food proteins most likely to be involved in its pathogenesis. These strategies may be implemented before birth or during breastfeeding, by focusing on the maternal diet, or it may directly target infant nutrition. In addition, there has been a focus on other nutritional factors or supplements that may modify the immune system in a positive direction.

In these guidelines, primary prevention of food allergy is defined as prevention of development of food allergy. A wide range of antenatal, perinatal, neonatal and childhood strategies have been investigated, and the development of the guidelines have been informed by a systematic review of interventions for the primary prevention of food allergy in children and adults (1) (see Chapter 2.1). This systematic review includes only studies with food allergy or food sensitization as outcomes. In instances where there is a lack of clear or consistent evidence, the findings of the literature review have been supplemented with expert consensual opinion. Even though only studies where food allergy or food sensitization was an outcome were included, other possible atopic/allergic symptoms such as atopic dermatitis are also reported. Not all studies reported on confirmed food allergy or sensitization to foods, and some reported food allergy in a combined outcome with other allergies.

Methods

These guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (2, 3). This is a structured approach to guideline production that is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal

Box 1 Key terms

Term	Definition
High risk	In the literature, this is defined as infants / children having at least one parent and/or sibling with a history of allergic disease sometimes also supplemented with an elevated cord blood IgE. Here, we have defined high-risk as having one or two parents and/or older siblings with a history of allergic disease (food allergy, atopic eczema/dermatitis, asthma or allergic rhinitis)
Unselected	Infants and children in an unselected population including families with and without allergic diseases i.e. low risk as well as high risk infants / children
Infancy	In the literature used to describe either first month or first year; here infancy is defined as the first year of life
Children	All age groups of children
Sensitization	A positive skin prick test (SPT) and/or detectable specific IgE (sIgE) irrespective of method or cut-off values and irrespective of clinical reactions
Food allergy	Adverse reaction to a food allergen caused by immunological mechanisms
Proven food allergy	Food allergy documented by controlled elimination / challenge procedures
Prebiotic	Non-digestible substances that provide a beneficial physiological effect for the host by selectively stimulating the favorable growth or activity of a limited number of indigenous bacteria
Probiotic	Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host

of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. We provide below an overview of the approach used.

Clarifying the scope and purpose of the guidelines

This process began in January 2012 with a meeting to discuss the overall approach to guideline development, including detailed discussions on the main aims of the guidelines, the target conditions, clarifying the target populations, to whom the recommendations applied, agreeing the intended end-user group, and ensuring adequate professional and lay representation in the guideline development process.

Ensuring appropriate stakeholder involvement

Participants represented a range of European countries, and disciplinary and clinical backgrounds (including medical secondary care, primary care and nursing), and patient groups. The Prevention Task Force continued to work together over the ensuing 18 months through email discussions, teleconferences and face-to-face meetings.

Systematic review of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree to one key over-arching question (Box 2) that were then pursued through a formal protocol (4) to a systematic review of the evidence (1) (Chapter 2.1). Seven bibliographic databases were searched from their inception to September 30, 2012 for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series and cohort studies. Cohort studies were included due to an inability to randomize with interventions such as breastfeeding. Excluded were reviews, discussion papers, non-research letters and editorials, qualitative studies, case studies, case series and animal studies.

Formulating recommendations

We graded the overall strength and consistency of the evidence to translate the key findings from the systematic review into evidence-linked recommendations (5) (Boxes 3, 4). This involved formulating clear recommendations and making clear the strength of evidence underpinning each recommendation. This ranged from consistent evidence derived from systematic reviews of randomized controlled trials through to evidence derived from expert consensus. Experts identified the resource implications of implementing the recommendations, barriers and facilitators to the implementation of each recommendation, advice on

Box 2 Key over-arching question addressed in the supporting systematic reviews (4)

What is the effectiveness of approaches for the primary prevention of food allergy?

Box 3 Assigning levels of evidence and recommendations (5)

LEVEL OF EVIDENCE	
Level I	Systematic reviews, meta-analysis, randomized control trials
Level II	Two groups, non-randomized studies (e.g. cohort, case-control)
Level III	One-group non-randomized (e.g. be-fore and after, pre test and post test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case-series)
Level V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
GRADES OF RECOMMENDATION	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from Level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level

Box 4 Recommendations for primary prevention of food allergy

Recommendation	Evidence level	Grade	Key references
Exclusive breastfeeding is recommended for all infants for the first 4-6 months	II - III	C	1, 30, 33, 36, 37, 60
Dietary restrictions are not recommended for all pregnant or lactating mothers	I - II	B	1
If breastfeeding is insufficient or not possible: • High-risk infants should receive a hypoallergenic formula with documented preventive effect for the first 4 months. Other infants may receive a standard formula. • After the age of 4 months a standard cow's milk based formula is recommended according to standard nutrition recommendations, irrespective of atopic heredity	I	A –B	1, 47-50, 60
Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity	II – III	C	1
No special dietary restrictions after the age of 4 months for infants with high risk for development of allergic disease No withholding or encouraging exposure to "highly allergenic" foods such as cow's milk, hens egg and peanuts irrespective of atopic heredity, once weaning has commenced	II – III	C	1

approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation (Table E1).

Peer review

A draft of these guidelines were externally peer-reviewed by experts from a range of organizations, countries and professional backgrounds. Additionally the draft guidelines were available on the EAACI website for a three-week period in June 2013 to allow all stakeholders to comment. All feedback was considered by the Prevention Task Force and, where appropriate, final revisions were made according to the feedback received.

Identification of evidence gaps

The process of developing these guidelines has identified a number of evidence gaps (Box 5) and we plan in the future to prioritize the questions that the Prevention Task Force believes should be most urgently addressed.

Editorial independence and managing conflict of interests

The production of these guidelines were funded and supported by EAACI. The funders did not have any influence on the guideline production process, its contents or on the decision to publish. Conflicts of interest statements were completed by all members of the Task Force and these were taken into account by Task Force chair as recommendations were formulated.

Updating the guidelines

We plan to update these guidelines in 2017 unless there are important advances before then.

Challenges in interpreting the evidence

Food allergy is a complex topic because the symptoms are diverse and allergies can manifest in many different forms. In children only around one third of parentally reported food allergy can be confirmed

Box 5 Research gaps

Gaps in the evidence	Plan to address	Priority
The effect of timing of weaning and introduction of different food antigens - while breastfeeding versus while not breastfeeding.	Prospective randomised controlled study with sufficient power and well accepted diagnostic criteria. Probably difficult to address sufficiently, at least in countries with high rate of breastfeeding.	1
The effect of maternal nutrition and environmental exposures during pregnancy and lactation on development of food allergy in the child.	Prospective randomised controlled study with sufficient power and well accepted diagnostic criteria.	2
The preventive effect of different hydrolyzed formulas on food allergy including long-term effects.	Prospective randomised controlled study with sufficient power and well accepted diagnostic criteria. Europe-wide cohort study looking at the ongoing childhood diet and allergy development (e.g. EuroPrevall follow-up, iFAAM)	3
The effect of pre- and probiotics on the incidence and prognosis of food allergy.	Prospective randomised controlled study with sufficient power and well accepted diagnostic criteria.	4

when appropriately investigated. In the population IgE sensitization to foods, as detected by skin prick test (SPT) or presence of specific IgE (sIgE), is not always associated with clinical reactions and food allergy (6-10). Because the diagnostic accuracy is suboptimal when based solely on history and/or sensitization, if possible a food allergy diagnosis needs to be confirmed by controlled elimination and challenge procedures. Unfortunately, most studies on the prevention of food allergy rely on reported reactions or surrogate markers of food allergy such as sensitization to foods (IgE and/or SPT) and disease outcomes e.g. eczema. Moreover, it is important to be aware of the natural course of food allergy, since food allergies develop in the order of exposure to different foods and many children with food allergies, e.g. cow's milk allergy, develop tolerance during the first years of life. It is therefore, important to investigate specific food allergies in the relevant age groups when they experience symptoms suggestive of food allergy, and to investigate the specific food allergens that are relevant to that age group and geographic location. Finally, most studies are not sufficiently powered to detect clinically important reductions in the incidence of food allergy.

There are additional ethical and logistical challenges to be considered when interpreting or undertaking food allergy research in young children and infants. For example, it is not ethical to randomize mothers to breastfeeding and evidence on this topic has therefore been based on high-quality observational studies. However, exclusively breastfed children may not be comparable to others due to self-selection and these mothers may be more motivated to exclusively breastfeed due to family history of allergic problems or early symptoms in their children. Thus, there is a risk of reverse causation, which is not taken into consideration in most studies.

It is important to note that the quality assessment in the systematic review was, in keeping with standard practice, undertaken on methodological grounds, rather than on the clinical relevance or overall validity of the studies. When extracting the relevant evidence for the guidelines it is also important to evaluate the scientific quality and clinical relevance of the studies.

Thus, for these recommendations on primary prevention of food allergy the above mentioned factors have been considered alongside the formal methodological quality assessment, and experimental studies reporting on confirmed food allergy are ranked highest, whereas studies with self-reported food allergy, atopic symptoms (which may represent food allergy) and sensitization as outcomes are included, but were ascribed less weight. Studies reporting only retrospective data were not included due to their high risk of bias.

Primary prevention

Almost all of the studies focused on dietary strategies of some type. The studies can be conceptually divided into those, which target pregnant women (dietary restrictions and supplements), those which target mothers while breastfeeding (dietary restrictions and supplements) and those, which directly target infants (breastfeeding and exclusive breastfeeding, cow's milk formula substitutes, supplements, delaying the introduction of complementary foods and dietary restrictions). Other preventive initiatives included vaccinations and multifaceted strategies combining dietary and environmental changes or targeting both mothers and infants simultaneously.

Almost all of the studies focused on preventing the development of food allergy from an early age, i.e. antenatal and infancy and many studies focused on infants at high-risk of allergic disease.

Antenatal prevention

Overall, there is no evidence to recommend that women modify their diet during pregnancy or take any supplements such as probiotics in order to prevent food allergy in their children (B).

High-risk families

Currently the evidence supporting the role of specific dietary modifications during pregnancy to prevent food allergy in high-risk children is lacking.

A systematic review (11) and two randomized controlled trials (12, 13) found no benefit from restricting common food allergens among pregnant women.

Fish oil supplements may deserve further investigation as two randomized controlled trials suggested trends towards reduced sensitization to egg (14-16).

One trial found that probiotic supplementation during pregnancy among high-risk families reduced allergic sensitization, but there was no evidence specific to food sensitization or food allergy (17).

Unselected families

In an unselected population (Box 1), one cohort study indicated that maternal intake of foods rich in n-6 polyunsaturated fatty acids and allergenic foods during late pregnancy may increase the risk of childhood sensitization, as opposed to foods rich in n-3 polyunsaturated fatty acids. Also high intake of celery and citrus fruits was associated with an increase in food sensitization, but there were no data on food allergy (18).

Prevention strategies for breastfeeding mothers

There is no evidence to recommend that breastfeeding women should modify their diet or take any supplements such as probiotics in order to prevent food allergy in their children (B).

High-risk families

There is no evidence to support intervention strategies for breastfeeding mothers. Two low quality non-randomized comparisons found that maternal dietary changes, i.e. avoidance of the allergenic foods while breastfeeding may not prevent food allergies (19, 20).

One randomized trial found no effect on food sensitization from probiotic supplement during late pregnancy and lactation (21, 22).

Unselected families

One systematic review (23) and two randomized controlled trials (24, 25) found no differences in most allergy outcomes from fish oil supplements taken by unselected populations of breastfeeding women.

Prevention strategies during infancy

Breastfeeding

Breast-feeding has many benefits for mother and child and is therefore recommended for all infants. There is a small amount of evidence to support breastfeeding as a means of preventing the development of food allergy (C).

The immunomodulatory components, e.g. long chain fatty acid content and oligosaccharides in breast milk may differ from one mother to another, making it complex to study the effect of breast milk per se on allergy prevention (26-28).

High-risk families

Although breastfeeding is widely promoted and has many other benefits, there is limited evidence to draw firm conclusions about the benefit for prevention of food allergies in infants at high-risk. One systematic

review (29) found that most studies identified some benefit of breastfeeding on the risk for food allergy and eczema. One randomized trial of preterm infants indicated a lower risk for cow's milk protein allergy in high-risk infants fed human bank milk as compared to preterm or term formula (30). However, a cohort study found that those who were exclusively breastfed for 5 months or more were more likely to be sensitized to eggs at one year, but not at two years; no data on food allergy was included (31). Another study found that breastfeeding for 6 months or longer and introducing solid foods after three months was associated with an increased risk for atopy including food sensitization at five years (32). However, the latter study was a part of a trial including other interventions, which makes it difficult to evaluate the effect of breastfeeding.

Unselected families

The evidence is also mixed in unselected populations. One systematic review (29) and four cohort studies (33-36) found that breastfeeding was associated with a reduced risk of food allergy or sensitization in childhood, three found no association in unselected populations (37-39) but one was not powered for food allergy prevention (37), and another was not targeted at food allergy (39). Furthermore, one cohort study suggested an increased risk for self-reported food allergy in those with high-risk only (40).

Infant formulas as alternatives to breastfeeding

There is evidence to recommend that hypoallergenic hydrolyzed cow's milk based formulas with proven clinical preventive efficacy, are used for infants at high risk, for the first four months, if breastfeeding is insufficient or not possible (B).

High-risk families

There is significant evidence regarding the benefits of hydrolyzed cow's milk formulas for infants. Two systematic reviews (29, 41) and five randomized trials (42-49) suggested that *extensively hydrolyzed whey or casein formulas* might have a protective effect. Although one of those (i.e. the GINI study) was not designed for evaluation of food allergy, it reported on atopic eczema/dermatitis and allergic manifestations including gastrointestinal food allergy (food allergy with manifestations in the gastrointestinal tract), and food sensitization (45, 46). Two other randomized comparisons failed to find a benefit (50, 51). However, in one of these, the children were breastfed for a long period and the formula was introduced after the age of six months (50), which may indicate that the window of opportunity for prevention with hydrolyzed formulas are likely to be restricted to the first six months. Another randomized trial combining extensively hydrolyzed casein based formula with avoidance of some foods for varying periods and maternal diet, also found a benefit of extensively hydrolyzed casein based formula on food allergy until three years of life (47-49), but is difficult to contribute the effect seen to the hydrolyzed formula only. In one of the systematic reviews food allergy were not reported separately, only as part of atopic symptoms (41). The Swedish study (50) reported on symptoms suggestive of food allergy, whereas the others reported on confirmed food allergy.

Partially hydrolyzed infant formula may also have a protective effect. Two systematic reviews (52, 53), two randomized controlled trials (45, 54) and two non-randomized comparisons (55, 56) found that partially hydrolyzed formula may protect against food allergy, and the latter two found that 'food allergy symptoms' or 'sensitization' may be reduced when compared to standard cow's milk formula. As described above, the GINI study (45) reported on eczema and allergic manifestations, including gastrointestinal food allergy, rather than food allergy (45, 46). One randomized trial (57) and one non-randomized comparison (58) failed to find any benefit. However, in one (57) outcomes were only assessed by telephone interview.

A few studies have compared the possible preventive effects of extensively and partially hydrolyzed formulas. They indicate that the preventive efficacy is dependent on the specific formula studied. The degree of hydrolysis alone may not correlate with the efficacy of prevention of food allergy (59), and also different extensively hydrolyzed formulas may have different effects. Thus, an extensively hydrolyzed whey formula used in the GINI study (45) was not effective for prevention, whereas another extensively hydrolyzed whey formula was effective in other studies (42, 43) and extensively hydrolyzed casein formula has been effective in several studies (42, 43, 47, 48, 60). A few studies indicated that some extensively hydrolyzed formulas (based on casein or whey) might have a better preventive effect as compared to partially hydrolyzed whey formula (42) or a blend of casein and whey (44), although a meta-analysis found no significant difference (53).

There was no evidence to support the use of soy-based formulas in allergy prevention. One systematic review (61) and two randomized trials (57, 62) found that soy-based formulas might not protect against food allergies when compared to cow's milk formula or to other alternatives. However, in one of the latter (57) outcome were assessed by telephone interview.

Unselected families

There were no available data, as these studies have not been performed.

Dietary supplements

There is no evidence to recommend pre- or probiotics or other dietary supplements based on particular nutrients to prevent food allergy (B).

Pre- and probiotic supplements

High-risk families

Probiotic supplements have been tested during infancy, but there is little evidence to support their effectiveness. Four randomized controlled trials (63-66) found no benefit against food allergy or sensitization.

Unselected families

There is no evidence to support prebiotics or probiotics to prevent food allergy in unselected or mixed-risk populations. One systematic review (67) found insufficient evidence about the benefits of prebiotics in infant formulas and one randomized trial using a particular blend of neutral oligosaccharides and pectin-derived acidic oligosaccharides (68) found benefit for eczema but not for food sensitization. Two systematic reviews (69, 70) and one randomized trial (71) found no benefit of using probiotics in unselected or mixed populations.

However, different microorganisms have been used in different studies, and it appears that different microbial strains may have different effects, which may explain the inconsistent results as regards a possible preventive effect of specific strains of probiotics.

Other supplements

One randomized trial (72) found no evidence to recommend or avoid cow's milk-based human milk fortifiers in premature infants, though the study may not be powered for food allergy as an outcome. One cohort study (73) found no evidence to recommend or avoid vitamins A and D as water-soluble or in peanut oil.

Introduction of complementary foods

There is insufficient evidence to make specific recommendations about the timing of the introduction of complementary foods and individual solid foods in regards of food allergy prevention for all children (C). However, a few studies indicate that it might be an advantage not to introduce solids before four months of age (C). In addition, other aspects have to be considered, such as the infant's developmental readiness, parental opinion/needs, the nutritional needs and the risk for developing very selective eating habits. Therefore, we recommend introducing complementary foods from 4-6 months of age according to standard local practices and the needs of the infant, irrespective of atopic heredity.

High-risk families

Another strategy has been to delay the introduction of solid foods. Infants may not need or may not be developmentally ready to start eating solid foods until sometime within the age range of 4-6 months, so this period is often considered as an appropriate minimum weaning age. Some studies suggest that introducing solid foods earlier than four months may increase the risk of food sensitization and eczema in infants with a family history of allergy. However, delaying the introduction of solid foods beyond four months does not seem to confer any additional protective benefits. Two low quality cohort studies (74, 75) found no evidence that introducing solid foods after four months in high-risk infants prevented food allergy. This finding is supported by the low prevalence of food allergy in randomized trials on hydrolyzed formulas without delaying introduction of solid foods after 4 - 6 months (42, 43).

Unselected families

One systematic review (76) and two cohort studies (77, 78) found that introducing solid foods after four months did not protect against food allergy; but one of these (77) found that introduction of solid foods before four months increased the risk of later allergy. Two cohort studies found reduced food sensitization

when solids were introduced earlier than four months (37, 79), in the latter only in those at high-risk.

Introduction of potential food allergens

The timing of potential food allergen introduction may be important, but there is insufficient rigorous scientific evidence in this regard; the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods during infancy (B-C). Therefore, for primary prevention we recommend no withholding or encouraging of exposure to "highly allergenic" foods such as cow's milk, hen's egg and peanuts irrespective of atopic heredity, once weaning has commenced.

Two randomized controlled trials (80-82) found that there was no increased risk of food allergy from early exposure to cow's milk protein in the first three days of life, but in one (80, 81) the diagnostic criteria for food allergy were weak and not documented by challenges, while for the other one (82) the symptoms were non-specific and food allergy was not reported. Another randomized trial (83) and one cohort study (36) suggested an increased risk of confirmed cow's milk allergy if children in unselected populations were fed cow's milk protein in the first few days.

There is little additional evidence about avoiding potential food allergens. One cohort study found (84) that consuming fish regularly during the first year of life may protect against food allergy or sensitization.

In a large cross-sectional study, not included in the systematic review because of its design, comparing Israeli and UK Jewish children, the prevalence of peanut allergy was 10-fold higher in the UK than in Israel whereas the median monthly consumption of peanuts in Israeli infants was very high but merely absent in the UK (85). This observation reports an interesting association, which awaits confirmation in further studies (86). Another cross-sectional study with retrospective data on introduction indicated that introduction of egg between 4-6 months might protect against egg allergy (87), but due to the methods, these data needs to be confirmed in other studies.

One recent nested control study, including children from a prospective birth-cohort study, found that children diagnosed with food allergy by two years were introduced solids earlier (≤ 16 weeks) and were less likely to be receiving breast milk when cow's milk protein was first introduced into their diet (88). Thus, introducing potential food allergens while continuing to breastfed may provide a reduced risk for development of food allergy. However, studies using rigorous design methodologies are required to answer this important question with greater certainty.

Combining dietary with environmental modifications

Although the quality of evidence is low, there is some evidence from six studies (89-95) to suggest that combining dietary with different environmental recommendations or modifications, such as reduction of exposure to house dust mite allergens, during infancy for high-risk families may be useful (B). Further research in this area would be helpful because there are few data about specific food allergy outcomes and it is difficult to differentiate cause and effect relationships in the available literature.

Prevention strategies during childhood and adulthood

Very little has been published about strategies to prevent food allergy targeting children and adults, and all available studies are in unselected populations. One systematic review (96) found that Bacillus Calmette–Guérin (BCG) vaccinations had no protective effect against food allergy and another systematic review (97) found no protective benefit from fish oil supplements. A cohort study (98) found that taking vitamins before age five may protect against food allergy, but the quality of evidence is very low (C).

Conclusions and future perspectives

Based on this evidence families can be provided with some practical advice about preventing food allergy, particularly amongst infants at high-risk due to parent and /or older siblings with allergic disease (Box 6). The advice for all mothers includes the consumption of a normal healthy diet without restrictions during pregnancy and lactation. For all infants exclusive breastfeeding is recommended for the first 4-6 months of life. If breastfeeding is insufficient or not possible for the first four months, infants at high-risk can be recommended a hypoallergenic formula

Box 6 Summary of recommendations for primary prevention of food allergy

Recommendations for all infants:

- No special diet during pregnancy or for the lactating mother
- Exclusively breastfeeding for 4 – 6 months

Further recommendations for high-risk infants:

- If supplement is needed during the first 4 months a documented hypoallergenic formula is recommended

Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity

with documented preventive effect for the first 4 months of life. There is no need to avoid introducing complementary foods beyond four months or for infants and children to take supplements such as prebiotics or probiotics. In addition, the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after the age of four months, once weaning has commenced, irrespective of atopic heredity.

Although no cost-effect or cost- benefit analysis has been published, the above recommendations are easy to follow, at low cost and are not detrimental (D). It may be necessary to consider the levels of evidence, as well as the price and the possibility for reimbursement of extra expenses for the different hydrolyzed formulas.

Whilst considering these recommendations, it should be remembered that a lack of evidence for some issues, does not necessarily mean they are not useful, merely that there is yet insufficient proof of a potential benefit. In this regard, there is a need for future studies.

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing these guidelines. We would like to thank Catherine Crowley and Lara Fioravanzo for their assistance in preparing the guidelines. We are grateful to the expert panel for providing expert feedback on the final draft of the paper (Prof Adnan Custovic, Prof Patrick G Holt, Dr. Susanne Lau, Dr. Ulugbek Nurmatov, Prof Hania Szajewska, Prof Andrea von Berg, Prof. Magnus Wickmann). We would also like to thank our EAACI members and the EAACI Executive Committee for their helpful comments and suggestions.

Authors' contribution

Antonella Muraro, Chair of the EAACI Food Allergy and Anaphylaxis Guidelines Initiative, has steered and coordinated the publication. Susanne Halken chaired the guidelines group with support from Arne Høst. Debra de Silva and Sukhmeet Panesar undertook the supporting systematic reviews under the supervision of Aziz Sheikh. All authors participated in the discussion of the systematic review, the evidence table, recommendations, gaps and specific sections and approved the final version.

Conflicts of interest

Susanne Halken has provided scientific advice for ALK-Abello. Antonella Muraro has provided scientific advice for Meda. Tony DuBois has provided scientific advice for ALK-Abello and received funding from ALK Abello to support his research activities. Philippe Eigenmann has provided scientific advice for Danone, Novartis, ALK, DBV technologies and Stallergenes; he has received funding for research activities from LETI, Nestlé and ThermoFisher. Arne Høst has provided scientific advice for ALK-Abello and Danone. Carina Venter has produced educational material for Danone, Mead Johnson and Nestlé and has received research funding from Thermofischer, Danone and Mead Johnson. Debra de Silva, Sukhmeet Panesar and Aziz Sheikh have received funding for coordinating guideline production, and generating the systematic reviews from EAACI. Aziz Sheikh has provided scientific advice to ALK-Abello, Meda, Lincoln Medical, ThermoFisher, Pfizer and Stallargenes; he is on the Anaphylaxis Campaign UK's Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee and the BSACI's Standard of Care Committee. Gideon Lack has no conflict of interests. Kirsten Beyer has received funding for research activities from the European Union, German Research Foundation, Berliner Sparkasse, BEA-Stiftung, Food Allergy and Anaphylaxis Network, Food Allergy Initiative, Danone, ThermoFisher, DST Diagnostics, Allergopharma and has received honoraria or consultation feed from Danone, MedaPharma, ALK-Abelló, Novartis, Unilever, Allergopharma, MedUpDate, ThermoFisher, HAL. Graham Roberts

and Hasan Arshad have provided scientific advice for Danone. Kate Grimshaw has provided scientific advice for Danone. Valérie Verhasselt has received research funding from Nestlé. Liam O'Mahony is a scientific consultant to Alimentary Health Ltd and has received research funding from GSK. George du Toit has received lecture fees from Nutricia and indirectly from the many sponsors of the KCL Allergy Academy. Cesmi A Akdis has received research grants from Allergopharma, Stallergenes, Actellion and Novarti. Besides, Cesmi A Akdis was President (2011-2013), Past President (2013-2015) and ExCom member in EAACI that has received financial support from several relevant business entities.

Reference List

1. de Silva D, Geromi M, Halken S, Host A, Panesar S, Muraro A *et al.* Primary prevention of food allergy in children and adults: systematic review. *Allergy* 2014 Jan 16 doi: 10.1111/all.12334.
2. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care* 2003;12:18-23.
3. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182:E839-E842.
4. de Silva D, Panesar SS, Thusu S, Rader T, Halken S, Muraro A *et al.* Preventing food allergy: protocol for a rapid systematic review. *Clin Transl Allergy* 2013;3:10.
5. Oxford Centre for Evidence-based medicine. Levels of Evidence and Grades of Recommendation. 2013; http://www.cebm.net/ accessed 2nd March 2014.
6. Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr Allergy Immunol* 2006;17:356-363.
7. Kjaer HF, Eller E, Host A, Andersen KE, Bindslev-Jensen C. The prevalence of allergic diseases in an unselected group of 6-year-old children. The DARC birth cohort study. *Pediatr Allergy Immunol* 2008;19:737-745.
8. Kjaer HF, Eller E, Andersen KE, Host A, Bindslev-Jensen C. The association between early sensitization patterns and subsequent allergic disease. The DARC birth cohort study. *Pediatr Allergy Immunol* 2009;20:726-734.
9. Matricardi PM, Bockelbrink A, Beyer K, Keil T, Niggemann B, Gruber C *et al.* Primary versus secondary immunoglobulin E sensitization to soy and wheat in the Multi-Centre Allergy Study cohort. *Clin Exp Allergy* 2008;38:493-500.
10. Matricardi PM, Bockelbrink A, Keil T, Gruber C, Niggemann B, Hamelmann E *et al.* Dynamic evolution of serum immunoglobulin E to airborne allergens throughout childhood: results from the Multi-Centre Allergy Study birth cohort. *Clin Exp Allergy* 2009;39:1551-1557.
11. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2012;9:CD000133.
12. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SG, Oman H. Effects of maternal diet during late pregnancy and lactation on the development of IgE and egg- and milk-specific IgE and IgG antibodies in infants. *Clin Exp Allergy* 1991;21:195-202.
13. Fälth-Magnusson K, Kjellman N-IM. Allergy prevention by maternal elimination diet during late pregnancy. *J Allergy Clin Immunol* 1992;89:709-713.
14. Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddle R, Gibson RA *et al.* Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. *BMJ* 2012;344:e184.
15. Denburg JA, Hatfield HM, Cyr MM, Hayes L, Holt PG, Sehmi R *et al.* Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. *Pediatr Res* 2005;57:276-281.
16. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG *et al.* Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol* 2003;112:1178-1184.
17. Huurre A, Laitinen K, Rautava S, Korkeamaki M, Isolauri E. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: a double-blind placebo-controlled study. *Clin Exp Allergy* 2008;38:1342-1348.
18. Sausenthaler S, Koletzko S, Schaaf B, Lehmann I, Borte M, Herbarth O *et al.* Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clin Nutr* 2007;85:530-537.
19. Lovegrove JA, Hampton SM, Morgan JB. The immunological and long-term atopic outcome of infants born to women following a milk-free diet during late pregnancy and lactation: a pilot study. *Br J Nutr* 1994;71:223-238.
20. Hattevig G, Kjellman B, Sigurs N, Bjorksten B, Kjellman NI. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989;19:27-32.
21. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357:1076-1079.
22. Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease:

4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361:1869-1871.

23. Klemens CM, Berman DR, Mozurkewich EL. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: a systematic review. *BJOG* 2011;118:916-925.
24. Manley BJ, Makrides M, Collins CT, McPhee AJ, Gibson RA, Ryan P *et al.* High-dose docosahexaenoic acid supplementation of preterm infants: respiratory and allergy outcomes. *Pediatrics* 2011;128:e71-e77.
25. Furuhjelm C, Warstedt K, Fageras M, Falth-Magnusson K, Larsson J, Fredriksson M *et al.* Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. *Pediatr Allergy Immunol* 2011;22:505-514.
26. Yu G, Duchen K, Bjorksten B. Fatty acid composition in colostrum and mature milk from non-atopic and atopic mothers during the first 6 months of lactation. *Acta Paediatr* 1998;87:729-736.
27. Sjogren YM, Duchen K, Lindh F, Bjorksten B, Sverremark-Ekstrom E. Neutral oligosaccharides in colostrum in relation to maternal allergy and allergy development in children up to 18 months of age. *Pediatr Allergy Immunol* 2007;18:20-26.
28. Kunz C, Rudloff S. Potential anti-inflammatory and anti-infectious effects of human milk oligosaccharides. *Adv Exp Med Biol* 2008;606:455-465.
29. van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LA *et al.* Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 2003;58:833-843.
30. Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomized prospective study. *BMJ* 1990;300:837-840.
31. Wetzig H, Schulz R, Diez U, Herbarth O, Viehweg B, Borte M. Associations between duration of breast-feeding, sensitization to hens' eggs and eczema infantum in one and two year old children at high risk of atopy. *Int J Hyg Environ Health* 2000;203:17-21.
32. Mihrshahi S, Ampon R, Webb K, Almqvist C, Kemp AS, Hector D *et al.* The association between infant feeding practices and subsequent atopy among children with a family history of asthma. *Clin Exp Allergy* 2007;37:671-679.
33. Kull I, Melen E, Alm J, Hallberg J, Svartengren M, van HM *et al.* Breast-feeding in relation to asthma, lung function, and sensitization in young schoolchildren. *J Allergy Clin Immunol* 2010;125:1013-1019.
34. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995;346:1065-1069.
35. Matheson MC, Erbas B, Balasuriya A, Jenkins MA, Wharton CL, Tang ML *et al.* Breast-feeding and atopic disease: a cohort study from childhood to middle age. *J Allergy Clin Immunol* 2007;120:1051-1057.
36. Høst A, Husby S, Østerballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. *Acta Paediatr Scand* 1988;77:663-670.
37. Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B *et al.* Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Pediatr Allergy Immunol* 2009;20:320-327
38. Kramer MS, Matush L, Vanilovich I, Platt R, Bogdanovich N, Sevkovskaya Z *et al.* Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. *BMJ* 2007;335:815.
39. Kramer MS, Matush L, Bogdanovich N, Aboud F, Mazer B, Fombonne E *et al.* Health and development outcomes in 6.5-y-old children breastfed exclusively for 3 or 6 mo. *Am J Clin Nutr* 2009;90:1070-1074.
40. Pesonen M, Kallio MJ, Ranki A, Siimes MA. Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years. *Clin Exp Allergy* 2006;36:1011-1018.
41. Hays T, Wood RA. A systematic review of the role of hydrolyzed infant formulas in allergy prevention. *Arch Pediatr Adolesc Med* 2005;159:810-816.
42. Halken S, Hansen Skamstrup K, Jacobsen HP, Estmann A, Engberg Fælling A, Hansen LG *et al.* Comparison of a partially hydrolyzed infant formula with two extensively hydrolyzed formulas for allergy prevention: A prospective, randomized study. *Pediatr Allergy Immunol* 2000;11:149-161.
43. Halken S, Høst A, Hansen LG, Østerballe O. Preventive effect of feeding high-risk infants a casein hydrolysate formula or an ultrafiltrated whey hydrolysate formula. A prospective, randomized, comparative clinical study. *Pediatr Allergy Immunol* 993;4:173-181.
44. Oldæus G, Anjou K, Björksten B, Moran JR, Kjellman N-IM. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. *Arch Dis Child* 1997;77:4-10.
45. Von Berg A, Filipiak-Pittroff B, Kramer U, Link E, Bollrath C, Brockow I *et al.* Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). *J Allergy Clin Immunol* 2008;121:1442-1447.
46. Von Berg A, Koletzko S, Grubl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP *et al.* The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol* 2003;111:533-540.
47. Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN *et al.* Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: A randomized study. *J Allergy Clin*

Immunol 1989;84:72-89.

48. Zeiger RS, Heller S, Sampson HA. Genetic and environmental factors affecting the development of atopy through age 4 in children of atopic parents: a prospective randomized controlled study of food allergen avoidance. *Pediatr Allergy Immunol* 1992;3:110-127.
49. Zeiger RS, Heller RS. The development and prediction of atopy in high-risk children: Follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995;95:1179-1190.
50. Odelram H, Vanto T, Jacobsen L, Kjellman N-IM. Whey hydrolysate compared with cow's milk based formula for weaning at about 6 months of age in high allergy-risk infants: effects on atopic disease and sensitization. *Allergy* 1996;51:192-195.
51. Mallet E, Henocq A. Long-term prevention of allergic diseases by using protein hydrolysate formula in at-risk infants. *J Pediatr* 1992;121:S95-100.
52. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;CD003664.
53. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. *Curr Med Res Opin* 2010;26:423-437.
54. Vandenplas Y, Hauser B, Van den Borre C, Clybouw C, Mahler T, Hachimi-Idrissi S *et al.* The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. *Eur J Pediatr* 1995;154:488-494.
55. Chirico G, Gasparoni A, Ciardelli L, De AM, Colombo A, Rondini G. Immunogenicity and antigenicity of a partially hydrolyzed cow's milk infant formula. *Allergy* 1997;52:82-88.
56. D'Agata A, Betta P, Sciacca P, Morano C, Pratico G, Curreri R, et. al. [Role of dietary prevention in newborns at risk for atopy. Results of a follow-up study]. *Pediatr Med Chir* 1996;18:469-472.
57. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB *et al.* Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2011;128:360-365.
58. de Seta L, Siani P, Cirillo G, Di Gruttola M, Cimaduomo L, Coletta S. [The prevention of allergic diseases with a hypoallergenic formula: a follow-up at 24 months. The preliminary results]. *Pediatr Med Chir* 1994;16:251-254.
59. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R *et al.* Dietary prevention of allergic diseases in infants and small children. Part I: immunologic background and criteria for hypoallergenicity. *Pediatr Allergy Immunol* 2004;15:103-111.
60. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R *et al.* Dietary prevention of allergic diseases in infants and small children. Part III: Critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004;15:291-307.
61. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;CD003741.
62. Kjellman NI, Johansson SG. Soy versus cow's milk in infants with a biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years of age. *Clin Allergy* 1979;9:347-358.
63. Morisset M, Aubert-Jacquin C, Soulaines P, Moneret-Vautrin DA, Dupont C. A non-hydrolyzed, fermented milk formula reduces digestive and respiratory events in infants at high risk of allergy. *Eur J Clin Nutr* 2011;65:175-183.
64. Kukkonen AK, Savilahti EM, Haahtela T, Savilahti E, Kuitunen M. Ovalbumin-specific immunoglobulins A and G levels at age 2 years are associated with the occurrence of atopic disorders. *Clin Exp Allergy* 2011;41:1414-1421.
65. Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpela R, Poussa T, Tuure T *et al.* Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol* 2009;123:335-341.
66. Marschan E, Kuitunen M, Kukkonen K, Poussa T, Sarnesto A, Haahtela T *et al.* Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. *Clin Exp Allergy* 2008;38:611-618.
67. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. *Cochrane Database Syst Rev* 2013;3:CD006474.
68. Gruber C, van Stuijvenberg M, Mosca F, Moro G, Chirico G, Braegger CP *et al.* Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. *J Allergy Clin Immunol* 2010;126:791-797.
69. Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev* 2007;CD006475.
70. Tang LJ, Chen J, Shen Y. [Meta-analysis of probiotics preventing allergic diseases in infants]. *Zhonghua Er Ke Za Zhi* 2012;50:504-509.
71. Prescott SL, Wiltschut J, Taylor A, Westcott L, Jung W, Currie H *et al.* Early markers of allergic disease in a primary prevention study using probiotics: 2.5-year follow-up phase. *Allergy* 2008;63:1481-1490.
72. Zachariassen G, Faerk J, Esberg BH, Fenger-Gron J, Mortensen S, Christesen HT *et al.* Allergic diseases among very preterm infants according to nutrition after hospital discharge. *Pediatr Allergy Immunol* 2011;22:515-520.
73. Kull I, Bergstrom A, Melen E, Lilja G, van Hage M, Pershagen G *et al.* Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood. *J Allergy Clin Immunol* 2006;118:1299-1304.
74. Kajosaari M. Atopy prevention in childhood: the role of

diet. Prospective 5-year follow-up of high-risk infants with six months exclusive breastfeeding and solid food elimination. *Pediatr Allergy Immunol* 1994;5:26-28.

75. Poysa L, Korppi M, Remes K, Juntunen-Backman K. Atopy in childhood and diet in infancy. A nine-year follow-up study. I. Clinical manifestations. *Allergy Proc* 1991;12:107-111.
76. Tarini BA, Carroll AE, Sox CM, Christakis DA. Systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease. *Arch Pediatr Adolesc Med* 2006;160:502-507.
77. Sausenthaler S, Heinrich J, Koletzko S. Early diet and the risk of allergy: what can we learn from the prospective birth cohort studies GINIplus and LISAplus? *Am J Clin Nutr* 2011;94:2012S-2017S.
78. Schoetzau A, Filipiak-Pittroff B, Franke K, Koletzko S, Von Berg A, Gruebl A *et al.* Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. *Pediatr Allergy Immunol* 2002;13:234-242.
79. Joseph CL, Ownby DR, Havstad SL, Woodcroft KJ, Wegienka G, MacKechnie H *et al.* Early complementary feeding and risk of food sensitization in a birth cohort. *J Allergy Clin Immunol* 2011;127:1203-1210.
80. de Jong MH, Scharp-Van Der Linden VT, Aalberse R, Heymans HS, Brunekreef B. The effect of brief neonatal exposure to cows' milk on atopic symptoms up to age 5. *Arch Dis Child* 2002;86:365-369.
81. de Jong MH, Scharp-van der Linden VTM, Aalberse RC, Oosting J, Tijssen JGP, de Groot CJ. Randomised controlled trial of brief neonatal exposure to cow's milk on the development of atopy. *Arch Dis Child* 1998;79:126-130.
82. Lindfors ATB, Danielsson L, Enocksson E, Johansson SGO, Westin S. Allergic symptoms up to 4-6 years in children given cow milk neonatally. A prospective study. *Allergy* 1992;47:207-211.
83. Saarinen KM, Juntunen-Backman K, Järvenpää A-L, Kultunen P, Lope L, Renlund M *et al.* Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: A prospective study of 6209 infants. *J Allergy Clin Immunol* 1999;104:457-461.
84. Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy* 2006;61:1009-1015.
85. du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR *et al.* Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-991.
86. du Toit G, Roberts G, Sayre PH, Plaut M, Bahnson HT, Mitchell H *et al.* Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol* 2013;131:135-143.
87. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN *et al.* Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010;126:807-813.
88. Grimshaw KE, Maskell J, Oliver EM, Morris RC, Foote KD, Mills EN *et al.* Introduction of Complementary Foods and the Relationship to Food Allergy. *Pediatrics* 18-11-2013.
89. Halmerbauer G, Gartner C, Schierl M, Arshad H, Dean T, Koller DY *et al.* Study on the Prevention of Allergy in Children in Europe (SPACE): allergic sensitization at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2003;14:10-17.
90. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007;119:307-313.
91. Scott M, Roberts G, Kurukulaaratchy RJ, Matthews S, Nove A, Arshad SH. Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. *Thorax* 2012;67:1046-1051.
92. Halken S, Høst A, Hansen LG, Østerballe O. Effect on an allergy prevention programme on incidence of atopic symptoms in infancy. A prospective study of 159 "high risk" infants. *Allergy* 1992;47:545-553.
93. Bardare M, Vaccari A, Allevie E, Brunelli L, Coco F, de Caspari GC *et al.* Influence of dietary manipulation on incidence of atopic disease in infants at risk. *Ann Allergy* 1993;71:366-371.
94. Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and enviromental prevention programme on the incidence of allergic symptoms in high risk infants: three years follow-up. *Acta Paediatr* 1996;85:1-22.
95. Bruno G, Milita O, Ferrara M, Nisini R, Cantani A, Businco L. Prevention of atopic diseases in high risk babies (long-term follow-up). *Allergy Proc* 1993;14:181-186.
96. Linehan MF, Nurmatov U, Frank TL, Niven RM, Baxter DN, Sheikh A. Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis. *J Allergy Clin Immunol* 2013; pii: S0091-6749:01265-01267
97. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. *Allergy* 2009;64:840-848.
98. Marmsjo K, Rosenlund H, Kull I, Hakansson N, Wickman M, Pershagen G *et al.* Use of multivitamin supplements in relation to allergic disease in 8-y-old children. *Am J Clin Nutr* 2009;90:1693-1698.

Appendix

Barriers and facilitators to implementation, audit criteria and resource implications of recommendations

<table>
<tr><td colspan="3" rowspan="2">Exclusive breastfeeding is recommended for all infants for the first 4-6 months</td><td>Barriers to implementation</td><td>Lack of support at the nursery, from family and friends
Lack of maternity leave</td></tr>
<tr><td>Facilitators to implementation</td><td>Breastfeeding is a general recommendation for nutrition of infants and young children
Human milk provides the nutritional needs for normal children until the age of 4-6 months
Very few contraindications to breastfeeding
It is easy and cheap</td></tr>
<tr><td>Evidence level</td><td>Grade</td><td>Key references</td><td rowspan="2">Audit criteria</td><td rowspan="2">≥ 75 % of all infants are breastfed for ≥ the first 4 months</td></tr>
<tr><td>II-III</td><td>C</td><td>1, 30, 33, 36, 37, 60</td></tr>
<tr><td colspan="3" rowspan="2">No dietary restrictions for all pregnant or the lactating mother for allergy preventive purposes</td><td>Barriers to implementation</td><td>Should be none</td></tr>
<tr><td>Facilitators to implementation</td><td>It is not an intervention, but normal unrestricted diet for women</td></tr>
<tr><td>Evidence level</td><td>Grade</td><td>Key references</td><td rowspan="2">Audit criteria</td><td rowspan="2">All pregnant and lactating women should have no dietary restriction to prevent allergy in their children</td></tr>
<tr><td>I-II</td><td>B</td><td>1</td></tr>
<tr><td colspan="3" rowspan="2">If breastfeeding is insufficient or not possible:
• High-risk infants should receive a hypoallergenic formula with documented preventive effect for the first 4 months. Other infants may receive a standard formula.
• After the age of 4 months a standard cow's milk based formula is recommended according to standard nutrition recommendations, irrespective of atopic heredity</td><td>Barriers to implementation</td><td>Limited access to documented hypoallergenic formulas with documented preventive effect
Costs for hypoallergenic formulas with documented preventive effect</td></tr>
<tr><td>Facilitators to implementation</td><td>It is a very little restrictive intervention
Limited need for hypoallergenic formula in breastfed children</td></tr>
<tr><td>Evidence level</td><td>Grade</td><td>Key references</td><td rowspan="2">Audit criteria</td><td rowspan="2">≥ 75 % high risk infants are breastfed for ≥ 4 months
≥ 75 % high risk infants have documented hypoallergenic formula if needed in the first 4 months
≥ 75 % high risk infants ≥ 4 month are offered normal and adequate nutrition without restrictions for preventive purposes</td></tr>
<tr><td>I</td><td>A-B</td><td>1, 47-50, 60</td></tr>
<tr><td colspan="3" rowspan="2">Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity</td><td>Barriers to implementation</td><td>Little, if any
Misleading advice</td></tr>
<tr><td>Facilitators to implementation</td><td>This is normal nutritional practice adequate for the particular age</td></tr>
<tr><td>Evidence level</td><td>Grade</td><td>Key references</td><td rowspan="2">Audit criteria</td><td rowspan="2">≥ 90% of all infants and children avoid unnecessary dietary restrictions</td></tr>
<tr><td>II-III</td><td>C</td><td>1</td></tr>
<tr><td colspan="3" rowspan="2">No special dietary restrictions after the age of 4 months for infants with high risk for development of allergic disease
No withholding or encouraging exposure to "highly allergenic" foods such as cow's milk, hens egg and peanuts irrespective of atopic heredity, once weaning has commenced</td><td>Barriers to implementation</td><td>Little if any
Misleading advice</td></tr>
<tr><td>Facilitators to implementation</td><td>This is normal nutritional practice adequate for the particular age</td></tr>
<tr><td>Evidence level</td><td>Grade</td><td>Key references</td><td rowspan="2">Audit criteria</td><td rowspan="2">≥ 90% of all infants and children avoid unnecessary dietary restrictions</td></tr>
<tr><td>II-III</td><td>C</td><td>1</td></tr>
</table>

SECTION 3

QUALITY OF LIFE IN FOOD ALLERGY

3.1

DISEASE-SPECIFIC HEALTH-RELATED QUALITY OF LIFE INSTRUMENTS FOR IgE-MEDIATED FOOD ALLERGY

SYSTEMATIC REVIEW

SA Salvilla[1], AEJ Dubois[2], BMJ Flokstra-de Blok[3], SS Panesar[1], A Worth[1], S Patel[4], A Muraro[5], S Halken[6], K Hoffmann-Sommergruber[7], A DunnGalvin[8], JO B'Hourihane[8], L Regent[9], NW de Jong[10], G Roberts[11-13], A Sheikh[1, 14], on behalf of the EAACI Food Allergy & Anaphylaxis Guidelines Group

On behalf of the EAACI Food Allergy and Anaphylaxis Group: C Bindslev-Jensen, V Cardona, P Eigenmann, N Papadopoulos, B Vlieg–Boerstra, CA Akdis

AFFILIATIONS

[1] Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, UK

[2] University of Groningen, University Medical Center Groningen, Department of Pediatric Pulmonology and Pediatric Allergy, and GRIAC Research Institute, Groningen, the Netherlands

[3]University of Groningen, University Medical Centre Groningen, Department of General Practice, GRIAC Research Institute, Groningen, The Netherlands;

[4]St. George's University, London, UK

[5]Padua General University Hospital, Padua, Italy

[6]Odense University Hospital, Odense C, Denmark

[7]Department of Pathophysiology and Allergy Research, Medical University of Vienna, Austria

[8]Department of Paediatrics and Child Health, University College, Cork, Ireland

[9]The Anaphylaxis Campaign, Farnborough, UK

[10]Dept. of Internal Medicine, section Allergology, ErasmusMC, Rotterdam, the Netherlands

[11]David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[12]NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[13]Human Development and Health and Clinical and Experimental Sciences Academic Units, University of Southampton, Faculty of Medicine, Southampton, UK

[14]Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA

***Background**: This is one of seven inter-linked systematic reviews undertaken on behalf of the European Academy of Allergy and Clinical Immunology as part of their Guidelines for Food Allergy and Anaphylaxis, which focuses on instruments developed for IgE-mediated food allergy. Disease-specific questionnaires are significantly more sensitive than generic ones in measuring the response to interventions or future treatments, as well as estimating the general burden of food allergy. The aim of this systematic review was therefore to identify which disease-specific, validated instruments can be employed to enable assessment of the impact of, and investigations and interventions for, IgE-mediated food allergy on health-related quality of life.*

***Methods**: Using a sensitive search strategy, we searched seven electronic bibliographic databases to identify disease-specific quality of life tools relating to IgE-mediated food allergy.*

***Results**: From the 17 eligible studies, we identified seven disease-specific health-related quality of life instruments, which were then subjected to detailed quality appraisal. This revealed that these instruments have undergone formal development and validation processes, and have robust psychometric properties, and therefore provide a robust means of establishing the impact of food allergy on quality of life.*

***Conclusions**: Suitable instruments are now available for use in children, adolescents, parents/caregivers, and adults. Further work must continue to develop a clinical minimal important difference for food allergy, and for making these instruments available in a wider range of European languages.*

Originally published as: Salvilla SA, Dubois AEJ, Flokstra-de Blok BMJ, Panesar SS, Worth A, Patel S, Muraro A, Halken S, Hoffmann-Sommergruber K, DunnGalvin A, B'Hourihane JO, Regent L, de Jong NW, Roberts G, Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Group. Disease-specific health-related quality of life instruments for IgE-mediated food allergy. *Allergy* 2014; DOI: 10.1111/all.12427. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

The term 'food allergy' refers to the sub-group of food-triggered reactions in which immunologic mechanisms have been implicated, whether IgE (Immunoglobulin E)-mediated, non-IgE-mediated, or involving a combination of IgE- and non-IgE-mediated etiologies (1). This review focuses on food allergy that is likely to have an IgE-mediated etiology.

