UNIVERSIDADE
BEIRA INTERIOR

Study of the prevalence and clinical features of food allergies in adults and adolescents from Beira Interior

Carlos Lozoya Ibáñez

Tese para obtenção do Grau de Doutor em
Medicina
(3º ciclo de estudos)

Orientador: Prof. Doutor Luís Taborda Barata

abril de 2020
(Versão definitiva, impressa no dia 27 de novembro de 2020)

Subdelego no professor Miguel Castelo Branco a presidência deste júri, a quem confiro os poderes necessários para votar conforme o estabelecido no despacho nº 2020/R/71 de 2 de setembro, conforme o nº 2 – 2.1, do referido despacho
Mário Marques Freire
16/11/2020

EDITAL

DOUTOR MÁRIO MARQUES FREIRE, Vice-Reitor da Universidade da Beira Interior e Presidente do júri, por delegação do Reitor, das provas de doutoramento (3º ciclo de estudos) no ramo de Medicina, requeridas por Carlos Lozoya Ibáñez.

Faz saber que:

1º O júri das referidas provas é constituído pela Doutora Maria Gabriela Canto Díez, professora associada da Faculdade de Medicina, da Universidade Complutense de Madrid, Doutora Ana Maria Pêgo Todo-Bom Ferreira da Costa, professora associada da Faculdade de Medicina da Universidade de Coimbra, Doutora Maria Belén de la Hoz Caballer, professora associada da Faculdade de Medicina da Universidade de Alcalá de Henares, Doutora Renata Sofia da Cunha Oliveira Barros, professor auxiliar da Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto, Doutor Jorge Luiz dos Santos, professor auxiliar da Universidade da Beira Interior.

2º As provas se realizarão de acordo com o seguinte calendário:

- Dia 23 de novembro de 2020, pelas 14,30 horas, apreciação e discussão da tese apresentada pelo candidato intitulada "**Study of the prevalence and clinical features of food allergies in adults and adolescents from Beira Interior**"

3º Serão arguentes da tese a Doutora Maria Gabriela Canto Díez e a Doutora Maria Belén de la Hoz Caballer.

4º As provas são públicas.

5º Findas as provas, o júri reunir-se-á para proceder à sua apreciação e decisão final, cujo resumo constará da respectiva ata, sendo a classificação do candidato, feita através de votação nos termos legais.

6º Todas as provas, sua apreciação e votação terão lugar na sala dos atos da Reitoria da Universidade da Beira Interior, de modo presencial e por videoconferência, nos termos do Art.º 5º da Lei 1-A/2020 de 19 de Março.

Covilhã e Universidade da Beira Interior, 11 de novembro de 2020.

O Presidente do Júri
Mário Marques Freire

Dedication

A mis padres y hermanos, a quienes todo os debo.

A mis hijos: Carlos y Valentina, por todos los días que no pudimos jugar juntos y que me privaron de vuestra compañía.

Acknowledgments

There is no labour that a person can have done on their own. Throughout these years of research, I have been fortunate to have had the help of many and exceptional people. Each one contributed as much as possible with their grain (or load) of sand for the construction of Everest, which is this thesis. I thank you all for your invaluable help. However, I want to highlight the collaboration of the following:

First and foremost, I would like to thank my supervisor, Professor Luís Taborda-Barata (FCS-UBI) for his invaluable support during my postgraduate studies, guidance, continuous help, friendship and help to solve every difficulty that appeared, even when it seemed to have no solution. It has been a privilege.

I would like to thank Dr. Fernanda Amaral, Dr. Mª José Pimenta, Dr. Eugénio Rodrigues, Dr.Teresa Mendes, Dr.Luís Fernandes and Dr. Mário Fernandes directors of the Community Health Centres in Castelo Branco, Vila Velha de Ródão, Idanha a Nova, Oleiros, Sertã and Proença a Nova, respectively, for allowing access to their patients' files. I would also like to thank Carlos Almeida, Graça Ventura, Jerónimo Barroso, Margarida Batista, Joaquim Abrantes and João Belém, the school directors of João Ruiz de Castelo Branco, Prof. Faria de Vasconcelos, Cidade de Castelo Branco, Nuno Álvares, Afonso de Paiva and Amato Lusitano de Castelo Branco respectively, for their invaluable help in distributing questionnaires to their students.

I would like to thank nurse Laura Silva (IPCB), students Marisa Padilha, Ana Martins and Mónica Lopes (FCS-UBI) for their collaboration in the application of the questionnaire.

I would like to thank the Pathology Technicians Cláudia Lobo and Patrícia Fernandes (ULSCB) for their invaluable support in collecting and processing blood samples.

I would like to thank Professors Ana Filipa Macedo (FCS-UBI), João Luís Belo and Sara Morgado-Nunes (IPCB) for the statistical processing of data.

I am most grateful for the help from Dr. Joana Belo (Allergy Department, Cova da Beira University Hospital Centre, Covilhã, Portugal), Dr María Luisa Somoza and Prof. Francisco Javier Ruano (Allergy Department, Infanta Leonor Hospital, Madrid, Spain),

Dr