Living with a food allergy is more difficult than is generally appreciated (2). Long-term management is focused on the avoidance of the food(s) that trigger the allergic reactions, which in turn places a psychological burden on patients and carers that can result in stress and anxiety. There is, in addition, often further anxiety relating to the burden of managing acute reactions – particularly if the decision to administer adrenaline (epinephrine) also falls on the patient and/or carer (3–6). In some cases, this can have a considerable impact on the day-to-day lives of patients and carers (7).

The importance of measuring health-related quality of life (HRQL) in patients is that such measurement allows for the estimation of the impact of the disease from a patient perspective; this is important because it is possible for two individuals with clinically similar disease severity to experience very different degrees of impairment in their everyday lives (8).

HRQL can be measured using generic or disease-specific questionnaires. Useful attributes of generic quality of life (QOL) questionnaires are that they allow comparison between different diseases as well as being sensitive to co-morbidities. However, associated limitations of generic instruments include the fact that they are less sensitive and responsive to change than disease-specific instruments, hence potentially important differences or changes may be missed. This is particularly relevant in the context of food allergy, where, unless individuals are exposed to the specific food, they may have no symptoms or problems other than the anxiety resulting from the need for continued avoidance (9). The disease-specific questionnaires that have been developed are significantly more sensitive in measuring the response to interventions or future treatments as well as estimating the general burden of food allergy (10).

This systematic review is one of seven inter-linked evidence syntheses that has been undertaken in order to provide a state-of-the-art synopsis of the current evidence base in relation to epidemiology, prevention, diagnosis and clinical management and impact on QOL. This will be used to inform clinical recommendations in the *EAACI Guidelines for Food Allergy and Anaphylaxis*. This review will consider only instruments developed for IgE-mediated food allergy.

Aims

We sought to identify which disease-specific, validated instruments can be employed to enable assessment of the impact of, and the effect of investigations and interventions for, food allergy on HRQL.

Methods

Registration and protocol

This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/prospero/) and has the reference number CRD42013003710. Detailed information on our methods, including the search strategy, study selection, quality assessment strategy, analysis, data synthesis and reporting have been reported in advance in our published protocol (11). We provide a brief synopsis of our methods below.

Search strategy

A sensitive search strategy was designed to retrieve all articles combining the concepts of food allergy, QOL and patient-reported outcomes from electronic bibliographic databases. The search strategy was devised on OVID MEDLINE and then adapted for the other databases (see Data E1 for full search strategies). In all cases, the databases were searched from January 1, 1990 to September 30, 2012. Our rationale for searching from 1990 onwards was that this marked the first publication of key allergy HRQL instruments such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Asthma Quality of Life Questionnaire (AQLQ) (12, 13).

Inclusion and exclusion criteria

We specified that the disease-specific HRQL questionnaire must have been specifically designed for use with patients and carers with food allergy. Any articles relating to the description, development and/or the validation of the above identified HRQLs were also eligible for inclusion. Excluded studies included

reviews, discussion papers, non-research letters, editorials, case studies and case series.

Study selection

The titles were checked independently by two reviewers (SAS and SSP) according to the selection criteria and categorized as: included, not included and unsure. For those papers in the unsure category, we retrieved the abstract and re-categorized. Any discrepancies were resolved by consensus and, if necessary, a third reviewer (AS) was consulted to arbitrate. Full text copies of potentially relevant studies were obtained and their eligibility for inclusion independently assessed.

Quality assessment strategy

We assessed the development of the instruments identified and their performance properties including: validity; generalizability; responsiveness; managing missing data; how variation in patient demography was managed; and cross-cultural and linguistic adaptation, using a previously reported quality assessment tool (14). Assessment of validity focused on identification of appropriate independent measures and their correlation with partial or total instrument scores. A team of researchers (SAS and SSP) independently assessed the articles against the defined criteria and any discrepancies were resolved by consensus and, if necessary, a third reviewer (AS) was consulted.

Analysis, data synthesis and reporting

Data were independently extracted onto a customized data extraction sheet by two reviewers (SAS and SSP), and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (AS). A descriptive summary with data tables was produced to summarise the literature. Quantitative pooling of data was not meaningful in the context of this review so a narrative synthesis of the data was undertaken.

Results

Study selection

The electronic database searches identified 1255 papers of potential interest. Seventeen studies met the inclusion criteria. The most frequent reason for exclusion was that the questionnaire was not a disease-specific HRQL instrument, was not validated or was inadequately validated (Figure 1).

From the 17 studies, seven disease-specific HRQL instruments were identified for food allergy as requiring full quality appraisal. Further details are found in Table 1. Four subtypes were identified: those to be completed by adults, adolescents, older children, and parent or caregiver. The characteristics of each of the HRQLs are presented in Table 2, a summary of their development is detailed in Table 3 and the psychometric properties of these instruments are summarised in Table 4.

Food allergy disease-specific HRQL for children

Food Allergy Quality of Life Questionnaire Child Form (FAQLQ-CF)

The food allergy QOL questionnaire child form (FAQLQ-CF) was developed as the first disease-specific HRQL questionnaire for food allergic children that can be self-administered, originally in the Dutch language. Four papers were reviewed for the development and validation of the FAQLQ-CF in this review (9, 10, 15-16).

The intended population was for children aged 8 to12 years and is a self-report; it contains 24 items and four domains. This instrument was developed as part of the EuroPrevall project, a European multi-centre research project on food allergy, to cover all age groups of patients with food allergy.

The FAQLQ-CF was developed following item generation and item reduction (12-14, 17). Cross-sectional validity was assessed through evaluation of its construct validity, convergent and discriminant validity, discriminative ability and reliability. Food Allergy Independent Measure (FAIM), a disease-specific objective instrument, was developed for the validation of the FAQLQ and included four expectation of outcome (EO) questions and two independent measure (IM) questions (18, 19). One study demonstrated moderate correlation between FAQLQ-CF and FAIM (rho = 0.60, p =<0.001) (9) and two studies showed similar internal consistency (Cronbach's α = 0.94 – 0.95) (7, 20). The instrument also demonstrated that it could discriminate between children who differed in number of food allergies (> 2 food allergies versus ≤ 2 food allergies, total FAQLQ-CF score 4.3 versus 3.6, p = 0.036). However, FAQLQ-CF could not discriminate between reported anaphylaxis or not (4.2 versus 3.9, p = 0.315) (9).

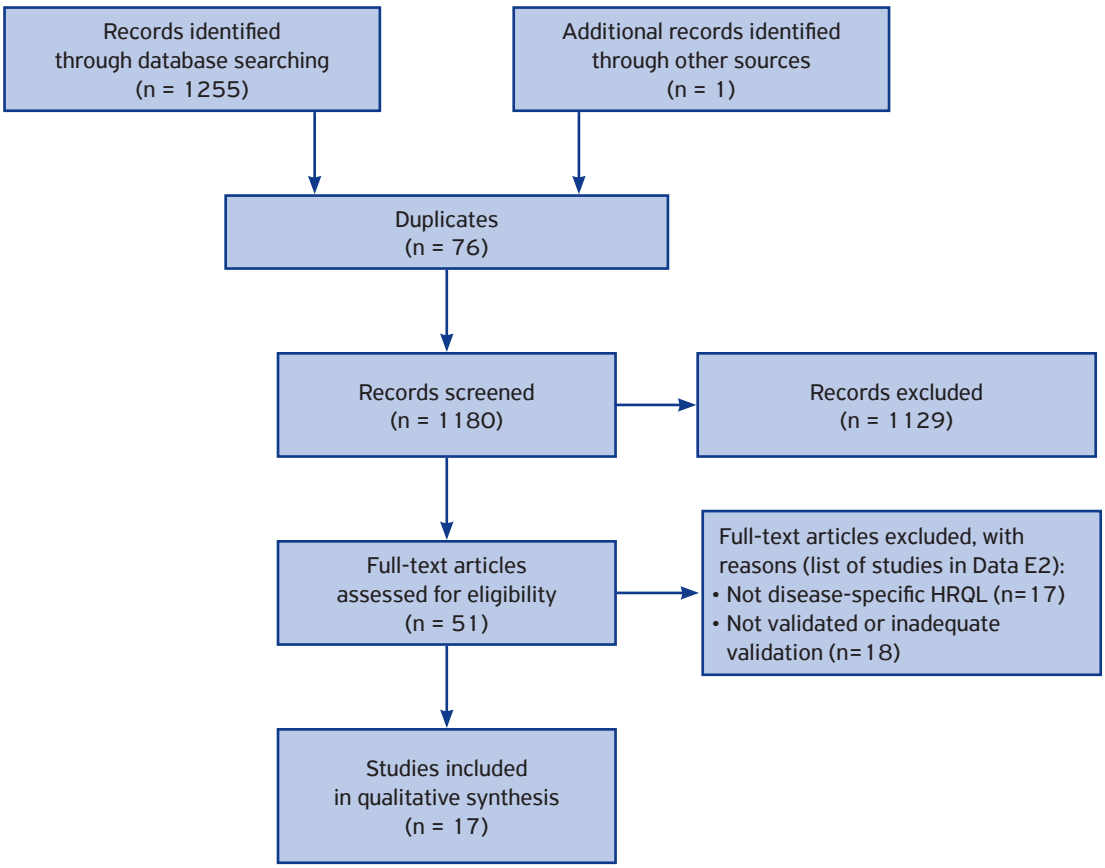


Figure 1 PRISMA flow diagram showing the study identification process. The diagram shows the process we followed to identify relevant studies, and the number of studies that were included or excluded at each stage

Table 1 Disease-specific HRQL instruments

Abbreviation (where stated)	Full name
CHILDREN	
FAQLQ-CF (9, 10, 15, 16)	Food Allergy Quality of Life Questionnaire Child Form
ADOLESCENT	
FAQLQ-TF (10, 20, 21)	Food Allergy Quality of Life Questionnaire Teenager Form
FAQL-teen (22)	Food Allergy Quality of Life Assessment Tool For Adolescents
You and Your Food Allergy (23)	You and Your Food Allergy
ADULTS	
FAQLQAF (10, 24, 25)	Food Allergy Quality of Life Questionnaire Adult Form
PARENT OR CAREGIVER	
FAQL-PB (19, 26-29)	Food Allergy Quality of Life Parental Burden
FAQLQ-PF (7, 15, 29, 30)	Food Allergy Quality of Life Questionnaire Parent Form

Table 2 Characteristics of included instruments

Instrument	Aim of the study and target population	No. items/domain	Mode of administration	Time to complete	Original language	Language available in
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR CHILDREN						
FAQLQ-CF (9, 10, 15, 16)	To develop and validate the Food Allergy Quality of Life Questionnaire – Child Form (FAQLQ-CF) Intended population: Children aged 8–12 years old	24 items and 4 domains: a- allergen avoidance b- risk of accidental exposure c- emotional impact d- dietary restrictions	Self-administered by children	Not published	Dutch	French Dutch English
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR ADOLESCENT						
FAQLQ-TF (10, 20, 21)	To develop and validate the Food Allergy Quality of Life Questionnaire – Teenager Form (FAQLQ-TF) Intended population : Adolescents aged 13-17 years old	28 items and 3 domains: a- dietary restrictions b- emotional impact c- risk of accidental exposure	Self-administered by adolescents	Not published	Dutch	Dutch English
FAQL-teen (9)	To develop a validated Food Allergy Quality of Life assessment tool for US adolescents (FAQL-teen) Intended population: Adolescents aged 13-19 years old	17 items. Domains not mentioned	Self-administered by adolescents	Not published	English	English
You and Your Food Allergy (23)	To develop and validate a disease-specific HRQL scale for teenagers living in the UK with food hypersensitivity (FHS). Intended population: Teenagers aged 13-18 years old	34 items and 5 domains: a- social well-being and independence b- support c- day-to-day activities d- family relations e- emotional well-being	Self-administered by adolescents	Not published	English	English
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR ADULTS						
FAQLQ-AF (10, 24, 25)	To report the development and cross-sectional validation of the first disease-specific HRQL questionnaire for adults with food allergy. Intended populations: Adults over 18 years old with food allergy excluding those with oral allergy syndrome	29 items and 4 domains: a- dietary restrictions b- emotional impact c- risk of accidental exposure d- food allergy-related health	Self-administered by adults	Not published	Dutch	Dutch English
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR PARENT OR CAREGIVER						
FAQL-PB (18, 26-29)	To create a validated, food allergy-specific HRQL instrument to measure parental burden associated with having a child with food allergy Intended population: Parents of children ≤17 years old	17 items and 3 domains: a- going on vacation b- social activities c- worries and anxieties	Self-administered by parents	Not published	English	Chinese English
FAQLQ-PF (7, 15, 29, 30)	To develop a sensitive, multi-dimensional measure to assess parental perception of the child's HRQL. Intended population: Parents of children aged 0–12 years old	30 items and 3 domains: a- emotional impact b- food-related anxiety c- social and dietary limitations	Self-administered by parents	Not published	Dutch	French Dutch English

Table 3 Summary of development properties of included HRQL instruments

Instrument	Pre-study hypothesis	Intended population	Actual content area (face validity)	Item identification	Item selection	Uni-dimensionality	Response scale	Scoring	Instrument translated and validated in English speaking population
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR CHILDREN									
FAQLQ-CF (9, 10, 15, 16)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR ADOLESCENTS									
FAQLQ-TF (10, 20, 21)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓
FAQL-teen (22)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓	✓	✓✓
You and Your Food Allergy (23)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓✓
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR ADULTS									
FAQLQ-AF (10, 24, 25)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓✓
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR PARENT OR CAREGIVER									
FAQL-PB (19, 26-29)	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
FAQLQ-PF (7, 15, 29, 30)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓✓

(For definitions refer to Table E2)

Table 4 Summary of psychometric properties of included HRQL instruments

Instrument	Convergent validity	Discriminant validity	Predictive validity	Other evidence for construct validity e.g. criterion, discriminant	Assessment of validity (cross-sectional, longitudinal or both)	Test-re-test agreement	Inter-observer agreement or inter-mode agreement	Person/ item separation reliability	Interpretation	Responsiveness
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR CHILDREN										
FAQLQ-CF (9, 10, 15, 16)	✓✓	✓✓	0	FAIM CHQ-CF87	Cross-sectional	✓✓	✓✓	0	✓	0
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR ADOLESCENTS										
FAQLQ-TF (10, 20, 21)	✓✓	✓✓	0	FAIM CHQ-CF87	Cross-sectional	✓✓	✓✓	0	✓	0
FAQL-teen (22)	✓✓	✓✓	0	PedsQL	Cross-sectional	0	0	0	✓	0
You and Your Food Allergy (23)	✓✓	✓✓	0	PedsQL	Cross-sectional	✓✓	✓✓	0	✓✓	0
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR ADULTS										
FAQLQ-AF (10, 24, 25)	✓✓	✓✓	0	FAIM RAND-36	Cross-sectional	✓✓	✓✓	0	✓	0
FOOD ALLERGY DISEASE-SPECIFIC HRQL FOR PARENT OR CAREGIVER										
FAQL-PB (19, 26-29)	✓✓	✓✓	0	CHQ-PF50	Cross-sectional	✓✓	✓✓	0	✓	0
FAQLQ-PF (7, 15, 29, 31)	✓✓	✓✓	0	FAIM	Both	✓✓	✓✓	0	✓✓	✓✓

(For definitions refer to Table E2)

One of the four studies also evaluated test-retest reliability of the FAQLQ-CF. The intraclass coefficient (ICC) was found to be excellent (ICC = 0.91) (10) and the same study identified the concordance correlation coefficient (CCC) as 0.907, as well as a Bland-Altman plot demonstrating that the mean differences of the test and re-test were close to zero for the FAQLQ-CF (10).

One study validated the French version of instrument. The results demonstrated the converted FAQLQ-CF had good internal consistency (Cronbach's α = 0.67) and a good correlation between FAQLQ-CF and FAIM-CF (r = 0.84) (15). One study identified in this review compared child self-reported and parent-proxy-reported HRQL in food allergic children (8-12 years old). The study assessed the FAQLQ-CF and FAQLQ Parental Form (PF) in Dutch food-allergic child-parent pairs. Child and parent proxy reports were correlated and tested for significant differences, including the comparison of the internal consistency and construct validity. The results demonstrated the correlation coefficient between the total FAQLQ-CF and FAQLQ-PF to be 0.56 (p = <0.001). The ICC was 0.57 (p = <0.001). The Bland-Altman plot showed that the mean between the FAQLQ-CF and FAQLQ-PF score was 1.06 (SD = 1.10) (15).

Food allergy disease-specific HRQL for adolescents

Food Allergy Quality of Life Questionnaire Teenager Form (FAQLQ-TF)

This tool was developed as the first disease-specific HRQL questionnaire for food allergic adolescents, originally in the Dutch language. Three papers were reviewed for the development and validation of the FAQLQ-TF (10, 20, 21).

The intended population included patients aged 13 to17 and is a self-report; it contains 28 items and three domains.

This instrument was developed as part of the EuroPrevall project and followed the development and validation method of the FAQLQ-CF. Assessment demonstrated correlation between FAQLQ-TF and FAIM (ρ = 0.57, p =<0.001) with an internal consistency (Cronbach's α = 0.92). Additionally, the instrument demonstrated that it could discriminate between adolescents who reported two or more food allergies compared to adolescents who only reported one (1 food allergies versus > 2 food allergies, total FAQLQ-TF score 4.3 versus 3.5, p = 0.037). However, FAQLQ-TF could not discriminate between those who did or did not have reported anaphylaxis (4.5 versus 4.0, p = 0.184) (20).

One of the three studies also evaluated the test-re-test reliability of the FAQLQ-TF, which was excellent (ICC = 0.976 and CCC = 0.975). The Bland-Altman plot also illustrated that the mean differences of the test and re-test was close to zero for the FAQLQ-TF (10). Another study identified in this review went on to further compare adolescent self-reported and parent-proxy-reported HRQL of food allergic adolescents and to investigate the factors that may influence any disagreements between the two; this was an area which had not been previously studied (21). This third study assessed the Teenager Form (TF) and Parental Form (PF) of the FAQLQ but also FAIM and brief-illness perception questionnaire (Brief-IPQ). The results comparing FAQLQ-TF and FAQLQ-PF showed that there was moderate correlation (ICC = 0.61, p = <0.001) and no significant difference (3.78 versus 3.56, p = 0.103) between adolescent-self reported and parent-proxy-reported HRQL at group level. The Bland-Altman plot showed relevant differences (exceeding the minimal important difference) for 63% of the adolescent-parent pairs (21).

Food Allergy Quality of Life Assessment Tool for Adolescents (FAQL-teen)

One study was identified which reviewed the development and validation of the FAQL-teen (22). The instrument was developed for adolescents in the United States (US) and the intended population was adolescents aged 13 to 19 years and is a self-report; it contains 17 items, but the domains were not mentioned in the study. The FAQL-teen was developed following guidelines available at the time; validation of the instrument included assessing the internal validity and discriminative ability (22).

This instrument showed strong internal validity (Cronbach's α = 0.90), as well as demonstrating discriminative ability by disease severity; adolescents with a history of anaphylaxis has significantly lower QOL than those without a history of anaphylaxis (mean FAQL-teen score for anaphylaxis was 2.5 versus 2.0 in those without anaphylaxis, p = 0.003). However, discriminative ability was not seen in adolescents with two or fewer food allergies (n = 95, mean score 2.2) versus those with greater than two food allergies (n = 108, mean score 2.5) (22).

You and Your Food Allergy

One study was identified which reviewed the development and validation a disease-specific HRQL scale of teenagers aged 13 to 18 years with food hypersensitivity living in the UK (17). It is a self-report and contains 34 items and five domains.

The HRQL scale was developed in four stages: stage one was the development of a preliminary HRQL scale and stage two involved pre-testing the preliminary scale. Stage three was the testing of the pilot scale to identify problematic items and stage four reduced the number of items in the field test scale to those best measuring HRQL.

The whole scale involved internal consistency (Cronbach's α = 0.92) and the test-re-test reliability (ICC = 0.87) (23). The scale correlated with a generic HRQL scale (PedsQL) and discriminated by disease severity. For the known-groups analysis, there was significant difference between the whole scale scores of those allergic to ≤ 2 foods [mean (s.d) = 71.7(13.1)] and those allergic to >2 foods [mean (s.d) = 67.5 (14.1)]. This supports the scales ability to distinguish between groups hypothesized to have differing HRQL (t = 2.459, df = 287, p <0.05) (23).

Food allergy disease-specific HRQL for adults

Food Allergy Quality of Life Adult Form (FAQLQ-AF)

The food allergy QOL adult form was developed, in Dutch, as the first disease-specific HRQL questionnaire for adults. Three papers were reviewed for the development and validation of the FAQLQ-AF in this systematic review (10, 24, 25). The intended population for the questionnaire was patients over the age of 18 years and is a self-report; it contains 29 items and four domains.

This instrument was developed as part of the EuroPrevall project and followed the development and validation method of the FAQLQ-CF and –TF. This instrument was the last of the HRQL questionnaires, in a series of questionnaires developed in the EuroPrevall project. The FAQLQ-AF was developed following item generation and item reduction (12-14, 17). Cross-sectional validity was assessed through evaluation of its construct validity, convergent and discriminant validity, discriminative ability and reliability. Assessment of this tool demonstrated good correlation between FAQLQ-AF and FAIM (ρ = 0.76, p =<0.001) with internal consistency (Cronbach's α = 0.97) (25).

Additionally, the instrument demonstrated that it could discriminate between patients who differ in severity of symptoms (anaphylaxis versus non-anaphylaxis, total FAQLQ-AF score 4.9 versus 4.1 p = 0.041) and number of food allergies (>3 food allergies versus ≤ 3 food allergies, total FAQLQ-AF score 5.2 versus 4.2, p = 0.008) (25). In addition, one of the studies evaluated the test-re-test reliability of the FAQLQ-AF which was excellent (ICC = 0.952 and CCC = 0.952).

In 2010, the FAQLQ-AF was translated from Dutch to English for an online version to be used in the US. One study identified in this review validated this translated instrument. The online FAQLQ-AF also demonstrated a good construct validity (correlation with FAIM ρ = 0.72; p = <0.001), internal consistency (Cronbach's α = 0.95) and was discriminative for anaphylaxis versus non-anaphylaxis (total FAQLQ-A score 5.4 versus 4.9 p = 0.03). Discriminative ability was also shown in American participants allergic to more than three foods versus participants allergic to three or fewer foods (5.7 versus 5.1; p = <0.001) (24).

Food allergy disease-specific HRQL for parent or caregiver

Food Allergy Quality of Life Parental Burden (FAQL-PB)

A total of five studies were identified describing the development and validation of the FAQL-PB instrument (18, 26-29). It is a self-report on the parent or caregiver's HRQL and contains 17 items and three domains.

One study focused on the creation and validation of a food allergy-specific HRQL instrument to measure parental burden associated with having a child with food allergy; the FAQL-PB (18).

The FAQL-PB was originally in English and was developed following item generation and item reduction (12-14, 17) resulting in a questionnaire with 17 items. The validation showed strong internal validity (Cronbach's α = 0.95) and a good correlation with expectation of outcome questions (r = 0.412, p = <0.01). FAQL-PB was also able to demonstrate the ability to discriminate by disease burden; parents whose children had multiple (more than 2) food allergies were more affected than parents whose children had fewer allergies (scores, 3.1 versus 2.6, p = <0.001) (18).

One study reviewed the impact of pediatric food allergy on caregiver QOL (21). One study showed that mother

and child reported lower anxiety (p = 0.043 and p <0.001) when the child was prescribed an epinephrine auto-injector (27).

One study tested the robustness of the Chinese food allergy QOL parental burden questionnaire (Chinese FAQL-PB). The internal validity of the instrument was excellent, (Cronbach's α = 0.976 and an ICC = 0.701, p<0.001). The authors did not use the FAIM tool to assess construct validity. However, confirmatory factor analysis (CFA) was undertaken to ensure that any domains found were genuinely present. The CFA revealed good correlations between the FAQL-PB items (28, 29).

Food Allergy Quality of Life Questionnaire Parental Form (FAQLQ –PF)

Four studies were reviewed for the development and validation of the FAQLQ-PF in this review (7, 15, 28, 30). The intended population is for parents of children aged 0 to 12 years with food allergy and is a proxy-report where parents report on their children's HRQL. It contains 30 items and three domains. This instrument was developed, initially in English, as part of the EuroPrevall project and followed the development and validation method of the FAQLQ-CF, –TF and –AF.

The FAQLQ-PF was developed following item generation and item reduction (12-14, 17). Cross-sectional validity was assessed through evaluation of its construct validity, convergent and discriminant validity, discriminative ability and reliability.

One study revealed the design of a sensitive multi-dimensional measure to assess parental perception of HRQL in children aged 0 to 12 years. This was developed in four stages; internal consistency was moderate (Cronbach's α >0.7) for subscales and total score. Construct validity was demonstrated by significant correlations between relevant scales of the Child Health Questionnaire (CHQ)-28 and FAQLQ-PF subscales (r = 0.69 - 0.77, p<0.01) and between FAQLQ-PF subscales and FAIM (r = 0.52 - 0.73, p = <0.01) (29).

One study compared child and parent proxy reports on HRQL in Dutch food allergic children (8–12 years old). Seventy-four child-parent pairs were included. The FAQLQ-CF score was significantly higher than the FAQLQ-PF score (3.74 versus 2.68, p<0.001, where 1 indicates no impairment and 7 indicates extreme impairment). The internal consistency for the FAQLQ-PF (α = 0.95) and the construct validity was confirmed for the Dutch translation of the FAQLQ-PF (ρ = 0.58, p <0.001) (7).

One study reviewed the validation of the FAQLQ-PF instrument in a French translation. The results demonstrated a strong correlation between FAQLQ-PF and FAIM (r = 0.85) and a good internal consistency (Cronbach's α = 0.748) (15).

The fourth study assessed the longitudinal measurement properties of the FAQLQ-PF instrument. The results showed that domains and total score improved significantly at post-challenge time-points for both groups (all p <0.05). Sensitivity was demonstrated by differences between positive and negative groups at six months [F (2, 59) = 6.221, p<0.003] and by differing improvement on relevant subscales (p<0.05). Minimally important difference (MID) was 0.45 on a seven-point response scale. Poorer QOL at baseline increased the odds by over 2.0 of no improvement in HRQL scores six-month time-point. The internal reliability of the overall score on the FAQLQ-PF (at six months) was found to be very good with a Cronbach's α of 0.89 – 0.9 and the reliability of the change score (ICC of change) in the instrument subscales and total score ranged from 0.90 to 0.92 (30). Hence FAQLQ-PF is sensitive to change, and has excellent longitudinal validity and reliability in a food-allergic patient population.

Discussion

Principal findings

This comprehensive systematic review has identified and formally appraised the underpinning evidence for available HRQL instruments for use in patients and parents of children with food allergy. We have found a number of instruments with good developmental and psychometric properties, and it is important that these are now widely used in research and clinical contexts. The inability at present to define a minimal clinically important difference remains a concern that needs urgently to be addressed, as does the need for making these instruments available in a wider range of European languages.

Strengths and limitations

The main strengths of this work include the use of formal systematic review methods, including the development of a formal systematic review protocol, which was

published in advance (11), and the involvement of a multi-disciplinary group of experts from a range of European countries.

The limitations of this work include the fact that our focus was on IgE-mediated food allergy (19), even though non-IgE-mediated and mixed IgE/non-IgE-mediated food allergy also occur and can have a profound impact on QOL. This decision, however, reflected the expert opinion that such instruments have yet to be developed; this therefore reflects an important outstanding research need.

In addition to Dutch and French, the FAQLQ-CF has been validated in English, Spanish and Polish (Goossens *et al.*, submitted) and translated into nine other European languages. In addition to Dutch and English, the FAQLQ-AF has been validated in French, Greek, Icelandic, Italian, Polish, Spanish, Swedish (Goossens *et al.*, in press) and translated into four other European languages. Also the FAQLQ-TF and –PF have been translated into a number of European languages and some of them are also validated (www.faqlq.com). A parent-administered instrument for adolescents (where parents report on their teenager's HRQL) is under development in the UK (29). After the time period of the search of this review, the FAQL-PB was validated in the UK (31) and a new pediatric food allergy quality of life questionnaire (PFA-QL) was validated in the UK (33). Additionally, the development of the Pediatric Quality of Life Inventory Eosinophilic Esophagitis Module by Franciosi *et al.* is currently undergoing multi-centre field-testing, but this tool does not limit itself to IgE-mediated food allergy (34).

The time period of the search excluded an important study assessing longitudinal validity and responsiveness of the FAQLQ-AF, FAQLQ-TF, and FAQLQ-CF and the impact of a double-blind, placebo-controlled food challenge (DBPCFC) on HRQL (34). The results of the study demonstrated responsiveness of the FAQLQs through improved HRQL scores after a DBPCFC, with greater improvements in HRQL scores after a negative outcome (food allergy ruled out) than a positive outcome (food allergy confirmed). Additionally, longitudinal validity of these questionnaires was supported by significant correlations between the change (follow-up minus baseline) in FAQLQ and FAIM. FAQLQ-AF (Pearson correlation coefficient = 0.71, $p<0.001$), FAQLQ-TF (Pearson correlation coefficient = 0.35, $p = 0.018$), and FAQLQ-CF (Pearson correlation coefficient = 0.51, $p< 0.001$) (34).

Interpretation of findings

The seven included HRQL questionnaires for food allergy were appraised as having relatively high quality of development properties (Table 3) and psychometric properties (Table 4). Regarding the development properties, the quality scores of the seven HRQL differed only slightly, ranging from 15 out of 18 (FAQL-teen) to 18 out of 18 (FAQLQ-PF). For the psychometric properties, more variance was seen in the quality scores with the FAQL-teen having the worst score (5 out of 16) and the FAQLQ-PF having the best score (12 out of 16). For the adolescent age group, three questionnaires are available. The FAQLQ-TF and the You and Your Food Allergy are comparable and have high quality development and psychometric properties. However, the FAQL-teen scored considerably lower on quality of psychometric properties and was specially developed for US adolescents which may limit its generalizability. It is also worth noting that cases of 'excellent' internal consistency ($\alpha>0.9$), redundancy possibly exists and some items may be measuring very similar things. This might mean that the scale is capturing quite a narrow range of quality of life issues and/or could be made shorter without losing internal reliability.

When selecting an HRQL questionnaire, it is important to choose a questionnaire that is appropriate for the setting, diagnosis and age of the patient. In addition, it should be available in the appropriate language. Choosing the appropriate HRQL questionnaire in food allergic patients will be extensively discussed in the guidelines of the European Academy of Allergy and Clinical Immunology on Food Allergy HRQL measures (Chapter 3.2).

Implications for research, policy and practice

To date, none of the instruments developed have provided a clinical minimal important difference (MID). One instrument (FAQLQ-PF) has ascertained the statistical MID, which is useful in deciding whether differences or changes are unlikely to be due to spontaneous variation in HRQL. It does not answer the question of whether patients find the difference or change in HRQL clinically important. This is therefore an unmet need in this area, as a clinical MID allow interventions to be assessed quantitatively by permitting calculation of numbers needed to treat

(NNT) resulting from the intervention being studied.

Since non-IgE mediated food allergies are not the focus of this study and have not been studied, we anticipate the problems patients encounter to be quite different from those with immediate-type symptoms or anaphylaxis. So we cannot make any specific suggestions or predictions about the HRQL tools used for non- IgE mediated symptoms, suffice to say that the construction of any such instrument should adhere to the methodological principles of making a quality of life instrument.

Disease-specific, rather than generic QOL tools are necessary to provide an in-depth picture of the day-to-day concerns of patients, particularly in the context of long-term conditions. Disease-specific measures are also able to capture small but potentially important changes in HRQL that may occur as a result of clinical treatment and care. Disease-specific instruments also allow separation of the effects of an intervention on a target disorder from the effects on co-morbid conditions. Since many patients with food allergy also suffer from asthma, allergic rhinitis and/or atopic eczema/dermatitis, having disease-specific instruments for food allergy is particularly relevant in this regard.

Conclusions

This is the first review, to our knowledge, that has systematically assessed the literature on disease-specific QOL tools for food allergy. This systematic review demonstrated that there are a limited number of health-related QOL tools specifically for IgE-mediated food allergy. It is unlikely that the instruments described here will be useful for non-IgE mediated food allergy where the problems patients face are quite different. Healthcare workers should be aware of the impact of food allergy on an individual's life and their families. Use of a HRQL questionnaire to evaluate HRQL in children, adolescent, adults with food allergy and their caregivers may be useful in clinical practice. For research purposes, use of properly validated instruments is critical to the accurate evaluation of HRQL in food allergic study participants.

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing this systematic review.

Funding

EAACI

Contributorship

AS, AM, GR and AEJD conceived this review. It was undertaken by SAS with the support of AEJD, BMJF-deB, SP and SSP. SAS and AEJD led the drafting of the manuscript and all authors critically commented on drafts of the manuscript.

Conflicts of interest

None known

References

1. Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al.* Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;303:1848-1856.
2. DunnGalvin A, Gaffney A, Hourihane JO. Developmental pathways in food allergy: a new theoretical framework. *Allergy* 2009;64:560-568.
3. Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Strategies for living with the risk of anaphylaxis in adolescence: qualitative study of young people and their parents. *Prim Care Respir J* 2012;21:392-397.
4. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. *Clin Exp Allergy* 2007;37:1213-1220.
5. Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. *Clin Exp Allergy* 2011;41:869-877.
6. Monks H, Gowland MH, MacKenzie H, Erlewyn-Lajeunesse M, King R, Lucas JS *et al.* How do teenagers manage their food allergies? *Clin Exp Allergy* 2010;40:1533-1540.
7. van der Velde JL, Flokstra-de Blok BM, Dunngalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Parents report better health-related quality of life for their food-allergic children than children themselves. *Clin Exp Allergy* 2011;41:1431-1439.
8. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med* 1993;118:622-629.
9. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO *et al.* Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children *Clin Exp Allergy* 2009;39:127-137.
10. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, Schouten JP, Dunngalvin A *et al.* Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults. *Qual Life Res* 2009;18:245-251.

11. Salvilla SA, Panesar SS, Patel S, Rader T, Muraro A, Roberts G *et al*; European Academy of Allergy, Clinical Immunology Food Allergy and Anaphylaxis Guidelines group. Disease-specific health-related quality of life (HRQL) instruments for food allergy: protocol for a systematic review. *Clin Transl Allergy* 2013;3:15.
12. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;21:77-83.
13. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76-83.
14. Pesudovs K, Burr JM, Harley C, Elliott DB. The development, assessment, and selection of questionnaires. *Optom Vis* 2007;84:663-674.
15. Wassenberg J, Cochard MM, Dunngalvin A, Ballabeni P, Flokstra-de Blok BM, Newman CJ *et al*. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol* 2012;23:412-419.
16. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. *Clin Exp Allergy* 2008;38:977-986.
17. Jaeschke R, Guyatt G. How to develop and validate a new quality of life instrument. In: Spilker B, editor. *Quality of life assessments in clinical trials.* New York: Raven Press, 1990:47-57.
18. Cohen BL, Noone S, Muñoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. *J Allergy Clin Immunol* 2004;114:1159-1163.
19. van der Velde JL, Flokstra-de Blok BMJ, Vlieg-Boerstra BJ, Oude Elberink JNG, Schouten JP, DunnGalvin A *et al*. Development, validity and reliability of the Food Allergy Independent Measure. *Allergy* 2010;65:630-635.
20. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO *et al*. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. *J Allergy Clin Immunol* 2008;122:139-144.
21. van der Velde JL, Flokstra-de Blok BM, Hamp A, Knibb RC, Duiverman EJ, Dubois AE. Adolescent-parent disagreement on health-related quality of life of food-allergic adolescents: who makes the difference? *Allergy* 2011;66:1580-1589.
22. Resnick ES, Pieretti MM, Maloney J, Noone S, Muñoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in adolescents with food allergy: the FAQL-teen. *Ann Allergy Asthma Immunol* 2010;105:364-368.
23. Mackenzie H, Roberts G, Van Laar D, Dean T. A new quality of life scale for teenagers with food hypersensitivity. *Pediatr Allergy Immunol* 2012;23:404-411.
24. Goossens NJ, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Duiverman EJ, Weiss CC, Furlong TJ *et al*. Online version of the food allergy quality of life questionnaire-adult form: validity, feasibility and cross-cultural comparison. *Clin Exp* 2011;41:574-581.
25. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ *et al*. Development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form. *Allergy* 2009;64:1209-1217.
26. Springston EE, Smith B, Shulruff J, Pongracic J, Holl J, Gupta RS. Variations in quality of life among caregivers of food allergic children *Ann Allergy Asthma Immunol* 2010;105:287-294.
27. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. *Pediatr Allergy Immunol* 2010;21:586-594.
28. Leung TF, Yung E, Wong YS, Li CY, Wong GW. Quality-of-life assessment in Chinese families with food-allergic children. *Clin Exp Allergy* 2009;39:890-896.
29. Knibb RC, Stalker C. Validation of the Food Allergy Quality of Life-Parental Burden Questionnaire in the UK. *Qual Life Res* 2013;22:1841-1849.
30. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire – Parent Form in children 0-12 years following positive and negative food challenges. *Clin Exp Allergy* 2010;40:476-485.
31. Hamp A, Hourihane JO, Knibb RC, Dubois A, deBlok-Flokstra B, DunnGalvin A. Developmental Specificity and Sensitivity between 2 Age Appropriate Health Related Quality of Life Measures in Food Allergic Children and Teenagers. *J Allergy Clin Immunol* 2008;121:S107.
32. Knibb RC, Ibrahim NF, Petley R, Cummings AJ, King RM, Roberts G *et al*. Validation of the Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL). *Pediatr Allergy Immunol* 2013;24:288-292.
33. Franciosi JP, Hommel KA, Greenberg AB, Debrosse CW, Greenler AJ, Abonia JP *et al*. Development of the Pediatric Quality of Life Inventory™ Eosinophilic Esophagitis Module items: qualitative methods. *BMC Gastroenterol* 2012;12:135.
34. van der Velde JL, Flokstra-de Blok BM, de Groot H, Oude-Elberink JN, Kerkhof M, Duiverman EJ *et al*. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. *J Allergy Clin Immunol* 2012;130:1136-1143.

3.2

FOOD ALLERGY HEALTH-RELATED QUALITY OF LIFE MEASURES

EAACI GUIDELINES

A Muraro[1*], AEJ Dubois[2, 3*], A DunnGalvin[4], J O'B. Hourihane[5], NW de Jong[6], R Meyer[7], SS Panesar[8], G Roberts[9-11], S Salvilla[8], A Sheikh [8, 12], A Worth[8], BMJ Flokstra-de Blok [3, 13], on behalf of The EAACI Food Allergy & Anaphylaxis Guidelines Group

AFFILIATIONS

[1] Department of Mother and Child Health, The Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region. - University of Padua. Padua, Italy

[2] University of Groningen, UniversityMedicalCenterGroningen, Department of Pediatric Pulmonology and Pediatric Allergy, Groningen, the Netherlands

[3] University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen, the Netherlands

[4] School of Applied Psychology, Department of Pediatrics and Child Health, School of Medicine, University College Cork, Ireland

[5] Department of Paediatrics and Child Health, University College, Cork, Ireland

[6] Department of Internal Medicine, Section of Allergology, Erasmus MC, Rotterdam, the Netherlands

[7] Department Gastroenterology, Great Ormond Street Hospital for Sick Children, London, UK

[8] Allergy& Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Scotland, UK

[9] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK

[10] NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, UK

[11] Human Development and Health and Clinical and Experimental Science Academic Units, Faculty of Medicine, University of Southampton, UK

[12] Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston, USA

[13] University of Groningen, University Medical Center Groningen, Department of General Practice, Groningen, the Netherlands

** Joint first author*

EXPERT PANEL

RC Knibb[1], M Masiello[2], I Baiardini[3], R Gerth Van Wijk[4], S Schnadt[5].

[1] Aston University, Birmingham, UK

[2] The Center for Health Promotion and Disease Prevention, Windber Research Institute and Windber Medical Center, Windber, PA

[3] Allergy and Respiratory Diseases Clinic, DIMI, University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy

[4] Department of Allergology, Erasmus MC, Rotterdam, the Netherlands

[5] Deutscher Allergie- und Asthmabund, Mönchengladbach, Germany

Instruments have been developed and validated for the measurement of health-related quality of life in patients with food allergy. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Guidelines for Food Allergy and Anaphylaxis Group. It draws on a systematic review of the literature on quality of life instruments for food allergy and the Appraisal of Guidelines for Research & Evaluation (AGREE II) guideline development process. Guidance is provided on the use of such instruments in research and the current limitations of their use in clinical practice is described. Gaps in current knowledge as well as areas of future interest are also discussed. This document is relevant to health care workers dealing with food allergic patients, scientists engaging in food allergy research and policy makers involved in regulatory aspects concerning food allergy and safety.

Originally published as: Muraro A, Dubois AEJ, DunnGalvin A, Hourihane JO'B, de Jong NW, Meyer R, Panesar SS, Roberts G, Salvilla S, Sheikh A, Worth A, Flokstra-de Blok BMJ. Food allergy health-related quality of life measures: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014; DOI:10.1111/all.12405. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

In recent decades, food allergy has emerged as a significant medical problem throughout Europe (1). As the medical morbidity and mortality associated with food allergy is limited to symptoms resulting from incidental ingestions of allergenic foods, conventional, symptom-based outcome measures fail to reflect the ongoing burden of this condition to patients' well being. Although health-related quality of life (HRQL) (Box 1) is an important outcome measure for many diseases, it is of particular importance for food allergy because there are no alternatives of sufficient sensitivity for use in most clinical situations. The relevance of HRQL measurement in allergy research, clinical practice and regulatory processes has been emphasized previously (2).

Scope and purpose of the guidelines

A number of studies have been undertaken in the last decade which broadly address the issue of quality of life in patients suffering from food allergy (3-9). Many of these studies have employed questionnaires designed to illuminate some aspect of the experience of patients with food allergy using both qualitative and quantitative approaches. These guidelines focus on instruments designed to measure HRQL in a quantitative and disease-specific fashion, and in particular, draws upon a systematic review of existing instruments, one of seven inter-linked evidence syntheses undertaken to provide a state-of-the-art synopsis of the current evidence base in this area (10). That review included a comprehensive search and quality assessment of instruments with special attention to the method of validation used. These guidelines examine the possible applications of these instruments and provides advice to clinicians and investigators on their proper use and interpretation of results. Current limitations will also be considered and gaps and areas of future interest identified.

Methods

These guidelines were produced using relevant principles detailed in the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (11). This is in essence a structured approach to guideline production that is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. We provide below an overview of the approach used.

Box 1 Key terms

Health-related quality of life (HRQL): the impact of an illness and its therapy upon a patient, as percieved by the patient

Validity is the degree to which an instrument measures what it is intended to measure. There are different types of validity of which construct validity is most important in HRQL measurement. *Construct validity* ensures that only that part of quality of life is being measured which is related to or driven by the disease in question. It is established by correlating measurements to one or more independent measures (IM) of the disease which provide an estimation of the extent and severity of patients' food allergy. An exact correlation is not expected as the HRQL instrument will not be measuring the same dimensions as the IM.

Reliability includes reproducibility and internal consistency. *Reproducibility* ensures that measurements taken under identical conditions are equivalent, and may be assessed by test re-test analysis. It is generally assessed by asking patients to complete the HRQL instrument twice, a few weeks apart, during a period when there is no change expected in their HRQL (e.g. when they have not experienced any food allergic reactions or received any relevant interventions). *Internal consistency* ensures that the items of a questionnaire are related to each other and to the total questionnaire, and is usaully assessed by Cronbach's alpha.

Responsiveness ensures that differences or changes of potential importance are not missed, and is examined by measuring differences or changes in groups where these are expected. It is often assessed in patients whose HRQL is expected to change (e.g. those who have experienced food allergic reactions or relevant interventions). *Interpretability* ensures that the relevance or clinical significance of measurements is apparent. This is ascertained by calculating the minimal clinically important difference (MCID), or the smallest change in HRQL score associated with a significant change in a global rating reported by patients.

Clarifying the scope and purpose of the guidelines

In January 2012, the scope of the intended guidelines was agreed upon, including the target allergy conditions and population, the end-user group and allowing for adequate academic, professional and lay presentation during guidelines development.

Ensuring appropriate stakeholder involvement

Participants represented a range of European countries, and academic and clinical backgrounds (including medical secondary care, primary care and nursing), and patient groups. The Food Allergy HRQL Taskforce continued to work together over the ensuing 18 months through email discussions, teleconferences and face-to-face meetings.

Systematic review of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree to a single key over-arching question – namely, 'Which disease-specific, validated instruments can be employed to enable assessment of the impact of, and investigations and interventions for, food allergy on HRQL?' The answer to this was then pursued through a formal systematic review of the evidence (12) (see Chapter 3.1).

Formulating recommendations

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (13) approach is a transparent, evidence-based approach to formulating recommendations for interventions and diagnostic tests. However, the GRADE approach is less suitable for use in the context of recommendations on the use of which quality of life instruments to select or how to use or interpret these. Therefore, following identification, critical appraisal and synthesis of relevant data, members of the Taskforce developed draft consensus recommendations on suitable validated instruments for use in the context of IgE-mediated food allergy, and the use of these instruments and interpretation of data for: (a) clinical and (b) research purposes.

Peer review

A draft of these guidelines were externally peer-reviewed by experts from a range of organizations, countries and professional backgrounds. In addition, these guidelines were posted on the EAACI website for public review for 3 weeks in June 2013. All feedback was considered by the Food Allergy HRQL Taskforce and, where appropriate, final revisions were made in the light of the feedback received. We will be pleased to continue to receive feedback on these guidelines, which should be addressed to the first author.

Identification of evidence gaps

The process of developing these guidelines has identified a number of evidence gaps and we plan in the future to prioritise the questions that the Food Allergy HRQL Taskforce believes should be most urgently addressed through formal consensus building techniques. We plan furthermore to draft outline research briefs that funders can use to commission research on these questions.

Editorial independence and managing conflict of interests

The production of these guidelines were funded and supported by EAACI. The funders did not have any influence on the guideline production process, its contents or on the decision to publish. Conflicts of interest statements were completed by all members of the Taskforce and these were taken into account by the Food Allergy HRQL Taskforce chair as recommendations were formulated.

Review of guidelines

The guidelines will be reviewed in 2017 and updated accordingly. However important advances will be incorporated prior to this date if required.

Results

The development of instruments used to measure HRQL should follow a specific methodology to ensure their validity, reproducibility, responsiveness (or sensitivity) and interpretability (3) (Box 1). All of these properties were examined in the systematic review (12) (Chapter 3.1). Particular emphasis was given to establishment of validity, which is of fundamental importance to proper instrument development.

Sixteen studies were quality appraised in the systematic review (12) and seven disease-specific HRQL instruments were identified as fulfilling the

Table 1 Summary of food allergy specific health related quality of life instruments

Abbreviation (where stated)	Key reference	Full name	Target population (age range in years)	Respondent (years)
FAQLQ-CF	4	Food Allergy Quality of Life Questionnaire -Child Form	Children (8 to 12)	Children (8 to 12)
FAQLQ-TF	5	Food Allergy Quality of Life Questionnaire -Teenager Form	Adolescents (13 to 17)	Adolescents (13 to 17)
FAQL-teen	15	Food Allergy Quality of Life Assessment Tool For Adolescents	Adolescents (13 to 19)	Adolescents (13 to 19)
You and Your Food Allergy	16	You and Your Food Allergy	Adolescents (13 to 18)	Adolescents (13 to 18)
FAQLQ-AF	6	Food Allergy Quality of Life Questionnaire -Adult Form	Adults (≥18)	Adults (≥18)
FAQL-PB	14	Food Allergy Quality of Life - Parental Burden	Parents	Parents
FAQLQ-PF	7	Food Allergy Quality of Life Questionnaire - Parent Form	Children (0 to 12)	Parents

criteria described above (4-8, 14-16). These included instruments for children, adolescents, adults and parent or caregiver, and were either self-reported or proxy-reported (see Table 1).

The Food Allergy Quality of Life Questionnaire (FAQLQ-CF, -TF, -AF and -PF) instruments have undergone the most thorough validation process, including assessment of their psychometric properties. These FAQLQs are available free of charge and several are available in multiple languages (www.faqlq.com).

Choosing an instrument

If HRQL instruments are to yield useful information in patients with food allergy, it is important to choose a tool that is appropriate for the setting, diagnosis and age of the patient (3, 17). Food allergy-specific HRQL questionnaires (Table 1) have been developed and validated for patients with IgE-mediated allergies (excluding Oral Allergy Syndrome (OAS)) and are therefore not suitable for non-IgE mediated food allergies. The food allergy-specific HRQL instruments have been designed to detect clinically important differences and changes in the disease-specific quality of life of patients with food allergy. As they are specific for IgE-mediated food allergy, they do not allow for comparison with other disorders.

The choice of food allergy-specific HRQL instrument should primarily be determined by the age of the patients, as highlighted in Table 1. In young children (i.e. those ≤8 years), a parent proxy questionnaire (which can be used up to the age of 12 years) is required (7, 8) whereas patient-administered instruments are appropriate for older children (>8 years) (4), adolescents (5, 15, 16) and adults (6), as they can express their own social/emotional and physical well-being. Language may also impact on the choice of instrument, not only because of differences between languages, but also because of cultural differences in various areas where the same language is spoken. The FAQLQ-AF has now been validated in several European countries and is available in English (18, 19), French, Spanish, Italian, Polish, Greek, Dutch and Icelandic (19). The FAQLQ-PF has been validated in French, Spanish, German, Dutch, Danish and Mandarin, although only the data on the first has been published in a full length paper to date (20). Also the FAQLQ-CF has also been translated and validated into a number of European languages (21). The FAQL-teen, FAQL-PB and You and Your Food Allergy questionnaire are only available in the language of development (English). Figure 1 provides an algorithm guiding the appropriate use of food allergy-specific HRQLQs and key factors to take into account are listed in Box 2. After the search period of the current review (1990 - September

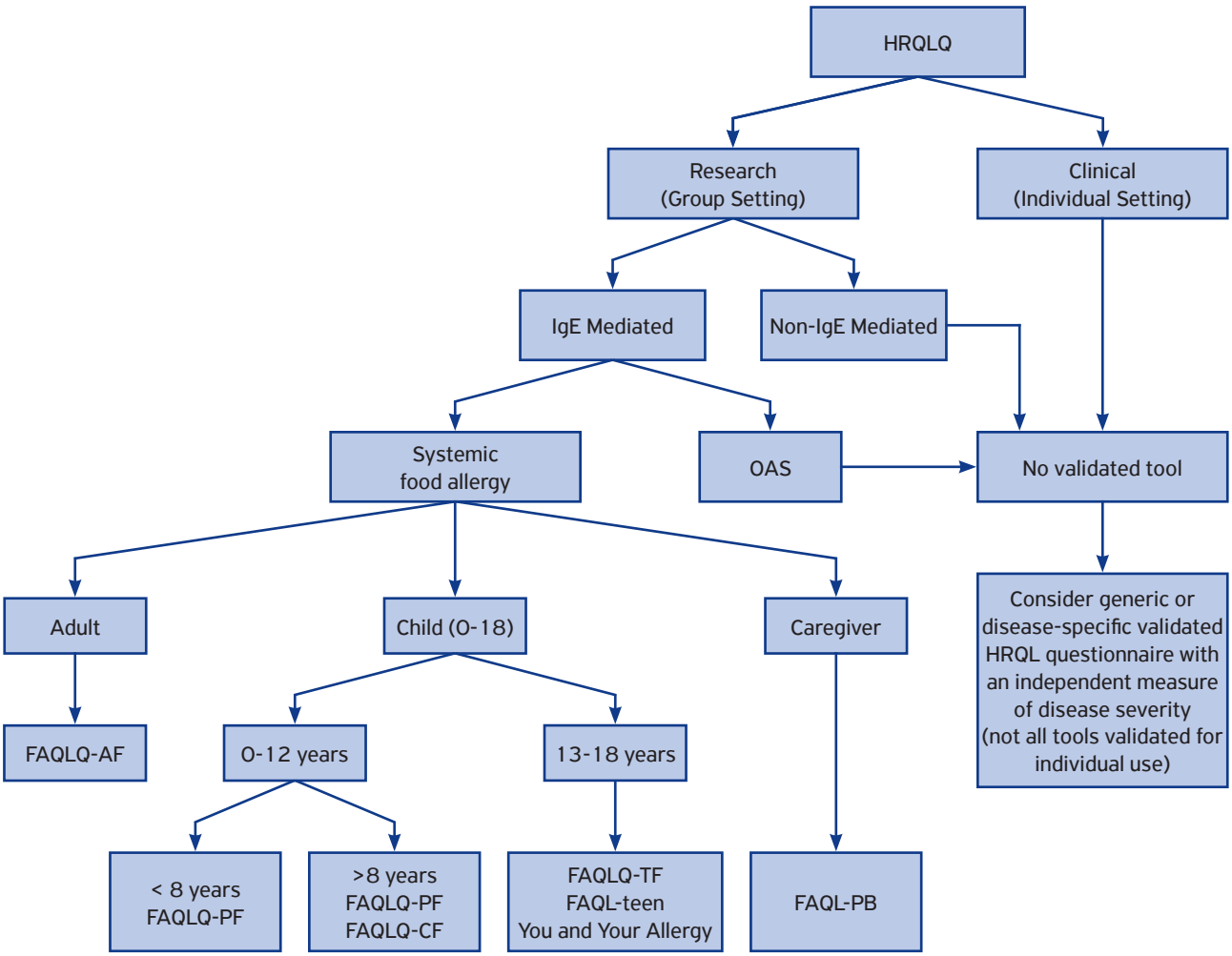


Figure 1 Choosing an appropriate Food Allergy HRQLQ

Box 2 Summary box of factors to take into account when choosing a HRQLQ for food allergy

- Type of food allergy (IgE mediated or not, OAS)
- Research or clinical application
- Inclusion or exclusion of effects of co-morbidities
- Patient age
- Language and cultural availability/appropriate-ness
- Preferred respondent: parent/caregiver as proxy, or child
- Target population/individual: parent/caregiver or child

2012), another disease-specific instrument has been validated in the UK for children with food allergy and their parents: the Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL) (22). In addition, the FAQLQ-CF, -TF and -AF were shown to be longitudinally valid and responsive (23).

Currently, there are no tools that can be used to gain insight on the contribution of the parent-child relationship on the HRQL of a food allergic child. There is some evidence that comparison of patient reported HRQL to parent (proxy) reported HRQL using the FAQLQs can offer some insights in this area (24, 25). In addition, an optional section in the FAQLQ-PF evaluates the amount of stress felt by mother, father, and family as a result of food allergy. Self-reported level of stress has been found to correlate significantly with

parent rated HRQL for the child (26). A parent (proxy) reported instrument is currently being developed for adolescents with food allergy which may increase our knowledge of the role that adolescent-parent relationships play in teenagers with food allergy. Finally, the dynamics of a family with a food allergic child may also be informed by assessing the parental burden using the FAQL-PB (14).

Currently, the FAQLQs have only been used in the research setting to provide quantitative information on the HRQL of patients with IgE-mediated food allergy, to assess the effect of interventions and determine outcomes (3). If they are to be used in clinic, the question arises as to whether they are a valid measure of HRQL at the level of individual patients and suitable to guide clinical practice. Methods to assess individual validity and patient acceptability of HRQL have been used in other diseases (27, 28). In essence, to be useful in clinical practice, reproducibility of the HRQLQ is required to be high and sensitive enough to detect the effects of differences in allergy management. In addition, the HRQLQ should be simple, easy to score and interpret and the information the instrument provides must be shown to affect patient management (29). Although the instruments described in these guidelines have characteristics suggesting they may be capable of providing valid HRQL assessments at the level of individual patients, more studies are required in this area. One recent study (30) evaluated the effectiveness of a developmentally appropriate cognitive behavioural therapy (CBT) intervention specifically developed to improve HRQL for children and teenagers with IgE mediated food allergy. The FAQLQ-PF, CF, and TF were used and the results showed that the measures were sensitive enough to detect improvement in HRQL in individual patients relative to a control group.

For patients with food allergy outside the remit of current validated food allergy-specific HRQLQ (e.g. those with non-IgE mediated food allergy or OAS) validated, generic HRQL questionnaires may be considered. However, these have not been designed to detect HRQL issues specific to food allergy and so are unlikely to be sensitive to small but potentially important differences or changes in food allergy HRQL. Moreover, generic HRQL questionnaires will be affected by any existing comorbid disorders. Another possibility, is to use a food allergy-specific HRQLQ and administer an appropriate independent measure of disease severity simultaneously in order to check the validity of this questionnaire in another population (e.g. non-IgE mediated food allergy or OAS).

Using an instrument

Ideally, HRQL instruments should be used in the setting (language, culture and age group) in which it was developed. In practice, instruments must often negotiate differences between the setting of their development and their ultimate application. It is thus often advisable to include an independent measure such as the Food Allergy Independent Measure (FAIM) (31) in the study in the new setting. Such a measure should be available in the same language and may help to differentiate between negative study outcomes due to lack of changes in HRQL from those due to loss of validity of the HRQL measure in the new setting.

HRQL measurements are imminently suited to determine whether interventions offer a benefit increment to patients which they find meaningful. In order to demonstrate this, the minimal clinically important difference (MCID) for the instrument used must be determined. The MCID is the smallest increment of difference or change in HRQL score which patients find clinically meaningful. Currently, none of the food allergy instruments have provided a MCID. This is thus an unmet need in this area, as it will allow interventions to be assessed quantitatively by permitting calculation of numbers needed to treat (NNT) resulting from the intervention studied.

Pharmaco-economic research is mostly used to identify, measure, and compare the costs, risks, and benefits of programs, services, or therapies and determine which alternative produces the best health outcome for the resources invested. Validated HRQL instruments for food allergy can be of value because they are able to measure the benefits of health care interventions from a patient perspective and ascertain whether the benefit of a particular intervention justify the resources required. Such measurements may be expressed as Quality-Adjusted Life Years (QALYs) that capture both the HRQL lost or gained and the time to which this change pertains. Such information is essential to cost-utility analyses which are important to policy makers.

Aside from the FAIM or similar independent measure and a global assessment, many other psychometric tools may be used concomitantly to gain insight into

the patient experience of disease and treatment. Of these, the burden of treatment (BoT) measurement deserves special mention, as it allows the evaluation of disease and treatment by asking patients to weigh these entities in their overall assessment of the benefits of a particular intervention. Together with HRQL, this can offer a comprehensive evaluation of the net benefits of an intervention.

The use of food allergy HRQL questionnaires to measure effect of interventions on HRQL of food allergic patients is increasing. Outcomes of these studies are described in the EAACI guidelines on diagnosis and treatment of food allergy (32).

Gaps in the evidence and recommendations

The healthcare system has traditionally focused on treating disease at point of failure, such as life-saving surgery or intensive medical therapy. In the case of food allergy, this occurs with accidental reactions and/or anaphylaxis. With health care professionals and governments now placing more of an emphasis on prevention, a different patient management model is required to assess cost-effectiveness within the continuum of care. Clinically, standardized HRQL measures can enhance screening patients for burdens associated with even asymptomatic periods of food allergy and can be used to monitor changes. Therefore, the development of high quality food allergy-specific HRQL instruments is a welcome advance in helping to assess the impact of IgE-mediated food allergy on patients' quality of life. That said, it is important to note that there remain a number of important research gaps in order to have a comprehensive set of tools for use in the everyday management of patients with food allergy across Europe. These are summarized below.

First, the MCID of existing instruments needs to be determined. This is essential to allow for calculation of NNT for clinical care and pharmaco-economic analysis.

Second, there are at present no tools for assessing HRQL in those with non-IgE-mediated food allergy or in those with OAS. Given that these manifestations of food allergy can have a substantial impact on the quality of life of patients and carers, there is a pressing need to develop appropriate instruments.

Third, the tools available for assessing HRQL in those with IgE-mediated food allergy are still only available in a fraction of the languages spoken across Europe. Given that food allergy affects people throughout Europe, formal validational work needs to be undertaken to make these instruments available across the full spectrum of relevant languages.

Fourth, how best to develop an efficient and integrated method of assessment and monitoring of HRQL in patients with co-existent allergic problems has been a matter of recent debate. In order to retain the advantages of a disease specific instrument, the use of information and communications technology may be an option. Unlike a paper questionnaire, electronic questionnaires can be developed that consist of a subgroup of questions from a much larger collection to provide personalised instruments that, for example, cater for type of allergy, multiple allergy, distance from medical centre, or co-morbid condition. Where appropriate, section(s) on coping, anxiety, risk, reactions, and management style could also be included. In addition, as electronic questionnaires could facilitate implementation in routine care contexts, it is important that these tools are validated for use across a range of platforms – for example, completion on patient portals, mobile phones, tablets, and personal computers. Given the increasing move to electronic health records across Europe (33), electronic data capture will also facilitate seamless transfer into patient records. A further advantage of an electronic system would be the ease with which a detailed database could be generated for health status of individual patients on a longitudinal basis. This would allow healthcare providers to target additional input to individual patients or families experiencing impaired HRQL due to particular circumstances.

Fifth, it should be noted that the available instruments have primarily been developed for use in research contexts. Using instruments in routine clinical contexts is potentially very valuable and is hence on the policy agendas of some European countries, but this does require the MCID of the instruments to be established in order to assess the impact of interventions/care provision on individual patients.

Sixth, how best to assess HRQL in the many patients with co-existent allergic problems is another related clinically important consideration. The main options are to either use an accompanying generic instrument (e.g. the EQ-5D) or to add in additional disease specific instruments for each co-morbidity. Whilst the

latter approach may be feasible in those with one co-morbdity (e.g. atopic eczema/dermatitis), it is likely to prove much more challenging in those with multiple co-morbdities (e.g. atopic eczema/dermatitis, allergic rhinitis and asthma).

Finally, efforts to link quality of life gains and optimal resource allocation has proved challenging in many areas of healthcare. However, how HRQL can aid policy decisions in allocating healthcare resources is an important issue for policy makers. Decisions are often taken based on the outcomes of an evaluation expressed as incremental costs per QALY gained, or disability-adjusted life years (DALY). Measuring HRQL in economic or monetary terms has not been attempted to date in the area of food allergy. Since QALYs need to be measured against some threshold (usually the monetary or consumption value of QALY gains), disease-specific, meaningful estimates of the value of QALY gains in food allergy need to be developed. Disease specific HRQL measures can be a key tool in such a development. Therefore, there is a need to identify relevant thresholds for costs per QALY and how these might vary across Europe in order to help inform policy considerations. In this respect, it is important that individual, family and societal perspectives are considered.

Based on the systematic review of HRQL instruments for IgE mediated food allergy, and the identification of needs and gaps in clinical practice and research, we make the following recommendations. These can be divided into general recommendations (Box 3), recommendations for clinicians (Box 4) and recommendations for research (Box 5).

Where next with HRQL instruments?

Some questions remain that impact on the future potential value of HRQL measures in allergy. Firstly, what are the correlates of HRQL in food allergy (e.g. anxiety, health beliefs, risk perception, information processing, coping behaviours) and how do they impact on the likelihood of adverse reactions and management? Which of these variables are causally related to HRQL status, and which variables are the effect of HRQL status? Lastly, as HRQL depends on subjective perception of the burden of food allergy, what are the underlying neuropsychological mechanisms (e.g. stress/immune interactions)? These questions have particular relevance for the interpretation and usefulness of HRQL measures in clinical practice. As our knowledge base grows, clarity will evolve about

Box 3 General recommendations

1. Only validated instruments as identified by this systematic review should be used to measure HRQL in food allergic subjects.
2. An independent measure (e.g. FAIM) should be used simultaneously as a correlating measure.
3. An established approach should be used when the validated questionnaires are translated into other languages, e.g. back translation and validation in the local language – there may be important linguistic or cultural issues that invalidate the tool in other countries.
4. To date, the FAQLQ (AF, TF, CF and PF) and FAQL-PB and –teen instruments and the You and Your Food Allergy instrument are the only tools sufficiently well-validated to be used in research contexts. The appropriate questionnaire will depend on the age of the patient.
5. Alterations to questions in the instrument are strongly discouraged, as these may compromise validity. If alterations are made, the instrument requires re-validation.
6. The instruments recommended in this review are specific to IgE-mediated food allergy and are not suited for use in patients with non-IgE mediated disease or oral allergy syndrome. Furthermore, for patients where measurement of HRQL due to comorbid conditions is desireable, appropriate disease-specific and/or a generic instrument may be required.

Box 4 Recommendations for clinicians

1. To date, the use of food-allergy specific HRQL tools in clinical practice has been little documented. Clinicians should be aware of this and be cautious when using HRQL measurements to guide mangement decisions.
2. There is currently also no information on the use of HRQL measurements as a form of bench-marking in food allergy.

Box 5 Recommendations for research

1. Research is needed on optimum methods of administration (e.g. paper, online, phone etc.), procedures (e.g. frequency) and interpretation (e.g. MCID).
2. Research is needed on which HRQL measures (if any) are valid at the level of individual patients to guide clinical practice.
3. Research is needed on the efficacy of disease specific HRQL instruments in the evaluation of medical and technological advances, patient satisfaction and quality of care and health and regulatory policy
4. The inclusion of HRQL in models to explain different pathways in the development, expression, and impact of chronic diseases.
5. Norms for age, gender, and country/culture need to be developed.
6. Research is needed on the relationship between responses to both proxy and self-report HRQL measures.
7. Research is needed on optimum methods (clinical and statistical) for evaluating HRQL in patients with co-morbid conditions.
8. Further work is needed to see how QALYs for food allergy can be developed to help inform policy.

how HRQL relates to other variables. Studies must be theory driven, well designed, multi-site, and build on previous work. It is important that we design studies that help to clarify the physiological mechanisms that underlie the psycho-social predictor and outcome variables in our models. For example, models should allow for bi-directional and causal pathways linking health to HRQL (including all significant variables and their weights). If the flow is bi-directional for some of the components, this has profound implications in terms of interpretation and application of HRQL results. The mechanisms responsible for any associations should be evaluated. Such models may be seen as a blueprint for exploration as well as a summary of available evidence.

Since the developmental process plays an important role in shaping and determining physical and psychological health and HRQL, an attempt to delineate a developmental pathway is also vital. Life transitions provide a naturalistic research opportunity to investigate adaptability to a diagnosis of food allergy and the link to health outcomes and HRQL. The pathway should take account of sensitive transition points when the interaction of biopsychosocial factors may create an increased vulnerability in terms of health and well-being (9, 34).

In addition to providing a meaningful way to assess the end results of health care services, including clinical and therapeutic interventions, and policy, HRQL measures can allow health professionals to pinpoint the time when both parents and children may need further support on issues such as diet, auto-injectors, risk management, managing anxiety, and changing developmental and practical challenges. It can also help us to identify unintended impacts of potential management options. The use of HRQL measures cross-culturally and across countries can delineate similarities, differences, and dynamic factors. Taken together, such findings, combined with research on variables related to HRQL, can provide a broader view than has hitherto often been the case on the impact of food allergy.

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing these guidelines. We would like to thank Catherine Crowley for their administrative help in preparing the guidelines. We would also like to thank our EAACI members and the EAACI Executive Committee for their helpful comments and suggestions.

Authors' contribution

Antonella Muraro, Chair of the EAACI Food Allergy and Anaphylaxis Guidelines Initiative, has steered and coordinated the publication. Anthony Dubois facilitated the guidelines group and edited the guidelines document. Bertine Flokstra-de Blok facilitated the identification of research questions for the systematic review and processed the feedback of the experts. Anthony Dubois, Audrey DunnGalvin, Rosan Meyer, Nicolette de Jong, Aziz Sheikh, Allison Worth and Bertine Flokstra-de Blok drafted specific sections. Sarah Salvilla and Sukhmeet Panesar undertook the supporting systematic review under the supervision of Aziz Sheikh. All authors participated in the discussion of the sections, recommendations, gaps and approved the final version.

Conflicts of interest

Antonella Muraro has provided scientific advice for Meda. Anthony Dubois has provided scientific advice for ALK-Abello and received funding from ALK Abello to support his research activities. Audrey DunnGalvin has received funding from Novartis for her research. Jonathan O'B. Hourihane has received speaker fees from Mead Johnson, Nutricia, MSD, Pfizer, ALK-Abello and Stallergenes; Thermo Fisher have provided consumables for his research activities. Nicolette W de Jong has no conlict of interests. Rosan Meyer has provided scientific advice for Danone, Nestle and Mead Johnson. Graham Roberts has provided scientific advice for Danone and ALK-Abello; Thermo Fisher and ALK-Abello have provided consumables for his research activities. Aziz Sheikh has provided scientific advice to ALK-Abello, Meda, Lincoln Medical, ThermoFisher, Pfizer and Stallargenes; he is on the Anaphylaxis Campaign UK's Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee and the BSACI's Standard of Care Committee and has received funding for coordinating guideline production, and generating the systematic reviews from EAACI. Sarah Salvillaand Sukhmeet Panesar have no conflict of interest. Allison Worth has received funding from ALK Abello, Meda and ThermoFisher to attend meetings and provide professional education. Bertine Flokstra-de Blok has no conflict of interest.

References

1. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V *et al.* The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014;69:62-75.
2. Baiardini I, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A *et al.* Recommendations for assessing patient-reported outcomes and health-related quality of life in clinical trials on allergy: a GA(2)LEN taskforce position paper. *Allergy* 2010;65:290-295.
3. Flokstra-de Blok BM, Dubois AE. Quality of life measures for food allergy. *Clin Exp Allergy* 2012;42:1014-1020.
4. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO *et al.* Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. *Clin Exp Allergy* 2009;39:127-137.
5. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO *et al.* Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. *J Allergy Clin Immunol* 2008;122:139-144, 144.e1-2.
6. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ *et al.* Development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form. *Allergy* 2009;64:1209-1217.
7. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. *Clin Exp Allergy* 2008;38:977-986.
8. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire - Parent Form in children 0-12 years following positive and negative food challenges. *Clin Exp Allergy* 2010;40:476-485.
9. Dunngalvin A, Hourihane JO. Developmental aspects of HRQL in food related chronic disease. *The International Handbook of Behaviour, Diet and Nutrition* New York, USA: Springer; 2011.
10. Salvilla SA, Panesar SS, Patel S, Rader T, Muraro A, Roberts G *et al.* Disease-specific health-related quality of life (HRQL) instruments for food allergy: protocol for a systematic review. *Clin Transl Allergy* 2013;3:15.
11. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *J Clin Epidemiol* 2010;63:1308-1311.
12. Salvilla SA, Panesar SS, Patel S, Rader T, Muraro A, Roberts G *et al.* Disease-specific health-related quality of life (HRQL) instruments for food allergy: protocol for a systematic review. *Clin Transl Allergy* 20131;3:15
13. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S *et al.* Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
14. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. *J Allergy Clin Immunol* 2004;114:1159-1163.
15. Resnick ES, Pieretti MM, Maloney J, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in adolescents with food allergy: the FAQL-teen. *Ann Allergy Asthma Immunol* 2010;105:364-368.
16. Mackenzie H, Roberts G, Van Laar D, Dean T. A new quality of life scale for teenagers with food hypersensitivity. *Pediatr Allergy Immunol* 2012;23:404-411.
17. Flokstra-de Blok BM, Dubois AE. Quality of life in food allergy: valid scales for children and adults. *Curr Opin Allergy Clin Immunol* 2009;9:214-221.
18. Goossens NJ, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Duiverman EJ, Weiss CC, Furlong TJ *et al.* Online version of the food allergy quality of life questionnaire-adult form: validity, feasibility and cross-cultural comparison. *Clin Exp Allergy* 2011;41:574-581.

19. Goossens NJ, Flokstra-de Blok BM, van der Meulen GN, Arnlind MH, Asero R, Barreales L *et al*. Health-related Quality of Life in Food Allergic Adults from Eight European Countries. *Ann Allergy Asthma Immunol,* in press.
20. Wassenberg J, Cochard MM, Dunngalvin A, Ballabeni P, Flokstra-de Blok BM, Newman CJ *et al*. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol* 2012;23:412-419.
21. Goossens NJ, Flokstra-de Blok BMJ, van der Meulen GN, Rokicka E, Starosta P, Jedrzejczak-Czechowicz M *et al*. Validation and Cross-Cultural Comparison of the 'Food Allergy Quality of Life Questionnaire – Child Form' in European Populations. 2014;Submitted.
22. Knibb RC, Ibrahim NF, Petley R, Cummings AJ, King RM, Roberts G *et al*. Validation of the Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL). *Pediatr Allergy* 2013;24:288-292.
23. van der Velde JL, Flokstra-de Blok BMJ, Duiverman EJ, Dubois AEJ. Longitudinal validity and responsiveness of the food allergy quality of life questionnaire-adult form; Quality of life improves significantly after double blind placebo controlled food challenges. *Allergy* 2010;65(s92):746.
24. van der Velde JL, Flokstra-de Blok BM, Dunngalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Parents report better health-related quality of life for their food-allergic children than children themselves. *Clin Exp Allergy* 2011; 41:1431-1439.
25. van der Velde JL, Flokstra-de Blok BM, Hamp A, Knibb RC, Duiverman EJ, Dubois AE. Adolescent-parent disagreement on quality of life of food allergic adolescents; Who makes the difference? *Allergy* ;66:1580-1589.
26. DunnGalvin A, Chang WC, Laubach S, Steele PH, Dubois AE, Burks AW *et al*. Profiling families enrolled in food allergy immunotherapy studies. *Pediatrics* 2009;124:e503-509.
27. Kocks JW, Kerstjens HA, Snijders SL, de Vos B, Biermann JJ, van Hengel P *et al*. Health status in routine clinical practice: validity of the clinical COPD questionnaire at the individual patient level. *Health Qual Life Outcomes* 2010;8:135.
28. Moores KL, Jones GL, Radley SC. Development of an instrument to measure face validity, feasibility and utility of patient questionnaire use during health care: the QQ-10. *Int J Qual Health Care* 2012;24:517-524.
29. Bjordal K. Impact of quality of life measurement in daily clinical practice. *Ann Oncol* 2004;15(Suppl 4):iv279-iv282.
30. DunnGalvin A, Hourihane J. Evidence-based efficacy of an intervention developed to moderate the psychological impact of food allergy, using a controlled design. 2014;Submitted.
31. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, DunnGalvin A, Hourihane JO *et al*. Development, validity and reliability of the food allergy independent measure (FAIM). *Allergy* 2010;65:630-635.
32. Muraro A, Werfel T, Beyer K, Bindslev Jensen C, Cardona V, Dubois A *et al*. Diagnosis and management of food allergy: Guidelines from the European Academy of Allergy and Clinical Immunology. Allergy, in press.
33. Sheikh A, Cornford T, Barber N, Avery A, Takian A, Lichtner V *et al*. Implementation and adoption of nationwide electronic health records in secondary care in England: final qualitative results from prospective national evaluation in "early adopter" hospitals. *BMJ* 2011;343:d6054.
34. DunnGalvin A, Gaffney A, Hourihane JO. Developmental pathways in food allergy: a new theoretical framework. *Allergy* 2009;64:560-568.

SECTION 4

ANAPHYLAXIS

4.1

THE EPIDEMIOLOGY OF ANAPHYLAXIS IN EUROPE

SYSTEMATIC REVIEW

SS Panesar[1], S Javad[2], D DeSilva[3], B I Nwaru[4], L Hickstein[5], A Muraro[6], G Roberts[7-9], M Worm[10], MB Bilò[11], V Cardona[12], AEJ Dubois[13], A DunnGalvin[14], P Eigenmann[15], M Fernandez-Rivas[16], S Halken[17], G Lack[18, 19], B Niggemann[20], A F Santos[18, 19, 21], BJ Vlieg–Boerstra[22], ZQ Zolkipli[8-9], A Sheikh[1]on behalf of the EAACI Food Allergy and Anaphylaxis Group

EAACI Food Allergy and Anaphylaxis Group: CA Akdis, A Bellou, C Bindslev-Jensen, K Brockow, A Clark, P Demoly, L Harada, K Hoffman-Sommergruber, L Poulsen, F Rueff, M Jutel, N Papadopoulos, F Timmermans, R Van Ree, T Werfel

AFFILIATIONS

[1] Allergy & Respiratory Research Group, Center or Population Health Sciences, The University of Edinburgh, Edinburgh, UK

[2] School of Public Health, Imperial College London, London, UK

[3] The Evidence Centre Ltd., London, UK

[4] School of Health Sciences, University of Tampere, Tampere, Finland

[5] Institute for Medical Informatics, Biometry and Epidemiology, University of Munich, Munich, Germany

[6] Department of Pediatrics, Center for Food Allergy Diagnosis and Treatment, Veneto Region, University of Padua, Padua, Italy

[7] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[8] NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[9] Human Development and Health and Clinical Experimental Sciences Academic Units, Faculty of Medicine, University of Southampton, UK

[10] Allergy-Center-Charité, Dpt of Dermatology and Allergy, Charité Universitätsmedizin, Berlin, Germany

[11] Allergy Unit, Dept. Internal Medicine, University Hospital, Ospedali Riuniti, Ancona, Italy

[12] Allergy Section, Department of Internal Medicine, Hospital UniversitariValld'Hebron, Barcelona, Spain

[13] University of Groningen, University Medical Center Groningen, Department of Pediatric Pulmonology and Pediatric Allergy, and GRIAC Research Institute, Groningen, the Netherlands

[14] Department of Paediatrics and Child Health, University College, Cork, Ireland

[15] University Hospitals of Geneva, Geneva, Switzerland

[16] Allergy Dept, Hospital Clinico San Carlos, IdISSC, Madrid, Spain

[17] Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[18] King's College London, King's Health Partners, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK

[19] Allergy Center Charité, University Hospital Charité, Berlin, Germany

[20] Department of Pediatric Allergy, Division of Asthma, Allergy & Lung Biology, King's College London

[21] MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK

[22] Immunoallergology Department, Coimbra University Hospital, Coimbra, Portugal

[23] Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, The Netherlands

Background: *Anaphylaxis is an acute, potentially fatal, multi-organ system, allergic reaction caused by the release of chemical mediators from mast cells and basophils. Uncertainty exists around epidemiological measures of incidence and prevalence, risk factors, risk of recurrence and death due to anaphylaxis. This systematic review aimed to: (1) understand and describe the epidemiology of anaphylaxis; and (2) describe how these characteristics vary by person, place, and time.*

Methods: *Using a highly sensitive search strategy, we identified systematic reviews of epidemiological studies, descriptive and analytical epidemiological investigations and studies involving analysis of routine data.*

Results: *Our searches identified a total of 5843 potentially eligible studies, of which 49 satisfied our inclusion criteria. Of these, three were suitable for pooled estimates of prevalence. The incidence rates for all-cause anaphylaxis ranged from 1.5 to 7.9 per 100000 person-years. These data indicated that an estimated 0.3% (95% CI 0.1, 0.5) of the population experience anaphylaxis at some point in their lives. Food, drugs, stinging-insects and latex were the most commonly identified triggers.*

Conclusions: *Anaphylaxis is a common problem; affecting an estimated 1 in 300 of the European population at some time in their lives. Future research needs to focus on better understanding trends across Europe and identifying those most likely to experience fatal reactions.*

Originally published as: Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, Roberts G, Worm M, Bilo MB, Cardona V, Dubois AEJ, Dunn Galvin A, Eigenmann P, Fernandez-Rivas M, Halken S, Lack G, Niggemann B, Santos AF, Vlieg-Boerstra BJ, Zolkipli ZQ & Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013; 68: 1353–1361. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

Anaphylaxis is a 'severe, life-threatening generalised or systemic hypersensitivity reaction'. Several working definitions of anaphylaxis have been formulated to aid diagnosis and management (1-4). The most well-known is the consensus clinical definition proposed by Sampson *et al.*, which involved representatives of a number of international allergy organisations, including the European Academy of Allergy and Clinical Immunology (EAACI) (Box 1) (5).

With anaphylaxis being a syndrome with variable symptoms, signs, and time course, none of the definitions are ideal and impede accurate epidemiological study (6). Additionally, the acute onset and transient nature renders it difficult to mount prospective investigations (7). Notwithstanding these inherent challenges, there is a need to improve our understanding of the epidemiology of anaphylaxis to understand the overall disease burden posed by the condition and obtain insights into its etiology, risk stratification and prognosis. Epidemiological measures of particular interest for anaphylaxis therefore include measures of incidence and prevalence, risk factors, and risk of recurrence and death (8) (Box 2). Other aspects of interest concern features of persons who experience anaphylaxis, temporal relationships, and the factors that lead to its development and recurrence (9).

This systematic review is one of seven inter-linked

Box 1 Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled

(1) Acute onset of an illness (minutes to hours) with involvement of

Skin/mucosal tissue (e.g. hives, generalized itch/flush, swollen lips/tongue/uvula)

AND

Airway compromise (e.g. dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow (PEF))

OR

Reduced BP or associated symptoms (e.g. hypotonia, syncope)

(2) Two or more of the following after exposure to known allergen for that patient (minutes to hours)

History of severe allergic reaction

Skin/mucosal tissue (e.g. hives, generalized itch/flush, swollen lips/tongue/uvula)

Airway compromise (e.g. dyspnea, wheeze/bronchospasm, stridor, reduced peak flow)

Reduced blood pressure (BP) or associated symptoms (e.g. hypotonia, syncope)

In suspected food allergy: gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

(3) Hypotension after exposure to known allergen for that patient (minutes to hours)

Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP*

Adults: systolic BP <100 mm Hg or >30% drop from their baseline

*Reproduced with permission from Sampson et al. (5) (C). *Low systolic BP for children is defined as <70 mm Hg from 1 month to 1 year; less than (70 mm Hg + [2 × age]) from 1 to 10 years; and <90 mm Hg from age 11 to 17 years.*

Box 2 Epidemiological definitions

Incidence: The number of new cases of anaphylaxis that occur during a given period in a defined population. Incidence will be studied as:

- *Incidence rate*: The number of new cases of anaphylaxis that occur during a defined period per unit person-time.
- *Cumulative incidence*: The number of new cases of anaphylaxis that occur during a given period per the population at risk.

Prevalence: The proportion of a defined population known to have experienced anaphylaxis. Care is required in defining the appropriate denominator. This epidemiological measure will be further divided into:

- *Point prevalence*: the proportion of the population that has experienced anaphylaxis at a specific time
- *Period prevalence*: the proportion of the population that has experienced anaphylaxis during a given period
- *Lifetime prevalence*: the proportion of the population that at some point in their life will have experienced anaphylaxis.

Case fatality rate: The proportion of cases of anaphylaxis that proves fatal (usually defined within a time period). This is also sometimes known as the case fatality ratio.

Definitions based on those proposed by Last (8).

evidence syntheses that have been undertaken to provide a state-of-the-art European synopsis of the current evidence base in relation to epidemiology, prevention, diagnosis and clinical management, and impact on quality of life. This will be used to inform clinical recommendations within the *EAACI Guidelines for Food Allergy and Anaphylaxis*.

Aims

The aims of this systematic review were to: (1) understand and describe the epidemiology of anaphylaxis, i.e. frequency, risk factors, and outcomes of anaphylaxis; and (2) describe how these characteristics vary by person, place, and time.

Methods

The protocol of this review has been published previously (10) and it is registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/prospero/, reference CRD42013003702).

Search strategy

A highly sensitive search strategy was designed (see Boxes E1-4 in supplementary material) to retrieve all articles combining the concepts of anaphylaxis and epidemiology from electronic bibliographic databases. We conceptualised the search to incorporate the three elements below as shown in Figure 1.

Inclusion criteria for study design

The following studies were included: systematic reviews +/-meta-analyses, cohort studies, cross-sectional studies, case-control studies and routine healthcare studies. These were chosen to ensure that the highest levels of evidence were pooled based on the aims of this review (11).

Exclusion criteria for study design

Reviews, discussion papers, non-research letters and editorials, case studies, and case series plus animal studies were excluded.

Study selection

The titles of the retrieved articles were checked independently by two reviewers (SSP, DdS) according to the selection criteria and categorised as: included, not included and unsure. The abstracts of unsure category papers were retrieved and they were re-categorised after discussion. Any discrepancies were resolved by consensus and, if necessary, a third reviewer (AS) was consulted to arbitrate. Full text copies of potentially relevant studies were obtained and their eligibility for inclusion assessed.

Quality assessment strategy

Each study was quality assessed independently by two reviewers (SSP, HH) using the relevant version of the Critical Appraisal Skills Programme (CASP) quality assessment tool for systematic reviews, (12) cohort

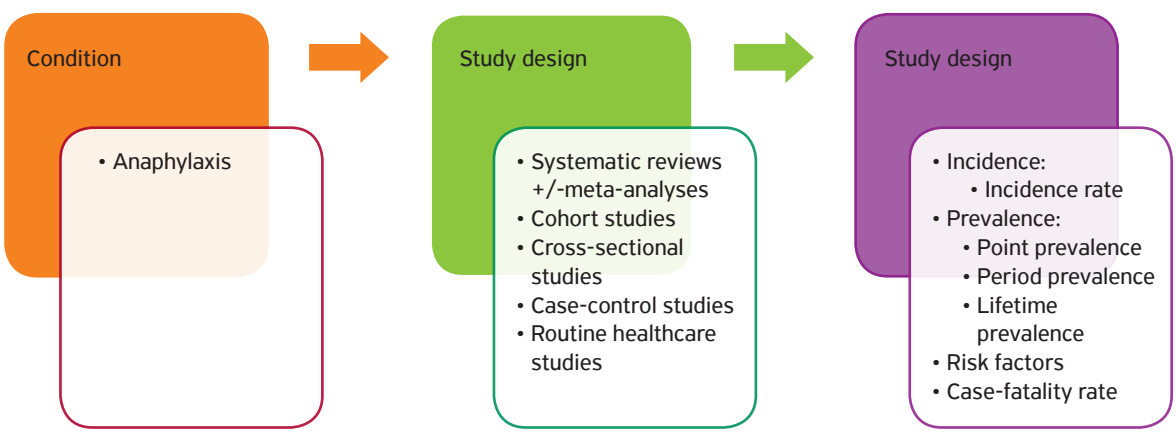


Figure 1 Conceptualisation of systematic review of the epidemiology of anaphylaxis

studies (13) and case-control studies (14) which involved an assessment of internal and external validity (15). Similarly, we used the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for assessing other forms of quantitative studies such as cross-sectional studies and routine healthcare studies (16). Any discrepancies were resolved by discussion or, where necessary, by arbitration by a third reviewer (AS).

Analysis, data synthesis and reporting

Data were independently extracted onto a customised data extraction sheet by two reviewers (DdS, SSP), any discrepancies were resolved by discussion or, were necessary, by arbitration by a third reviewer (AS). A descriptive summary with data tables was produced to summarise the literature. Meta-analysis was undertaken using random-effects modelling and adopting methods suggested by Agresti and Coul. Heterogeneity was assessed using Cochrane's Q, a statistic based on the chi-square test with corresponding Z- and p-values. As this test is known to have low power, the I2 statistic was also calculated: a value of 25% corresponds to low heterogeneity, 50% to moderate and 75% to high (17). Comprehensive Meta-Analysis (Biostat, Englewood, NJ) was used for these analyses. A narrative synthesis of the data was also undertaken. The PRISMA checklist was used to guide the reporting of the systematic review (see Box E5) (18).

Results

Overview of results

The searches identified a total of 5843 potentially eligible studies, of which 49 satisfied our eligibility criteria and were therefore included in this review (see Figure 2) (19-67). The key characteristics and main findings of all included studies are detailed in Table E1 and the quality assessment of these studies is summarised in Table E2. The main findings are further discussed in more detail below.

Incidence, prevalence and trends over time

Incidence

Ten studies offered varying estimates of incidence rates as shown in Table E1 (24, 31, 44, 50-52, 56-59). These ranged from 1.5 per 100000 person-years (24) to 32 per 100000 person-years (45). In one study, over a four-year period, anaphylaxis was the cause of 0.1% of children's hospital admissions and 0.3% of adult admissions (50). Pooled analysis was not possible due to the heterogeneity of the populations and the different approaches to reporting incidence in these studies.

Prevalence

The descriptions used in studies typically failed to differentiate clearly between measures of point, period and lifetime prevalence. Quantitative data were available for pooling from three population-based studies (26, 39, 57); in which estimates of prevalence ranged from 1/1333 (0.1%) (57) to 37/6676 (0.6%) (39). Meta-analysis (I2 = 99.9%) yielded a pooled prevalence estimate of 0.3% (95% CI 0.1 to 0.5), as shown in Figure 3.

Variations by person, place and time

Person: In a study of 325046 people, a peak incidence of 313.58 per 100000 person-years was noted in the 0–4 years old group; this was significantly different ($p<0.05$) to other age groups. For affected people over 10 years of age, incidence tended to be higher for females (58). A review of 816/401152 (0.2%) ambulance calls for anaphylaxis found that 180/816 (22%) involved children (26). Secondary analyses of various healthcare databases found that 4.1 per 100000 admissions to hospitals were in the 0–14 years group, 3.9 per 100000 in the 15–44 years group and 3.5 per 100000 in the 45 years and older group (52).

Place: The study by Sheikh *et al.* reviewed 13.5 million emergency hospital admissions (2323 for anaphylaxis) over a five-year period. A north-south divide existed in the UK with a higher frequency of anaphylaxis admissions in the south (rate ratio 1.35, 95% CI 1.25 to 1.47). A rural to urban rate ratio of 1.35 (95% CI 1.17 to 1.59) and a non-deprived to deprived rate ratio of 1.32 (95% CI 1.19 to 1.46) were also noted (56).

Time: Increases in the incidence rate of anaphylaxis have been reported (44, 51, 57). The incidence of hospital admissions for anaphylaxis increased from 5.6 per 100000 discharges in 1991-92 to 10.2 per 100000 discharges in 1994-95 (44). Age-sex standardised incidence was estimated as 6.7 per 100000 person-years in 2001, rising to 7.9 per

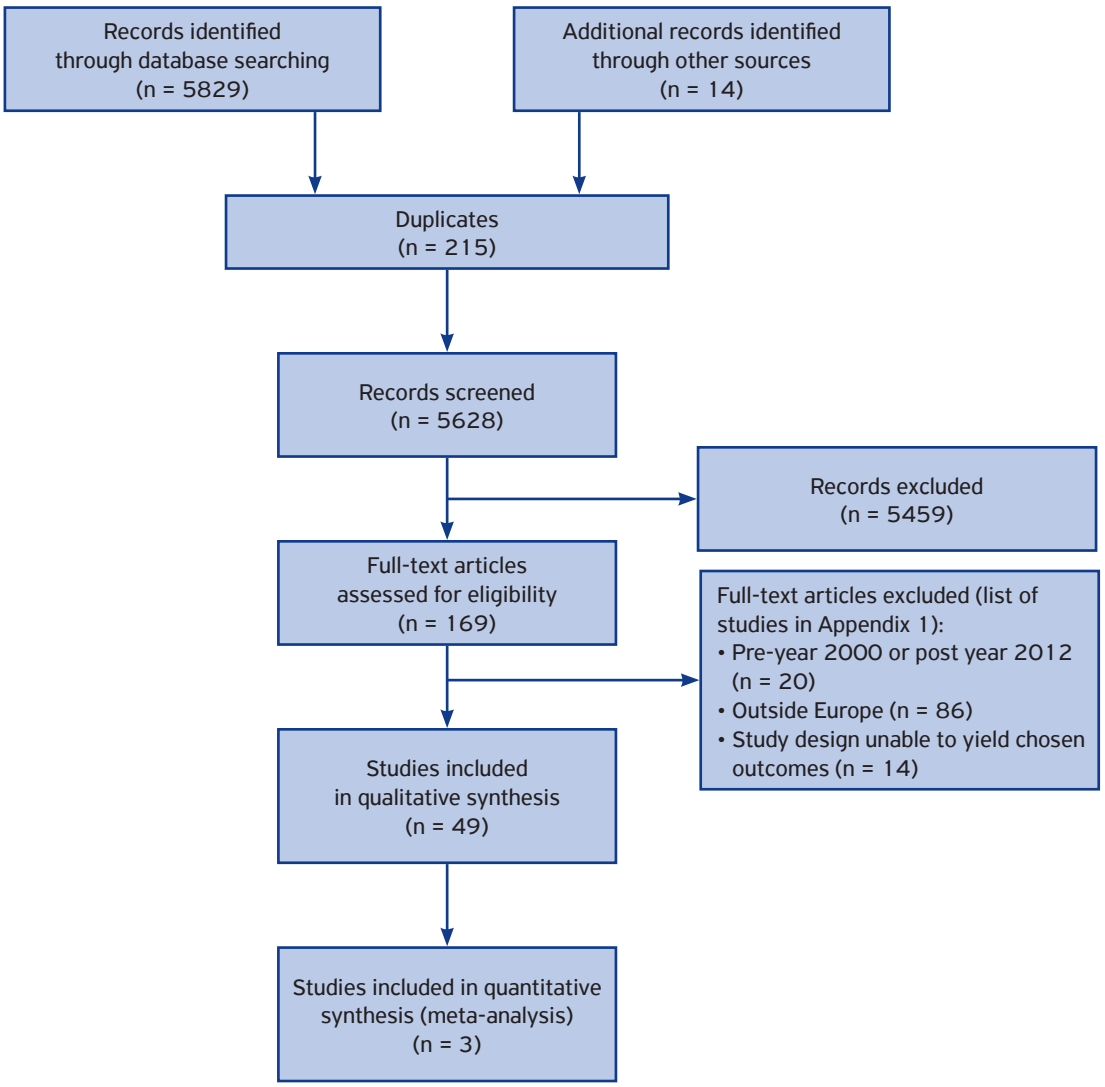


Figure 2 PRISMA diagram for epidemiology of anaphylaxis

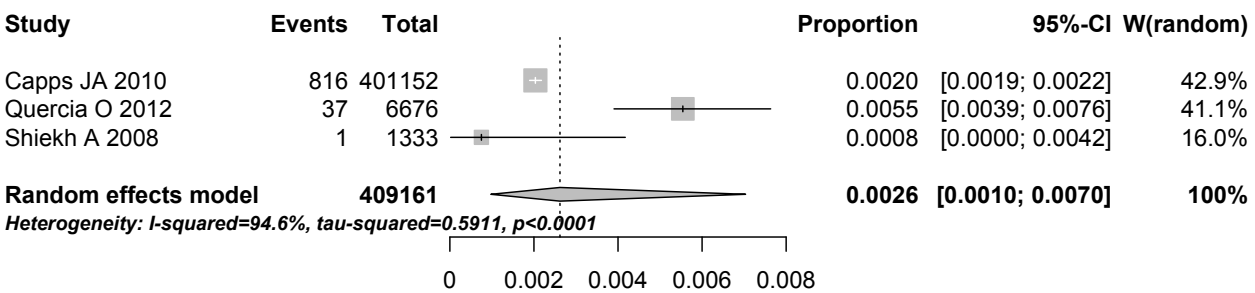


Figure 3 Pooled estimate for the prevalence of anaphylaxis

100000 person-years in 2005 (57). Anaphylaxis rates rose from 6 to 41 per million admissions between 1990-91 and 2000-01 (51). On a similar note, the lifetime age-sex standardised prevalence of recorded diagnosis of anaphylaxis was 50 per 100000 in 2001, rising to 75.5 per 100000 in 2005 (57).

Triggers (elicitors) and co-morbidities

The key triggers identified in these studies included foods, medications, stinging insects and latex. Co-morbidities such as atopic eczema/dermatitis and asthma were also found to be important (30). For example, in a case-control study of co-existing asthma, atopic eczema/dermatitis was the only factor associated with a significantly increased risk of anaphylaxis within the asthma free cohort (odds ratio (OR) 2.83, 95% CI 1.51 to 5.29). Within the cohort with asthma, the following co-morbidities were associated with increased occurrence of anaphylaxis: allergic rhinitis (OR 1.76, 95% CI 1.35 to 2.30), atopic eczema/dermatitis (OR 1.69, 95% CI 1.13 to 2.51) and osteoarthritis (OR 1.50, 95% CI 1.05 to 2.14) (30).

Food triggered reactions

The proportions of food allergy reactions that resulted in anaphylaxis varied markedly (28, 32, 41, 46, 64), 67 with estimates ranging from 12/2716 (0.4%) (41) to 65/163 (39.9%) (Table E1) (64). Different estimates of the most frequent food allergens implicated in anaphylaxis have been provided by the studies. For example, peanuts and tree nuts (27.6%), hen's egg (8.6%) and foods cross-reacting with latex (11%) were the most commonly identified food triggers in one study (64). The food allergens that most commonly resulted in anaphylaxis in another study of 163 children were cow's milk (47/163, 29%), hen's egg (25/163, 25%), hazelnut (9/163, 5%), peanut (6/163, 4%), kiwi (7/163, 4%), walnut (6/163, 4%), pine nut (5/163, 3%), fish (5/163, 3%), wheat (4/163, 2%), soy (3/163, 2%), shrimp (3/163, 2%), apricot (3/163, 2%) and sesame (3/163, 2%) (28). Exposure to airborne allergens increased the risk of anaphylaxis due to food with children with pollen allergy being at increased risk of being admitted with food-related anaphylaxis during the pollen season (46).

Medication and therapeutic agent triggered reactions

The systematic review by Nybo *et al.* (2008) (36) included 25 studies, only two of which met our inclusion criteria (35, 54). Five studies provided estimates for medication-triggered anaphylaxis, (22, 23, 33, 36, 48, 69) which ranged from 3/1446 (0.2%) (33) to 3 of 96, 3.1% (22). There was wide variation in the frequency of anaphylaxis associated with different medications. For example, the rate per 100000 exposed cases was 2.1 for aspirin, 32.0 for parenteral penicillin, and 378.0 for parenteral plasma. These plasma reactions are considered to be infusion reactions rather than true cases of anaphylaxis. There was a relatively low risk for dipyrone, diclofenac, paracetamol, ampicillin, cloxacillin, and cephalosporins. In contrast, parenteral penicillin, dextran, contrast media, blood, and pentoxifylline were associated with intermediate risks. The highest incidences were observed in those receiving plasma and streptokinase (34). However, given the diverse nature of the studies, it is difficult to make conclusions on the true frequency of anaphylaxis in this category.

Stinging insect triggered reactions

One study found that 6.5% of beekeepers had a systemic reaction to bee sting in the past 12 months; 9/494 (2%) of these reactions resulted in anaphylaxis (27). The risk of systemic reactions increased when atopic disease was present: seasonal allergic rhinitis (OR 4.4, 95% CI 1.2 to 11.5), perennial rhinitis (OR 4.6, 95% CI 1.2 to 18.2), food allergy (OR 7.0, 95% 2.0 to 25.0), physician-diagnosed asthma (OR 8.0, 95% CI 2.5 to 25.6), and any atopic disease (OR 10.9, 95% CI 3.5 to 33.8).

Latex triggered reactions

Focusing on pregnant women undergoing surgery in hospital, 2/588 (0.34%) experienced anaphylaxis due to latex allergy (29).

Prognosis

Case fatality rates were noted in three studies at 0.000002% (52), 0.00009% (56), and 0.0001% (31).

Studies in progress

We are aware of one study in progress which is investigating the epidemiology and healthcare utilization in children and adults with anaphylaxis in Denmark; this is expected to report in 2014.

Discussion

Summary of main findings

The population-based incidence of anaphylaxis in Europe is estimated at 1.5 to 7.9 per 100000 person-years (57). There is some evidence that the incidence of anaphylaxis may be increasing but this may be due to changing clinical definitions or thresholds for presentation or admission. Studies would suggest that approximately 0.3% (95% CI 0.1 to 0.5) of the European population have experienced anaphylaxis at some point in their lives. These figures vary by age, geographical regions and exposure. They also depend on the source of data, for example historical medical records, national databases and data collected by general practitioners or specialists, and the definitions used (68). It was beyond the scope of this review to ascertain these factors. This review has also found that foods, drugs/therapeutic agents, stinging insects and latex are the most common triggers of anaphylaxis. Overall, the case fatality ratio from anaphylaxis was low, estimated at under 0.0001%.

Strengths and limitations

This is, as far as we are aware, the first systematic review of the epidemiology of anaphylaxis in European populations. Key strengths of this work include searches of a range of relevant databases, independent critical appraisal of studies, and, where appropriate, quantitative synthesis of data.

Our systematic review does not include studies prior to 2000 and is limited to Europe; this review may therefore not be generalisable to non-European settings. For example, it has excluded a recent epidemiological investigation from Turkey consisting of 114 patients hospitalised due to anaphylaxis over a one-year period giving a lifetime prevalence of 1.95 per 100000 person-years (95% CI 1.30 to 3.77) (69). The varying estimates of epidemiological frequency are likely to be due to varying study designs, approaches and definitions used by the authors. It was beyond the scope of this review to ascertain severity of anaphylaxis; milder systemic reactions which are successfully treated by self-medication may never be captured and this could result in an underestimate of our figures. Most of the studies reviewed relied on the clinical history along with sensitisation for case finding. Experience with challenge testing has shown that there will be an overestimation of prevalence in studies using this method of case finding. While this may suggest transient forms of anaphylaxis, there may also be other unrecognised pathology accounting for symptoms in an unknown number of cases.

Interpreting findings in the context of the wider literature

A review by a Working Group of the American College of Allergy, Asthma and Immunology summarised the findings from some principal studies published in English. Most of these were outside the time period of interest and included a number of non-European studies. This Working Group concluded that the overall incidence of anaphylaxis was between 30-60 cases per 100000 person-years and 950 cases per 100000 person-years, with a lifetime prevalence 0.05-2.0%. Even the higher figure could be an underestimate due to under-diagnosis and under-reporting (6). There may also be factors associated with poor diagnosis by non-specialists in allergy (70). Our pooled estimates are somewhat lower, although the range is very wide, perhaps reflecting differences in diagnostic criteria for anaphylaxis between Europe and North America.

Implications for research, policy and practice

The occurrence of anaphylaxis can have a profound effect on the quality of life of the sufferer and their family (71). The risk of recurrence may be high and some attacks prove fatal. Successfully identifying those at greatest risk of an initial attack, and a recurrence, could reduce morbidity, but this has proved difficult in practice using demographic and clinical markers. Genetic factors may have the potential to help fill this gap by identifying those at particularly high risk of severe reactions.

Secondary analyses of routine sources of data have proved helpful in describing the epidemiology of anaphylaxis, although the estimates generated would be considered more reliable if the data could be validated and linked across primary and secondary care sectors (72). Such validation work needs to be prioritised. Vigilance is needed as new drugs or foods are introduced. National reporting systems of adverse drug reactions or adverse reactions to foods associated with anaphylaxis may need reinforcing, perhaps through the use of prompts during patient consultations (73).

Conclusions

Improved data capture in and across routine health databases is required if we are to obtain more accurate estimates of the burden of anaphylaxis. This may be obtained through agreement on an acceptable definition of anaphylaxis (73) use of standard coding conventions (e.g. ICD-10, SNOMED-CT). At present, the best epidemiological estimates appear to come from north-west Europe, but more information is needed from southern and eastern Europe.

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing these systematic review. We would also like to thank the EAACI Executive Committee for their helpful comments and suggestions. Lastly we thank Dana Fawzi, Ibrahim Ali and Hala Hamadah for their assistance in obtaining some of the studies used in the systematic review.

Funding

EAACI

Contributorship

AS, AM and GR conceived this review. It was undertaken by SSP with the support of SJ and DdS. SSP and AS led the drafting of the manuscript and all authors critically commented on drafts of the manuscript.

Conflicts of interest

None known

References

1. American Academy of Pediatrics, Committee on School Health. Guidelines for urgent care in school. *Pediatrics* 1990;86:999-1000.
2. International Collaborative Study of Severe Anaphylaxis. An epidemiologic study of severe anaphylactic and anaphylactoid reactions among hospital patients: methods and overall risks. *Epidemiology* 1998;9:141-146.
3. Australasian Society of Clinical Immunology and Allergy Inc. (ASCIA). Guidelines for EpiPen prescription. ASCIA Anaphylaxis Working Party 2004. Available online at http://www.allergy.org.au/anaphylaxis/epipen_guidelines.htm. Last accessed 20 September 2012.
4. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; and Joint Council of Allergy, Asthma, and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115(3 suppl): S483-S523.
5. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock A, Branum A *et al.* Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-397.
6. Lieberman P, Camargo CA, Bohlke K, Jick H, Miller RL, Sheikh A *et al.* Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;97:596–602.
7. Simons FE, Sheikh A. Evidence-based management of anaphylaxis. *Allergy* 2007;62:827-829.
8. Last JM, editor. *A dictionary of epidemiology.* 4th ed. New York, NY: Oxford University Press, 2000.
9. Simons FE, Sheikh A. Anaphylaxis: the acute episode and beyond. *BMJ* 2013;346:f602.
10. Panesar SS, Nwaru BI, Hickstein L, Rader T, Hamadah H, Ali DF *et al.*, European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines group. The epidemiology of anaphylaxis in Europe: protocol for a systematic review. *Clin Transl Allergy* 2013;3:9.
11. OCEBM Levels of Evidence Working Group. 'The Oxford 2011 Levels of Evidence'. Oxford Centre for Evidence-Based Medicine. Available online at http://www.cebm.net/index.aspx?o=5653. Last accessed 28 September 2012.
12. CASP checklist for systematic reviews. http://www.casp-uk.net/wp-content/uploads/2011/11/CASP_Systematic_Review_Appraisal_Checklist_14oct10.pdf. Last accessed 10 October 2012.
13. CASP checklist for cohort studies. http://www.casp-uk.net/wp-content/uploads/2011/11/CASP_Cohort_Appraisal_Checklist_14oct10.pdf. Last accessed on 10 October 2012.
14. CASP checklist for case-control studies. http://www.casp-uk.net/wp-content/uploads/2011/11/CASP_Case-Control_Appraisal_Checklist_14oct10.pdf. Last accessed 10 October 2012.
15. Appraisal Tools http://www.phru.nhs.uk/Pages/PHD/resources.htm. Last accessed 20 September 2012.
16. Effective Public Health Practice Project Quality Assessment Tool. http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf. Last accessed on October 2012.
17. Agresti A, Coull BA. Approximate is better than 'exact' for interval estimation of binomial proportions. *Am Statis* 1998;52:119–126.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6: e1000097.
19. Alvarado MI, Perez M. Study of food allergy in the spanish

population. *Allergol Immunopathol* 2006;34:185-193.

20. Asero R, Antonicelli L, Arena A, Bommarito L, Caruso B, Colombo G *et al.* Causes of food-induced anaphylaxis in Italian adults: A multi-centre study. *Int Arch Allergy Immunol* 2009;150:271-277.
21. Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol* 2006;98:357-362.
22. Bousquet PJ, Kvedariene V, Co-Minh HB, Martins P, Rongier M, Arnoux B *et al.* Clinical presentation and time course in hypersensitivity reactions to beta-lactams. *Allergy* 2007; 62:872-876.
23. Calvani M, Di Lallo D, Polo A, Spinelli A, Zappala D, Zicari AM. Hospitalizations for pediatric anaphylaxis. *Int J Immunopathol Pharmacol* 2008;21:977-983.
24. Calvani M, Cardinale F, Martelli A, Muraro A, Pucci N, Savino F *et al.* Risk factors for severe pediatric food anaphylaxis in italy. *Pediatr Allergy Immunol* 2011;22:813-819.
25. Capps JA, Sharma V, Arkwright PD. Prevalence, outcome and pre-hospital management of anaphylaxis by first aiders and paramedical ambulance staff in manchester, UK. *Resuscitation* 2010; 81:653-657.
26. Celikel S, Karakaya G, Yurtsever N, Sorkun K, Kalyoncu AF. Bee and bee products allergy in Turkish beekeepers: Determination of risk factors for systemic reactions. *Allergologia et Immunopathol* 2006;34:180–184.
27. Derby CJ, Gowland MH, Hourihane JO. Sesame allergy in britain: A questionnaire survey of members of the anaphylaxis campaign. *Pediatr Allergy Immunol* 2005; 16:171-175.
28. Draisci G, Zanfini BA, Nucera E, Catarci S, Sangregorio R, Schiavino D *et al.* Latex sensitization: A special risk for the obstetric population? *Anesthesiology* 2011;114:565-569.
29. Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LAG. Anaphylaxis epidemiology in patients with and patients without asthma: A united kingdom database review. *J Allergy Clin Immunol* 2010;125:1098-1104.e1.
30. Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: A study over a 3-year period comprising 940000 inhabitants of the swiss canton bern. *Clin Exp Allergy* 2004;34:285-290.
31. Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of food allergy in France. *J Allergy Clin Immunol* 2001;108:133-140.
32. Lange L, Koningsbruggen SV, Rietschel E. Questionnaire-based survey of lifetime-prevalence and character of allergic drug reactions in German children. *Pediatr Allergy Immunol* 2008;19:634-638.
33. Laporte JR, de Latorre FJ, Laszlo A, Retsagi G, Gadgil DA, Chandrasekhar DV *et al.* Risk of anaphylaxis in a hospital population in relation to the use of various drugs: An international study. *Pharmacoepidemiol Drug Saf* 2003; 12:195-202. (International Collaborative Study of Severe Anaphylaxis)
34. Laxenaire MC, Mertes PM, Groupe d'Etudes des Reactions Anaphylactoides, Peranesthesiques. Anaphylaxis during anaesthesia. results of a two-year survey in france. *Br J Anaesth* 2001;87:549-558.
35. Nybo M, Madsen JS. Serious anaphylactic reactions due to protamine sulfate: A systematic literature review. *Basic Clin Pharmacol Toxicol* 2008;103:192-196.
36. Pastorello EA, Rivolta F, Bianchi M, Mauro M, Pravettoni V. Incidence of anaphylaxis in the emergency department of a general hospital in Milan. *J Chromatogr B Biomed Sci Appl* 2001;756:11-17.
37. Perez Pimiento AJ, PrietoLastra L, Rodriguez Cabreros MI, Vasquez Bautista AA, Garcia Cubero A, Calvo Manuel E. Systemic reactions to wasp sting: Is the clinical pattern related to age, sex and atopy? [erratum appears in allergolimmunopathol (madr). 2007 mar-apr;35(2):51]. *Allergol Immunopathol* 2007;35:10-14.
38. Quercia O, Incorvaia C, Puccinelli P, Scurati S, Emiliani F, Frati F *et al.* Prevalence of allergic disorders in italy: The cotignola population study. *Eur Ann Allergy & Clin Immunol* 2012; 44:5-11.
39. Quiralte J, Blanco C, Delgado J, Ortega N, Alcntara M, Castillo R *et al.* Challenge-based clinical patterns of 223 spanish patients with nonsteroidal anti-inflammatory-drug-induced-reactions. *J Investig Allergol Clin Immunol* 2007; 17:182-188.
40. Rance F, Grandmottet X, Grandjean H. Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. *Clin Exp Allergy* 2005;35:167-172.
41. Rasmussen TA, Jorgensen MRS, Bjerrum S, Jensen-Fangel S, Stovring H, Ostergaard L *et al.* Use of population based background rates of disease to assess vaccine safety in childhood and mass immunisation in Denmark: Nationwide population based cohort study. *BMJ* 2012;345:e5823.
42. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clini-Toxicol: Offic J Amer Acad Clin Toxicol & Eur Assoc Poisons Centr & Clin Toxicolo* 2009; 47:81-88.
43. Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: Time trend study. *BMJ* 2000;320:1441.
44. van Puijenbroek EP, Egberts ACG, Meyboom RHB, Leufkens HGM. Different risks for NSAID-induced anaphylaxis *Ann Pharmacother* 2002; 36:24-29.
45. Vetander M, Helander D, Flodstrom C, Ostblom E, Alfven T, Ly DH *et al.* Anaphylaxis and reactions to foods in children - a population-based case study of emergency department visits. *Clin Exp Allergy* 2012;42:568-577.
46. Worm M, Edenharter G, Rueff F, Scherer K, Pfohler C, Mahler V *et al.* Symptom profile and risk factors of anaphylaxis in central europe. *Allergy* 2012;67:691-698.
47. Ayala F, Fabbrocini G, Bartiromo F, Barberio E, Rescigno O, Di Simone L *et al.* Adverse drug reactions: Dermatological experience. *G Ital di Dermatol Venereol* 2006;141:17-20.
48. Dietrich W, Ebell A, Busley R, Boulesteix A. Aprotinin and

anaphylaxis: Analysis of 12,403 exposures to aprotinin in cardiac surgery *Ann Thorac Surg* 2007;84:1144-1150.

49. Gibbison B, Sheikh A, McShane P, Haddow C, Soar J. Anaphylaxis admissions to UK critical care units between 2005 and 2009. *Anaesthesia* 2012;67:833-838.
50. Gupta R, Sheikh A, Strachan D, Anderson HR. Increasing hospital admissions for systemic allergic disorders in England: Analysis of national admissions data. *BMJ* 2003; 327:1142-1143.
51. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: Secondary analyses of national databases. *Clin Exp Allergy* 2004;34:520-526.
52. Hopf Y, Watson M, Williams D. Adverse-drug-reaction related admissions to a hospital in Scotland. *Pharm World Sci* 2008;30:854-862.
53. Mertes PM, Laxenaire M, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. *Anesthesiology* 2003;99:536-545.
54. Mertes PM, Alla F, Trechot P, Auroy Y, Jougla E, Groupe d'Etudes des Reactions Anaphylactoides, Peranesthesiques. Anaphylaxis during anesthesia in france: An 8-year national survey. *J Allergy & Clin Immunol* 2011;128:366-373.
55. Sheikh A, Alves B. Age, sex, geographical and socioeconomic variations in admissions for anaphylaxis: Analysis of four years of english hospital data. *Clin Exp Allergy* 2001;31:1571-1576.
56. Sheikh A, Hippisley-Cox JJ, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. *J R Soc Med* 2008; 101:139-143.
57. Tejedor Alonso MA, Moro Moro M, Mugica Garcia MV, Esteban Hernandez J, Rosado Ingelmo A, Vila Albelda C *et al*. Incidence of anaphylaxis in the city of Alcorcon (Spain): A population-based study. *Clin Exp Allergy* 2012; 42:578-589.
58. Tejedor Alonso MA, Moro MM, Hernandez JE, Mugica Garcia MV, Albelda CV, Ingelmo AR *et al*. Incidence of anaphylaxis in hospitalized patients. *Int Arch Allergy Immunol* 2011;156:212-220.
59. Pakravan N, Waring WS, Sharma S, Ludlam C, Megson I, Bateman DN. Risk factors and mechanisms of anaphylactoid reactions to acetylcysteine in acetaminophen overdose. *Clin Toxicol: Offic J Amer Acad Clin Toxicol & Eur Assoc Poisons Cent & Clin Toxicolo* 2008;46:697-702.
60. Waring WS, Stephen AF, Robinson OD, Dow MA, Pettie JM. Lower incidence of anaphylactoid reactions to N-acetylcysteine in patients with high acetaminophen concentrations after overdose. *Clin Toxicol* 2008;46:496 -500.
61. Moneret-Vautrin DA, Kanny G, Parisot L. Serious food allergy-related accidents in france: Frequency, clinical and etiological characteristics. First enquiry carried out by the french 'allergovigilance network'. [French] Accidents graves par allergiealimentaire en france: Frequence, caracteristiquescliniques et etiologiques. Premiereenquete du reseau d'allergovigilance, avril-mai 2001. *Revue Francaise d'Allergologie et d'Immunologie Clinique* 2001; 41:696-700.
62. Michalska-Krzanowska G, Kurek M, Ratajski R. The incidence of anaphylactic reactions in 3560 patients undergoing TIVA with propofol, fentanyl and different neuromuscular blocking agents: A one-year retrospective study. *Anestezjologia Intensywna Terapia* 2006;38:125-128.
63. Mulier S, Hanssens L, Chaouat P, Casimir G. [Child food allergy: results of a Belgian cohort]. [French] L'allergie alimentaire chez l'enfant: etude d'une cohorte belge. *Rev Med Brux* 2006; 27 Spec No:Sp 82-86.
64. Rymarczyk B, Gluck J, Jozwiak P, Rogala B. Incidence and variety of clinical manifestation of food hypersensitivity in the population of Silesia - A questionnaire based study. [Polish]Czestosc wystepowania i charakterystyka reakcji nadwrazliwosci na pokarmy w populacji Slaskiej - Badanie ankietowe. *Alergia Astma Immunol* 2009;14:248-251.
65. Couto M, de Almeida MM. Allergic disease diagnosis in Portugal: An exploratory study. Diagnostico da doenca alergica em Portugal: Um estudo exploratorio. *Revista Portuguesa de Imunoalergol* 2011;19:23-32.
66. Branellec A, Thomas M, Fain O, Kettaneh A, Stirnemann J, Letellier E. [Frequency of self-reported penicillin allergy in the area of Seine-Saint-Denis (France)]. *Rev Med Interne.* 2008;29:271-276.
67. Lynch RM, Robertson R. Anaphylactoid reactions to intravenousN-acetylcysteine: a prospective case controlled study. *Accid Emerg Nurs* 2004;12:10-15.
68. Worm M. Epidemiology of anaphylaxis. Ring J (ed): *Anaphylaxis.* Chem Immunol Allergy. Basel, Karger, 2010, vol 95, pp 12–21.
69. Cetinkaya F, Incioglu A, Birinci S, Karaman BE, Dokucu AI, Sheikh A. Hospital admissions for anaphylaxis in Istanbul, Turkey. *Allergy* 2013;68:128-130.
70. Worm M, Hompes S, Vogel N, Kirschbaum J, Zuberbier T. Care of anaphylaxis among practising doctors. *Allergy* 2008;63:1562-1563.
71. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. *Clin Exp Allergy* 2007;37:1213-1220.
72. Anandan C, Simpson CR, Fischbacher C, Sheikh A. Exploiting the potential of routine data to better understand the disease burden posed by allergic disorders. *Clin Exp Allergy* 2006;36:866-871.
73. Clark S, Camargo CA. Epidemiology of anaphylaxis. *Immunol Allergy Clin N Am* 2007;27:145-163.

4.2

MANAGEMENT OF ANAPHYLAXIS

SYSTEMATIC REVIEW

S Dhami[1], SS Panesar[2], G Roberts[3-5], A Muraro[6], M Worm[7], MB Bilò[8], V Cardona[9], AEJ Dubois[10], A DunnGalvin[11], P Eigenmann[12], M Fernandez-Rivas[13], S Halken[14], G Lack[15, 16], B Niggeman[17], F Rueff[18], AF Santos[15, 16, 19], B Vlieg–Boerstra[20], ZQ Zolkipli [3, 4] and A Sheikh[2, 21]

On behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group: CA Akdis, A Bellou, C Bindslev-Jensen, K Brockow, A Clark, P Demoly, L Harada, M Jutel, N Papadopoulos, K Hoffman-Sommergruber, L Poulsen, F Timmermans, R Van Ree

AFFILIATIONS

[1] Evidence-Based Health Care Ltd, Edinburgh, UK

[2] Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK

[3] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[4] NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, UK

[5] Human Development and Health and Clinical and Experimental Sciences Academic Units, Faculty of Medicine, University of Southampton, Southampton, UK

[6] Padua General University Hospital, Padua, Italy

[7] Allergy-Center-Charité, Dpt of Dermatology and Allergy, Charité-Universitätsmedizin, Berlin, Germany

[8] University Hospital Ospedali Riuniti, Ancona, Italy

[9] Hospital Valld'Hebron, Barcelona, Spain

[10] Department of Paediatrics, Division of Paediatric Pulmonology and Paediatric Allergy, and GRIAC Research Institute University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[11] Department of Paediatrics and Child Health, University College, Cork, Ireland

[12] Children's Hospital, Geneva, Switzerland

[13] Allergy Dept, Hospital Clinico San Carlos, IdISSC, Madrid, Spain

[14] Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[15] Department of Pediatric Allergy, Division of Asthma, Allergy & Lung Biology, King's College London , London, UK

[16] King's College London, King's Health Partners, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK

[17] Allergy Center Charité, University Hospital Charité, Berlin, Germany

[18] Department of Dermatology and Allergy, Ludwig-Maximilian University, Munich, Germany

[19] Immunoallergology Department, Coimbra University Hospital, Coimbra, Portugal

[20] Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, The Netherlands

[21] Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston MA, USA

***Background**: Anaphylaxis is an acute, potentially fatal, multi-organ system, allergic reaction. This systematic review aimed to assess the effectiveness of (1) interventions for the acute management of anaphylaxis and (2) pharmacological and non-pharmacological approaches for the longterm management of anaphylaxis.*

***Methods**: Seven databases were searched for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-after studies, and interrupted time series and–only in relation to adrenaline–case-series investigating the effectiveness of interventions in managing anaphylaxis.*

***Results**: Fifty-five studies satisfied the inclusion criteria. We found no robust studies investigating the effectiveness of adrenaline (epinephrine), H1-antihistamines, systemic glucocorticosteroids or methylxanthines to manage anaphylaxis. There was evidence regarding the optimum route, site and dose of administration of adrenaline from trials studying people with a history of anaphylaxis. This suggested that administration of intramuscular adrenaline into the middle of vastuslateralis muscle is the optimum treatment. Furthermore, fatality register studies have suggested that a failure or delay in administration of adrenaline may increase the risk of death. The main long-term management interventions studied were anaphylaxis management plans and allergen-specific immunotherapy. Management plans may reduce the risk of further reactions, but these studies were at high risk of bias. Venom immunotherapy may reduce the incidence of systemic reactions in those with a history of venom-triggered anaphylaxis.*

***Conclusions**: There is at present little in the way of robust evidence to guide decisions on the acute or long-term management of anaphylaxis. Given the risk of death and the considerable morbidity associated with anaphylaxis, these evidence gaps need to be filled.*

Originally published as: Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilo MB, Cardona V, Dubois AEJ, DunnGalvin A, Eigenmann P, Fernandez-Rivas M, Halken S, Lack G, Niggeman B, Rueff F, Santos AE, Vlieg-Boerstra B, Zolkipli ZQ & Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group. Management of anaphylaxis: a systematic review. *Allergy* 2014;69:168–175. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

Anaphylaxis can be defined as a "severe, life-threatening generalised or systemic hypersensitivity reaction" (1, 2). Several working definitions of anaphylaxis have been formulated to aid clinical diagnosis and management (1-4). The most well-known of these is the consensus clinical definition proposed by Sampson *et al*., which involved representatives of a number of international allergy organisations, including the European Academy of Allergy and Clinical Immunology (EAACI) (1).

Care of patients with anaphylaxis involves consideration of both the acute, emergency treatment of reactions and long-term care, which aims to reduce the risk of further reactions and improve outcomes if, despite these measures, a further reaction ensues (1). It remains very difficult to predict the severity of a reaction and, in fatal episodes, death may occur within minutes of an anaphylactic reaction, these observations underscoring the importance of effective, emergency management.

This systematic review is one of seven inter-linked evidence syntheses that were undertaken in order to provide a state-of-the-art synopsis of the current evidence-base in relation to epidemiology, prevention, diagnosis and clinical management, and impact on quality of life. There were used to inform clinical recommendations for the *EAACI Guidelines for Food Allergy and Anaphylaxis*.

Aims

The aims of this systematic review were to assess the effectiveness of (1) interventions for the acute management of anaphylaxis and (2) pharmacological and non-pharmacological approaches for the long-term management of anaphylaxis.

Methods

Details of the methodology for the identification, selection, and inclusion of the studies have been previously reported (9,10). In summary, our inclusion criteria were systematic reviews with or without meta-analyses, randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), controlled before-after (CBA) designs, interrupted time series (ITS) studies, and case-series, with a minimum of 10 patients, for studies investigating the use of adrenaline (Figure 1).

Standard methods for performing systematic reviews were used. A descriptive summary with data tables was produced to summarize the literature. Quality assessments of studies were undertaken using appropriate tools (see online supplement). We preferentially extracted data on risk ratios and mean differences. Because data were not suitable for meta-analysis (11), a narrative synthesis of the data was undertaken.

Further details can be found in the online supplement.

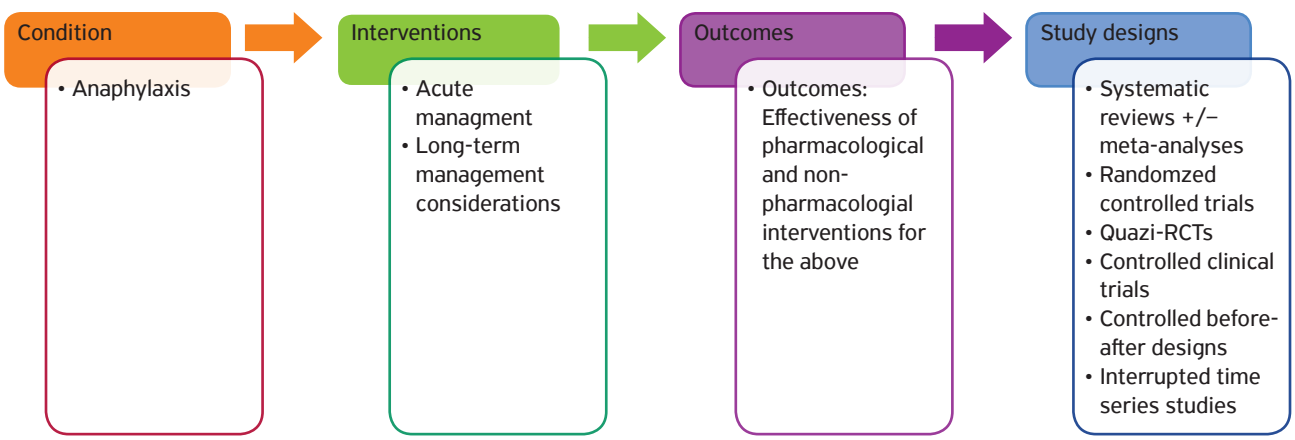


Figure 1 Conceptualization of systematic review of interventions for the acute and long- term management of anaphylaxis

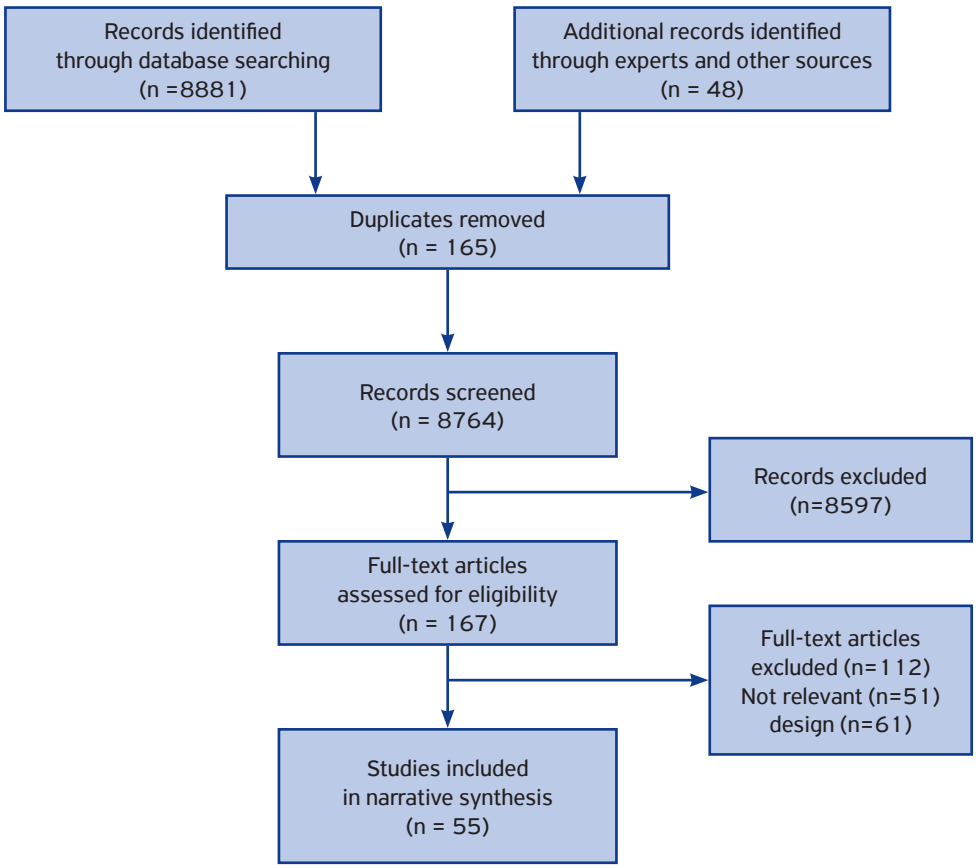


Figure 2 PRISMA diagram for searches on the acute and long-term management of anaphylaxis

Results

The searches identified a total of 8929 potentially eligible studies, of which 55 satisfied our eligibility criteria and were therefore included in this review (Figure 2). The key characteristics and main findings of all included studies are detailed in online Table E1 and the quality assessment of these studies is summarized in Tables E2 (systematic reviews) and E3 (primary studies). The main findings are further discussed below.

ACUTE MANAGEMENT OF ANAPHYLAXIS

Adrenaline

We identified 14 studies: four systematic reviews (12-15) (including one update), four RCTs (16-19), two case-series (20, 21) and five fatality register-based reports (22-26) (including two updates) on the effectiveness of adrenaline.

Effectiveness and timing

Three well conducted systematic reviews (19-21) that looked at the use of adrenaline for the treatment of anaphylaxis and adrenaline auto-injectors found no RCTs or quasi-RCTs. Weaker evidence from a case series of 27 patients receiving emergency pre-hospital treatment found that prompt use of adrenaline may reduce the risk of fatality (26). The second case series found that a fifth of children experiencing anaphylaxis needed more than one dose of adrenaline; healthcare professionals administered this second dose in 94% of cases. The five fatality register-based reports (22-26) provided important insights into the difficulties of predicting the severity of subsequent reactions,

risk factors for fatality, co-existing asthma and the under-issuing, poor carriage, under-use, delayed use and incorrect use of adrenaline auto-injectors. These reports revealed that fatalities can occur, even if adrenaline is used correctly.

Site and route of delivery

Two RCTs (22, 24) found that, in both children and adults, maximal plasma concentration occurs quicker with the intra-muscular than subcutaneous route. The latter trial in adults also concluded that the optimum site of injection was the vastuslateralis muscle. A systematic review of poor quality found that the use of subcutaneous adrenaline was not contraindicated in patients older than 35 years without a history of coronary artery disease (17).

Dose in children

One RCT compared the effectiveness of the previous designs of the Epipen Junior and Epipen in children weighing 15-30 kgs. The authors concluded that children should be prescribed the 0.3mg Epipen from 30kgs (17).

Glucocorticosteroids

Two systematic reviews investigating the use of glucocorticosteroids in the acute management of anaphylaxis (27, 28) failed to identify any RCTs or quasi-RCTs and so were unable to make any recommendations.

Antihistamines

Two systematic reviews investigating the use of H1-antihistamines in the acute management of anaphylaxis (29, 30) identified no suitable RCTs or quasi-RCTs. Two RCTs that investigated the use of H1- and H2-antihistamines in acute allergic reactions (only a small proportion had anaphylaxis) (31, 32) revealed that the combination of H1- and H2-antihistamines was superior to H1-antihistamines alone in treating urticaria, but not angioedema; the second showed that pruritus was better controlled by H1-antihistamines than H2-antihistamines, and that combined treatment offered no advantage.

Methylxanthines

We found one systematic review investigating the effectiveness of methylxanthines in the acute management of anaphylaxis; this found no trials in humans (33).

LONG-TERM MANAGEMENT OF ANAPHYLAXIS

Anaphylaxis management plans

We identified two systematic reviews investigating anaphylaxis management plans (34, 35). The first found no evidence from RCTs or quasi-RCTs investigating the clinical effectiveness of anaphylaxis management plans for the prevention of recurrences or improvement in outcomes from anaphylaxis. The second systematic review had a wider focus including qualitative, epidemiological and experimental studies undertaken with or without a control group. This demonstrated that there were no universally accepted anaphylaxis management plans. It however identified four studies, which suggested that anaphylaxis management plans may substantially reduce the risk of future, severe reactions.

Venom immunotherapy (VIT)

We found three systematic reviews and meta-analyses (36-38) and one further systematic review without a meta-analysis investigating the effectiveness of VIT. These four systematic reviews included a total of 23 unique studies of varying quality. Twelve of these studied patients with a history of anaphylaxis using eligible study designs and have therefore also individually been assessed (see Tables E1 and E3) (40-51).

The high-quality systematic review by Boyle *et al.*, identified six RCTs and 1 quasi-RCT (392 participants) (36). Five studies involved subcutaneous immunotherapy and one sublingual immunotherapy. Patients treated with VIT had less systemic allergic reactions (RR=0.10, 95% CI 0.03 to 0.28) and better quality of life (mean difference=1.21 points on a 7-point scale (95% CI 0.75 to 1.67)). Subcutaneous VIT treated patients had more systemic adverse reactions (RR=8.16, 95% CI 1.53 to 43.46). One systematic review of low quality showed that VIT was effective in reducing the risk of further systemic reactions (49).

The systematic review by Hockenhull *et al.* (39) investigated the clinical- and cost-effectiveness of a specific VIT subcutaneous preparation (Pharmalgen), and included nine trials (four RCTs and five quasi-RCTs), all judged to be of poor quality. They modelled cost-effectiveness showing a cost of £8-20 (€10-25)

million/life year gained, assuming a base-case scenario of no improvement in quality of life. A sensitivity analysis showed that VIT was more cost-effective in those at high risk of further stings or if improvements in quality of life and anxiety associated with VIT were included in the model.

Educational interventions

A quasi-experimental trial evaluated whether an educational intervention could improve compliance with carrying an in-date adrenaline auto-injector in high school children with food allergy (52). The intervention failed to demonstrate any significant difference in carriage rates in the intervention and control groups.

Psychological interventions

One systematic review of low quality investigated the management of anxiety related to children with a history of anaphylaxis (53). It concluded that anaphylaxis can place a substantial psychological burden on children, adolescents and carers, and that dealing with this anxiety may improve outcomes.

Prophylactic interventions

Interventions have been studied to prevent anaphylaxis. A major limiting factor with these studies is the fact that the groups studied were not known to be at high risk of anaphylaxis.

Adrenaline admixture with snakebite anti-venom

A systematic review and meta-analysis demonstrated that adrenaline premedication reduces adverse reactions when administering snakebite anti-venom (54) (RR=0.32, 95% CI 0.18 to 0.58). A subsequent factorial designed RCT investigated the use of adrenaline, antihistamines and glucocorticosteroids given alone or in combination (55). This also found adrenaline, but not other interventions, to be effective in reducing the risk of anaphylaxis.

Pharmacological interventions for the prevention of anaphylaxis to iodinated contrast media

One systematic review of nine trials involving 10011 unselected patients failed to demonstrate that premedication with glucocorticosteroids, H1-antihistamines or a combination of H1- and H2-antihistamines prevented anaphylaxis triggered by iodinated contrast media (56).

Discussion

This comprehensive review of the international literature has found little robust evidence for the acute or long-term management of anaphylaxis. The only trial evidence uncovered for the emergency management of anaphylaxis was in relation to adrenaline, but these trials have been undertaken in patients who were at the time not experiencing anaphylaxis (22-25). Taken together with the methodologically lower quality evidence from case-series and fatality registers, there is some evidence to support the use of adrenaline for the emergency management of anaphylaxis. The evidence points to the importance of injecting this by the intramuscular route into the antero-lateral aspect of the thigh. In relation to longer-term management considerations, anaphylaxis management plans may be effective in reducing the risk of recurrence. VIT reduces the severity of reactions to subsequent stings and improves quality of life and concerns around cost-effectiveness remain.

Acute management of anaphylaxis

Case fatality register studies have demonstrated that deaths can occur within minutes of the onset of a reaction and have highlighted how difficult it is to predict the severity of reactions (12). It is therefore consistently advocated by guidelines that all reactions are promptly managed by initiating a range of pharmacological and non-pharmacological interventions. This review failed to identify any high-quality studies investigating the role of non-pharmacological interventions such as the role of cardiopulmonary resuscitation and posture. In contrast, we found some evidence investigating the role of adrenaline – the main drug treatment advocated in guidelines. This evidence was derived from case series, fatality registers and a limited number of trials in people not experiencing anaphylactic reactions. Overall, this body of evidence was weak, but pointed to the importance of the early administration of adrenaline, in an appropriate dose, administered by the intramuscular route into the anterolateral aspect of the thigh. Given the considerable ethical and logistical challenges in undertaking trials of parenteral adrenaline in patients experiencing anaphylaxis, it is unlikely that stronger evidence will be forthcoming.

We found no evidence from primary studies for other potential treatments, such as fluid replacement, oxygen, glucocorticosteroids, antihistamines, methylxanthines

and bronchodilators, and it is therefore not possible to offer any recommendations for the use of these treatments.

Long-term management of anaphylaxis

The long-term management of anaphylaxis centres on the need to identify triggers and co-factors, providing advice on how to minimise further reactions, and equipping individuals with the skills and equipment needed to manage further reactions (57). Consideration also needs to be given to ameliorate any psychological consequences of a diagnosis of anaphylaxis. Researchers have therefore thus far focused attention on the role of anaphylaxis management plans, immune-modulatory interventions, and a variety of educational and psychological interventions.

The formal experimental evidence in support of anaphylaxis management plans is limited. Studies that have, however, used before-after designs and which therefore did not satisfy our inclusion criteria have found that these may result in substantial reductions in the risks of further reactions (58, 59). Given the high risk of confounding with such study designs, this evidence must be interpreted with caution.

The single educational study included failed to show a positive effect on carriage of in-date adrenaline auto-injectors by high school children with previous anaphylaxis. A study with a before-after design found that the input of a multi-disciplinary allergy clinic was effective in improving parents' knowledge of food allergy and in reducing subsequent reactions (60). This evidence is encouraging, but due to the high inherent risk of bias associated with such a design these findings need to be treated with caution until more evidence from studies employing more robust study designs are forthcoming. The systematic review on psychological interventions for children with a history of anaphylaxis and their parents/carers was difficult to interpret because of its poor quality and reporting. Whilst clearly demonstrating that a number of studies have found that a diagnosis of anaphylaxis can be associated with anxiety and impaired quality of life, there was very little in the way of primary evidence demonstrating that intervening could improve outcomes in such individuals/families.

Immuno-modulatory approaches are of considerable interest as these have the potential to modify the disease course and may possibly prove curative. We found a modest body of evidence in relation to VIT in relation to the management of those with stinging-insect anaphylaxis, although much of this was judged to be at high risk of bias. This body of evidence did however consistently demonstrate that VIT can significantly reduce the severity of subsequent systemic reactions to insect stings, but given the infrequency of further stings and the low number of fatalities, it was not possible to assess whether VIT reduced the risk of fatal reactions to insect stings. There were no formal cost-effectiveness studies identified, the only potentially relevant evidence emerging from modelling studies in relation to a specific product: this found that VIT is most likely to be cost-effective in populations at high risk of further exposure (e.g. bee keepers, their family members and those who live near bee farms) or if likely benefits to quality of life are accounted for. VIT is a treatment which has been shown to reduce subsequent reactions and although the treatment may give rise to adverse effects it is a treatment patients prefer over the long-term carriage of an adrenaline auto-injector. In state-funded health services, however, the cost implications of such an intervention may prevent widespread availability limiting its use to high-risk patients only where its cost-effectiveness profile is likely to be much more favorable.

We found no eligible studies investigating the role of desensitization therapy in the management of those with anaphylaxis to drugs or latex. Studies investigating the effectiveness of oral and sublingual immunotherapy have mainly been undertaken in those without a history of anaphylaxis to foods; these studies are therefore reviewed in the companion systematic review on the management of food allergy.

Prophylactic approaches can also potentially play a role in those with a history of anaphylaxis. The evidence we uncovered did not however directly focus on this population. Rather, the approaches studied have been used in the general population and have found that: prophylactic use of adrenaline can substantially reduce the risk of anaphylaxis associated with anti-snake venom and that adding antihistamines or glucocorticosteroids conferred no additional advantage; and that antihistamines and glucocorticosteroids were of questionable value in preventing anaphylaxis associated with iodinated contrast media based diagnostic investigations in unselected populations.

Implications for future research

This review has underscored the dearth of high quality research to guide everyday clinical decision making. There is then a pressing need to develop the evidence-base for both the acute and long-term management of this potentially life-threatening disorder. In relation to acute management, it is widely accepted that it would be unethical to undertake studies investigating the effectiveness of adrenaline when compared with placebo, but trials could potentially be undertaken investigating the optimum dose, site, route and timing of administration of adrenaline. Other important questions that need to be addressed include establishing the role of H1- and H2-antihistamines and glucocorticosteroids and these could also potentially be investigated using formal experimental designs. Similarly, there are a range of interventions delivered with the aim of improving longer-term outcomes – for example, provision of adrenaline auto-injectors, anaphylaxis management plans, immunotherapy – and these can all potentially also be studied using formal trial designs. Ideally, these studies should investigate the impact of interventions on the outcomes that have been carefully described in recent Cochrane and other systematic reviews (12, 14, 28, 29, 35). A fuller discussion of the research agenda will be made available in the forthcoming EAACI Anaphylaxis Guidelines (Chapter 4.3).

Conclusions

There is at present little in the way of robust evidence to guide decisions on the acute or long-term management of anaphylaxis. Key recommendations from this review have been summarized in Box 1. Given the risk of death and the considerable morbidity associated with anaphylaxis these evidence gaps need to be filled wherever possible (61). These gaps include the need for educational interventions for patients, carers and healthcare professionals, lack of data on the pharmacodynamics of adrenaline and the ideal dosage in children and to some extent adults, and a lack of effective study designs on the benefits of educational plans (62).

Box 1 Key recommendations

- There is some evidence that prompt administration of adrenaline may be life-saving; it should therefore be used as the drug of first choice in the acute management of anaphylaxis.
- Adrenaline should be administered by the intramuscular route into the anterolateral aspect of the mid-thigh.
- Anaphylaxis management plans may reduce the severity of subsequent reactions.
- VIT may reduce the severity of subsequent reactions and improve quality of life, but cost-effectiveness considerations should be considered, particularly in those at low risk of further stings.
- Adrenaline used prophylactically can reduce severe adverse effects associated with anti-snake venom administration.

Acknowledgments

We would like to acknowledge the support of the EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in supporting the undertaking of this systematic review. We would also like to thank the EAACI Executive Committee for their helpful comments and suggestions.

Contributorship

AS, AM and GR conceived this review. It was undertaken by SD with the support of SSP, GR and AS. SD, AS and GR led the drafting of the manuscript and all authors critically commented on drafts of the manuscript.

Funding

EACCI.

Conflicts of interest

None known.

References

1. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier B, Lockey R *et al.* A revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of World Allergy Organization. *J Allergy Clin Immunol* 2004;113:832–836.
2. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G *et al.*; EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy* 2007;62:857-871.
3. American Academy of Pediatrics, Committee on School Health. Guidelines for urgent care in school. *Pediatrics* 1990;86:999-1000.

4. International Collaborative Study of Severe Anaphylaxis. An epidemiologic study of severe anaphylactic and anaphylactoid reactions among hospital patients: methods and overall risks. *Epidemiology* 1998;9:141-146.
5. Australasian Society of Clinical Immunology and Allergy Inc. (ASCIA). Guidelines for EpiPen prescription. ASCIA Anaphylaxis Working Party 2004. Available online at http://www.allergy.org.au/anaphylaxis/epipen_guidelines.htm. Last accessed 20 September 2012.
6. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; and Joint Council of Allergy, Asthma, and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;15(3 suppl):S483-S523.
7. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock A, Branum A *et al.* Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-397.
8. Walker S, Sheikh A. Managing anaphylaxis: effective emergency and long-term care are necessary. *Clin Exp Allergy* 2003;33:1015-1018.
9. Dhami S, Panesar SS, Rader T, Muraro A, Roberts G, Worm M, Sheikh A; EAACI Food Allergy and Anaphylaxis Guidelines group. The acute and long-term management of anaphylaxis: protocol for a systematic review. *Clin Transl Allergy* 2013;3:14.
10. International Prospective Register of Systematic Reviews (PROSPERO http://www.crd.york.ac.uk/prospero): CRD42 013003703.
11. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. *Am Statis* 1998;52:119-126.
12. Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev* 2008;CD006312.
13. Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev* 2012:CD006312.
14. Sheikh A, Simons FER, Barbour V, Worth A. Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community. *Cochrane Database Syst Rev* 2012;8. DOI: 10.1002/14651858.CD008935.pub2
15. Safdar B, Cone D, Pham K. Subcutaneous epinephrine in the prehospital setting. *Prehosp Emerg Care* 2000;5:200-207.
16. Simons FE, Roberts J, Gu X, Simons K. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;101:33-37.
17. Simons FE, Gu X, Simons K. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001;108:871-873.
18. Simons FE, Gu X, Johnston L, Simons K. Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis? *Pediatrics* 2000;106:1040-1044.
19. Simons FER, Gu X, Silver N, Simons K. EpiPenJr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. *J Allergy Clin Immunol* 2002;109:171-175.
20. Jarvinen K, Sicherer S, Sampson H, Nowak-Wegrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 2008;122:133-138.
21. Soreide E, Buxrud T, Harboe S. Severe anaphylactic reactions outside hospital: etiology, symptoms and treatment. *Acta Anaesthesiol* 1988:32:339-342.
22. Bock S, Munoz-Furlong, Sampson H. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-193.
23. Bock S, Munoz-Furlong, Sampson H. Further fatalities caused by anaphylactic reactions to food, 2001-2006. Letter *J Allergy Clin Immunol* 2007;119:1016-1018.
24. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30:1144-1150.
25. Pumphrey RH, Gowland H. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol* 2007;119:1018-1019.
26. Sampson HA, Mendelson L, Rosen JP, Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-384.
27. Choo K, Simons FE. Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2010;65:1205-1211.
28. Choo K, Simons FE. Sheikh A. Glucocorticoids for the treatment of anaphylaxis. lucocorticoids for the treatment of anaphylaxis: *Cochrane Database Syst Rev* 2012; CD007596.
29. Sheikh A, Ten Broek V, Brown GA, Simons FE. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2007;62:830-837.
30. Sheikh A, Ten Broek V, Brown GA, Simons FE. H1-antihistamines for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev* 2012; CD006160.
31. Lin RY, Curry A, Pesola GR *et al.* Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antihistamines. *Ann Emerg Med* 2000;36:462-468.
32. Runge J, Martinez JC, Caravati E, Williamson S, Hartsell S. Histamine antihistamines in the treatment of acute allergic reactions. *Ann Emerg Med* 1992;21:237-242.
33. Ernst ME, Graber MA. Methylxanthine use in anaphylaxis: what does the evidence tell us? *Ann Pharmacoth* 1999;33:1001-1004.

34. Choo K, Sheikh A. Action plans for the long-term management of anaphylaxis: systematic review of effectiveness. *Clin Exp Allergy* 2007;37:1090-1094.
35. Nurmatov U, Worth A, Sheikh A. Anaphylaxis management plans for the acute and long-term management of anaphylaxis: a systematic review. *J Aller Clin Immunol* 2008; 22:353-361, 361.e1-3.
36. Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M, Oude Elberink JN. Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev* 2012;10:CD008838.
37. Ross R, Nelson H, Finegold I. Effectiveness of specific immunotherapy in the treatment of hymenoptera venom hypersensitivity: a meta-analysis. *Clin Ther* 2000;22: 351-358.
38. Watanabe A. Specific-immunotherapy using Hymenoptera venom: systematic review. *Sao Paulo Med J* 2010;128: 30-37.
39. Hockenhull J, Elremeli M, Cherry MG, Mahon J, Lai M, Darroch J *et al.* A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen for the treatment of bee and wasp venom allergy. *Health Technol Assess* 2012;16;1-110.
40. Brown S, Wiese M, Blackman K and Heddle R. Ant venom immunotherapy: a double-blind, placebo-controlled, cross-over trial. *The Lancet* 2003;361:1001-1006.
41. Golden D, Valentine M, Kagey-Sobotka A, Lichtenstein L. Regimens of hymenoptera venom immunotherapy. *Ann Int Med* 1980;92:620-624.
42. Hunt K, Valentine M, Sobotka A, Benton A, Amodio F, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *New Eng J Med* 1978;299:157-161.
43. Mosbech H, Malling H, Biering I, Bowadi H, Soborg M *et al.* Immunotherapy with Yellow Jacket Venom. A comparative study including three different extracts, one adsorbed to Aluminium Hydroxide and two unmodified. *Allergy* 1986;41:95-103.
44. Muller U, Lanner A, Schmid P, Bischof MM, Dreborg S. *et al.* A double blind study on immunotherapy with chemically modified honey bee venom: monomethoxy polyethylene glycol-coupled versus crude honey bee venom. *Int. Arch Allergy Appl Immunol* 1985;77:201-203.
45. Muller U, Rabson A, Bischof M, Lomnitzer R, Dreborg S, Hoigne R. A double-blind study comparing glycol-modified honeybee venom and unmodified honeybee venom for immunotherapy. *J Allergy Clin Immunol* 1987;80:252-261.
46. Oude Elberink J., de Monchy J., van der Heide S., Guyatt H., Dubois A. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol* 2002;110:174-182.
47. Oude Elberink J, van der Heide S, Guyatt H, Dubois A. Analysis of the burden of treatment in patients receiving an Epipen for yellow jacket anaphylaxis. *J Allergy Clin Immunol* 2006;118:174-182.
48. Quercia O, Rafanelli S, Puccinelli P, Stefanini F. The safety of cluster immunotherapy with aluminium hydroxide-adsorbed honey bee venom extract. *J Invest Allergol Clin Immunol* 2001;11:27-33.
49. Golden D, Kagey-Sobotka A, Valentine M, Lichtenstein L. Prolonged maintenance interval in Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1981;67:482-484.
50. Muller U, Thurnheer R, Patrizzi R, Spiess J, Hoigne R. Immunotherapy in bee sting hypersensitivity. *Allergy* 1979;34:369-378.
51. Thurnheer U, Muller U, Stoller R, Lanner A, Hoigne R. Venom Immunotherapy in hymenoptera sting allergy. *Allergy* 1983;38:465-475.
52. Spina J, Mcintyre L, Pulcini J. An intervention to increase high school students compliance with carrying auto-injectable epinephrine: a MASNRN Study. *J Sch Nurs* 2012;28:230-237.
53. Manassis K. Managing anxiety related to anaphylaxis in childhood: A systematic review. *J Allergy (Cairo)* 2012;2012:316296 doi: 10.1155/2012/ 316296.
54. Habib A. Effect of premedication on early adverse reactions following antivenom use in snakebite: A Systematic Review and meta-analyses. *Drug Saf* 2011;34:869-880.
55. De Silva H, Pathmeswaran A, Ranasinha C, Jayamanne S, Samarakoon B, Hittharage A *et al.* Low-Dose Adrenaline. Promethazine, and Hydrocortisone in the Prevention of Acute Adverse Reactions to Antivenom following Snakebite: A Randomized, Double-Blind, Placebo=controlled Trial. *PLOS Med* 2011;8:e1000435.
56. Tramer M, von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ* 2006;333:675.
57. Walker S, Sheikh A. Managing anaphylaxis: effective emergency and long-term care are necessary. *Clin Exp Allergy* 2003;33:1015-1018.
58. Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. *Lancet* 2001;357:111-115.
59. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. *Clin Exp Allergy* 2005;35:751-756.
60. Kapoor S, Roberts G, Bynoe Y, Gaughan M, Habibi P, Lack GAllergy. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy* 2004;59:185-191.
61. Kastner M, Harada L, Waserman S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. *Allergy* 2010;65:436-444.
62. Papadopoulos NG, Agache I, Bavbek S, Bilo BM, Braido F, Cardona V *et al.* Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;2:21.

4.3

ANAPHYLAXIS

EAACI GUIDELINES

A Muraro[1*], G Roberts[2-4*], M Worm[5*], MB Bilò[6], K Brockow[7], M Fernández Rivas[8], AF Santos[9-11], ZQ Zolkipli[2-4], A Bellou[12], K Beyer [13], C Bindslev-Jensen[14], V Cardona[15], AT Clark[16], P Demoly[17], AEJ Dubois[18], A DunnGalvin[19], P Eigenmann[20], S Halken[21], L Harada[22], G Lack[9, 10], M Jutel[23], B Niggemann[24], F Ruëff[25], F Timmermans[26], BJ Vlieg–Boerstra[27], T Werfel[28], S Dhami[29], SS Panesar[29], CA Akdis[30], A Sheikh[31], on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group

AFFILIATIONS

[1] Department of Department of Mother and Child Health, Padua General University Hospital, Padua, Italy

[2] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK

[3] NIHR, Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[4] Human Development in Health and Clinical and Experimental Sciences Academic Units, University of Southampton Faculty of Medicine, Southampton, UK

[5] Allergy-Center-Charité, Dept of Dermatology and Allergy, Charité Universitätsmedizin, Berlin, Germany

[6] Allergy Unit, Dept. Internal Medicine, University Hospital, Ospedali Riuniti, Ancona, Italy

[7] Department of Dermatology and Allergy, Biederstein, Technische Universität München, Munich, Germany.

[8] Allergy Department, Hospital Clinico San Carlos, IdISSC, Madrid, Spain

[9] Department of Pediatric Allergy, Division of Asthma, Allergy & Lung Biology, King's College London, London, UK

[10] King's College London, King's Health Partners, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK

[11] Immunoallergology Department, Coimbra University Hospital, Coimbra, Portugal

[12] European Society for Emergency Medicine and Emergency Department, University Hospital and Faculty of Medicine, Rennes, France

[13] Department of Pediatric, Pneumology and Immunology, Charité, Universitatsmedizin Berlin, Berlin, Germany

[14] Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark

[15] Allergy Section, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[16] Allergy section, Department of Medicine, University of Cambridge, Cambridge, UK.

[17] Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France

[18] University of Groningen, University Medical Center Groningen, Department of Pediatric Pulmonology and Pediatric Allergy, and GRIAC Research Institute, Groningen, the Netherlands

[19] Department of Paediatrics and Child Health, University College, Cork, Ireland

[20] University Hospitals of Geneva, Geneva, Switzerland

[21] Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[22] Anaphylaxis Canada

[23] Wroclaw Medical University, Wroclaw, Poland

[24] University Hospital Charité, Berlin, Germany

[25] Department of Dermatology and Allergology, Ludwig-Maximilians-Universität, München, Germany

[26] Nederlands Anafylaxis Netwerk – European Anaphylaxis Taskforce, Dordrecht, the Netherlands

[27] Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, the Netherlands

[28] Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany

[29] Evidence-Based Health Care Ltd, Edinburgh, UK.

[30] Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.

[31] Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK

** Joint first author*

EXPERT PANEL

C Camargo[1], J Gardener[2], G Hedlin[3], M Levine[4], P Lieberman[5], R Loh[6], H Mosbech[7], J Ring [8], M Said[9], E Simons[10], J Soar [11], M Triggiani [12]

[1] Department of Emergency Medicine and the Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA

[2] Royal Free Hospital, London, UK

[3] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden; Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden

[4] Division of Allergy, School of Child and Adolescent Health, Red Cross War Memorial Children's Hospital, Cape Town, South Africa

[5] Department of Medicine, Nova Southeastern University, Davie, Fla, USA

[6] Princess Margaret Hospital, Child and Adolescent Health Service, Subiaco, Western Australia, Australia

[7] Allergy Clinic, Copenhagen University Hospital, Gentofte, Copenhagen, Denmark.

[8] Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein der TU München, Munich, Germany

[9] Allergy & Anaphylaxis Australia Inc, Australia

[10] Professor in the Department of Pediatrics and Child Health and the Department of Immunology at the University of Manitoba, Winnipeg, Manitoba, Canada

[11] Consultant in Intensive Care, North Bristol NHS Trust, Bristol, UK

[12] Dipartimento di Medicina Clinica, Scienze Cardiovascolari ed Immunologiche, Università degli Studi di Napoli "Federico II", Napoli, Italy.

Anaphylaxis is a clinical emergency and all healthcare professionals should be familiar with its recognition and acute and ongoing management. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on Anaphylaxis. They aim to provide evidence-based recommendations for the recognition, risk factor assessment and the management of patients who are at risk of, are experiencing, or have experienced anaphylaxis. While the primary audience is allergists, these guidelines are also relevant to all other healthcare professionals. The development of these guidelines has been underpinned by two systematic reviews of the literature, on the epidemiology and clinical management of anaphylaxis. Anaphylaxis is a potentially life-threatening condition whose clinical diagnosis is based on recognition of a constellation of presenting features. First-line treatment for anaphylaxis is intramuscular adrenaline. Useful second-line interventions may include removing the trigger where possible, calling for help, correct positioning of the patient, high flow oxygen, intravenous fluids, inhaled short-acting bronchodilators and nebulized adrenaline. Discharge arrangements should involve an assessment of the risk of further reactions, a management plan with an anaphylaxis emergency action plan and, where appropriate, prescribing an adrenaline auto-injector. If an adrenaline auto-injector is prescribed, education on when and how to use the device should be provided. Specialist follow-up is essential to investigate possible triggers, to perform a comprehensive risk assessment and prevent future episodes by developing personalized risk reduction strategies including, where possible, commencing allergen immunotherapy. Training for the patient and all caregivers is essential. There are still many gaps in the evidence base for anaphylaxis.

Originally published as: Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, Santos AF, Zolkipli ZQ, Bellou A, Beyer K, Bindslev-Jensen C, Cardona V, Clark AT, Demoly P, Dubois AEJ, DunnGalvin A, Eigenmann P, Halken S, Harada L, Lack G, Jutel M, Niggemann B, Ruëff F, Timmermans F, Vlieg–Boerstra BJ, Werfel T, Dhami S, Panesar S, Akdis CA, Sheikh A, on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014; DOI: 10.1111/all.12437. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

Anaphylaxis is a clinical emergency and all healthcare professionals should be familiar with its management. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Anaphylaxis and are part of the *EAACI Guidelines for Food Allergy and Anaphylaxis*. The guidelines aim to provide evidence-based recommendations for the recognition, risk assessment and management of patients who have experienced, are experiencing or are at risk of experiencing anaphylaxis. The primary audience is allergists but they are also likely to be of relevance to all other healthcare professionals (e.g. doctors, nurses and paramedics) in emergency departments (ED), hospital and primary care. Development of the guidelines have been informed by two systematic reviews of the epidemiology and clinical management of anaphylaxis (1, 2) with weaker forms of evidence being used where there were insufficient data or where high level evidence is practically or ethically unobtainable. These guidelines build on the previous EAACI Position Paper on Anaphylaxis in Childhood (3) and are complementary to other current anaphylaxis guidelines (4-6). Distinctive features include a European focus and the placing of particular emphasis on the practical issues associated with long-term management.

Anaphylaxis is defined as a "severe, life-threatening systemic hypersensitivity reaction" (7) (Box 1). This is characterized by being rapid in onset with potentially life-threatening airway, breathing or circulatory problems; it is usually, but not always, associated with skin and mucosal changes (5). These guidelines focus mainly on allergic anaphylaxis involving specific-immunoglobulin-E (IgE) but are also relevant to anaphylaxis involving other mechanisms.

Methods

These Guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (8, 9), a structured approach to guideline production. This is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. The process began in January 2012, ensuing over 18 months, with in detail discussion of the frame of guidelines for clinical practice, the main aims of the guidelines, the target conditions, agreeing the intended end-user for the recommendations, agreeing the intended end-user group, and ensuring adequate professional and lay representation in the guidelines development process. The process involved:

Clarifying the scope and purpose of the guidelines

The scope of these EAACI guidelines is multi-faceted providing statements that assist clinicians

Box 1 Key terms

Term	Definition
Anaphylaxis	Severe, potentially life-threatening systemic hypersensitivity reaction (6, 7). This is characterized by being rapid in onset with life-threatening airway, breathing or circulatory problems, and is usually, although not always, associated with skin and mucosal changes.
Adrenaline (epinephrine)	A drug with combined α- and β-agonist actions which result in (i) peripheral vasoconstriction thereby reversing hypotension and mucosal edema, (ii) increased rate and force of cardiac contractions thereby reversing hypotension, and (iii) reversal of bronchoconstriction and reduction in release of inflammatory mediators.
Adrenaline auto-injector	Device designed to be used by a non-medical person to give a pre-defined dose of intramuscular adrenaline.
Co-factors	Patient-related or external circumstances that are associated with more severe allergic reactions. They are also known as augmentation factors.
Management plans	Lay summary of the clinical plan that patients should follow. It will have an emergency action plan with likely presenting symptoms and how to respond to each. It should also provide additional information such as avoidance advice if applicable and contact details for further advice from allergy clinic and patient support groups.

in the management of anaphylaxis in daily practice, harmonizing the approach to this clinical emergency among stakeholders across Europe and advocating for further research.

Ensuring appropriate stakeholder involvement

Participants in the Anaphylaxis Taskforce represented a range of 14 European countries, and disciplinary and clinical backgrounds, for example emergency physicians (A B Bellou), primary care (A Sheikh), psychology (A DunnGalvin), patient groups (F Timmermans, L Harada) and dietitians (BJ Vlieg–Boerstra).

Systematic reviews of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree to three key questions that were then pursued through two formal systematic reviews of the evidence (1, 2, 10, 11) (see Box 2) (see Chapters 4.1, 4.2).

Formulating recommendations

We graded the strength and consistency of key findings from these systematic reviews to formulate evidence-linked recommendations for care (12) (Box 3). This involved formulating clear recommendations and making clear the strength of evidence underpinning each recommendation. Experts identified the resource implications of implementing the recommendations, barriers and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation.

Peer review and public comment

A draft of these guidelines was externally peer-reviewed by invited experts from a range of organizations, countries and professional backgrounds. Additionally the draft guidelines were made available on the EAACI website for a 3-week period in June 2013 to allow all stakeholders to comment. All feedback was considered by the Anaphylaxis Taskforce and, where appropriate, final revisions were made in light of the feedback received. We will be pleased to continue to receive feedback on these guidelines, which should be addressed to the first author.

Identification of evidence gaps

The process of developing these guidelines has identified a number of evidence gaps and we plan in future to formally prioritize these. We plan to draft outline research briefs that funders can use to commission research on these questions.

Box 2 Key questions addressed in the two supporting systematic reviews (1, 2)

- What is the epidemiology (i.e. frequency, risk factors and outcomes) of anaphylaxis and how do these vary by time, place and person?
- What is the effectiveness of interventions for the acute management of anaphylaxis?
- What is the effectiveness of interventions for the long-term management of those at high risk of further episodes of anaphylaxis?

Box 3 Assigning levels of evidence and recommendations (12)

LEVEL OF EVIDENCE	
Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, non-randomized studies (e.g. cohort, case-control)
Level III	One-group non-randomized (e.g. before and after, pre test and post test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case-series)
Level V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
GRADES OF RECOMMENDATION	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level

Editorial independence and managing conflict of interests

The production of these guidelines was funded and supported by EAACI. The funder did not have any influence on the guidelines production process, its contents or on the decision to publish. Taskforce members' conflicts of interest were taken into account by the Taskforce chair as recommendations were formulated.

Updating the Guidelines

We plan to update these guidelines in 2017 unless there are important advances before then.

Epidemiology

A detailed description of the epidemiology of anaphylaxis can be found in the underpinning systematic review referred to above (1) (Chapter 4.1). The exact incidence and prevalence of anaphylaxis in Europe is challenging to establish due to a number of factors. The current definition of anaphylaxis is complex and difficult to use in epidemiological studies (13). Additionally, the World Health Organization's International Classification of Diseases codes (ICD-9 and current ICD-10) focus on anaphylactic shock and do not cover the full range of triggers meaning that not all allergy cases are likely to be captured in routine data systems. ICD-11 is in development but still seems to miss major triggers (14). Additionally, anaphylaxis has an acute and unexpected onset, may vary in severity, and may resolve spontaneously (15). For all these reasons under-diagnosis and under-reporting are likely to be common and as a result epidemiological measures are likely to underestimate the true disease burden.

The results of 10 European studies suggest an incidence of 1.5 to 7.9 per 100000 person-years (1) with studies from the UK showing an increase in admissions with anaphylaxis over the last two decades (1). Based on three European population-based studies, prevalence is estimated at 0.3% (95% CI, 0.1-0.5) (1). Overall, the case fatality rate for anaphylaxis is low, below 0.001% (1).

Key triggers include food, drugs and stinging insects; in up to 20% the elicitor is not identified. Their relative importance varies with age and geography studied. For ED presentations, drugs and foods are the most common elicitors of anaphylaxis, with age-related differences (1, 16). Foods are the most frequent cause of anaphylaxis in children, with pollen allergy and asthma being important risk factors (1). Drug and Hymenoptera venom triggered anaphylaxis are more common in adults than in children. Compared to males, adult females have a higher frequency of anaphylaxis (1) in general, and specifically to plant foods and non-steroidal anti-inflammatory drugs (NSAID) (1). Drugs are the most frequent cause of anaphylaxis in hospitalized patients (1). For anaphylaxis during anesthesia, neuromuscular blocking agents are the most frequent triggers in adult patients in most countries, with a higher incidence in females (1).

Clinical presentation and diagnosis

The clinical manifestations of anaphylaxis depend on the organ systems involved. Widely accepted criteria to help clinicians identify likely anaphylaxis (17, 18) (Box 4) emphasize the rapid onset of its multiple symptoms and signs. These criteria significantly improve the identification of anaphylaxis (19) and demonstrate excellent sensitivity (96.7%) and good specificity (82.4%) for the diagnosis of anaphylaxis in a retrospective ED study (20). Symptoms and signs of anaphylaxis usually occur within two hours of exposure to the allergen (21), usually within 30 minutes for food allergy and even faster with parenteral medication or insect stings. In a large case series of fatal anaphylaxis, the median time from symptoms to arrest has been reported as 30, 15 and 5 minutes for food, insect venom and parenteral medication respectively (22).

Among the symptoms of anaphylaxis, cutaneous manifestations occur in most cases (23, 24). In a recent study describing a cohort of 2012 pediatric and adult patients with anaphylaxis, the skin was the most frequently affected organ (84%), followed by cardiovascular symptoms (72%) and respiratory symptoms (68%) (25). Anaphylaxis however can develop in the absence of cutaneous manifestations. Respiratory or cardiovascular symptoms or signs are the potentially life-threatening features of anaphylaxis (26). Respiratory symptoms occur more frequently in children and cardiovascular symptoms predominate in adults (25-31). Nausea and vomiting may also be associated with anaphylaxis (22) (Figure 1).

Box 4 Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)

   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Reproduced with permission from Sampson et al. (17) (C).
**Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.*

Biphasic anaphylactic reactions have been reported to develop in up to 20% of reactions (24, 32-34) although the evidence for this is of low quality. They usually occur within 4-12 hours of the first symptoms or signs and may be more severe. A delay in giving adrenaline (epinephrine), insufficient adrenaline or failure to administer a glucocorticosteroid may increase the risk of biphasic reactions (33-37).

Anaphylaxis is a clinical diagnosis that builds on the criteria shown in Box 4. Retrospectively the diagnosis may be supported if serum tryptase is elevated within a few hours after the reaction when compared with the patient's baseline levels; levels are often normal especially in food-triggered reactions in children (38). Evidence of IgE sensitization on skin prick (39) or in vitro testing may also aid the diagnosis; provocation testing, ideally with any potential co-factors (40), may be required if diagnostic doubt remains (26). Children may outgrow their food allergy, even if severe (41).

The differential diagnosis of anaphylaxis includes medical diseases, which affect the organ systems most frequently involved in anaphylaxis (Box 5).

Factors increasing the risk of severe allergic reactions

Risk factors for anaphylaxis include individual patient related factors and circumstances (25, 26, 42-46) (Box 6). We do not have precise data on the magnitude of risk associated with each.

Concomitant diseases

Co-existing asthma is a risk factor for anaphylaxis and fatal anaphylaxis, especially if severe and uncontrolled (47, 48). Mast cell disorders, and probably underlying cardiovascular disease, are also associated with an increased risk of severe or fatal anaphylaxis (24, 49, 50).

Specific allergens

Patients with peanut and tree nut allergy are at increased risk for a severe reaction (51). In patients with insect venom allergy, increased severity has been reported for older age, pre-existing cardiovascular disease, mast cell disorder, including mastocytosis and mast cell activation syndrome (52, 53), elevated baseline serum tryptase concentrations, concomitant treatment with a beta-adrenergic-blocker and/or angiotensin converting enzyme (ACE) inhibitor and a previous severe reaction (54-57).

Co-factors

Co-factors increase the risk of an allergic reaction occurring or its severity. They have been described in nearly 20% of young patients in a prospective registry study (28) (Table 1) and include exercise, fever, acute infection, premenstrual status and emotional stress. NSAID and alcohol also seem to enhance some food allergic reactions (40). Exercise-induced anaphylaxis (EIA) and food-dependent, exercise-induced

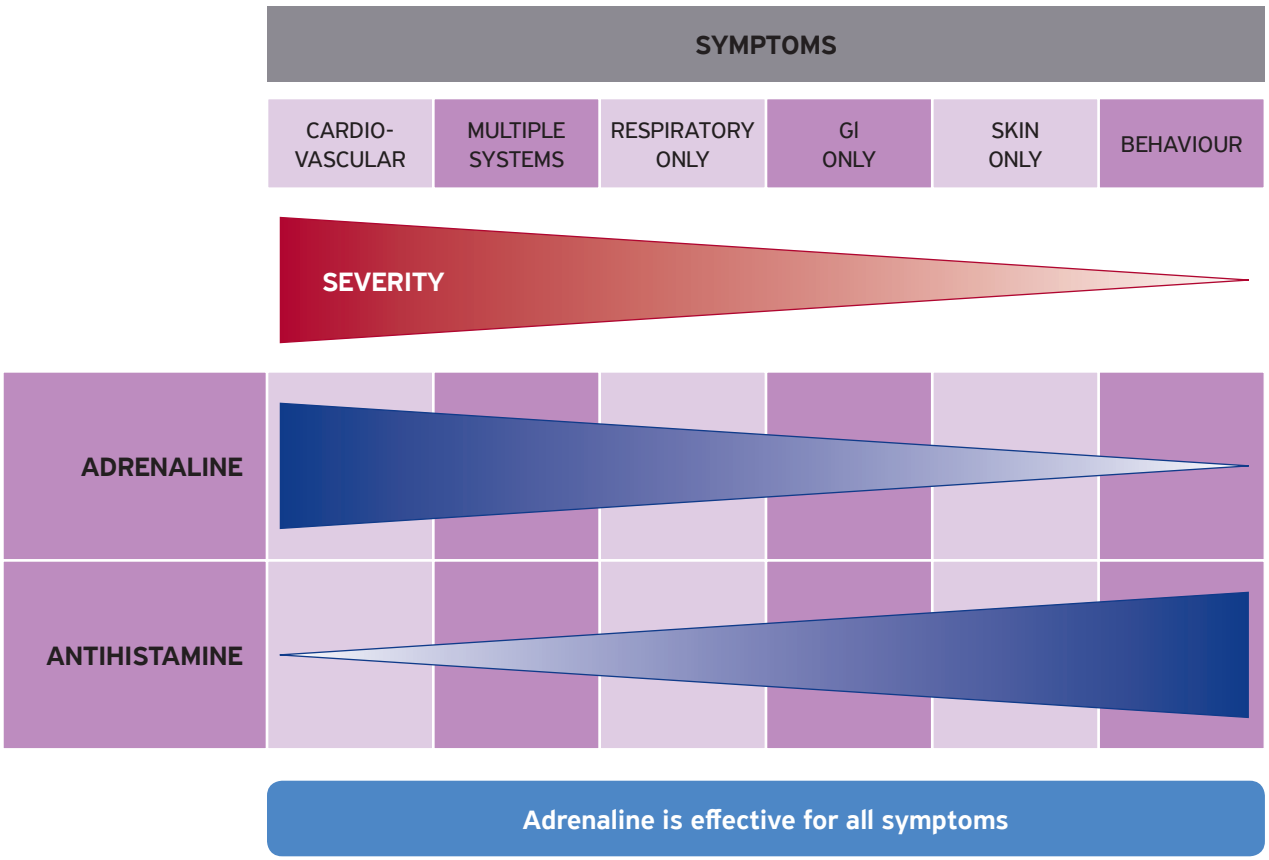


Figure 1 Symptoms associated with anaphylaxis

anaphylaxis (FDEIA) are more often seen in adults than in children. The association with exercise is crucial for the onset of symptoms or signs (58-60). The range of triggering physical activities and intensities is broad. EIA is not fully reproducible so that same exercise may not always result in anaphylaxis in a given patient.

Emergency management of anaphylaxis

Patients with anaphylaxis require immediate assessment using an Airway, Breathing, Circulation, Disability and Exposure approach. Problems should be treated as they are found and a call put out for emergency services (Box 7). Deaths result from upper airway, lower respiratory and/or cardiovascular compromise so emergency management must focus on these manifestations. We recommend first-line treatment with intramuscular adrenaline before instituting other interventions as adrenaline is still underutilized in anaphylaxis (61) although it is potentially lifesaving. Cardiopulmonary resuscitation should be immediately instituted if cardiorespiratory arrest occurs. An overview is presented in Figure 2 and check list in Box 8.

First-line intervention

Adrenaline

Adrenaline must be administered to all patients experiencing anaphylaxis; it should also be administered to those with clinical features that are likely to evolve into anaphylaxis (22, 45, 46, 62-64) (C). In an effort to increase the use of adrenaline, these guidelines place adrenaline as the first intervention for anaphylaxis. Adrenaline exerts effects on (i) α-1 receptors causing peripheral vasoconstriction thereby reversing hypotension and mucosal edema, (ii) β-1 receptors by increasing both the rate and force of cardiac contractions thereby reversing hypotension, and (iii) β-2 receptors reversing bronchoconstriction and reducing the release of inflammatory mediators (62).

Box 5 Differential diagnosis of anaphylaxis (D)

Skin or mucosal	• chronic remittent or physical urticaria and angioedema • pollen-food syndrome
Respiratory diseases	• acute laryngotracheitis • tracheal or bronchial obstruction (e.g. foreign substances, vocal cord dysfunction) • status asthmaticus (without involvement of other organs)
Cardiovascular diseases	• vasovagal syncope • pulmonary embolism • myocardial infarction • cardiac arrhythmias • hypertensive crisis • cardiogenic shock
Pharmacological or toxic reactions	• ethanol • histamine (e.g. scombroid fish poisoning) • opiates
Neuropsychiatric diseases	• hyperventilation syndrome • anxiety and panic disorder • somatoform disorder (e.g. psychogenic dyspnea, vocal cord dysfunction) • dissociative disorder and conversion (e.g. globus hystericus) • epilepsy • cerebrovascular event • psychoses • artifact (factitious disorder) • Hoigné's syndrome • coma (e.g. metabolic, traumatic)
Endocrinological diseases	• hypoglycemia • thyrotoxic crisis • carcinoid syndrome • vasointestinal polypeptide tumours • pheochromocytoma

Adapted from Simons *et al.* (6) and Muraro *et al.* (3).

Box 6 Examples of risk-and co-factors of anaphylaxis

Lifestyle factors	• physical exertion • alcohol
Drugs	• NSAIDs • ACE inhibitors • β-blockers
Patient-specific factors	• adolescence, advanced age and sex • infections • hormonal status • psychogenic stress
Pre-existing conditions	• asthma and other IgE dependent diseases • cardiovascular disease • mastocytosis and/or increased basal tryptase

There are no absolute contra-indications to treatment with adrenaline in a patient experiencing anaphylaxis; benefits outweigh the risks in the elderly and patients with pre-existing cardiovascular disease (6).

Adrenaline should be given by intramuscular injection into the mid-outer thigh (65, 66) (A). The safety profile of intramuscular adrenaline is excellent although patients may experience transient pallor, palpitations and headache. Intramuscular adrenaline (1 mg/ml) should be given at a dose of 0.01 ml/kg of body weight to a maximum total dose of 0.5 ml (3). When using adrenaline auto-injectors, patients weighing between 7.5-25 kg should receive a 0.15 mg dose with patients being a 0.3 mg dose at 25-30 kg (67). There are no data to inform us which patients should receive a 0.5 mg dose auto-injector, if this is available. The adrenaline dose can be repeated after at least a 5 minute interval (D).

Patients who require repeated intramuscular doses of adrenaline may benefit from an adrenaline infusion (64) (D). Adrenaline infusion must be given by those experienced in the use of vasopressors in their daily clinical practice, for example anesthetists, ED and critical care doctors. Intravenous adrenaline in patients with adequate circulation may cause life-threatening hypertension, myocardial ischemia, and arrhythmias. Patients who are given intravenous adrenaline should be monitored with continuous ECG, pulse oximetry and frequent non-invasive blood pressures.

The use of subcutaneous or inhaled adrenaline in the treatment of anaphylaxis is not recommended (68, 69). One caveat is stridor from laryngeal edema where nebulized adrenaline (2–5 ml, 1 mg/ml) can be used in addition to intramuscular adrenaline (3) (D).

Box 7 Emergency management: recommendations

Recommendation	Evidence level	Grade	Key references
FIRST-LINE INTERVENTION: ADRENALINE			
Adrenaline is potentially life-saving and must therefore promptly be administered as the first-line treatment for the emergency management of anaphylaxis.	IV	C	22, 45, 46, 63, 64
Earlier administration of adrenaline should be considered on an individual basis when an allergic reaction is likely to develop into anaphylaxis.	V	D	Expert consensus
Adrenaline should be administered by intramuscular injection into the mid-outer thigh.	I	B	65, 66
In patients requiring repeat doses of adrenaline, these should be administered at least 5 minutes apart	V	D	66 expert consensus
With inadequate response to 2 or more doses of intramuscular adrenaline, adrenaline may be administered as an infusion by appropriately experienced intensive care, emergency department and critical care physicians, with appropriate cardiac monitoring.	IV	D	64
SECOND-LINE INTERVENTIONS			
Trigger of the anaphylaxis episode should be removed.	V	D	Expert consensus
Help should be called promptly and simultaneously with patient's assessment.	V	D	Expert consensus
Patients experiencing anaphylaxis should be positioned supine with elevated lower extremities if they have circulatory instability, sitting up if they have respiratory distress and in recovery position if unconscious.	V	D	45
High flow oxygen should be administered by face mask to all patients with anaphylaxis.	V	D	Expert consensus
Intravenous fluids (crystalloids) should be administered (boluses of 20 ml/kg) in patients experiencing cardiovascular instability.	V	D	Expert consensus
Inhaled short-acting beta-2 agonists should additionally be given to relieve symptoms of bronchoconstriction.	V	D	22
THIRD-LINE INTERVENTIONS			
Oral H1- (& H2)-antihistamines may relieve cutaneous symptoms of anaphylaxis.	I	B	73, 74
Systemic glucocorticosteroids may be used as they may reduce the risk of late phase respiratory symptoms. High dose nebulized glucocorticoids may be beneficial for upper airway obstruction.	V	D	Expert opinion
MONITORING AND DISCHARGE			
Patients who presented with respiratory compromise should be closely monitored for at least 6-8 hours and patients who presented with circulatory instability require close monitoring for 12-24 hours.	V	D	Expert opinion
Before discharge, the risk of future reactions should be assessed and an adrenaline auto-injector should be prescribed to those at risk of recurrence.	V	D	Expert opinion
Patients should be provided with a discharge advice sheet, including allergen avoidance measures (where possible) and instructions for the use of the adrenaline auto-injector. Specialist and food allergy specialist dietitian (in food anaphylaxis) follow-up should be organized. Contact information for patient support groups should also be provided.	V	D	Expert opinion

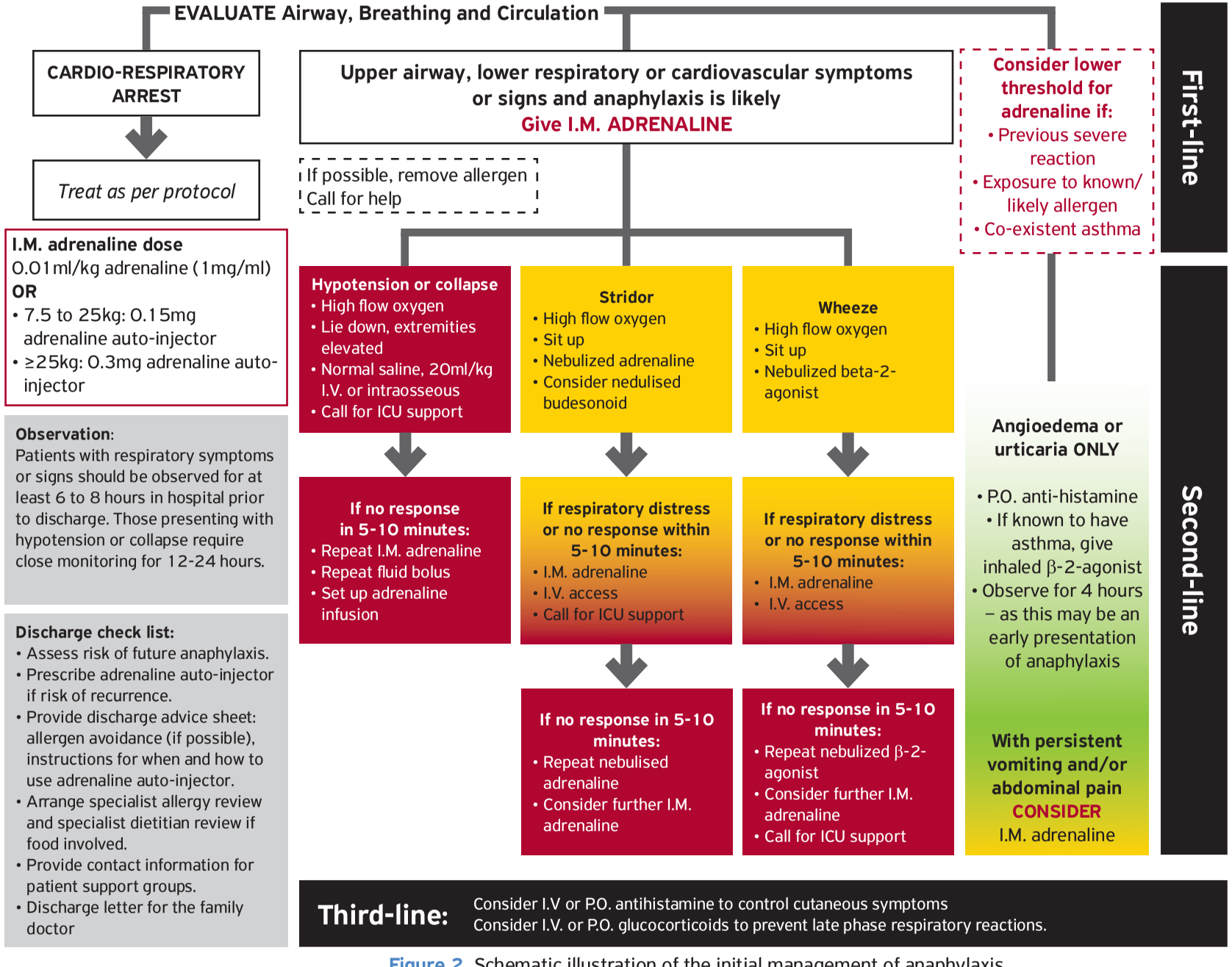


Figure 2 Schematic illustration of the initial management of anaphylaxis

Box 8 Checklist for managing anaphylaxis

1. Stay with patient
2. Look for signs of anaphylaxis
3. Administer adrenaline if signs of anaphylaxis
4. Repeat adrenaline as necessary
5. Other treatments as indicated (eg oxygen, beta-2 agonist, fluids, antihistamine, corticosteroid)
6. Look for trigger (eg food, drug, venom)

Adrenaline is effective for all symptoms

Second-line interventions

Removal of the trigger and call for help

The likely trigger of the anaphylaxis should be immediately removed, if possible (69) (D). Help should be called from the emergency medical services in the community or resuscitation team in hospital (69) (D).

Posture

Patients experiencing anaphylaxis should be kept still and positioned according to their presenting features: (i) with the most frequent presentation of respiratory distress, position sitting up (D); (ii) with circulatory instability, position lying on back with the lower extremities elevated to conserve the circulatory volume (45) (D); (iii) if pregnant, place semi-recumbent on the left side with lower extremities elevated (70) (D); and (iv) where unconscious, place in the recovery position (D). Patients should avoid sudden abrupt change to a more upright posture (D).

Oxygen

High flow oxygen should be administered by face mask to all patients with anaphylaxis (D).

Fluid support

Intravenous fluids should be administered to patients with cardiovascular instability (71), as adrenaline may not be effective without restoring the circulatory volume (D). Crystalloids are the fluid of choice and should be given in boluses of 20 ml/kg (D).

Inhaled short-acting beta-2-agonists

Inhaled short-acting beta-2 agonists can be additionally given to relieve symptoms of bronchoconstriction in patients with anaphylaxis (22) (D). Although intramuscular adrenaline is first-line treatment in the emergency setting, in controlled circumstances in hospital with clinical staff experienced in managing anaphylaxis (e.g. oral food challenge in an allergy clinic), mild wheeze may initially be treated with inhaled short-acting beta-2 agonists alone; intramuscular adrenaline should be given if there is no response within 5 minutes (D).

Third-line interventions

H1- and H2-antihistamines

Systemic antihistamines are commonly used in anaphylaxis but have only been demonstrated to relieve cutaneous symptoms in studies where only a minority of participants were experiencing anaphylaxis (72). The combination of systemic H1- and H2-antihistamines may confer additional benefits over-and-above systemic H1-antihistamines alone in relieving some cutaneous symptoms in those experiencing acute allergic reactions (73, 74). There are case reports that intravenous antihistamines may cause hypotension; this may be related to the speed of administration (75). Oral H1- (& H2)-antihistamines are therefore only recommended for the relief of cutaneous symptoms of anaphylaxis (B).

Glucocorticosteroids

Oral or intravenous glucocorticosteroids are commonly used in anaphylaxis and are thought to possibly prevent protracted anaphylaxis symptoms, particularly in patients with concomitant asthma, and also biphasic reactions; however, this has not been proven and they have a slow onset of action. Oral or parenteral glucocorticosteroids may be given once first- and second-line therapies have been administered (D). High doses of nebulized budesonide may be effective for airway oedema (D); this is therefore recommended for patients presenting with stridor.

Other potential treatments

Glucagon

Parenteral administration of glucagon may be useful in treating patients with anaphylaxis who are unresponsive to adrenaline, particularly in those taking beta-blockers (76) (D).

Monitoring and discharge arrangements

Patients who presented with respiratory compromise should be closely monitored for at least 6-8 hours

and patients who presented with hypotension require close monitoring for at least 12-24 hours (D). Before discharge, the risk of future reactions should be assessed and an adrenaline auto-injector prescribed to those at risk of recurrence (D). Patients should be provided with a discharge advice sheet, including allergen avoidance measures (where possible), instructions for when and how to use the adrenaline auto-injector; referral to an allergy specialist to investigate possible triggers, assess and, where possible, to intervene to minimize the risk of further reactions and ensure that patients and caregivers are optimally equipped and trained to manage any further reactions, and, if food is involved, referral to a specialist dietitian (D). Contact information for patient support groups should ideally be provided to signpost sources of further useful information.

Long-term management of anaphylaxis

The long-term management of patients who have experienced anaphylaxis starts with the confirmation of triggering allergens using validated in-vivo and/or in-vitro tests interpreted in the light of a detailed allergy history. Preventive strategies to avoid recurrence include allergen avoidance (3) and allergen immunotherapy where possible should be implemented. Finally, education should be provided covering self-treatment of anaphylaxis recurrence in the community, and management of relevant concomitant diseases (6) (Box 9). An allergy specialist dietitian can help identify food triggers and provide avoidance advice. Patients should be carefully instructed about hidden allergens, cross-reactions to other allergens and situations that constitute a special hazard such as eating out (see for further details, Chapter 1.5) (77) (Box 9). Most recommendations are based on expert opinion (Box 10).

Anaphylaxis management plans

Anaphylaxis management plans should cover avoidance advice, contact details for advice plus an anaphylaxis emergency action plan with likely presenting symptoms and how to respond to each. Studies have shown that after the inception of a management plan, accidental reactions are less common, at least in children with peanut or tree nut allergies (78, 79). A management plan used by a multi-disciplinary allergy clinic had a positive effect on parental knowledge of avoidance measures and emergency treatment of reactions in another study (80). Anaphylaxis management plans should be used from diagnosis to aid recognition and treatment of any further reactions and should be regularly updated (81, 82) (C) (Box 11).

Box 9 Summary of the long-term management in the community of patients at risk of anaphylaxis

- Provision of individualized management plan written clearly in simple, non-medical language; it should include:
  - » personal identification data: name and address; contact details of the parents, guardian or next of kin, allergist, family doctor and the local ambulance service; and preferably a photograph
  - » clear identification of the source of the allergens to be avoided and allergen avoidance advice
  - » clear identification of any non-allergen triggers or co-factors, such as exercise, and avoidance advice
  - » anaphylaxis emergency action plan

  Copy of plan should be kept by the patient, any caregivers, school staff and family doctor.
- Provision of emergency kit with copy of anaphylaxis emergency action plan and medications for self-treatment, e.g.
  - » adrenaline auto-injector for treating anaphylaxis, where appropriate
  - » fast acting, non-sedating, antihistamine for treating cutaneous allergic reactions, where appropriate
- Venom immunotherapy and desensitisation in drug allergy as appropriate.
- Training of patients and caregivers, this should include:
  - » instructions on appropriate allergen avoidance measures, including consultation with an allergy dietitian, where appropriate
  - » instructions on prompt recognition of symptoms of anaphylaxis
  - » training on when and how to use an adrenaline auto-injector, where appropriate
  - » reinforcement with revision at regular yearly intervals
- Psychological support as required
- Implementation of the patient's management plan in the community (e.g. nursery, school)

Indications for adrenaline auto-injectors

There are six absolute indications for a prescription of an adrenaline auto-injector (Box 12): (i) previous

Box 10 Long-term management: recommendations

Recommendation	Evidence level	Grade	Key references
ANAPHYLAXIS MANAGEMENT PLAN			
An anaphylaxis management plan should be used from the time of diagnosis to prevent future reactions, and aid recognition and treatment of any further reactions.	III	C	79, 80
VENOM IMMUNOTHERAPY			
Subcutaneous venom immunotherapy is recommended in venom allergic patients with a previous episode of anaphylaxis and adults with systemic cutaneous reactions.	I	A	56, 90, 91, 92, 93
TRAINING			
Training in the recognition and management of anaphylaxis should be offered to all patients and caregivers of children at risk of anaphylaxis ideally from the time of diagnosis.	V	D	3, 6
Training in the recognition and management of anaphylaxis, including use of adrenaline auto-injectors, should be offered to all professionals dealing with patients at risk of anaphylaxis.	IV	C	115
Training packages should be developed with the target groups.	V	D	Expert opinion
Training should cover allergen avoidance, symptoms of allergic reactions, when and how to use an adrenaline auto-injector and what other measures are needed within the context of an anaphylaxis management plan.	V	D	3, 6, 79, 125
Training may involve more than one session to allow revision, an interactive scenario-based approach, a standardized program with manual and educational material and simulation tools. Content and language should be tailored to be understood and memorized.	V	D	3, 126
PSYCHOLOGICAL INTERVENTIONS			
Educational interventions should ideally incorporate psychological principles and methods to address anxiety so that children and families may function well at home, at school/work, and socially despite their risk of future reactions and should ideally be part of their educational training. This can be done in a group format. Some patients, with severe anxiety of ongoing duration, may need more in-depth one to one psychological intervention.	V	D	110, 123, 124

anaphylaxis with food, latex, aeroallergens such as animals or other unavoidable triggers (C); (ii) exercise-induced anaphylaxis (C); (iii) previous idiopathic anaphylaxis (C); (iv) co-existent unstable or moderate to severe, persistent asthma with food allergy (C); (v) venom allergy in adults with previous systemic reactions (unless receiving maintenance VIT) and children with more than systemic cutaneous reactions (C); and (vi) underlying mast cell disorder and any previous systemic reaction (C). The asthma indication is extrapolated from data emerging from retrospective studies (15, 83-86).

There are a large number of relative indications based on case series or expert opinion (Box 12). As a guide, the presence of one should lead to the consideration of the prescription of an adrenaline auto-injector; in the presence of two or more, strong consideration should be given to prescription; a specialist allergy review may help to balance the advantages and disadvantage of prescribing. Prescription practices differ considerably (87) and there may be additional local indications such as lipid transfer protein sensitisation in the Mediterranean region.

Box 11 Example of an individualized anaphylaxis emergency action plan

If you think you/your child/other are having an anaphylactic reaction after possible contact with an allergic trigger.

Or after possible contact with an allergic trigger, any of the following symptoms may indicate that you/your child/other is experiencing an anaphylactic reaction:

- **Airway problems**:
  - » swelling of tongue
  - » swelling/tightness in the throat
  - » difficulty swallowing
  - » difficulty talking and/or hoarse voice
- **Breathing problems**:
  - » difficulty breathing
  - » noisy breathing, wheeze and/or persistent cough
- **Consciousness**:
  - » feeling faint, dizziness, confused state or loss of consciousness
  - » pale and floppy (young children)

Then:

1. **Immediately administer adrenaline auto-injector** into the upper outer thigh
2. **Call an ambulance** stating that the patient is having an anaphylactic reaction
3. Lay person having the reaction down (with legs up if possible); if there is difficulty in breathing, allow them to sit up but not stand
4. If no improvement after 5 minutes, administer a second adrenaline auto-injector.

When in doubt, administer the adrenaline auto-injector.

This is only one example of an anaphylaxis action plan. The plan should be individualized, for example, patients with previous rapid onset life-threatening anaphylaxis may be instructed to use their self-injectable adrenaline earlier in the development of any subsequent allergic reaction.

There are no high quality data to help decide how many adrenaline auto-injectors should be available to individual patients. The percentage of patients who required a further dose of intramuscular adrenaline after the administration of an auto-injector was 0-15-32% in different patient groups (15, 83, 84, 61, 88-89) (Box 13) with the additional adrenaline given by healthcare professionals in over 80% of cases. Co-existent asthma was found to be a risk factor for additional adrenaline in one study (84). The challenge is therefore to identify the patients who need to have access to more than one auto-injector. Indications for two auto-injectors are suggested in Box 14. There may also be practical, psychological or policy considerations as to why a specific patient needs more than one auto-injector.

Immunomodulatory approaches

Venom immunotherapy

Systematic reviews (90-92) and meta-analyses (93) have demonstrated the effectiveness of subcutaneous venom immunotherapy (VIT) in children and adults (A). Patients treated with VIT have a better health-related quality of life than those just provided with an adrenaline auto-injector (94, 95). Subcutaneous VIT is therefore recommended in venom allergy for both children and adults with anaphylaxis plus adults with systemic cutaneous reactions (A). Some children with cutaneous sting reactions, where VIT is not indicated, may benefit from having access to an autoinjector (56). The recent systematic review has found VIT to only be cost-effective in populations at high risk of further exposure (93) but the analysis did not incorporate quality of life (96). Rush protocols (i.e. over a few days) are as equally efficacious as slower regimens (97). More adverse effects have been reported with an ultra-rush (few hours) compared to a rush protocol (52) and with rush compared to cluster protocols (98).

Drug desensitization

Drug desensitization is defined as the induction of a temporary state of clinical tolerance of a compound responsible for a hypersensitivity reaction. It is undertaken by administering increasing doses of the medication concerned (e.g. antibiotic, insulins, sulphonamides, chemotherapeutic and biological agents) over a short period of time (from several hours to a few days), until the total cumulative therapeutic dose is achieved and tolerated. It should only be used by trained doctors when alternatives are less effective, not available or contraindicated after considering the risks and benefits. It is mainly undertaken in IgE-mediated reactions, but also in reactions where drug-specific IgE have not been demonstrated (e.g. acetyl salicylic acid). Desensitization induces a temporary tolerant state, which can only be maintained by continuous administration of the medication.

Box 12 Indications for prescription an adrenaline auto-injector

Recommendation	Evidence level	Grade	Key references
ABSOLUTE INDICATIONS FOR AT LEAST ONE ADRENALINE AUTO-INJECTOR			
Previous anaphylaxis triggered by food, latex or aeroallergens	IV	C	127, 128
Previous exercise-induced anaphylaxis	IV	C	58
Previous idiopathic anaphylaxis	IV	C	61
Co-existing unstable or moderate to severe, persistent asthma and a food allergy*	IV	C	15, 83, 84, 85, 86
Venom allergy in adults with previous systemic reactions (not receiving maintenance VIT) and children with more than cutaneous/ mucosal systemic reactions	IV	C	56, 129, 130
Underlying mast cell disorders or elevated baseline serum tryptase concentrations together with any previous systemic allergic reactions to insect stings, even in VIT treated patients	IV	C	52, 56, 103, 130
CONSIDER PRESCRIBING AT LEAST ONE ADRENALINE AUTO-INJECTOR WITH ANY OF THE FOLLOWING ADDITIONAL FACTORS (ESPECIALLY IF MORE THAN ONE IS PRESENT):			
Previous mild-to-moderate allergic reaction* to peanut and/or tree nut	IV	C	51, 79
Teenager or young adult with a food allergy*	IV	C	22, 46, 63, 45, 131
Remote from medical help and previous mild to moderate allergic reaction to a food, venom, latex or aeroallergens	V	D	131 Expert opinion
Previous mild-to-moderate allergic reaction to traces of food*	V	D	22, 45, 46, 63, 131

*excluding pollen food syndrome (oral allergy syndrome)

Box 13 Rate of usage of adrenaline auto-injectors by patients

Reference	Study design	Auto-injector prescription	Used an auto-injector during follow up*	Reactions where initial intramuscular adrenaline dose was followed by additional doses**
61	Retrospective clinic population	All	4% (41/969) over a 12 month period	32% (13/41)
88	Retrospective clinic population	All	22% (15/68) over a 20 month period	15% (2/13)
89	Prospective clinic population	Not all	3% (23/785) over an average of 48 months	0% (0/23)
84	Prospective clinic population	Not all	19% (78/413) over an average of 24 month	19% (18/95)
15	Patient survey	Not all	27% (500/1885)	18% (90/500)
83)	Patient survey	Not all	35% (22/63)	18% (4/22)

*Refers to individual patients. **Refers to individual allergic reactions (often more than one per patient). Additional doses were usually given by a healthcare professional.

Box 14 Suggested indications for prescription of a second adrenaline auto-injector

Suggested indications for prescribing a second auto-injector for the patient to carry include:	Evidence level	Grade	Key references
Co-existing unstable or moderate to severe, persistent asthma and a food allergy*	IV	C	(84)
Co-existing mast cell diseases and/or elevated baseline tryptase concentration	IV	C	(129), (130)
Lack of rapid access to medical assistance to manage an episode of anaphylaxis due to geographical or language barriers	V	D	Expert opinion
Previous requirement for more than one dose of adrenaline prior to reaching hospital	V	D	Expert opinion
Previous near fatal anaphylaxis	V	D	Expert opinion
If available auto-injector dose is much too low for body weight	V	D	Expert opinion

*excluding pollen food syndrome (oral allergy syndrome)

Food oral immunotherapy

There are currently no established oral immunotherapy treatment protocols for food-induced anaphylaxis. Recent data suggest that immunotherapy may increase the amount of a tolerated dose over time (99). Significant systemic side effects can occur and currently these protocols are not recommended in clinical practice (see related food allergy guidelines (77) (Chapter 1.5)).

Prophylaxis

Adrenaline admixture with snakebite anti-venom

The use of subcutaneous adrenaline alone as a pre-medication with snakebite anti-venom reduces the risk of anaphylaxis to the snake anti-venom administration (100, 101) (A). The use of hydrocortisone alone does not reduce severe adverse reaction to snake anti-venom (102) (A).

Pharmacological interventions for the prevention of anaphylaxis to iodinated contrast media

The routine use of prophylactic systemic pre-medication (H1- and/or H2-antihistamines or glucocorticosteroids) cannot be recommended in unselected people undergoing procedures with radio-contrast media as they do not prevent life-threatening reactions (103) (A). There are no available data to support the use of premedication in patients with a previous reaction to another allergen (104).

Training

Who should be trained

As anaphylaxis usually occurs in the community (105-107), all patients at risk of anaphylaxis and their caregivers should be provided with educational resources and training to be able to self-manage reactions ideally from the time of diagnosis (D) (Box 9). Adolescent patients require particular attention given the challenges associated with this period of life (108-111).

What training should cover

Training should cover patient-specific avoidance strategies at home, in the social environment and when traveling (112) (D), recognition of symptoms and warning signals, when and how to administer self-injectable adrenaline and other measures needed to manage the reaction (e.g. call for help, positioning) (D). Training should emphasize the need to continually carry the auto-injector where one has been prescribed (113) (D).

How they should be trained

Several studies indicate that for most patients, the standard prescription and formal instruction on how to prevent and treat anaphylaxis by a physician are insufficient to achieve compliance with respective practical measures, including carrying an adrenaline auto-injector (114) and appropriately using it (61).

This is compounded by the inability of many clinicians to correctly use an adrenaline auto-injector (3, 115). Training should be offered to all professionals dealing with patients at risk of anaphylaxis (C). Educational training has been shown to be clinically effective in chronic allergic diseases such as asthma and atopic eczema or dermatitis (116, 117). Patient education programs are especially effective when using a written action plan (118), a multidimensional and multidisciplinary approach (119), or involved repeated regular medical reviews (120) in other conditions. A multi-disciplinary approach (80) and the provision of educational printed and online materials for food allergy (121) have both been shown to improve knowledge, correct use of auto-injectors and reduce reactions using a before and after study design. Repeated instructions on how to use an adrenaline auto-injector improved correct use in one center (122).

Psychological interventions

Information about the future risk of anaphylaxis may lead to stress and anxiety in patients and caregivers (110, 123, 124). Research suggests that this should be addressed by alleviating uncertainty using psychological principles and methods to maximize quality of life as part of the educational training (123) (Box 11) (D). This can be done in a group format. Some patients, with severe anxiety of ongoing duration, may need more in-depth one to one psychological intervention (123) (D).

Summary and future perspectives

Anaphylaxis is an important clinical emergency which all healthcare professionals should be able to recognise and manage. Anaphylaxis is a clinical diagnosis based on a constellation of presenting features. Allergy tests are usually helpful in accurately identifying the trigger. First-line treatment is intramuscular adrenaline, which may be repeated if required. Second-line interventions include removing the trigger, calling for help, correct positioning of the patient, high flow oxygen, intravenous fluids, inhaled short-acting bronchodilators and nebulized adrenaline. The evidence base for these and other potential interventions is neither comprehensive nor robust. Patients should be monitored after recovery to observe for possible biphasic reactions. Before discharge, an assessment should be made of the risk of further reactions; where appropriate, the patient should be equipped with an adrenaline auto-injector. The absolute indications for an adrenaline auto-injector are (i) previous anaphylaxis with food, latex, aeroallergens such as animals and other unavoidable triggers; (ii) previous exercise-induced anaphylaxis; (iii) previous idiopathic anaphylaxis; (iv) co-existent unstable or moderate to severe, persistent asthma with food allergy; (v) untreated venom allergy in adults with previous systemic reactions (unless on maintenance VIT) and children with more than systemic cutaneous reactions; and (vi) underlying mast cell disorder and any previous systemic reaction. Specialist allergy follow-up is essential to investigate possible triggers as well as potential co-factors, to perform a risk assessment, prevent future episodes by developing personalized risk reduction strategies, including allergen immunotherapy where indicated, as well as a personalised emergency response plan for future allergic reactions. Patients with food allergy should also have advice from a dietitian. Training the patient and caregivers is essential and should cover avoidance strategies, recognition of symptoms and warning signals, when and how to administer medication including self-injectable adrenaline. Other professionals within healthcare, education and childcare should also be trained to recognize and appropriately manage anaphylaxis.

Two recent, related EAACI systematic reviews of the anaphylaxis literature (1, 2) have revealed a lack of high quality evidence in this area preventing the development of firm recommendations. It is important that these gaps are prioritized to maximize the benefit of future research to patient care (132). Large prospective cohort studies of patients at risk of anaphylaxis in real life settings are required to provide a clearer understanding of the magnitude of risk associated with each factor to allow us to personalize avoidance advice and auto-injector prescription (Box 15). For patients experiencing anaphylaxis, we need further pharmacokinetic studies to determine the optimal dose and dosing interval, especially for adult patients (Box 15). Further work on other routes of adrenaline administration should be encouraged as adjuvants to intramuscular adrenaline. Additionally, randomized controlled studies are required to assess the effectiveness of systemic glucocorticosteroids in preventing late manifestations of anaphylaxis and whether the addition of antihistamines improves the respiratory and/or cardiovascular features of anaphylaxis. Finally we need evidence to assess the

Box 15 Anaphylaxis: gaps in the evidence

Gap	Plan to address	Priority
ANAPHYLAXIS EPIDEMIOLOGY AND CLINICAL PRESENTATION		
Clinical definition and diagnostic criteria for allergic anaphylaxis that are easy to use in practice by emergency room medical staff.	Consensus process	2
Universally accepted, epidemiological definition and associated coding criteria to allow accurate modeling of anaphylaxis cases.	Consensus process	3
Accurate estimation of the incidence, prevalence, burden and mortality rate of anaphylaxis in different populations across Europe.	Application of new definition and criteria plus study of routine clinical diagnostic data	4
Clearer understanding of the magnitude of risk factors for future occurrence of anaphylaxis.	Large prospective cohort studies of patients at risk of anaphylaxis	1
EMERGENCY MANAGEMENT		
First-line intervention: adrenaline		
Optimal dose and dosing intervals of intramuscular adrenaline in patients experiencing anaphylaxis.	Pharmacokinetics studies	1
Role of other routes of adrenaline (e.g. inhaled, sublingual) in anaphylaxis.	Randomized controlled trials	2
Data comparing the pharmacokinetics of different adrenaline auto-injector devices	Randomized controlled trials	4
Second-line interventions		
Role of second-line drugs in the treatment of anaphylaxis, namely oxygen and inhaled beta-2 agonists	Randomized controlled trials	5
Comparative efficacies of crystalloids and colloids in the treatment of cardiovascular instability during anaphylaxis	Randomized controlled trials	6
Third-line interventions		
Role of third-line interventions in the treatment of anaphylaxis, namely H1-antihistamines and systemic glucocorticosteroids.	Randomized controlled trials	3
LONG-TERM MANAGEMENT, TRAINING AND PSYCHOLOGICAL INTERVENTIONS		
Anaphylaxis management plans		
Multiple different anaphylaxis management plans and emergency action plans in use.	Consensus process with all stakeholders	5
Evidence on the effectiveness of anaphylaxis management plans, particularly in different subgroup (e.g. age, allergy type, different risk levels).	Pragmatic large randomized controlled trials	2
Evidence on the utility of management plans (e.g. with quality of life questionnaires)	Pragmatic randomized controlled trials	7

Box 15 (continued)

Gap	Plan to address	Priority
ADRENALINE AUTO-INJECTORS		
Who should have an adrenaline auto-injector and how many should they have access to?	Large prospective studies, well phenotyped participants, clear criteria for anaphylaxis	1
Whether a stock supply of adrenaline auto-injectors in locations such as schools might improve the management of anaphylaxis in the community?	Large cluster randomized controlled trials	8
VENOM IMMUNOTHERAPY		
It is unclear if venom immunotherapy is able to prevent fatal reactions, because of the rarity of this outcome	Controlled studies would be unethical.	
Cost-effective evaluation of the treatment in relation to quality of life rather than survival rate	Health economic analysis	9
Comparative studies on the effect of different build-up protocols (traditional versus rush and ultra-rush) with the same extract focusing on safety	Randomized controlled trials comparing approaches	10
PROPHYLACTIC INTERVENTIONS		
Studies to compare the effectiveness of prophylactic pre-medication to prevent life-threatening reactions due to iodinated contrast media in patients with a history of a previous immediate reactions or potential risk factors for reactions	Large randomized controlled trial	11
Studies looking at the impact of other immunomodulatory interventions on reducing the risk of further episodes of anaphylaxis, for example monoclonal anti-IgE (e.g. omalizumab).	Randomized controlled trials to assess	
TRAINING		
Evidence on the efficacy of training of patients and direct caregivers/ parents of children and other groups such as teachers, day care workers, nurses, and physicians.	Randomized controlled trial to assess impact of training	3
Evidence on the optimal content, trainers (e.g. physicians, allergy specialist dietitians), duration, repetition and format of training and whether it should vary for patients of different ages and different future risk.	Development of training program with stakeholders and formal assessment of effectiveness	4
PSYCHOLOGICAL INTERVENTIONS		
Short- and long-term efficacy of different psychological interventions and their influence on quality of life, knowledge, anxiety, compliance with carriage of in-date adrenaline auto-injectors, performance in an emergency situation, and social functioning in at risk patients and their caregivers and how differing personalities impact the efficacy of the interventions.	Randomized controlled trial assessing impact of approach	6

effectiveness of training and anaphylaxis management plans in improving outcome in patients (Box 15).

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines Group in developing these guidelines. We would like to thank Toby Pitts-Tucker and Catherine Crowley for their assistance in preparing the guidelines. We would also like to thank our expert panel and everyone who provided comments on the draft guidelines (in particular Moira Austin, Carlo Caffarelli, Rollo Clifford, Lene Heise Garvey, Lars Gottberg, Joanna Lange, Barbara Rogala, Francesca Saretta, Peter Standring, Alessandra Ometto and David Reading) and the EAACI Executive Committee for their helpful comments and suggestions.

Authors' contribution

Antonella Muraro, Chair of the EAACI Food Allergy and Anaphylaxis Guidelines Initiative, has steered and coordinated the publication. Graham Roberts facilitated the anaphylaxis guidelines group and edited the guidelines document with support from Margitta Worm. M. Beatrice Bilò, Knut Brockow, Montserrat Fernández-Rivas, Alexandra F. Santos, Zaraquiza Zolkipli and Aziz Sheikh coordinated drafting of the evidence table, recommendations, gaps and text for specific sections. Sangeeta Dhami and Sukhmeet Panesar undertook the supporting systematic reviews under the supervision of Aziz Sheikh. All authors participated in the discussion of the evidence table, recommendations, gaps and specific sections and approved the final version.

Conflicts of interest

Graham Roberts has provided scientific advice for Danone and ALK-Abelló; Thermo Fisher and ALK-Abelló have provided consumables for his research activities. Antonella Muraro has provided scientific advice for Meda. Margitta Worm has provided scientific advice for ALK-Abelló. M. Beatrice Bilò has provided scientific advice for Meda. Knut Brockow has provided scientific advice for ALK-Abelló, Meda, Thermo Fisher and Stallergenes. Montserrat Fernández-Rivas has provided scientific advice to GSK; ALK-Abelló has provided consumables for her research activities. Carsten Bindslev-Jensen has received funding from Thermo Fisher, HAL, Stallergenes and Anergis, ALK, Novartis, MSD, Schering-Plough for his research activities. Victoria Cardona has provided scientific advice for ALK-Abelló. Pascal Demoly has provided scientific advice for Stallergenes, ALK-Abelló, Circassia, Allergopharma, Chiesi, Menarini and Pierre Fabre Médicament, Tony DuBois has provided scientific advice for ALK-Abelló and received funding from ALK-Abelló to support his research activities. Audrey DunnGalvin has received funding from Novartis for her research. Philippe Eigenmann has provided scientific advice for Danone, Novartis, ALK, DBV technologies and Stallergenes; he has received funding for research activities from LETI, Nestlé and Thermo Fisher. Susanne Halken has provided scientific advice for ALK-Abelló. Marek Jutel has been an investigator for clinical studies led by Allergopharma, Stallergenes, Novatis, GSK and Medimmune. Franziska Ruëff has been an investigator for clinical studies led by Allergopharma, HAL, Novartis and Pierre Fabre and has received travel grants and honoraria as a speaker from ALK-Abelló, Bencard, HAL, Novartis and Thermo Fisher. Frans Timmermans has received unrestricted grants from ALK-Abello, MSD, MEDA for the activities of European Anaphylaxis Taskforce – Nederlands Anafylaxis Netwerk which he manages. Berber Vlieg–Boerstra has provided scientific advice for Danone and Mead Johnson; she has received research grants from Nutricia Advanced Medical Nutrition and ALK-Abelló. Sukhmeet Panesar, Sangeeta Dhami and Aziz Sheikh have received funding for coordinating guidelines production, and generating the systematic reviews from EAACI. Aziz Sheikh has provided scientific advice to ALK-Abelló, Meda, Lincoln Medical, Thermo Fisher, Pfizer and Stallergenes; he is on the Anaphylaxis Campaign UK's Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee and the BSACI's Standard of Care Committee. Laurie Harada works for Anaphylaxis Canada whose educational activities have been supported by Pfizer and Sanofi. Alexandra F. Santos, Zaraquiza Zolkipli, Cezmi Akdis, Kirsten Beyer, Abdul Bellou, Gideon Lack, Bodo Niggemann, Andy Clark and Thomas Werfel have no conflict of interests.

References

1. Panesar SS, Javad S, De Silva D, Nwaru BI, L Hickstein, Muraro A *et al.* on behalf of the EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013;68:1353-1361.

2. Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilò B *et al*. Management of anaphylaxis: a systematic review. *Allergy* 2014;69:159-167.
3. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G *et al*. The management of anaphylaxis in childhood: Position paper of the European academy of allergology and clinical immunology. *Allergy* 2007;62:857-871.
4. Soar J, Perkins GD, Abbas G, Alfonzo A, Barelli A, Bierens JJLM *et al*. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation* 2010;81:1400-1433.
5. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P *et al*; Working Group of the Resuscitation C. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. *Resuscitation* 2008;77:157-169.
6. Simons FE, Ardusso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J *et al*; World Allergy Organization. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;127:587-593.e1-e22.
7. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF *et al*. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-836.
8. Agree Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care* 2003;12:18-23.
9. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G *et al*. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182:E839-E842.
10. Panesar SS, Nwaru B, Hickstein L, Rader T, Hamadah H, Ali D *et al*. The epidemiology of anaphylaxis in Europe: protocol for a systematic review. *Clin Transl Allergy* 2013;3:9.
11. Dhami S, Panesar SS, Rader T, Muraro A, Roberts G, Worm M *et al*; EAACI Food Allergy and Anaphylaxis Guidelines group. The acute and long-term management of anaphylaxis: protocol for a systematic review. *Clin Transl Allergy* 2013;3:14.
12. Oxford Centre for Evidence-based Medicine. Levels of Evidence and Grades of Recommendation. http://www cebm net/index aspx?o=1025. Last accessed 25 March 2013.
13. Simons FER, Ardusso LRF, Bilò MB, El-Gamal YM, Ledford DK, Ring J *et al*; for the World Allergy Organization. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;4:13-37.
14. Tanno LK, Ganem F, Demoly P, Toscano CM, Bierrenbach AL. Undernotification of anaphylaxis deaths in Brazil due to difficult coding under the ICD-10. *Allergy* 2012;67:783-789.
15. Simons FER, Clark S, Camargo CA, Jr. Anaphylaxis in the community: learning from the survivors. *J Allergy Clin Immunol* 2009;124:301-306.
16. Moro Moro M, Tejedor Alonso MA, Esteban Hernandez J, Mugica Garcia MVM, Rosado Ingelmo A, Vila Albelda C. Incidence of anaphylaxis and subtypes of anaphylaxis in a general hospital emergency department. *J Investig Allergol Clin Immunol* 2011;21:142-149.
17. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease / Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-397.
18. Sampson HA, Munoz-Furlong A, Bock SA, Schmitt C, Bass R, Chowdhury BA *et al*. Symposium on the definition and management of anaphylaxis: Summary report. *J Allergy Clin Immunol* 2005;115:584-591.
19. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. *J Allergy Clin Immunol* 2010;126:98-104.
20. Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF *et al*. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. *J Allergy Clin Immunol* 2012;129:748-752.
21. de Silva IL, Mehr SS, Tey D, Tang MLK. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy* 2008;63:1071-1076.
22. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30:1144-1150.
23. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol* 2004;113:536-542.
24. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371-376.
25. Worm M, Edenharter G, Rueff F, Scherer K, Pfohler C, Mahler V *et al*. Symptom profile and risk factors of anaphylaxis in Central Europe. *Allergy* 2012;67:691-698.
26. Simons FER, Ardusso LR, Bilo MB, Dimov V, Ebisawa M, El-Gamal YM *et al*; World Allergy Organization. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2012;12:389-399.
27. Steele R, Camacho-Halili M, Rosenthal B, Davis-Lorton M, Aquino M, Fonacier L. Anaphylaxis in the community setting: Determining risk factors for admission. *Ann Allergy Asthma Immunol* 2012;109:133-136.

28. Hompes S, Kohli A, Nemat K, Scherer K, Lange L, Rueff F *et al*. Provoking allergens and treatment of anaphylaxis in children and adolescents - data from the anaphylaxis registry of German-speaking countries. *Pediatr Allergy Immunol* 2011;22:568-574.
29. Braganza SC, Acworth JP, McKinnon DRL, Peake JE, Brown AFT. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child* 2006;91:159-163.
30. Vetander M, Helander D, Flodstrom C, Ostblom E, Alfven T, Ly DH *et al*. Anaphylaxis and reactions to foods in children--a population-based case study of emergency department visits. *Clin Exp Allergy* 2012;42:568-577.
31. Beyer K, Eckermann O, Hompes S, Grabenhenrich L, Worm M. Anaphylaxis in an emergency setting - elicitors, therapy and incidence of severe allergic reactions. *Allergy* 2012; 67:1451-1456.
32. Douglas DM, Sukenick E, Andrade WP, Brown JS. Biphasic systemic anaphylaxis: an inpatient and outpatient study. *J Allergy Clin Immunol* 1994;93:977-985.
33. Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: A prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 2007;98:64-69.
34. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* 2000;106:762-766.
35. Sampson HA. Fatal food-induced anaphylaxis. *Allergy* 1998;53:125-130.
36. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 2005;95:217.
37. Mehr S, Liew WK, Tey D, Tang MLK. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. *Clin Exp Allergy* 2009;39:1390-1396.
38. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T *et al*. Usefulness and Limitations of Sequential Serum Tryptase for the Diagnosis of Anaphylaxis in 102 Patients. *Int Arch Allergy Immunol* 2013;160:192-199.
39. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U *et al*. The skin prick test - European standards. *Clin Transl Allergy* 2013;3:3.
40. Cardona V, Luengo O, Garriga T, Labrador-Horrillo M, Sala-Cunill A, Izquierdo A *et al*. Co-factor-enhanced food allergy. *Allergy* ;67:1316-1318.
41. Vlieg-Boerstra BJ, Duiverman EJ, Van Der Heide S, Bijleveld CMA, Kukler J, Dubois AEJ. Should children with a history of anaphylaxis to foods undergo challenge testing? *Clin Exp Allergy* 2008;38:1935-1942.
42. Mertes PM, Alla F, Trechot P, Auroy Y, Jougla E, Groupe d'Etudes des Reactions Anaphylactoides P. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011;128:366-373.
43. Park HJ, Kim SH. Factors associated with shock in anaphylaxis. *Am J Emerg Med* 2012;30:1674-1678.
44. Moneret-Vautrin DA. Drugs as risk factors of food anaphylaxis in adults. [French] Facteurs de risque d'anaphylaxie alimentaire severe Role confirme de certaines classes de medicaments. *Med Sci (Paris)* 2010;26:719-723.
45. Pumphrey RSH GM. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol* 2007;119:1018-1019.
46. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol* 2007;119:1016-1018.
47. Calvani M, Cardinale F, Martelli A, Muraro A, Pucci N, Savino F *et al*.; Italian and members Members of the Italian Society of Pediatric Allergy and Immunology (SIAIP) Anaphylaxis' Study Group. Risk factors for severe pediatric food anaphylaxis in Italy. *Pediatr Allergy Immunol* 2011;22:813-819.
48. Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LAG. Anaphylaxis epidemiology in patients with and patients without asthma: A United Kingdom database review. *J Allergy Clin Immunol* 2010;125:1098-1104.
49. Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. *Clin Exp Immunol* 2008;153:7-11.
50. Wimazal F, Geissler P, Shnawa P, Sperr WR, Valent P. Severe life-threatening or disabling anaphylaxis in patients with systemic mastocytosis: a single-center experience. *Int Arch Allergy Immunol* 2012;157:399-405.
51. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr* 2000;137:749-755.
52. Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W *et al*. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol* 2009;124:1047-1054.
53. Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations. *J Allergy Clin Immunol* 2011;128:147-152.
54. Bilo MB. Anaphylaxis caused by Hymenoptera stings: From epidemiology to treatment. *Allergy* 2011;66:35-37.
55. Rueff F, Przybilla B, Dugas-Breit S. Mastocytosis - clinical symptoms. *Allergologie* 2009;32:214-223.
56. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE *et al*; Joint Task Force on Practice Parameters, American Academy of Allergy A&IA, American College of Allergy A&IA, Joint Council of Allergy AaI. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol* 2011;127:852-854.
57. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis

in patients with mastocytosis: A study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;63:226-232.

58. Shadick NA, Liang MH, Partridge AJ, Bingham C, Wright E, Fossel AH *et al*. The natural history of exercise-induced anaphylaxis: Survey results from a 10-year follow-up study. *J Allergy Clin Immunol* 1999;104:123-127.
59. Tewari A, Du TG, Lack G. The difficulties of diagnosing food-dependent exercise-induced anaphylaxis in childhood -- a case study and review. *Pediatr Allergy Immunol* 2006; 17:157-160.
60. Aihara Y, Takahashi Y, Kotoyori T, Mitsuda T, Ito R, Aihara M *et al*. Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students. *J Allergy Clin Immunol* 2001;108:1035-1039.
61. Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J *et al*. The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy* 2012;42:284-292.
62. Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In Brunton LL, Lazo JS, Parker KL, editors. *Goodman & Gilman's The Pharmacological Basis of Therapeutics 11th ed.* New York: Mc Graw-Hill, 2006;215-268.
63. Bock SA, Muoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-193.
64. Soreide E B. Severe anaphylactic reactions outside hospital: etiology, symptoms and treatment. *Acta Anaesthesiol Scand* 1988;32:339-342.
65. Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;101:33-37.
66. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001;108:871-873.
67. Simons FER, Gu X, Silver NA, Simons KJ. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. *J Allergy Clin Immunol* 2002;171-175.
68. Simons FER, Gu X, Johnston LM, Simons KJ. Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis? *J Allergy Clin Immunol* 2000;106:1040-1044.
69. Simons FER, Sheikh A. Anaphylaxis: the acute episode and beyond. *BMJ* 2013;346:602.
70. Simons FER, Schatz M. Anaphylaxis during pregnancy. *J Allergy Clin Immunol* 2012;130:597-606.
71. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2012;6:CD000567.
72. Nurmatov UB, Rhatigan E, Simons FER, Sheikh A. H2 antihistamines for the treatment of anaphylaxis with and without shock: a systematic review. *Ann Allergy Asthma Immunol* 2014;112:126-131.
73. Runge JW, Martinez JC, Caravati EM, Williamson SG, Hartsell SC. Histamine antagonists in the treatment of acute allergic reactions. *Ann Emerg Med* 1992;21:237-242.
74. Lin RY CA. Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med* 2000;36:462-468.
75. Ellis BC, Brown SG. Parenteral antihistamines cause hypotension in anaphylaxis. *Emerg Med Australas* 2013; 25:92-3.
76. Thomas M. Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. *Emerg Med J* 2005;22:272-273.
77. Muraro A, Werfel T, Beyer K, Bindslev Jensen C, Cardona V, Dubois AEJ *et al*. EAACI Food Allergy and Anaphylaxis Guidelines. Diagnosis and management of food allergy. *Allergy* 2014, submitted.
78. Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. *Lancet* 2001;357:111-115.
79. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: Proposal for good practice. *Clin Exp Allergy* 2005;35:751-756.
80. Kapoor S, Roberts G, Bynoe Y, Gaughan M, Habibi P, Lack G. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy* 2004;59:185-191.
81. Choo K, Sheikh A. Action plans for the long-term management of anaphylaxis: Systematic review of effectiveness. *Clin Exp Allergy* 2007;37:1090-1094.
82. Nurmatov U, Worth A, Sheikh A. Anaphylaxis management plans for the acute and long-term management of anaphylaxis: A systematic review. *J Allergy Clin Immunol* 2008;122:353-361.
83. Uguz A, Lack G, Pumphrey R, Ewan P, Warner J, Dick J *et al*. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy* 2005;35:746-750.
84. Järvinen KM, Sicherer SH, Sampson HA, Nowak-Wegrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 2008;122:133-138.
85. Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JT, Decker WW. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. *Ann Allergy Asthma Immunol* 2009;103:395-400.
86. Rudders SA, Banerji A, Corel B, Clark S, Camargo CA, Jr. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. *Pediatrics* 2010;125:e711-e718.
87. Johnson MJ, Foote KD, Moyses HE, Roberts G. Practices in the prescription of adrenaline autoinjectors. *Pediatr Allergy Immunol* 2012;23:124-127.
88. Gold MS, Sainsbury R. First aid anaphylaxis management in

children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000;106:171-176.

89. Clark AT, Ewan PW. Good prognosis, clinical features, and circumstances of peanut and tree nut reactions in children treated by a specialist allergy center. *J Allergy Clin Immunol* 2008;122:286-289.
90. Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M *et al*. Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev* 2012;10:CD008838.
91. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity: A meta-analysis. *Clin Ther* 2000;22:351-358.
92. Watanabe AS, Fonseca LAM, Galvao CES, Kalil J, Castro FFM. Specific immunotherapy using Hymenoptera venom: systematic review. *Sao Paulo Med J* 2010;128:30-37.
93. Hockenhull J, Elremeli M, Cherry MG, Mahon J, Lai M, Darroch J *et al*. A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen for the treatment of bee and wasp venom allergy. *Health Technol Assess* 2012;16:III-IV, 1-110.
94. Oude Elberink JNG, De Monchy JGR, Van Der Heide S, Guyatt GH, Dubois AEJ. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol* 2002;110:174-182.
95. Oude Elberink JNG, van der Heide S, Guyatt GH, Dubois AEJ. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. *J Allergy Clin Immunol* 2006;118:699-704.
96. Rueff F, Bilo MB, Cichocka-Jarosz E, Muller U, Elberink HO, Sturm G. Immunotherapy for Hymenoptera venom allergy: too expensive for European health care? *Allergy* 2013;68:407-408.
97. Golden DBK, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera Venom Immunotherapy. *Ann Intern Med* 1980;92:620-624.
98. Mosbech H, Muller U, Behalf Of The Study Group. Side-effects of insect venom immunotherapy:results from an EAACI multicenter study. *Allergy* 2000;55:1005-1010.
99. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LCL *et al*. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;126:83-91.
100. Habib A. Effect of Pre-Medication on Early Adverse Reactions Following Antivenom Use in Snakebite. *Drug-Safety* 2011;34:869-880.
101. de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A *et al*. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. *PLoS medicine* 2011;e1000435.
102. Gawarammana IB, Kularatne SA, Dissanayake WP, Kumarasiri RP, Senanayake N, Ariyasena H. Parallel infusion of hydrocortisone +/- chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites.[Erratum appears in Med J Aust. 2004 Apr 19;180(8):428]. *Med J Aust* 2004;180:20-23.
103. Tramer MR, von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ* 2006;675.
104. Brockow K, Ring J. Anaphylaxis to radiographic contrast media. *Curr Opin Allergy Clin Immunol* 2011;11:326-331.
105. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children--a questionnaire-based survey in Germany. *Allergy* 2005;60:1440-1445.
106. Clark S, Bock SA, Gaeta TJ, Brenner BE, Cydulka RK, Camargo CA. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 2004;113:347-352.
107. Grabenhenrich L, Hompes S, Gough H, Rueff F, Scherer K, Pfohler C *et al*. Implementation of anaphylaxis management guidelines: a register-based study. *PLoS One* 2012;7:e35778.
108. MacKenzie H, Roberts G, van LD, Dean T. Teenagers' experiences of living with food hypersensitivity: a qualitative study. *Pediatr Allergy Immunol* 2010;21(4:Pt 1):595-602.
109. Monks H, Gowland MH, MacKenzie H, Erlewyn-Lajeunesse M, King R, Lucas JS *et al*. How do teenagers manage their food allergies? *Clin Exp Allergy* 2010;40:1533-1540.
110. DunnGalvin A, Gaffney A, Hourihane JOB. Developmental pathways in food allergy: a new theoretical framework. *Allergy* 2009;64:560-568.
111. Worth A, Regent L, Levy M, Ledford C, East M, Sheikh A. Living with severe allergy: an Anaphylaxis Campaign national survey of young people. *Clin Transl Allergy* 2013;3:2.
112. Barnett J, Botting N, Gowland M, Lucas J. The strategies that peanut and nut-allergic consumers employ to remain safe when travelling abroad. *Clin Transl Allergy* 2012;2:12.
113. Macadam C, Barnett J, Roberts G, Stiefel G, King R, Erlewyn-Lajeunesse M *et al*. What factors affect the carriage of epinephrine auto-injectors by teenagers? *Clin Transl Allergy* 2012;2:3.
114. Kastner M, Harada L, Waserman S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: A systematic review of the literature. *Allergy* 2010;65:435-444.
115. Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. *Pediatrics* 2000;105:359-362.

116. Guevara JP, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. *BMJ* 2003;326:1308-1309.

117. Staab D, Diepgen TL, Fartasch M, Kupfer J, Lob-Corzilius T, Ring J *et al*. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ* 2006;332:933-938.

118. Ducharme FM, Bhogal SK. The role of written action plans in childhood asthma. *Curr Opin Allergy Clin Immunol* 2008;8:177-188.

119. Lagger G, Pataky Z, Golay A. Efficacy of therapeutic patient education in chronic diseases and obesity. *Patient Educ Couns* 2010;79:283-286.

120. Powell H, Gibson PG. Options for self-management education for adults with asthma. *Cochrane Database Syst Rev* 2003;(1):CD004107.

121. Sicherer SH, Vargas PA, Groetch ME, Christie L, Carlisle SK, Noone S *et al*. Development and validation of educational materials for food allergy. *J Pediatr* 2012;160:651-656.

122. Segal N, Garty BZ, Hoffer V, Levy Y. Effect of instruction on the ability to use a self-administered epinephrine injector. *Isr Med Assoc J* 2012;14:14-17.

123. Manassis K. Managing anxiety related to anaphylaxis in childhood: A systematic review. *J Allergy (Cairo)* 2012:316296. doi:10.1155/2012/316296.

124. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. *Clin Exp Allergy* 2007;37:1213-1220.

125. Vickers DW, Maynard L, Ewan PW. Management of children with potential anaphylactic reactions in the community: a training package and proposal for good practice. *Clin Exp Allergy* 1997;27:898-903.

126. Patel BM, Bansal PJ, Tobin MC. Management of anaphylaxis in child care centers: Evaluation 6 and 12 months after an intervention program. *Ann Allergy Asthma Immunol* 2006;97:813-815.

127. Anagnostou K, Harrison B, Iles R, Nasser S. Risk factors for childhood asthma deaths from the UK Eastern Region Confidential Enquiry 2001-2006. *Prim Care Respir J* 2012;21:71-77.

128. Hourihane JO, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997;27:634-639.

129. Bonifazi F, Jutel M, Bilo BM, Birnbaum J, Muller U, Hypersensitivity EIGoIV. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005;60:1459-1470.

130. Krishna MT, Ewan PW, Diwakar L, Durham SR, Frew AJ, Leech SC *et al*; British Society for Allergy and Clinical Immunology. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clin Exp Allergy* 2011; 41:1201-1220.

131. Sicherer SH, Simons FER. Quandaries in prescribing an emergency action plan and self-injectable epinephrine for first-aid management of anaphylaxis in the community. *J Allergy Clin Immunol* 2005;115:575-583.

132. Papadopoulos N, Agache I, Bavbek S, Bilo B, Braido F, Cardona V *et al*. Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;2:21.

SECTION 5

COMMUNITY

5.1

MANAGING PATIENTS WITH FOOD ALLERGY IN THE COMMUNITY

EAACI GUIDELINES

A Muraro[1*], I Agache[2*], A Clark[3*], A Sheikh[4-6], G Roberts[7-9], CA Akdis[10, 11], LM Borrego[12], J Higgs[13], JO'B Hourihane[14], P Jorgensen[15], A Mazon[16], D Parmigiani[17, 18], M Said[19], S Schnadt[20], H van Os-Medendorp[21], B Vlieg-Boestra[22], M Wickman[23-25] on behalf of the EAACI Food Allergy & Anaphylaxis Guidelines Group

AFFILIATIONS

[1] The Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, Department of Mother and Child Health, Padua General University Hospital, Padua, Italy

[2] Theramed Medical Center, Brasov, Romania

[3] Allergy Department, Cambridge University Hospitals, Cambridge, UK

[4] Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK

[5] Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, MA, USA

[6] Department of Medicine, Harvard Medical School, Boston MA, USA

[7] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK

[8] Human Development in Health and Clinical and Experimental Sciences Academic Units, University of Southampton Faculty of Medicine, Southampton, UK

[9] Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[10] Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[11] Christine Kühne–Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

[12] Centro de Alergia, Hospital CUF Descobertas and Departamento de Imunologia, NOVA Medical School, Lisboa, Portugal

[13] Health Education Trust, Greens Norton, Northamptonshire, United Kingdom

[14] Paediatrics and Child Health, University College, Cork, Ireland

[15] Allergy, Auckland, New Zealand

[16] Pediatric Allergy and Pneumology Unit. Children's Hospital La Fe. Instituto de Investigacion Sanitaria La Fe, Valencia, Spain

[17] Association for Teacher Education in Europe, Bruxelles, Belgium

[18] Department of Education, University of Genoa, Italy

[19] Allergy & Anaphylaxis Australia, Hornsby, New South Wales, Australia

[20] Deutscher Allergie- und Asthmabund e.V., Mönchengladbach, Germany

[21] UMC Utrecht, Department of Dermatology & Allergology, Utrecht, the Netherlands

[22] Department of Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

[23] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[24] Department of Pediatrics, Sachs' Children's Hospital, Stockholm, Sweden

[25] Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden

** Joint first authorship*

The European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines, managing patients with food allergy in the community, intend to provide guidance to reduce the risk of accidental allergic reactions to foods in the community. This document is intended to meet the needs of early childhood and school settings as well as providers of non-pre-packaged food (e.g. restaurants, bakeries, take-away, deli counters, and fast-food outlets) and targets the audience of individuals with food allergy, their families, patient organizations, the general public, policy makers and allergists.

Food allergy is the trigger of anaphylaxis in the community. Providing children and caregivers with comprehensive information on food allergen avoidance, and prompt recognition and management of allergic reactions are of the utmost importance. Provision of adrenaline auto-injector devices and education on how and when to use these, are essential components of a comprehensive management plan.

Managing patients at risk of anaphylaxis raises many challenges, which are specific to the community. This includes the need to interact with third parties providing food (e.g. school teachers and restaurant staff) to avoid accidental exposure and to help individuals with food allergy to make safe and appropriate food choices. Education of individuals at risk and their families, their peers, school nurses and teachers as well as restaurant and other food retail staff can reduce the risk of reactions. Increased awareness among policy makers may improve decision making on legislation at local and national level.

Originally published as: Muraro A, Agache I, Clark A, Sheikh A, Roberts G, Akdis CA, Borrego LM, Higgs J, Hourihane JO'B, Jorgensen P, Mazon A, Parmigiani D, Said M, Schnadt S, van Os-Medendorp H, Vlieg-Boestra B, Wickman M on behalf of the EAACI Food Allergy & Anaphylaxis Guidelines Group. EAACI Food Allergy and Anaphylaxis Guidelines. Managing patients with food allergy in the community. *Allergy* 2014. DOI: 10.1111/all.12441. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Background

Food allergy reactions commonly occur outside the home (1) (Box 1). This section of EAACI Food Allergy and Anaphylaxis Guidelines is intended to provide guidance to all stakeholders in order to reduce the risk of accidental allergic reactions to foods in the community. These guidelines are therefore intended to assist those working in school and early childhood settings (e.g. kindergarten) as well as providers of non-pre-packaged food (e.g. restaurants, bakeries, take-away, deli counters, and fast-food outlets). Furthermore, we hope it will help children with food allergy, their families, schools, and their specialist and non-specialist healthcare providers (Table 1). These guidelines have been prepared by EAACI's Taskforce on the Community and builds on the previous EAACI Position Paper on Management of the Allergic Child at School (2).

Methods

These guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (4, 5). This is a structured approach to guideline production that is designed to ensure appropriate representation of the wide range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. We provide below an overview of the approach used.

Clarifying the scope and purpose of the guidelines

The process began in January 2012 with a meeting to discuss the overall approach to guideline development. This included detailed discussions on the main aims of the guidelines, the target conditions, agreeing the intended end-user for the recommendations, agreeing the intended end-user group, and ensuring adequate professional and lay representation in the guidelines development process.

Ensuring appropriate stakeholder involvement

Participants represented 20 European countries,

Table 1 Target audience

Children with food allergy and their caregivers
Healthcare providers
Food service staff and managers
Early childhood settings staff and managers
School principals, teachers, school staff and volunteers
Patient organizations
Government and policy makers

Box 1 Key terms

Term	Definition
Food allergy	An adverse reaction to food triggered by an immunological mechanism, involving specific IgE (IgE mediated) or cell–mediated mechanisms (non IgE mediated) or both IgE and cell mediated mechanisms (mixed IgE and non IgE mediated). Food allergy is a subgroup of food hypersensitivity reactions.
Anaphylaxis	"Severe, life-threatening generalized or systemic hypersensitivity reaction"(3) which is characterized by being rapid in onset with life-threa-tening airway, breathing or circulatory problems, usually associated with skin and mucosal changes
Adrenaline (epinephrine)	Drug with combined alpha- and beta-agonist causing peripheral vasoconstriction (reversing hypotension and mucosal oedema), increased rate and force of cardiac contractions (reversing hypotension), reversal of bronchoconstriction and reduction in release of inflammatory mediators in case of anaphylaxis.
Adrenaline auto-injectors	Devices that patients, caregivers or professionals can be trained to use to give a pre-defined dose of intramuscular adrenaline
Personalized emergency management plan	A written plan tailored to the individual patient's clinical characteristics of reaction, to be implemented when a reaction occurs

from different disciplinary and clinical backgrounds, including medical tertiary, secondary and primary care, dietitians, nursing and teachers and patient groups. Primary Care: Aziz Sheikh; Nurse: van Os-Medendorp; Dietitians: Berber Vlieg-Boestra, Jeanette Higgs; Association of Teacher for Education in Europe – ATEE: Davide Parmigiani, Patient's Organizations representatives: Sabine Schnadt (Germany), Penny Jorgensen (New Zealand), Maria Said (Anaphylaxis Australia)

Formulating recommendations

The following recommendations are the result of expert opinion consensus following previous systematic reviews of literature on epidemiology, diagnosis and management of food allergy and anaphylaxis (6, 7, 8, 9) and extensive narrative review of the relevant literature (Box 2). They result also from consultations with all the stakeholders involved in management of food allergy and anaphylaxis, such as primary care physicians, nurses, dietitians, patient organizations and teachers associations.

Experts identified the resource implications of implementing the recommendations, barriers and facilitators to the implementation of each recommendation, advised on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation.

Peer review

A draft of these guidelines were externally peer-reviewed by experts from a range of organizations, countries and professional backgrounds. All feedback was considered by the Community Task Force and, where appropriate, final revisions were made in the light of the feedback received. We will be pleased to continue to receive feedback on these guidelines, which should be addressed to the first author.

Identification of evidence gaps

The process of developing these guidelines identified a number of evidence gaps and we plan in future to prioritize the questions that the Community Task Force believes should be urgently addressed through formal consensus building techniques. We plan furthermore to draft outline research briefs that funders can use to commission research on these questions.

Editorial independence and managing conflict of interests

The production of these guidelines was funded and supported by EAACI. The funders did not have any influence on the guideline production process, its contents or on the decision to publish. All members of the Community Task Force completed conflicts of interest statements and these were taken into account by the Community Task Force chair as recommendations were formulated.

Updating the guidelines

We plan to update these guidelines in 2017 unless there are important advances before then.

Box 2 Assigning levels of evidence and recommendations (10)

LEVEL OF EVIDENCE	
Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, non-randomized studies (e.g. cohort, case-control)
Level III	One-group non-randomized (e.g. before and after, pre test and post test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case-series)
Level V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
GRADES OF RECOMMENDATION	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from Level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level

Why the community is important

Food allergy is a common and increasing problem (11, 12) with the main burden occurring in childhood (13). In Europe, at least 25% of school-age children live with allergic disease, and food allergy affects up to 4-7% of primary school children (6). The estimate will vary depending on point or lifetime prevalence and whether this is self-reported, based on oral food challenge or other methods. The pooled lifetime and point prevalence of self-reported FA were 17.3% (95% CI: 17.0-17.6) and 5.9% (95% CI: 5.7-6.1), respectively. The point prevalence of sensitization to ≥1 food as assessed by specific IgE was 10.1% (95% CI: 9.4-10.8) and skin prick test 2.7% (95% CI: 2.4-3.0), food challenge positivity 0.9% (95% CI: 0.8-1.1).

Food allergy, particularly to peanuts, tree nuts, egg and milk, is the leading cause of anaphylaxis (14-17). Allergen avoidance education is often targeted at avoidance within the home, with less emphasis on how to avoid community exposure. Anaphylaxis often presents at home, and this as an important situation to manage (1). However, there is also significant risk from community exposure (1). The location for anaphylaxis to occur in the community is school or kindergarten, accounting for 16-22% of reactions (18, 19-23). Between 10-18% of food allergy or reactions occur at school (1, 24). In a United Kingdom (UK) survey, 61% of schools had at least one child at risk of anaphylaxis (i.e. had a reported history of anaphylaxis or carried an AAI (25). Reactions also occur in a wide variety of other community locations including restaurants, sports fields, beaches, and gymnasiums (21). Fatalities due to food allergy are equally likely to occur at home or in community locations such as a restaurant/take away (26), friend's home, school/nursery (27-29), camp and work (30, 31).

The management of food allergic children should therefore to protect against the risk of allergen exposure outside the home. Avoidance of community reactions depends on complex factors and interaction with third parties providing food (e.g. schools) when parents are not present. Anaphylaxis is in adolescents and young adults, an age when they begin to take over responsibility for making food choices outside the home (32), and carrying emergency medication (33-36). Improved education of individuals at risk and their families, peers, school staff and restaurant and other food service staff about reducing risk can help to prevent fatalities (18). Increased awareness of policy makers may improve care at local and national levels. Harmonized legislation is urgently required for the generic availability and administration of adrenaline at school as well as for educational multidisciplinary programmes aimed at general practitioners and targeting the family as a whole, the restaurant, canteen and school staff (37).

Families, caregivers and the allergist

Families of children require guidance on managing this potentially long-lasting condition, balancing safety against social and emotional restrictions. Equal weight should be given to protecting children against community and home reactions. Parents and caregivers have primary responsibility for coordinating care for their children. As children reach adolescence, they begin to make food choices by themselves outside the home, and take responsibility for carrying their own emergency medication. This coincides with the time of life severe reactions and deaths due to anaphylaxis. Education should be focused on providing a comprehensive package of age-appropriate avoidance, advice, provision and training in how and when to use emergency medication.

The first principle is correct diagnosis of the allergy by clinical history, serum specific IgE and skin prick testing and challenge, if necessary, to identify relevant trigger and tolerated foods (7, 8). The allergist and or the dietitian should provide comprehensive advice on allergenic foods to be avoided, interpretation of food allergen labelling (including precautionary labelling) and identification of potential sources of cross-contamination. Patients and their families should be advised of the common pitfalls and situations where accidental reactions are particularly frequent or severe, and contingencies for these situations should be discussed. Advice should include guidance for relevant community-specific situations, for example, how to manage food allergy with reference to school meals, school camps or social gatherings. Management should also focus on good control of co-existing asthma. Other allergic conditions such as eczema and allergic rhinitis should also be addressed.

The use of comprehensive personalized emergency management plans (PEMP) is associated with a

decreasing frequency of severe reactions following their implementation (31, 38). Regular follow-up is an essential part of any management plan. The ability of parents to assess the risk and manage their child's condition is highly dependent on their own knowledge, attitudes, and beliefs about food allergy (13). Not surprisingly, misconceptions are held about prevalence and triggers. Also, many families report an adverse effect of the food allergy on their personal relationships, with some experiencing outright hostility from others when trying to accommodate their child's food allergy (39).

Provision of adrenaline auto-injector devices to those at risk of anaphylaxis is an essential part of the comprehensive PEMP. Indications for provision of AAIs are discussed in detail in the anaphylaxis (9). According to the Health Council of the Netherlands 1450 to 1700 children in the Netherlands are prescribed an adrenaline auto-injector device (AAI) yearly 50-75% of children two devices, one on their person and one stored at day care or school (40). However, an alarming under-prescription of AAIs was reported in school-going adolescents: although the auto-injector was indicated in 3.0%, only 0.09% of the adolescent evaluated owned a device (41). In a study of children from 14 allergy clinics throughout UK, only 16.7% used their prescribed AAI during anaphylaxis (42). These data emphasize the importance of repeated education and assessment of the knowledge on how and when to use of AAI devices (9).

Education is clearly important. Factors associated with greater knowledge are a prior practical demonstration, consultation with an allergy specialist rather than a general physician and independently seeking additional information from a patient organization (43). Factors correlating with confidence to administer auto-injectors are prior administration, regular training and empowerment by healthcare professionals to manage a severe allergic reaction (44).

School

Food allergy is a common health issue in the school setting (45, 46) will be exposed to when out of their parents' direct care and require adrenaline administration. All schools should therefore have a policy to protect such children. The reality is that many facilities are poorly prepared to protect students. Essential components of policies for the prevention of food allergen exposure are often missing (1, 47), teachers have poor knowledge of anaphylaxis triggers, symptoms, and adrenaline auto-injectors (23, 48, 49, 50) and PEMPs are not currently consistently provided for the majority of students with food allergy (23).

In one series of school children, only 54% had a personalized emergency management plan, 72% an AAI, and 60% a complete emergency kit (51, 52). Where PEMPs are provided studies have shown that up to two-thirds of patients and caregivers are unable to administer AAI devices, or even have them available (52).

In a study on a large university campus only 6.6% of food allergic students reported always carrying an AAI (48); in addition, only 39.7% avoided a self-identified food allergen (48).

The goals in school are to create a network of support and a self-sustaining environment of awareness that reduces the likelihood of reactions, and enables staff to recognize and treat emergencies. The ideal approach is for schools to develop a formal policy, with the aim of achieving these goals, which is informed by the available expertise (Box 3).

The school principal should take overall responsibility for provision and delivery of the policy. Early liaison with local expertise such as allergists, paediatricians, allergy nurses and patient organizations is essential to the implementation of a well-informed, comprehensive policy. There may be significant barriers to be overcome in this regard as 'education' and 'health' are often governed by different municipal government bodies. Therefore, fostering a cooperative partnership between doctors, community nurses, dietitians, parents and the school community is essential (50).

A named person should be responsible for development of a personalised care plan (PCP) for individual children. This should ideally be a school nurse, but if not available then another appropriately trained individual (e.g. teacher) could be identified. There may be no such person, in which case the principal is encouraged to seek help in training staff using suitable allergy resources (Box 4). All staff are responsible for implementation of the policy.

Teachers and school staff responsible for student supervision should be properly instructed to recognize the onset of an allergic reaction, including anaphylaxis, and know how and when to get help. In many schools there is a lack of full-time school nurses and teachers

Box 3 Suggested elements of food allergy policy for schools (53-55)

- Formal school policy
- Led by principal
- All staff (including non-teaching) responsible for implementation
- Specify named personnel for coordination of management plans and training staff in emergency medication use
- Engage with local expertise (allergist, nurse, paediatrician)
- Process to identify FA children at school entry
- System to identify food-allergic children to school staff, especially catering or new/temporary staff
- Clear communication line to parents
- Protocol to provide PEMP
- Approach to allergen avoidance in school
- Include extra-curricular activities (e.g. school trips)
- Integrate food allergy into bullying/child protection policy
- Periodic checks of AAI availability and expiry
- Protocol to deliver AAI from storage to site of emergency treatment

Box 4 Suggested source of expertise for help in developing policy and training staff

- Paediatric allergist
- Paediatrician
- Allergy nurse
- Allergy-trained school nurse
- National or local allergy patient organization
- Expert patient/parent
- Online resources

feel overwhelmed when the responsibility is placed upon them to care for children. It is imperative that teachers receive a comprehensive and practical educational program on food allergies whether a school nurse is available or not.

Ideally, school nurses should play a key role in coordinating management of students with food allergies. It is essential they themselves have received sufficient training in food allergy. These school nurses can then train the entire school staff. A train-the-trainer anaphylaxis education program providing school nurses with curriculum, lesson plans, teaching-learning activities, and resources for anaphylaxis education of all school staff has been suggested in Europe (and the US) through patient organizations (56, 57) (http://www.anaphylaxis.org.uk)

The nominated individual should adapt the PEMP for each student. Parents need to be included in discussions on school management (including PEMPs) as they are well practiced in managing their child's food allergy by the time they reach school age. When school staff and parents cannot agree on an important issue, it can be taken to the specialist.

Another important component of the policy is to have systems in place to identify children to school staff, especially catering or new/temporary staff. Any food provided by the school should have clear allergen labelling; menus including allergen information should be available to the families in advance. Appropriate food handling procedures should be put in place to minimise the risk of cross-contamination. A general 'allergen-ban' in isolation is inadequate, falling short of a 'whole school management' approach to instil allergy awareness throughout the school. Measures in line with these approaches include cleaning faces, hands and the floor after meals, making sure the has own treats.

Bullying, teasing, and harassment of children with food allergy together with denial of their condition is also frequently encountered (53, 54). Policies should be structured around ethical principles of confidentiality (where appropriate), fairness, avoiding stigmatization, and empowerment of those affected (55).

Primary and secondary/tertiary school policies should differ in order to reflect the needs and developmental level of their students. Primary school children tend to be in a more protective environment. In secondary schools pupils should be supported as they become

more responsible for their allergies. During the teenage years adolescents should be positively encouraged to self-manage their condition whilst still in a 'semi-protected' environment, in preparation for adulthood (58, 59). An "adolescent-centred" approach empowers secondary pupils in a process that is meaningful and relevant to their lives (60).

Secondary schools should educate the peers of students with food allergy in good practice, risk awareness and management of emergencies. This may help counteract the ignorance, stigma and bullying associated with allergies.

Prompt administration of adrenaline is the first-line treatment for anaphylaxis. Scheduled checks for the availability of AAIs are essential, to identify AAI expiry and ensure timely replacement, in liaison with the family (61). Quick and easy access to adrenaline is also an issue since in many cases the device is stored in a remote office causing a delay. School policy should specify a protocol to bring the device to the student promptly during an emergency. Storage in the class or cafeteria or other unlocked and easily accessible locations is recommended for primary school students. As soon as the student achieves a proper level of maturity they can be encouraged to self-carry the device.

AAIs are not always subsidized by public health insurance, limiting their availability (62). In such cases government support for reimbursement of adrenaline auto-injectors in low-income households is desirable. Some US and Australian, though not European legislatures, are now permitting the patient non-specific availability of AAIs in schools, which may address this issue of children and adolescents having to always carry their own AAIs. However students will still need to carry their own AAI to protect them from the effects of food sharing and food accidents on the way to and from school, or on school trip (Box 5).

Providers of non-prepacked foods

Restaurants and other food establishments, such as bakeries, take-aways, deli counters and fast-food outlets, pose a number of potential dangers for individuals with food allergy, particularly due to cross-contamination and unexpected ingredients.

A telephone survey of US patients who suffered reactions to peanut and tree nut in restaurants, bakeries and shops showed that only 45% with previously diagnosed food allergy notified the establishment of their allergy. In the remainder of cases, reported reactions resulted from ingestion of food not intended for them, ingestion of food selected from buffet/food bars, or skin or inhalational contact (e.g. residual food on tables; peanut shells covering floors; being within a metre of the cooking of the food). For 78% of all reported reactions, someone in the establishment knew that the food contained the allergen as an ingredient. In 50% of these incidents, the food item was "hidden" (e.g. in sauces and dressings). In 22% cases, exposures were reported from contamination caused primarily by shared cooking or serving supplies (63).

Social considerations such as peer pressure, embarrassment, stigma, alcohol ingestion, choice and spontaneity may hamper a parent or adolescent's ability to apply appropriate avoidance behaviour (64). The individual or family should clearly state the allergy to the provider on each occasion and if possible should preview the menu online. This should be repeated on every visit to take account of change in recipes or staff. The food providers have a responsibility to provide clear, comprehensive information on potential allergenic ingredients so the individual/family can make an informed decision about food consumption. Where the risk is unknown, this should also be stated, and the restaurant should be avoided.

At present current food allergen legislation requires any of the 14 EU regulatory allergens, where used as ingredient, to be clearly declared within the ingredients list of prepacked foods (65). From December 2014, the Food Information for Consumers Regulation (EU Regulation No. 1169/2011) will also require businesses selling food sold non-prepacked to provide information about allergenic ingredients deliberately used in the food they serve to consumers. The allergens which have to be declared are mentioned in the Annex II of the Regulation. They include most of the major allergens, but not every food allergen. There are examples of voluntary best practice advice for such businesses (66).

Food preparation and handling techniques in catering establishments can increase the risk of a food allergic reaction due to the possibility of cross-contamination. The frequency of accidental allergic reactions as a result of cross-contamination in food establishments

Box 5 Families, healthcare professionals, schools, food outlets: recommendations

Recommendation	Evidence level	Grade	Key references
THE INDIVIDUAL / FAMILY			
Implement allergen strategies recommended by the allergist, nurse and dietitian both within the home and the wider community	V	D	Expert consensus
For children, inform the school/early-years settings of the allergy and provide them with a food allergy management plan from the allergist.	V	D	Expert consensus
Keep regular follow up with the allergist and school nurse and dietitian and forward new copies of treatment plans to the school as they are updated	V	D	Expert consensus
Monitor medication expiry dates and replace adrenaline auto-injectors as required	V	D	Expert consensus
THE ALLERGIST (ALLERGY SPECIALIST OR OTHER HEALTHCARE PROFESSIONAL WITH THE APPROPRIATE TRAINING AND COMPETENCY):			
Provide a comprehensive food allergy management plan incorporating the following features: diagnosis, risk assessment, allergen avoidance advice, provision and training in emergency medication, including adrenaline auto-injectors.	V	D	Expert consensus
Provide a written management plan incorporating relevant allergen avoidance advice and use of emergency medication PEMP. This should be passed to the school to form be incorporated into a personalized care plan (PCP).	V	D	Expert consensus
Liaise with educational services (for children) to develop/maintain a comprehensive school allergy policy and individual PCPs.	V	D	Expert consensus
SCHOOLS: RECOMMENDATIONS			
The school principal should develop a comprehensive school policy for allergy aware management and a staff member should be identified to coordinate allergy care and liaise with local allergy services.	IV	D	Expert Opinion
The school should identify all children with food allergy in its care, and each should have a PCP. The care plan should clearly state which foods are to be avoided, and what action is to be taken in the event of an accidental reaction.	IV	D	Expert Opinion
The school should engage with local allergy specialists to provide input into PCPs, training staff on food allergen avoidance, and how to treat reactions PEMP.	IV	D	Expert Opinion
The school should store emergency medication for each child as recommended by the allergist. Medication should be readily available.	IV	D	Expert Opinion
Allergy awareness should be applied to cooking and handling of food anywhere in the school	IV	D	Expert Opinion
The scope of the comprehensive school policy should extend to school trips, exchanges and excursions	IV	D	Expert Opinion
SUPPLIERS AND PROVIDERS OF NON-PACKAGED FOODS:			
Seek training and obtain competency in serving customers who have food allergy	IV	D	Expert Opinion
Implement policy and procedures to reduce cross-contamination	IV	D	Expert Opinion
Provide information to customers about food allergen content or possible cross contamination	IV	D	Expert Opinion

is unknown, though it is frequently encountered in clinical practice. Ignorance of the ingredients in a recipe by serving staff also poses significant risk (67). Good communication between staff preparing food and front-of-house serving staff is essential to prevent this

Some food allergic individuals can react to ingestion of trace levels of the offending food, although highly variable ranges of threshold doses exist. The magnitude of the risk depends, amongst other factors, on the dose of exposure to cross-contaminated foods, and the individual's threshold reactivity (68). Other co-factors at the time of the reaction such as poor asthma control, type of food allergen, exercise, infection, menstruation, NSAIDs, and alcohol use may contribute to severity (68-71). One study showed that for peanut allergy, threshold levels decreased with increasing age and increasing sIGE (72). However, in most fatal reactions, the allergen was deliberate ingredient in the food and not due present to cross contamination, and adrenaline was not available or not administered (18, 73). Insufficient threshold dose information within the food allergic population restricts the advice on safe levels of contamination allergenic foods.

The need for more training for restaurant staff and consumer caution on staff knowledge gaps remains high. Studies from the US and the UK of an assortment of staff from a wide variety of restaurants and fast-food outlets suggest a high degree of confidence, but a low level of knowledge, and a desire for further training (74-76)

Travelling abroad may be perceived as a potential risky situation for severe food allergic reactions. Difficulties with airlines or restaurants are frequently quoted (76). The data from studies reporting reactions on airplanes is limited (77); but a small number, of reactions occur in this context, some of them severe. Airline companies show inconsistency, e.g. regarding provision of peanuts on board aircraft, and requests for special assistance (78-82). Allergic reactions constituted only 2.2% of medical emergencies during commercial passenger flights in the US (83).

In the survey performed by Greenhawt *et al.* although 76% of food allergic patients who had an in-flight reaction reported carrying an AAI only 10.6% of these individuals used their device, and overall, only 10% received adrenaline (from the auto-injector or via syringe) as treatment. Despite the reaction, 52.4% reported not making any changes in their behaviour. However some protective behaviour was reported by the other half: 25.7% reported they no longer consume food served on board, 23.8% now clean their personal seating area, and 20% request a peanut or tree nut–free flight. Twelve percent reported no longer flying commercially as a result of this reaction (80).

The approach to eating on an aircraft should be the same as that for any restaurant, ensuring the cabin staff are aware of the allergy (preferably inform the airline before the flight and the cabin staff on the day), and the contents of any meal served during the flight should be carefully checked. Emergency medication should be carried in the aircraft cabin and not packed into the luggage hold.

At the destination, individuals can use a variety of strategies to remain safe including visiting familiar environments, carrying allergy information cards in the host language and possibly preparing their own food (84). They should also carry a sufficient supply of emergency medication, bearing in mind it may be difficult to replace, and be prepared to use it.

General public

The general public plays a significant role in the well being of individuals with food allergy. The emergence of food allergy as a significant public health problem has been relatively recent and is accompanied by increasing interest from the mass media and the commercial sector, as policy-makers respond to the demands of affected individuals (84). Food allergy has become an important issue on the regulatory agenda, particularly in the UK, Canada, the USA, New Zealand and Australia (85). In order to respond appropriately to the growing prevalence of food allergies, decision-makers must balance protecting the affected population, whilst accommodating the general public's needs.

Improved food allergy knowledge among the general public is desirable. A web-based survey of the general US population showed that familiarity and prior training in food allergy management were associated with higher knowledge scores. However, respondents tended to minimize the stigma associated with food allergy and oppose food allergy policies in schools (86).

The introduction of public health policies to protect food-allergic individuals should be based on the best available data and expert consensus. Currently, many policies and regulations are being implemented in

public spaces (schools, restaurants) despite the lack of scientific consensus (87). Consequently, these policies are often perceived as extreme in the literature, in the media, and by the non-allergic population (88). The inflated perception of risk for severe food allergies in the general population (87, 89) has resulted in several debates related to protection versus rights, particularly around the policies developed in response to the disproportionate burden of food allergies in children (90).

In addition social exclusion (such as parents to invite an a child with allergies, prohibited trips and activities or reduced career options in the longer term) is a growing problem that needs to be addressed at the societal level. In the meantime, careful planning such as training the staff who will be accompanying the allergic child in the trip in allergen avoidance on symptoms recognition and emergency medication should overcome some situations of social exclusion.

Concluding remarks

Food allergy reactions commonly occur outside the home environment. Food allergies are now seen as a health risk and there is a growing interest from the general public, media and the commercial sector. Community exposure, traveling abroad and lack of information from health care providers are factors that place patients at greater risk of severe or fatal anaphylaxis. In the community, many stakeholders need to work together to reduce the risk of allergic reactions to foods and to manage any that occur.

The ability of the parents of children with food allergies to assess the risk and manage their child's condition is highly dependent on the parental knowledge, attitudes, support of family/friends/others including support organisations and beliefs of food allergy. School nurses and teachers play a key role in managing young students with food allergies. For older students self-management should be encouraged. Policies regarding food allergy management in schools range widely, and are often inadequate if not made in conjunction with an informed clinician.

Many retail catering facilities are poorly prepared to handle the advent of anaphylaxis and staff often have poor knowledge on preventive management of food allergy. Businesses such as restaurants and take-aways have no legal obligation to warn customers about potential allergen content. The need for more training for restaurant/cafeteria/fast-food/take-away staff and consumer caution on food allergen content and staff knowledge gaps remains high.

Communication patterns of within the general community may be hampered by legitimate everyday social considerations such as embarrassment, choice, spontaneity and discrimination. Increased food allergy knowledge among the general public is required, nevertheless the needs and rights of the non-allergic population should be taken into consideration as well. Policies should be structured around ethical principles of confidentiality and anonymity, fairness, avoiding stigmatization, and empowerment of patients.

However, implementing proper risk management strategies should be evidence based. The paucity of randomized–controlled studies on evaluation of effectiveness and cost-effectiveness of such interventions has so far restricted the grade of recommendations to the level of expert consensus (Box 6). As a consequence, the adoption of procedures has been limited to very few countries. The time has come to undertake efforts to address these issues in the community at- large worldwide (Box 7).

Expert Panel

We are grateful to the expert panel for providing expert feedback on the final draft of the paper: Magnus Borres (Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden), Anna Bręborowicz (Department of Pathophysiology, Poznan University of Medical Sciences, Poznan, Poland), Chun-Han Chan (Food Allergy Branch, Chemical Services Division, Food Standards Agency, London, UK), M. Hazel Gowland (Anaphylaxis Campaign, Farnborough, UK), Matt Greenhawt (Department of Internal Medicine, Division of Allergy and Clinical Immunology, The University of Michigan Food Allergy Center, The University of Michigan Medical School, and the University of Michigan Health System, Ann Arbor, Michigan, USA), Ruchi Gupta (Northwestern University Feinberg School of Medicine, Chicago, Ill; Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA), Marcia Podestà (Food Allergy Italia).

Acknowledgements

We would like to acknowledge the support of EAACI and the EAACI Food Allergy and Anaphylaxis Guidelines

Box 6 Research gaps

Gaps in the evidence	Plan to address	Priority
Epidemiology of food-induced anaphylactic reactions in the community (incidence and risk assessment)	Disease registries and large epidemiological trials with a common methodology	High
Population thresholds for common food allergens and interaction with co-factors	Studies to estimate population thresholds and actions levels for common food allergens, including estimating the effect of co-factors (e.g. exercise) on the action levels	High
Objective measurement of interventions aimed to reduce in the community	Pragmatic (RCTs) to prevent food allergic reactions in the community including quality of life / anxiety score as outcome measure.	High
Comparison between various intervention methods for efficacy and cost-effectiveness	RCTs of various media (smartphone apps and websites) to implement/reinforce training packages for prevention and acute management of reactions. Especially useful for evaluation of specific target groups, such as teenagers/young adults and teachers.	High
	Trials of efficacy and cost-effectiveness of different models of school training implementation, e.g. web based school nurse training versus face-face.	High
	Trials of efficacy and cost-effectiveness of different models to improve knowledge base of community food providers.	High

Group in developing these guidelines. We would like to thank Dr. Cristina Ranzato for her insights and advice on public health issues and Ms Catherine Crowley for her administrative help in preparing the guidelines. We would also like to thank our EAACI taskforce members and the EAACI Executive Committee for their helpful comments and suggestions.

Authors' contribution

Antonella Muraro, Chair of the EAACI Food Allergy and Anaphylaxis Guidelines Initiative, has steered and coordinated the publication. Ioana Agache and Andy Clark wrote the first draft of the manuscript. All authors participated in the revision of the manuscript including the discussion of the recommendations and gaps.

Conflicts of interest

Antonella Muraro has provided scientific advice for Meda. Graham Roberts has provided scientific advice for Danone and ALK-Abelló; Thermo Fisher and ALK-Abelló have provided consumables for his research activities. Jonathan O'B. Hourihane has received speaker fees from Mead Johnson, Nutricia, MSD, Pfizer, ALK-Abelló and Stallergenes; Thermo Fisher have provided consumables for his research activities. Luis Miguel Borrego has received honoraria for lectures from MSD. Sabine Schnadt has support for travel to EAACI congress from Peanut Council and Novartis. Ioana Agache, Jennette Higgs, Angel Mazon, Magnus Wickman, Maria Said, Davide Parmigiani, Andrew Clark, Cezmi Akdis, Berber Vlieg-Boerstra, Penny Jorgensen, Harmieke van Os-Medendorp and Aziz Sheikh have no conflict of interests in relation to this manuscript.

References

1. Eigenmann PA, Zamora SA. An internet-based survey on the circumstances of food-induced reactions following the diagnosis of IgE-mediated food allergy. *Allergy* 2002;57: 449-453.
2. Muraro A, Clark A, Beyer K, Borrego LM, Borres M, Lødrup Carlsen KC *et al.* The management of the allergic child at school: EAACI/GA2LEN Task Force on the allergic child at school. *Allergy* 2010;65:681-689.
3. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF *et al.* Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin*

Box 7 Families, healthcare professionals, schools, food outlets: implementation and audit

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
THE INDIVIDUAL / FAMILY					
Implement allergen strategies recommended by the allergist, nurse and dietitian both within the home and the wider community	V	D	Lack of trained personnel to explain the indications	Education of the family as a whole, including caregivers through specific educational courses	% of families receiving proper advice
For children, inform the school/early-years settings of the allergy and provide them with a food allergy management plan from the allergist.	V	D	Lack of allergists Lack of time and adequate knowledge among primary care physicians Fear of stigma Lack of proper legislation implementing guidelines for school	Education and training of nurses and medical students Education on psychological issues and proper communication Implementation of specific legislation	% of patients with food allergy management plans at school
Keep regular follow up with the allergist and school nurse and dietitian and forward new copies of treatment plans to the school as they are updated	V	D	Lack of communication among stakeholders Lack of trained personnel Long waiting lists	Implementation of communication flow e.g. web based	% of school receiving updates directly
Monitor medication expiry dates and replace adrenaline auto-injectors as required	V	D	Lack of knowledge that adrenaline auto-injectors expire, availability and cost of auto-injectors	Alert systems as reminder, check at each physician's visit	% of patient with adrenaline auto-injector
THE ALLERGIST (ALLERGY SPECIALIST OR OTHER HEALTHCARE PROFESSIONAL WITH THE APPROPRIATE TRAINING AND COMPETENCY)					
Provide a comprehensive food allergy management plan incorporating the following features: diagnosis, risk assessment, allergen avoidance advice, provision and training in emergency medication, including adrenaline auto-injectors.	V	D	Lack of knowledge among healthcare professionals, lack of training	Education to primary care physicians, nurses, dietitians and medical students	% of patients receiving an adequate comprehensive consultation
Provide a written management plan incorporating relevant allergen avoidance advice and use of emergency medication. This should be passed to the school to form a basis for the personalized care plan (PCP).	V	D	Lack of trained personnel, lack of adequate communication with the school	Education to primary care physicians, nurses, dietitians and medical students	% of patients receiving management plans
Liaise with educational services (for children) to develop/maintain a comprehensive school allergy policy and individual PCPs.	V	D	Lack of time and resources	Compensation for time spent for educational activity	% of consultations to school

Box 7 (continued)

Recommendation	Evidence level	Grade	Barriers to implementation	Facilitators to implementation	Audit criteria
SCHOOLS: RECOMMENDATIONS					
The principal should develop a comprehensive school policy for allergy aware management and a staff member should be identified to coordinate allergy care and liaise with local allergy services.	IV	D	Lack of specific national guidelines for school Liability issues for school staff to be addressed	Implementing national guidelines for school	% of national countries with guidelines for school % of schools with management plans
The school should identify all children with food allergy in its care, and each should have a comprehensive PCP.	IV	D	Lack of specific national guidelines for school	Implementing national guidelines for school	% of national countries with guidelines for school % of children correctly identified
The school should engage with local allergy specialists to provide input into PCPs and staff training.	IV	D	Lack of specific national guidelines for school	Implementing national guidelines for school	% of national countries with guidelines for school % of school staff trained
The school should store emergency medication for each child as recommended by the allergist. Medication should be readily available.	IV	D	Lack of specific national guidelines for school	Implementing national guidelines for school	% of staff aware of the medication storage and expiry date
Allergy awareness should be applied to cooking and handling of food anywhere in the school	IV	D	Lack of specific national guidelines for school Liability issues for school staff to be addressed	Implementing national guidelines Implementing procedures	% of school with proper procedures
The scope of the comprehensive school policy should extend to school trips, exchanges and excursions	IV	D	Lack of specific national guidelines for school Liability issues for school staff to be addressed	Implementing national guidelines Implementing procedures	% of school with proper procedures
SUPPLIERS AND PROVIDERS OF NON-PACKAGED FOODS					
Seek training and obtain competency in serving customers who have food allergy	IV	D	Lack of awareness, knowledge and training, lack of legislation	Educational courses	% of staff with adequate knowledge
Implement policy and procedures to reduce cross-contamination	IV	D	Lack of awareness, knowledge and training, lack of legislation, lack of funding for educational activities	Educational courses on national basis funded by the Government or charities Implementation of policies and procedures	% of policies and procedures developed and implemented
Provide information to customers about food allergen content or possible cross contamination	IV	D	Lack of awareness, knowledge and training, lack of legislation	Educational courses on national basis funded by the Government or charities Implementation of policies and procedures	% of customers receiving proper management

Immunol 2004;113:832-836.

4. Agree Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care* 2003;12:18-23.
5. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G *et al*. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182: E839-E842.
6. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V *et al*. EAACI Food Allergy and Anaphylaxis Guidelines Group. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014;69:62-75.
7. Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K *et al*. The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy* 2014;69:76-86.
8. de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K *et al*. Acute and long-term management of food allergy: systematic review. *Allergy* 2014;69:159-167.
9. Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilò MB *et al*. Management of anaphylaxis: a systematic review. *Allergy* 2014;69:168-175.
10. Oxford Centre for Evidence-based Medicine. Levels of Evidence and Grades of Recommendation. http://www cebm net/index aspx?o=1025. Last accessed 25 March 2013.
11. Gupta R, Sheikh A, Strachan D, Anderson HR. Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. *BMJ* 2003;327:1142–1143.
12. Nowak-Wegrzyn A, Sampson HA. Adverse reactions to foods. *Med Clin North Am* 2006;90:97-127.
13. Bidat E. Food allergy in children. *Arch Pediatr* 2006;13: 1349-1353.
14. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children-a questionnaire-based survey in Germany. *Allergy* 2005;60:1440-1445.
15. Vetander M, Helander D, Flodström C, Ostblom E, Alfvén T, Ly DH *et al*. Anaphylaxis and reactions to foods in children--a population-based case study of emergency department visits. *Clin Exp Allergy* 2012;42:568-577.
16. Beyer K, Eckermann O, Hompes S, Grabenhenrich L, Worm M. Anaphylaxis in an emergency setting - elicitors, therapy and incidence of severe allergic reactions. *Allergy* 2012;67:1451-1456.
17. Cox HE. Food allergy as seen by an allergist. *J Pediatr Gastroenterol Nutr* 2008;47 Suppl 2:S45-S48.
18. Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagni G *et al*. Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 1998;101:E8.
19. Moneret-Vautrin DA, Kanny G, Morisset M, Flabbee J, Guénard L, Beaudouin E *et al*. Food anaphylaxis in schools: evaluation of the management plan and the efficiency of the emergency kit. *Allergy* 2001;56:1071-1076.
20. Rankin KE, Sheikh A. Serious shortcomings in the management of children with anaphylaxis in Scottish schools. *PLoS Med* 2006;3:e326.
21. McIntyre CL, Sheetz AH, Carroll CR, Young MC. Administration of epinephrine for life-threatening allergic reactions in school settings. *Pediatrics* 2005;116:1134-1140.
22. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy ClinImmunol* 2007;119:1016-1018.
23. Young MC, Muñoz-Furlong A, Sicherer SH. Management of food allergies in schools: a perspective for allergists. *J Allergy Clin Immunol* 2009;124:175-182.
24. Burks W, Ballmer-Weber BK. Food allergy. *Mol Nutr Food Res* 2006;50:595-603.
25. Allen KJ, Hill DJ, Heine RG. Food allergy in childhood. *Med J Aust* 2006;185:394-400.
26. Uguz A, Lack G, Pumphrey R, Ewan P, Warner J, Dick J *et al*. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy* 2005;35:746-750.
27. AAAAI Board of Directors. American Academy of Allergy, Asthma and Immunology. Anaphylaxis in schools and other childcare settings. *J Allergy ClinImmunol* 1998;102:173-176.
28. School guidelines for managing students with food allergies. *School Nurse News* 2007;24:8:11.
29. Robinson JM, Ficca M. Managing the student with severe food allergies. *J Sch Nurs* 2012;28:187-194.
30. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin* 2007;119:1018-1019.
31. Kapoor S, Roberts G, Bynoe Y, Gaughan M, Habibi P, Lack G. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy* 2004;59:185-191.
32. Muñoz-Furlong A, Weiss CC. Characteristics of food-allergic patients placing them at risk for a fatal anaphylactic episode. *Curr Allergy Asthma Rep* 2009;9:57-63.
33. Imamura T, Kanagawa Y, Ebisawa M. A survey of patients with self-reported severe food allergies in Japan. *Pediatr Allergy Immunol* 2008;19:270-274.
34. Sampson MA, Muñoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. *J Allergy ClinImmunol* 2006;117:1440-1445.
35. Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. *Clin Exp Allergy* 2011;41:869-877.
36. Gallagher M, Worth A, Cunningham-Burley S, Sheikh

A. Strategies for living with the risk of anaphylaxis in adolescence: qualitative study of young people and their parents. *Prim Care Respir J* 2012;21:392-397.

37. http://www.cdc.gov/healthyyouth/foodallergies/pdf/13_243135_A_Food_Allergy_Web_508.pdf. Last accessed 1 May 2014.
38. Clark AT, Ewan PW. Good prognosis, clinical features, and circumstances of peanut and tree nut reactions in children treated by a specialist allergy center. *J Allergy Clin Immunol* 2008;122:286-289.
39. Knibb RC, Semper H. Impact of suspected food allergy on emotional distress and family life of parents prior to allergy diagnosis. *Pediatr Allergy Immunol* 2013;24:798-803.
40. Health Council of the Netherlands. Food allergy. The Hague: Health Council of the Netherlands, 2007; publication no. 2007/07.
41. Flokstra-de Blok BM, Doriene van Ginkel C, Roerdink EM, Kroeze MA, Stel AA, van der Meulen GN *et al.* Extremely low prevalence of epinephrine autoinjectors in high-risk food-allergic adolescents in Dutch high schools. *Pediatr Allergy* 2011;22:374-377.
42. Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J *et al.* The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy* 2012;42:284-292.
43. Arkwright PD, Farragher AJ. Factors determining the ability of parents to effectively administer intramuscular adrenaline to food allergic children. *Pediatr Allergy Immunol* 2006;17:227-229.
44. Kim JS, Sinacore JM, Pongracic JA. Parental use of EpiPen for children with food allergies. *J Allergy ClinImmunol* 2005;116:164-168.
45. Gupta RS, Springston EE, Smith B, Kim JS, Pongracic JA, Wang X *et al.* Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the United States. *Pediatr Allergy Immunol* 2010;21:927-934.
46. Weiss C, Muñoz-Furlong A, Furlong TJ, Arbit J. Impact of food allergies on school nursing practice. *J Sch Nurs* 2004;20:268-278.
47. Polloni L, Lazzarotto F, Toniolo A, Ducolin G, Muraro A. What do school personnel know, think and feel about food allergies? *Clin Transl Allergy* 2013;3:39.
48. Greenhawt MJ, Singer AM, Baptist AP. Food allergy and food allergy attitudes among college students. *J Allergy Clin Immunol* 2009;124:323-327.
49. Ercan H, Ozen A, Karatepe H, Berber M, Cengizlier R. Primary school teachers' knowledge about and attitudes toward anaphylaxis. *Pediatr Allergy Immunol* 2012;23:428-432.
50. Behrmann J. Ethical principles as a guide in implementing policies for the management of food allergies in schools. *J Sch Nurs* 2010;26:183-193.
51. Pouessel G, Deschildre A, Castelain C, Sardet A, Sagot-Bevenot S, de Sauve-Boeuf A *et al.* Parental knowledge and use of epinephrine auto-injector for children with food allergy. *Pediatr Allergy Immunol* 2006;17:221-226.
52. Clark S, Camargo CA Jr. Emergency management of food allergy: systems perspective. CurrOpin Allergy Clin Immunol. 2005;5:293-8.
53. Pulcini JM, Sease KK, Marshall GD. Disparity between the presence and absence of food allergy action plans in one school district. *Allergy Asthma Proc* 2010;31:141-146.
54. Shemesh E, Annunziato RA, Ambrose MA, Ravid NL, Mullarkey C, Rubes M, *et al.* Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics* 2013 ;131:e10-e17
55. Lieberman JA, Weiss C, Furlong TJ, Sicherer M, Sicherer SH. Bullying among pediatric patients with food allergy. *Ann Allergy Asthma Immunol* 2010;105:282-286.
56. Cavanaugh R, Strickland CJ. Research to practice: developing an integrated anaphylaxis education curriculum for school nurses. *J Sch Nurs* 2011;27:197-208.
57. http://www.anaphylaxis.org.uk/healthcare/allergywise-training/allergywise-online-training-and-resources-for-healthcare-professionals. Last accessed 1 May 2014.
58. Gådin KG, Weiner G, Ahlgren C. Young students as participants in school health promotion: an intervention study in a Swedish elementary school. *Int J Circumpolar Health* 2009;68:498-507.
59. Standage M, Cumming SP, Gillison FB. A cluster randomized controlled trial of the be the best you can be intervention: effects on the psychological and physical well-being of school children. *BMC Public Health* 2013;13:666. doi: 10.1186/1471-2458-13-666.
60. Fenton NE, Elliott SJ, Cicutto L, Clarke AE, Harada L, McPhee E. Illustrating risk: anaphylaxis through the eyes of the food-allergic child. *Risk Anal* 2011;31:171-183.
61. Spina JL, McIntyre CL, Pulcini JA. An intervention to increase high school students' compliance with carrying auto-injectable epinephrine: a MASNRN study. *J Sch Nurs* 2012;28:230-237.
62. Frost DW, Chalin CG. The effect of income on anaphylaxis preparation and management plans in Toronto primary schools. *Can J Public Health* 2005;96:250-253.
63. Furlong TJ, DeSimone J, Sicherer SH. Peanut and tree nut allergic reactions in restaurants and other food establishments. *J Allergy ClinImmunol* 2001;108:867-870.
64. Leftwich J, Barnett J, Muncer K, Shepherd R, Raats MM, Hazel Gowland M, Lucas JS. The challenges for nut-allergic consumers of eating out. *Clin Exp Allergy* 2011;41:243-249.
65. Anandan C, Sheikh A. European developments in labelling allergenic foods. *BMJ* 2005;331:1155-1156.
66. http://www.food.gov.uk/business-industry/guidancenotes/labelregsguidance/nonprepacked#.URJ5846D7IY. Last accessed 1 May 2014.
67. Zurzolo GA, Mathai ML, Koplin JJ, Allen KJ. Hidden

allergens in foods and implications for labelling and clinical care of food allergic patients. *Curr Allergy Asthma Rep* 2012;12:292-296.

68. Taylor SL, Baumert JL. Cross-contamination of foods and implications for food allergic patients. *Curr Allergy Asthma Rep* 2010;10:265-270.
69. Eller E, Hansen TK, Bindslev-Jensen C. Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges. *Ann Allergy Asthma Immunol* 2012;108:332-336.
70. Hompes S, Dölle S, Grünhagen J, Grabenhenrich L, Worm M. Elicitors and co-factors in food-induced anaphylaxis in adults. *Clin Transl Allergy* 2013;3:38.
71. Cardona V, Luengo O, Garriga T, Labrador-Horrillo M, Sala-Cunill A, Izquierdo A *et al*. Co-factor-enhanced food allergy. *Allergy* 2012;67:1316-1318.
72. van der Veen MJ, van Ree R, Aalberse RC, Akkerdaas J, Koppelman SJ, Jansen HM *et al*. Poor biologic activity of cross-reactive IgE directed to carbohydrate determinants of glycoproteins. *J Allergy Clin Immunol* 1997;100:327–334.
73. Ferreira CT, Seidman E. Food allergy: a practical update from the gastroenterological viewpoint. *J Pediatr (Rio J)* 2007;83:7-20.
74. Ahuja R, Sicherer SH Food-allergy management from the perspective of restaurant and food establishment personnel. *Ann Allergy Asthma Immunol* 2007;98:344-348.
75. Bailey S, Albardiaz R, Frew AJ, Smith H. Restaurant staff's knowledge of anaphylaxis and dietary care of people with allergies. *Clin Exp Allergy* 2011;41:713-717.
76. Leitch IS, Walker MJ, Davey R. Food allergy: gambling your life on a take-away meal. *Int J Environ Health Res* 2005;15:79-87.
77. Shehata Y, Sheikh A, Flight anaphylaxis emergencies: lessons gained from attempting a questionnaire pilot study. *Prim Care Respir J* 2007;16:321.
78. Comstock SS, DeMera R, Vega LC, Boren EJ, Deane S, Haapanen LA *et al*. Allergic reactions to peanuts, tree nuts, and seeds aboard commercial airliners. *Ann Allergy Asthma Immunol* 2008;101:51–56.
79. Moore BR, Ping JM, Claypool DW. Pediatric Emergencies on a US-Based Commercial Airline. *Pediatr Emerg Care* 2005;21:725–729.
80. Greenhawt MJ, McMorris MS, Furlong TJ. Self-reported allergic reactions to peanut and tree nuts occurring on commercial airlines. *J Allergy Clin Immunol* 2009;124:599–600.
81. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. Self-reported allergic reactions to peanut on commercial airliners. *J Allergy Clin Immunol* 1999;104:186-189.
82. Barnett J, Botting N, Gowland M H, Lucas J S. The strategies that peanut and nut-allergic consumers employ to remain safe when travelling abroad. *Clin Transl Allergy* 2012;2:12.
83. Peterson DC, Martin-Gill C, Guyette FX, Tobias AZ, McCarthy CE, Harrington ST *et al*. Outcomes of Medical Emergencies on Commercial Airline Flights. *N Engl J Med* 2013;368:2075-2083.
84. Nettleton S, Woods B, Burrows R, Kerr A. Food allergy and food intolerance: Towards a sociological agenda. *Health (London)* 2009;13:647–664.
85. Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ *et al*. Diagnosing and managing common food allergies. *JAMA* 2010;303:1848–1856.
86. Gupta RS, Kim JS, Springston EE, Smith B, Pongracic JA, Wang X *et al*. Food allergy knowledge, attitudes, and beliefs in the United States. *Ann Allergy Asthma Immunol* 2009;103:43-50.
87. Harrington DW, Elliott SJ, Clarke AE, Ben-Shoshan M, Godefroy S. Exploring the Determinants of the Perceived Risk of Food Allergies in Canada. *Hum Ecol Risk Assess* 2012;18:1338–1358.
88. Harrington DW, Elliott SJ, Clarke AE. Frames, claims and audiences: Construction of food allergies in the Canadian media. *Public Underst Sci* 2012;21:724-739.
89. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E *et al*. The prevalence of food allergy: A meta-analysis. *J Allergy Clin Immunology* 2007;120:638–646.
90. Madsen CB, Crevel R, Chan CH, Dubois AE, DunnGalvin A, Flokstra-de Blok BM *et al*. Food allergy: Stakeholder perspectives on acceptable risk. *Regul Toxicol Pharmacol* 2010;57:256-265.

SECTION 6

FOOD INDUSTRY

6.1

PROTECTING CONSUMERS WITH FOOD ALLERGIES

EAACI GUIDELINES

A Muraro[1*], K Hoffmann-Sommergruber[2*], T Holzhauser[3], LK Poulsen[4], MH Gowland[5], CA Akdis[6, 7], ENC Mills[8], N Papadopoulos[9, 10], G Roberts[11-13], S Schnadt[14], R van Ree[15], A Sheikh[16-18], S Vieths[3], on behalf of the EAACI Food Allergy & Anaphylaxis Guidelines Group

AFFILIATIONS

[1] The Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region. Department of Mother and Child Health, Padua General University Hospital, Padua, Italy

[2] Dept of Pathophysiology and Allergy Research, Medical University Vienna, Vienna, Austria

[3] Division of Allergology, Paul-Ehrlich Institute, Langen, Germany

[4] Allergy Clinic, Copenhagen University Hospital, Copenhagen, Denmark

[5] Allergy Action, St Albans, UK

[6] Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[7] Christine Kühne–Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

[8] Institute of Inflammation and Repair, Manchester Academic Health Science Centre, Manchester Institute of Biotechnology, University of Manchester, UK

[9] Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

[10] Centre for Pediatrics and Child Health Institute of Human Development The University of Manchester, Manchester, UK

[11] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[12] Human Development in Health and Clinical and Experimental Sciences Academic Units, University of Southampton Faculty of Medicine, Southampton, UK

[13] NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[14] Deutscher Allergie- und Asthmabund e.V., Mönchengladbach, Germany

[15] Departments of Experimental Immunology and Otorhinolaryngology, Academic Medical Center, Amsterdam University, Amsterdam, The Netherlands

[16] Allergy and Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK

[17] Department of Medicine, Harvard Medical School, Harvard, USA

[18] Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Boston, USA

** Joint first author*

Individuals suffering from IgE-mediated food allergy usually have to practice life-long food allergen avoidance. This chapter aims to provide an overview of recent evidence-based recommendations for allergen risk assessment and management in the food industry and discusses unmet needs and expectations of the consumer with food allergies in that context. There is a general duty of care on the food industry and obligations in European Union legislation to reduce and manage the presence of allergens alongside other food hazards. Current evidence enables quantification of allergen reference doses which can be used to set up reliable food safety management plans for some foods. However, further work is required to include a wider variety of foods and to understand the impact of the food matrix as well as additional factors which affect the progression and severity of symptoms as a function of dose. Major concerns have been raised by patients/carers and patient groups about the perceived over-use of precautionary 'may contain' labelling to address the issue of the unintended presence of allergens; these therefore need to be reconsidered. New and improved allergen detection methods should be evaluated for their application in food production. There is an urgent requirement for effective communication between healthcare professionals, patient organizations, food industry representatives and regulators to develop a better approach to protecting consumers with food allergies.

Background

IgE-mediated food allergy is an important chronic disease manifested by a range of symptoms which can sometimes become life-threatening (1, 2). In the absence of a cure, individuals with food allergy usually have to practice life-long food allergen avoidance. Those at risk of severe allergic reactions must be equipped with rescue medication in case they accidentally consume or have contact with the culprit food. As most common allergenic foods provide valuable nutrition and dietary variety, it is neither practical nor desirable to eliminate these from all food products. Therefore, allergens are ubiquitous elements in food manufacturing environments. In order to support consumers with food allergy in avoiding food allergens, European Union (EU) food legislation requires the labelling of allergenic food components which are used as ingredients (3). It also imposes a general duty of care on the food industry to reduce and manage, control and communicate the presence of allergens alongside other food hazards (Box 1). This requires allergenic ingredients to be managed rather than eliminated completely from the food supply (4). However, the majority of foods are processed on shared equipment and so-called allergen cross-contact may lead to the unintended presence of allergens. To date, the frequency and extent of cross-contact in commercial food items is generally unknown. As a consequence, precautionary labelling, such as “may contain…” is frequently used. This is partly for product liability reasons but also to provide additional consumer safety information, even though application of the precautionary labelling may not be evidence-based. In addition, important gaps in knowledge regarding the allergen risk management of manufactured food

Box 1 Key terms

Term	Definition
Allergen	Any substance to which IgE may react causing triggering of effector cells via FcERI-crosslinking; usually a protein. For allergen management this term usually refers to the food.
Clinical threshold doses	The lowest dose of an allergenic food to elicit an objective allergic reaction in an individual during a food challenge test.
Co-factors	Patient related circumstances that may modify allergic reactions to be more severe. They are known also as augmentation factors .
Cross-contact / cross-contamination	Unintentional transfer of an allergenic food/ingredient into another food even despite existing GMP. Applies for both, prepacked and whole foods.
Food	Any substance, whether processed, semi-processed or raw, which is intended for human consumption, and includes drink, chewing gum and any substance which has been used in the manufacture, preparation or treatment of "food" but does not include cosmetics or tobacco or substances used only as drugs (Codex Alimentarius).
Food label	Any tag, brand, mark, pictorial or other descriptive matter, written, printed or stencilled on the packaging or container of food (5).
Reference dose	The amount of the allergenic food (mg protein) below which adverse reactions are unlikely.
Risk assessment	A scientifically based process consisting of four steps: hazard identification, hazard characterization, exposure assessment and risk characterization (5).
Risk communication	The interactive exchange of information and opinions throughout the risk analysis process with regard to hazards and risks, related factors and perceptions among risk assessors, managers, consumers, the academic community and other interested parties (5).
Risk management for food safety	A network of inter-related elements ensuring that food does not cause adverse human health effects. These elements include programmes, plans, policies, processes, methods, controls, responsibilities, documents, records and resources (6).

remain. Proper, improved and novel tools that enable food industry to develop and implement effective allergen management strategies are urgently required. In parallel, efficient training strategies for food manufacturing and catering companies have to be developed. Last, but not least, adequate support for consumers with food allergy needs to be developed. It is necessary to understand consumer attitudes to allergens in foods, and to appreciate who is avoiding which foods and why. This decision depends on each individual's potential severity of symptoms, their age, their understanding and social circumstances. For effective and personalized food allergen avoidance, providing the essential information is a key element, as well as adequate training of the patients to read and interpret the labels of pre-packed and non pre-packed foods as well as talking to food suppliers for further information.

METHODS

Clarifying the scope and purpose of this document

The process began in January 2012 with a meeting to discuss the overall approach to guideline development. This included detailed discussions on the main aims of the guidelines, the target conditions, agreeing the intended end-user for the recommendations, agreeing the intended end-user group, and ensuring adequate professional and lay representation in the guidelines development process.

Ensuring appropriate stakeholder involvement

Participants represented different disciplinary and clinical backgrounds, including medical tertiary, secondary and primary care (Aziz Sheikh) and patient groups (Sabine Schnadt (Germany), Hazel Gowland (UK)).

Formulating recommendations

This chapter aims to provide an overview of recent evidence-based recommendations for allergen risk assessment and management in the food industry and discusses unmet needs and expectations of the food allergic consumer in that context. Key issues are summarised with regard to food allergens and the food allergic consumer, including the perceived excessive use of precautionary labelling, (7) the lack of common standards for risk assessment, the suboptimal analytical methodology and the communication between consumers at risk, food manufacturers and regulators to establish a common understanding of the risk. In order to build on the current status quo and improve experiences and outcomes for patients/carers, there is a need to agree common standards and develop clear risk-based use of precautionary labelling, which provide a valid and reliable communication of risk, and support the issuing of clear allergen management advice for use in the food manufacturing area. The target audience for this review comprises patients' organizations, regulators, allergists and healthcare professionals as well as food manufacturers, retailers and caterers. The following recommendations are the result of expert opinion consensus following previous systematic reviews of literature on epidemiology, diagnosis and management of food allergy and anaphylaxis (8-11) (see Chapters 1.1, 1.2, 1.3, 4.1, 4.2) and extensive narrative review of the relevant literature. They result also from consultations with all stakeholders involved in management of food allergy and anaphylaxis including primary care physicians and patient organizations. The most important goals are summarized in Box 2.

Box 2 Major goals

- To identify best practice for allergen risk assessment in food manufacturing and catering.
- To examine the evidence-base that underpins allergen management plans and risk communication strategies, including application of precautionary labelling.
- To examine education / training strategies for food manufacturing and catering companies.
- To identify relevant analytical tools and enforcement practices of regulatory authorities.
- To identify best education and training strategies for food allergic consumers to assess the information presented on food labels relevant for their allergic condition.

Editorial independence and managing conflict of interests

The production of these guidelines was funded and supported by EAACI. The funders did not have any influence on the guideline production process, its contents or on the decision to publish. All members of the Community Task Force completed conflicts of interest statements and these were taken into account by the Community Task Force chair as recommendations were formulated.

Updating the guidelines

We plan to update this document in 2017 unless there are important advances before then.

Risk assessment: towards evidence-based reference doses

Within the last two decades, great efforts have been undertaken in assessing the risk arising from allergenic ingredients in food products for consumers with food allergies. Due to the fact that the range of reactivity to allergens is very wide (up to 6 orders of magnitude, calculated from controlled food challenge studies; (12)) it is evident that the development of an evidence-based risk assessment for food allergens is a challenging task. The overall uncertainty of the risk due to even very small residual amounts of allergen and the consequent effect for a consumer who is highly sensitive, with or without co-factors, has led to the introduction of precautionary labelling (13).

Recently, the Australian Voluntary Incidental Trace Allergen Labelling (VITAL) initiative and the ILSI Europe Food Allergy Task Force reviewed data sets from previous food challenges with regard to reactions to low doses of different allergenic foods and performed a probabilistic risk assessment approach (13-15). The eliciting dose for inducing an allergic reaction in 1% of the specific allergic population (ED01) was estimated for peanut as 0.2 mg protein, i.e. 1% of the peanut allergic individuals would react to a dose of 0.2 mg peanut protein (Table 1). Other ED01 levels have been developed for cow's milk, hen's egg, and hazelnut (13). ED05 values have been identified for wheat, mustard, lupin, cashew, sesame seed, shrimp and fish (14, 15). So far, doses for celery and tree nuts, other than hazelnut and cashew, are lacking (15). Depending on the allergenic food, doses ranged from 0.03 mg (egg) to 10 mg (shrimp). The availability of these reference doses provides the foundations for an evidence-based approach for redesigning efficient risk assessment applicable to food production.

Table 1 Suggested reference doses for allergenic foods*

Food	Reference dose (mg protein)	Required analytical sensitivity**
Peanut[1]	0.2	4
Cow's milk[1]	0.1	2
Egg[1]	0.03	0.6
Hazelnut[1]	0.1	2
Soy[2]	1.0	20
Wheat[2]	1.0	20
Cashew[2]	2.0	40
Mustard[2]	0.05	1
Lupin[2]	4.0	80
Sesame seed[2]	0.2	4
Shrimp[2]	10.0	200
Fish[2, #]	0.1	2

* (modified from Taylor *et al.* (15); Allen *et al.* (13) and Alvarez and Boye (43), the respective serving size and the detection limit of cross-contamination as assessed by ELISA.
** Required analytical sensitivity (mg/kg, ppm) of a method to detect a protein reference dose in a defined amount of a serving size, e.g. 50 gram.
[1] eliciting doses for 1% of food allergic population (ED01).
[2] eliciting doses for 5% of food allergic population (ED05).
[#] provisional data

The VITAL approach is designed for situations where the unintended allergen is distributed evenly (homogenously) in the product. In cases where allergens are present in a particulate form (e.g. nut pieces, sesame seeds) and not evenly distributed, this approach is not applicable (16). For these cases, the use of precautionary labelling is the only current option when the risk is unacceptable.

Allergen management: part of existing food safety management

The need to set standards and procedures for

allergen management and to incorporate them into existing overall food safety assurance strategies in compliance with good manufacturing practices (GMP) is well recognized by the food industry and includes a management plan to identify, prevent and control food safety hazards (HACCP – hazard analysis critical control point).

Recently, FoodDrinkEurope published a guidance document (6) for food producers, to harmonize and disseminate robust and evidence-based information on good practice in risk management of allergenic foods. This guidance document drew on various national guidance documents, as well as research results from the European Commission funded research project EuroPrevall, recommendations from the MoniQA EU Network of Excellence, and from ILSI International Life Sciences Institute, Europe. Key elements of allergen risk management included: correct training of the personnel involved in the production procedures; complete information of raw materials; adequate production facilities; state-of-the-art manufacturing; provision of accurate and reliable/trustworthy information for the consumer at risk, product development and parallel updates of relevant information and continuous documentation (6). Correct cleaning procedures for the processing plant to avoid cross contamination are particularly critical.

Labelling

Food allergen labelling: Issues relating to the deliberate use of allergenic ingredients

Within the current EU legislation ((European Directive 2007/68/EC (17) amending Directive 2000/13/EC (18) the labelling of 13 allergenic foods (or food groups) and derived products thereof, as specified in annex IIIa of directive 2007/68/EC, is mandatory when used as ingredients for pre-packed foods, regardless of the concentration of the potentially allergenic ingredient. The 13 allergenic foods (or food groups) include the most important foods (Table 2) that cause IgE mediated and non IgE mediated allergies, coeliac disease due to reactivity to gluten. Sulphur dioxide and sulphites, also listed in this Directive, cause intolerances and are therefore not further discussed in this review.

Certain products derived from the foods on the list may be exempted from the labelling requirement if they can be assessed and found to be non-allergenic. For example wheat based glucose syrups, including dextrose or maltose, do not require labelling. Other exceptions are fish gelatin used as a carrier for vitamins or carotenoids, fully refined soybean oil, and alcoholic distillates derived from nuts.

Regulation 1169/2011(19) on the provision of food information (FIR) to consumers, that will be effective from 13 December 2014, will replace the existing labelling directive, including its provisions for allergens. The FIR provides detailed information on how to present allergen information and clearly states the nature of the allergy-inducing substance or product on the respective labels and extends allergen labelling to non-prepackaged foods. A systematic re-examination and potential update of the allergen list by the EU-Commission is also foreseen (19). Since this EU-legislation is enforced by the national legislation of its member states (19), differences across countries regarding the type of labelling are likely, and strategies to harmonise these activities are needed as examples have shown in the past. For non-prepacked food products that lack an ingredient list, provision of allergen information is also required at the point of sale after the end of the regulatory transition period in December 2014. Also the information on allergenic ingredients is mandatory. However, the means through which information about the presence of these allergenic compounds is to be made available to consumers has been derogated to the EU member states. Issues remain regarding the inadvertent presence of so-called “cross-contact” allergens which are not covered by Directive 1169/2011 and may therefore result in the ongoing application and over-use of precautionary labelling statements, such as “may contain”, or “trace amounts of“ (see below).

Similar activities on allergen labelling legislation have been performed in other parts of the world and are summarised in Table 2. The EU list is currently the most comprehensive one and was followed by other countries such as Switzerland, Argentina and Ukraine (20). In contrast, Japan only requires mandatory labelling for wheat, buckwheat, egg, milk, peanut and crustaceans. However, an additional 19 foods are listed for “recommended labelling”.

The allergenic foods cited in almost all labelling regulations are milk, egg, gluten containing cereals, crustaceae, peanuts and tree nuts. Others, such as mustard, mollusc, lupin and buckwheat seem to be restricted to certain geographic areas, possibly

Table 2 Labelling of allergenic foods according to regulatory frameworks

	Codex[1]	European Union[2]	Australia/ New Zealand	Canada	China	Hong Kong	Japan	Korea	Mexico	United States
Wheat / cereals[3]	X	X	X	X	X	X	X[4]	X[4]	X	X
Eggs	X	X	X	X	X	X	X	X	X	X
Milk	X	X	X	X	X	X	X	X	X	X
Peanut	X	X	X	X	X	X	X	X	X	X
Fish	X	X	X	X	X	X		X[6]	X	X
Crustaceans	X	X	X	X	X	X	X[5]	X	X	X
Soy	X	X	X	X	X	X		X	X	X
Tree nuts	X	X[9]	X	X[10]	X	X			X	X
Sesame		X	X	X						
Shellfish/ mollusks		X	X	X						
Mustard		X		X						
Celery		X								
Lupine		X								
Other							X[7]	X[8]		

Table modified from Gendel S. Reg. Toxicol and Pharmacol. 2012; (20)

1. The following countries use CODEX regulations: Barbados, Chile, Papua Neuginea, Philippines, St. Vincent and The Grenadines.
2. Argentina, Switzerland and Ukraine also use The European legislation.
3. Cereals containing gluten
4. Wheat and buckwheat
5. Shrimp and crab listed under crustaceans
6. Mackerel as the only fish listed
7. Foods recommended for labelling: abalone, squid, salmon roe, salmon, mackerel, chicken, beef, pork, gelatin, matsutake mushroom, walnut, orange, kiwifruit, soybean, banana, peach, apple, kiwifruit, yam.
8. "Other" includes pork, peach, tomatoe.
9. European Union listed the following tree nuts: almonds, brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pistachio nuts and walnuts.
10. Canada listed the following tree nuts: almonds, brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachio nuts and walnuts

reflecting the different dietary habits and thus risk of exposure.

Precautionary labeling: impact on food avoidance strategies of consumers at risk

In cases of unintended presence of allergens, voluntary allergen labelling information is applied by the food manufacturer in order to inform and protect consumers with allergies, and is guided by Article 36. However, precautionary labelling indicating the unintentional presence of allergens should only be used when there is a significant probability of allergen cross contamination representing an unacceptable risk to the allergic consumer. However, detailed guidance on quantitative risk assessment remains to be developed and needs to be underpinned by a transparent evidence base. A recent study from Crotty and Taylor (21) analysed precautionary labelling for milk in 100 food products.

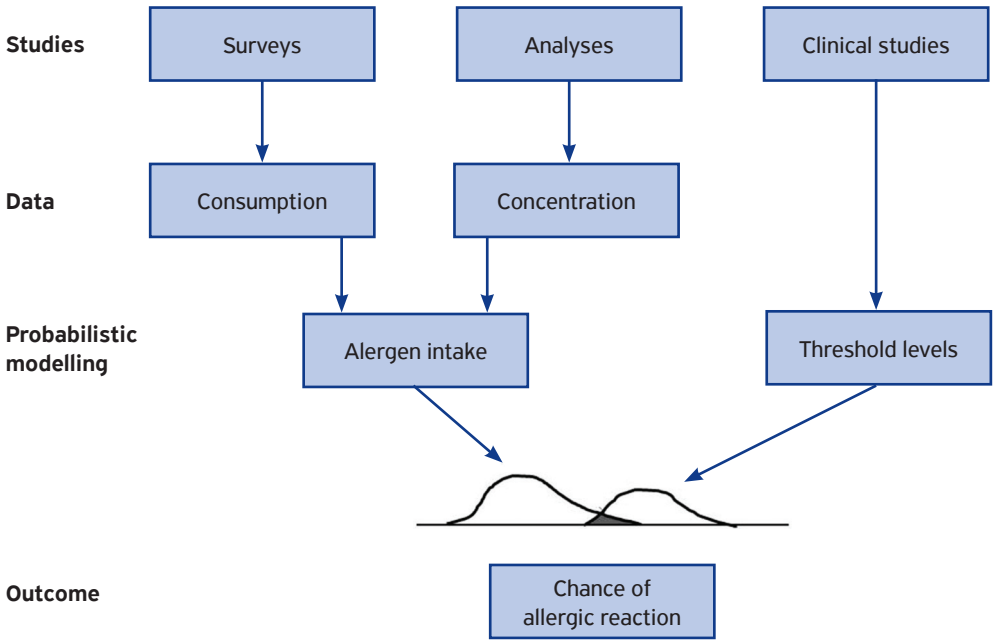


Figure 1 Food Allergen risk management: a probabilistic approach according to Spanjersberg *et al.* (44)

Forty percent of products labelled with "may contain milk ingredients" had detectable milk residues, with a wide range of concentrations (3.4 - 15000ppm, (21)). In products with labels indicating "shared equipment" or "shared facility" the frequency of detected milk ingredients was lower. Finally 40% of products listing milk as a minor ingredient did not have any detectable milk. Comparing different food matrices, dark chocolate was identified as a high risk product for milk allergic consumers. Another study from Ford *et al.* (22) compared food products with precautionary labelling for 3 allergen sources, peanut, milk and egg. Detectable amounts of allergenic foods were identified in 5.3% of products with precautionary labels and in 1.9% of products without precautionary labelling. Therefore, the authors conclude that the avoidance of product with advisory statements should be recommended for the consumer at risk, even if the detectable amounts of culprit allergen source may be rather low (22). A recent Irish study on peanut containing foods with advisory labels detected low levels of peanut in only 2 out of 38 products (23). Based on their data the authors discussed whether there is a sufficient risk warranting the use of advisory labelling. However, they also concluded that for the sake of patients with peanut allergy and their avoidance strategies, advisory nut statements should still be recommended.

Recent studies have highlighted the fact, that due to the excessive use of precautionary labelling, the perception, opinions and behaviour of patients with food allergies have changed (24-26). In general, they are rather complacent about this type of labelling (27). However, they also assume that different statements reflect different levels of risk with statements such as "shared facility" implying a lower risk than "may contain", for example (27).

Tools for effective allergen risk management

Allergen risk assessment is an integral part of allergen risk management and estimates the impact of a health hazard as a function of dose and exposure (Figure 1 (14)). As a consequence, the definition of an acceptable versus unacceptable risk needs to be defined and agreed upon. Therefore, an effective allergen risk management strategy relies on the information of threshold levels for clinical reactivity. While threshold levels for toxic substances are generally available, threshold levels for allergens have, until recently, remained elusive (28). It is known that allergic individuals can respond to a very wide range of doses, and generally accepted levels are not yet agreed. Despite the individual differences in threshold doses, Crevel *et al.* have suggested

identifying an "eliciting dose" for a specified fraction of the allergic population, for instance 5 or 10% (ED05 or ED10 (13-15, 29)) as the amount of an allergen, known to produce a reaction in defined proportion of the allergic population. This parameter could be used for the concept of "protection of the vast majority" and representing the basis for food safety objectives. It also acknowledges the fact that complete protection of the allergic population, absolute safety ('zero risk'), is not possible (30). Convincing data on threshold levels have been generated for 11 allergenic food sources, for other allergenic food sources lack these data (see also section above (15)). Within EuroPrevall great efforts were undertaken, to develop harmonized challenge protocols, apply standardized challenge meals to assess threshold levels for the most important food allergen sources in a multicentre study, and forthcoming results are expected to provide necessary information on threshold doses for both the food industry and regulators (31, 32). It should be recognized however that threshold levels are determined under optimal experimental conditions and little is known about changes in individuals' threshold due to co-factors such as infectious diseases, drug intake (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) are known to increase intestinal permeability and antacids to interfere with the physiological breakdown of food proteins), alcohol, stress and exercise.

An integral part of implementation of allergen risk management in food manufacturing and retailing is the ability to validate and then verify, for example, that cleaning practices are effective and that finished food products comply with the quality criteria laid out in allergen management plans. This applies with even more force when a claim, as in "free-from" foods, is made. Thus a suite of analytical methods are required ranging from rapid and easy-to-use qualitative and semi-quantitative methods that can be applied in a food manufacturing environment to more rigorous quantitative methods. In general, analytical methods that target the hazard are preferable, and hence those able to determine the presence of the allergenic proteins are considered to be the best available methodology. However, most use a methodology based on the detection of indicative proteins, peptides or nucleic acids rather than the actual allergen. Clearly, the detection of peptides or proteins is more closely related to the presence of allergenic proteins. Independently, various studies have demonstrated the successful application of nucleic acid-based methods, such as PCR (polymerase chain reaction), which correlates well with protein-based methods (33).

The detection of specific proteins and even allergens by specific antibodies using ELISA techniques is most frequently applied (34-36). These highly sensitive methods are widely used, and detect cross-contaminants in foods at or below the ppm (mg allergen per kg food) level (Table 1).

Recently, mass spectrometry (MS) approaches have been developed to detect peptide and proteins even in complex food matrices with high sensitivity (37, 38). In the case of hazelnut detection, a recent project demonstrated comparability between the available techniques, ELISA, PCR, and MS (39). Further development of such orthogonal methodology is needed before routine application is possible. Analytical methods do not detect absolute amounts of allergen doses but quantify the concentration of an allergenic protein or food (e.g. peanut) in a reference size such as a serving size (e.g. 50 gram) of the composed food (e.g. chocolate). Depending on: a) the reference dose for the allergenic food that is summarized in Table 1; and b) the serving size, the methods need to be sufficiently sensitive to reliably detect or quantify the respective concentration. The limit of detection of the methods needs to be below this concentration (Table 1).

When performing analytical methods for allergen detection in foods, the impact of food processing and the food matrix on the individual allergens should be taken into account. Processing and matrix factors may induce unpredictable effects, making analytical results difficult to interpret. Allergenic food proteins are part of the diet and interact with the respective food matrix. Furthermore, these proteins may undergo changes due to food processing treatments which in turn affect their allergenicity. Data on potential changes in allergenicity are thus relevant for refined allergen risk assessment in food production and detection assays should be extended with "processed" allergenic molecules. The influence of processing on allergenicity should be assessed in clinical food challenge studies. Only limited data from such studies in humans are currently available (40).

These issues are further confounded by the lack of agreed reference doses for allergens in foods, making it impossible to set effective parameters for optimal analytical performance, such as limit of quantification.

Furthermore, the lack of reference materials, in particular for naturally-incurred materials, for allergen detection has meant there is a lack of consensus regarding reporting units for allergens, and also that it is not currently possible to undertake the necessary inter-laboratory trials to select the best-practice methodology. The development of such reference materials will also need to ensure that the allergenic molecules are present in a relevant form. As proof of concept, a recent multi-laboratory trial used a dessert matrix already validated for clinical use which was tested as a quality control material for allergen analysis, in order to compare a range of commercially available immunoassays for egg and milk content (41).

Communication and training

Consumers purchase products on the basis of trust, experience and recommendation, expecting that they are for safe use, unless specific information is given on the labels. The food industry is increasingly recognizing its role in implementing preventive measures to protect the allergic consumer from having reactions though accidental consumption of their problem food. However, it is also evident that key knowledge and skills are essential to support them in undertaking effective food avoidance. In this context, the indiscriminate use of precautionary labelling has led to loss of confidence from the allergic consumer in this risk communication tool (12). Therefore appropriate communication strategies are needed. For example, communicating that reference doses – if available – are associated with a certain risk of reaction. This in turn requires adequate training of the patients with allergies to obtain the relevant information on the food product and from the food suppliers. Therefore the key element is the close cooperation and effective communication between patient organizations, food industry representatives and regulators. Moreover, adequate training of individuals who have contact with customers – from helplines, to those in the retailing and catering sectors – is of great importance. This also extends to those involved in caring for individuals with food allergies in the extended community including personnel in day care centres, nurseries and teachers. This is needed to increase awareness about food allergies and thus reduce the risk of accidental exposure of food allergens as well as prompt action in the event of such exposure (see also food allergy guidelines, Chapter 1.5).

Box 3. Gaps in the evidence

- Need for harmonization in labeling activities with regard to layout, terminology.
- Need for generally agreed reference doses for most important food allergen sources.
- Need for certified reference material and standardized detection assays.
- Definition of tolerable risk level in food allergy.
- Best practices to train and support the food allergic consumer and to select optimal communication for both consumer at risk and third party.

Gaps in the evidence

There is an urgent need for agreement on threshold levels for individual food allergens sources based on double-blind, placebo-controlled food challenges (DBPCFC) studies, as well as generation of further challenge data for allergens for which currently available data are insufficient (Box 3). In this context, the VITAL 2.0 system developed in Australia has generated much interest. For allergen detection assays standardized and certified reference materials are still lacking. Novel analytical methods and their applicability in reliable allergen detection in various food matrices should be investigated. Novel insights into food matrices, food processing and their impact on the allergenicity of foods should also be incorporated into allergen risk management once a sound knowledge base has been developed. Although important, limited data are available on the impact of food avoidance on the quality of life and the related costs to allergic consumers. (42)

Summary and recommendations

It is now well recognized that protecting the allergic consumer from unintended exposure to allergenic food is a shared responsibility, in which each stakeholder must play their part. EU legislation on allergen labelling is in place and is implemented and enforced through the respective national laws. As a result, differences in the layout, terminology used, and practices arise. To harmonize labelling issues, industry has started efforts for disseminating best practices among food producers. Labelling of non-packaged (or indeed

prepackaged) foods is not yet available in all countries, although the relevant legislation will apply in the near future. In general, precautionary labelling should be avoided whenever possible, since every additional 'may contain' warning diminishes the impact of those already used, thereby increasing the risk of unnecessary risk taking and hence exposure. As a matter of principle, it should not be applied without a thorough risk management plan based on a transparent evidence base. Adequate training of the personnel working in the food manufacture, catering, nurseries and schools is critical. Lastly access to relevant information on food allergy is an essential resource to improve the quality of life of the allergic consumer.

The food industry has started to integrate allergen management in existing food safety management procedures. However, there is an urgent need for certified reference materials. It is of concern that agreement around management threshold levels for key food allergen sources is still lacking. Implementation of such thresholds could ensure a high degree of protection while avoiding excessive food choice restriction for allergic consumers. Close cooperation is needed between regulators, food industry representatives and consumer organizations in order to define tolerable risk levels in food allergy.

Acknowledgements

The group is extremely grateful to Rene Crevel, Safety and Environmental Assurance Centre, Unilever, Colworth House, Sharnbrook, Bedford, UK for continuous valuable input. We would also like to thank our EAACI taskforce members and the EAACI Executive Committee for their helpful comments and suggestions. We would like to thank Ms Daniela Brombin for her administrative help in preparing this document.

Conflict of interests

Antonella Muraro has provided scientific advice for Meda. Karin Hoffmann-Sommergruber has received honoraria from Thermo Fisher and Milupa. Lars Poulsen has provided scientific advice to Nvozymes and has received funding for research from ALK-Abelló, Anergis, Biomay, Stallergenes. Graham Roberts has provided scientific advice for Danone and ALK-Abelló; Thermo Fisher and ALK-Abelló have provided consumables for his research activities. Sabine Schnadt has received support for travel to EAACI congress from Peanut Council and Novartis. Aziz Sheikh has received funding for coordinating guidelines production, and generating the systematic reviews from EAACI. He has provided scientific advice to ALK-Abelló, Meda, Lincoln Medical, Thermo Fisher, Pfizer and Stallergenes; he is on the Anaphylaxis Campaign UK's Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee and the BSACI's Standard of Care Committee. Cezmi A Akdis has received research grants from Allergopharma, Stallergenes, Actellion, and Novartis. Besides, Cezmi A Akdis was President (2011–2013), Past President (2013–2015), and ExCom member in EAACI, which has received financial support from several relevant business entities. Ronald van Ree has provided scientific advice for HAL Allergy, Stallergenes, BIAL, Ventria Bioscience, Pharming; he has provided contract research services to HAL Allergy, Stallergenes and Ventria Bioscience and has received consumables from Thermo Fischer. Hazel Gowland is a researcher on Food Standards Agency funded projects and unpaid adviser to other FSA funded studies. Clare Mills has received funding from the European Food Safety Authority, sits on the UK Food Standards' Agency's Advisory Committee and is a cofounder of the start-up company Reacta Biotech Ltd. Nikos Papadopoulos is currently EAACI President (2013-2015) and has provided consulting for several relevant business entities. Thomas Holzhauser had consultant arrangements with Institut für Produkt Qualität, Berlin and scientific consultant arrangements with Monsanto Company. Stefan Vieths has no conflicts in relation to this document

References

1. Panesar SS, Javad S, De Silva D, Nwaru BI, Hickstein L, Muraro A *et al.* on behalf of the EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013;68:1353-1361.
2. Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilò B *et al.* Management of anaphylaxis: a systematic review. *Allergy* 2014;69:168-175.
3. Anandan C, Sheikh A, European developments in labelling allergenic foods. *BMJ* 2005;331:1155-1156.
4. Ward R, Crevel R, Bell I, Khandke N, Ramsay C, Paine S. A vision for allergen management bes practice in the food industry. *Trends in Food Science & Technology* 2010;21:619-625.
5. Codex Alimentarius. Recommended International Code of

Practice: General Principles of Food Hygiene. *CAC/RCP 1-1969* Rev. 3 (197) Amended 1999.

6. FoodDrinkEurope. Guidance on Food Allergen Management for Food Manufacturers. Brussels, 2013.
7. Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Strategies for living with the risk of anaphylaxis in adolescence: qualitative study of young people and their parents. *Prim Care Respir J* 2012;21:392-397.
8. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V *et al.* EAACI Food Allergy and Anaphylaxis Guidelines Group. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014;69: 62-75.
9. Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K *et al.* The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy* 2014;69:76-86.
10. de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K *et al.* Acute and long-term management of food allergy: systematic review. *Allergy* 2014;69:159-167.
11. Crevel RW, Baumert JL, Baka A, Houben GF, Knulst AC, Kruizinga AG *et al.* Development and evolution of risk assessment for food allergens. *Food Chem Toxicol* 2014; 67C:262-276.
12. Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S *et al.* Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol* 2014;133:156-164.
13. Crevel RW, Baumert JL, Luccioli S, Baka A, Hattersley S, Hourihane JO *et al.* Translating reference doses into allergen management practice: Challenges for stakeholders. *Food Chem Toxicol* 2014;67C:277-287.
14. Taylor SL, Baumert JL, Kruizinga AG, Remington BC, Crevel RW, Brooke-Taylor S *et al.* Establishment of Reference Doses for residues of allergenic foods: report of the VITAL Expert Panel. *Food Chem Toxicol* 2014;63:9-17.
15. Roder M, Ibach A, Baltruweit I, Gruyters H, Janise A, Suwelack C *et al.* Pilot plant investigations on cleaning efficiencies to reduce hazelnut cross-contamination in industrial manufacture of cookies. *J Food Prot* 2008;71:2263-2271.
16. COMMISSION DIRECTIVE 2007/68/EC of 27 November 2007 amending Annex IIIa to Directive 2000/13/EC of the European Parliament and of the Council as regards certain food ingredients. *Official Journal of the European Union* 2007;L310:11-14.
17. Union E. Directive 2000/13/EC of the European Parliament and of the Council of 20 March 2000 on the approximation of the laws of the Member States relating to the labelling, presentation and advertising of food stuffs. *Official J Europ Commun* 2000;109:0029-0042.
18. Parliament E. Regulation (EU) 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers. *Official J Europ Commun* 2011; L 304:18:63.
19. Gendel SM. Comparison of international food allergen labeling regulations. *Regul Toxicol Pharmacol* 2012;63:279-285.
20. Crotty MP, Taylor SL. Risks associated with foods having advisory milk labeling. *J Allergy Clin Immunol* 2010;125: 935-937.
21. Ford LS, Taylor SL, Pacenza R, Niemann LM, Lambrecht DM, Sicherer SH. Food allergen advisory labeling and product contamination with egg, milk, and peanut. *J Allergy Clin Immunol* 2010;126:384-385.
22. Robertson ON, Hourihane JO, Remington BC, Baumert JL, Taylor SL. Survey of peanut levels in selected Irish food products bearing peanut allergen advisory labels. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2013;30:1467-1472.
23. Hefle SL, Furlong TJ, Niemann L, Lemon-Mule H, Sicherer S, Taylor SL. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *J Allergy Clin Immunol* 2007;120: 171-176.
24. Noimark L, Gardner J, Warner JO. Parents' attitudes when purchasing products for children with nut allergy: a UK perspective. *Pediatr Allergy Immunol* 2009;20:500-504.
25. Turner PJ, Kemp AS, Campbell DE. Advisory food labels: consumers with allergies need more than "traces" of information. *BMJ* 2011;343:d6180.
26. Zurzolo GA, Koplin JJ, Mathai ML, Tang MK, Allen KJ. Perceptions of precautionary labelling among parents of children with food allergy and anaphylaxis. *Med J Aust* 2013;198:621-623.
27. Crevel RW, Ballmer-Weber BK, Holzhauser T, Hourihane JO, Knulst AC, Mackie AR *et al.* Thresholds for food allergens and their value to different stakeholders. *Allergy* 2008;63: 597-609.
28. Madsen CB, Hattersley S, Buck J, Gendel SM, Houben GF, Hourihane JO *et al.* Approaches to risk assessment in food allergy: report from a workshop ''developing a framework for assessing the risk from allergenic foods". *Food Chem Toxicol* 2009;47:480-489.
29. Madsen CB, Hattersley S, Allen KJ, Beyer K, Chan CH, Godefroy SB *et al.* Can we define a tolerable level of risk in food allergy? Report from a EuroPrevall/UK Food Standards Agency workshop. *Clin Exp Allergy* 2012;42:30-37.
30. Mills EN, Mackie AR, Burney P, Beyer K, Frewer L, Madsen C *et al.* The prevalence, cost and basis of food allergy across Europe. *Allergy* 2007;62:717-722.
31. Cochrane SA, Salt LJ, Wantling E, Rogers A, Coutts J, Ballmer-Weber BK *et al.* Development of a standardized low-dose double-blind placebo-controlled challenge vehicle for the EuroPrevall project. *Allergy* 2012;67:107-113.
32. Holzhauser T, M R. PCR methods for detection of allergens in foods. In: Flanagan S, editor. Handbook of food allergen detection and control. Cambridge: Woodhead Publishing,

2014.

33. Koppelman S, Hefle S. Detecting allergens in food. Cambridge: Woodhead, 2006.
34. Flanagan S. Handbook of food allergen detection and control. Cambridge: Woodhead Publishing, 2014.
35. Mills C, Wichers H, Hoffmann-Sommergruber K. Managing Allergens in Food Cambridge: Woodhead Publishing, 2007.
36. Lutter P, Parisod V, Weymuth H. Development and validation of a method for the quantification of milk proteins in food products based on liquid chromatography with mass spectrometric detection. *J AOAC Int* 2011;94:1043-1059.
37. Heick J, Fischer M, Kerbach S, Tamm U, Popping B. Application of a liquid chromatography tandem mass spectrometry method for the simultaneous detection of seven allergenic foods in flour and bread and comparison of the method with commercially available ELISA test kits. *J AOAC Int* 2011;94:1060-1068.
38. Costa J, Ansari P, Mafra I, Oliveira MB, Baumgartner S. Assessing hazelnut allergens by protein- and DNA-based approaches: LC-MS/MS, ELISA and real-time PCR. *Anal Bioanal Chem* 2014;406:2581-2590.
39. Ballmer-Weber BK, Hoffmann A, Wuthrich B, Luttkopf D, Pompei C, Wangorsch A *et al*. Influence of food processing on the allergenicity of celery: DBPCFC with celery spice and cooked celery in patients with celery allergy. *Allergy* 2002;57:228-235.
40. Johnson PE, Rigby NM, Dainty JR, Mackie AR, Immer UU, Rogers A *et al*. A multi-laboratory evaluation of a clinically-validated incurred quality control material for analysis of allergens in food. *Food Chem* 2014;148:30-36.
41. Muraro A, Dubois AEJ, DunnGalvin A, Hourihane JO'B., de Jong NW, Meyer R *et al*. Food allergy health-related quality of life measures: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014; DOI: 10.1111/all.12405.
42. Alvarez PA, Boye JI. Food production and processing considerations of allergenic food ingredients: a review. *J Allergy (Cairo)* 2012;2012:746125.
43. Spanjersberg MQ, Kruizinga AG, Rennen MA, Houben GF. Risk assessment and food allergy: the probabilistic model applied to allergens. *Food Chem Toxicol* 2007;45:49-54.

SECTION 7

SUMMARY AND FUTURE PERSPECTIVES

Antonella Muraro[1] and Graham Roberts [2-4]

[1] Department of Mother and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment, Veneto Region, University of Padua, Italy

[2] David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[3] NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[4] Human Development and Health and Clinical and Experimental Sciences Academic Units, Faculty of Medicine, University of Southampton, UK

The *EAACI Food Allergy and Anaphylaxis Guidelines* Group has worked over the last 2 years to generate a comprehensive set of guidelines. In this unprecedented project, the evidence base for food allergy and anaphylaxis has been systematically reviewed with the results being used to generate a comprehensive collection of 6 guidelines to inform the management of patients. The guidelines group consisted of over 70 individuals and was truly pan European and multidisciplinary with representation from primary care, secondary and tertiary care, health professionals including clinicians, nurse, and dieticians and psychologists as well as food scientists, patient group representatives and regulators. The guidelines group has worked within the context of the EAACI Food Allergy and Anaphylaxis Campaign which has sought to raise the profile of food allergy and anaphylaxis in Europe, to advocate for better care for patients and to improve the education of health professionals and the public.

The systematic reviews of the epidemiology of food allergies (Chapters 1.1, 1.2) summarize the burden of food allergy in European children, adolescents and adults. While the point prevalence of self-reported food allergy was found to be around 6%, the prevalence of food challenge proven food allergy was under 1%. This still though represents around 7.5 millions of affected individuals across Europe, with a large proportion of children. The key food allergens in Europe are cow's milk, egg, wheat, peanut, tree nut, and fish and shell fish. The risk factors for food allergy frequently differ between studies. This may be due to local population differences but is more likely to be due to differences in study design. It is important that future studies adopt a uniform design with food challenges being used to make a gold standard diagnosis of food allergy. This will enable data from future studies to meta-analyzed in order to improve our ability to understand the pathogenesis of food allergy. Additionally, further epidemiological data is required from eastern and southern Europe, as they are very poorly represented in the current literature, to determine whether the burden of food allergy is similar across the whole of Europe.

There are now considerable data in the literature characterizing the performance of skin prick testing and specific IgE testing for food allergy (Chapter 1.3). Both skin prick testing and specific IgE testing have good sensitivity but relatively poor specificity for diagnosing food allergy. This means that they are good for ruling out food allergy but not so good for ruling the diagnosis in. However, most of the studies were very small with high risk of bias and there was a lack of head to head comparisons of skin prick testing and specific IgE testing. Additionally there was relatively little real life diagnostic data focused on component testing. These should be the focus of future studies.

Chapter 1.4 focused on the management of food allergy. This whole area is characterized by a lack ofevidence, both for the acute management of non-life threatening allergic reactions and longer term management. This makes developing evidence based recommendations difficult. The EAACI food allergy guidelines (Chapter 1.5) covers history taking, determination of sensitisation to food, elimination diets, oral food challenges and the acute and long term management of food allergy. Apart from for skin prick testing, specific IgE testing and the use of hypoallergenic formulae, there is no high level evidence to guide management. Therefore many recommendations rely on extrapolations from other data or expert opinion. Of the many evidence gaps, high priority ones include: better approaches to identify patients at risk of developing severe reactions, evidence on the efficacy of modified food allergens (e.g. baked milk or egg) to accelerate the development of tolerance; evidence on the efficacy of oral induction of tolerance (OIT) for common food allergens; and better data on the role of monoclonal anti-IgE for managing food allergy with or without the concurrent use of OIT.

The current lack of a routine curative therapy for food allergy, emphasizes the need to develop effective preventive strategies. Chapter 2.1 summarizes the available data on the prevention of food allergy in a systematic review. The literature is difficult to interpret for many reasons: challenge based outcomes are rarely used resulting in the likely over diagnosis of food allergy; IgE sensitization status is often not taken into account avoiding consideration of the existence of multiple food allergy phenotypes; randomization to breast feeding, as a factor that is likely to be critical in the development of food allergy, is not ethical. Future studies need to be better designed. Therefore, only limited conclusions can be drawn from the data: a special diet is not required in pregnancy nor with lactation; infants should be exclusively breast fed for 4-6 months; if a high risk infant needs a formula feed, a proven hypoallergenic formula should be used; and complementary foods should be introduced from 4

months according to local weaning practices. Of the many evidence gaps in this area, perhaps the greatest priority for further data is on the effect of timing of weaning on the development of food allergy and whether concurrent breast feeding modifies the impact

Given the overload of food allergy on life, it is important to understand the quality of life of individuals with food allergy. The systematic review of the literature in Chapter 3.1 identified seven validated food allergy-specific, health-related quality of life questionnaires for children, adolescents, adults and parents. These can be used to quantify quality of life and the impact of interventions. Further work though is required to generate minimal important differences for these questionnaires to help interpret results. These questionnaires also need to be validated in a wider range of European countries. Recommendations for the development and use of quality of life questionnaires are made in Chapter 3.2.

Food allergy is the commonest cause of anaphylaxis. The systematic review of the literature in Chapter 4.1 found an incidence rate ranging from 1.5 to 7.9 per 100000 person-years. This broad range is likely to reflect both differing definitions of anaphylaxis and variation in different populations due to genetic or environmental factors. Better linkage of health data bases across primary and secondary sectors would facilitate better data collection and understanding of the epidemiology of anaphylaxis. The second systematic review focused on the management of anaphylaxis (Chapter 4.2). The lack of studies evaluating acute interventions in anaphylaxis is notable making it difficult to generate evidence based recommendations. The best data are for the pharmacokinetics of adrenaline, but not during an episode of anaphylaxis, and for venom immunotherapy as a means of preventing future severe reactions. The EAACI anaphylaxis guidelines (Chapter 4.3) stress adrenaline as the first intervention in anaphylaxis to tackle the under and delayed use of adrenaline. A full allergy assessment, the development of an individualized management plan and training are emphasized, although the evidence base for these is poor. Given the burden associated with anaphylaxis, this is an obvious priority area for further research studies. Key priorities would be better diagnostic criteria for emergency department staff to facilitate early identification of anaphylaxis; optimal dose and dosing interval for patients experiencing anaphylaxis; investigation of the role of sublingual adrenaline as an adjunct to intramuscular administration; understanding which components are required for an optimal individualize management plan; and assessment of the best approach to training patients and carers.

Most allergic reactions to food occur in the community, this should therefore be the focus of strategies to prevent future reactions and procedures need to be in place to manage any reactions that do occur (Chapter 5.1). Schools are an important component and policies need to be in place to assist teachers and other staff. Healthcare professionals and patient organizations need to work with schools to support them to maintain the safety of pupils with food allergies.

The food industry is another major component to the safety of patients with food allergies (Chapter 6.1). Food allergen management by the food industry suffers from a lack of knowledge on the level of allergen required to precipitate a significant allergic reaction plus suboptimal analytical systems to detect small amounts of allergenic foods. This has led to the frequent, and probably overuse of precautionary "may contain ...." labels resulting in many patients ignoring such messages. There is an urgent need for evidence-based references doses for all allergenic foods and data about the impact of co-factors on these doses. These data would inform improved allergen management systems. It is then critical that the food industry works with patient groups and regulators to develop labelling that better communicates the risk of individual products, while acknowledging that risk can never be zero. This would allow patients to make better decisions minimizing risk while maximizing their quality of life.

Great discoveries have been made in the last decade resulting in the improved understanding and clinical management of patients with food allergy and at risk of anaphylaxis. These have been documented in the *EAACI Food Allergy and Anaphylaxis Guidelines.* Many children, adolescents and adults continue to be affected by food allergy and continue to be at risk of anaphylaxis. There is therefore a continued need to focus resources on food allergy and anaphylaxis to better understand these clinical problems and how to better prevent and manage them. Major advances are expected in the next decade. For this purpose these guidelines are planned to be updated by 2017 or even earlier if significant progress will be available beforehand.

European Academy of Allergy and Clinical Immunology

Hagenholzstrasse 111
3rd Floor
8050 Zurich
Switzerland

info@eaaci.org
www.eaaci.org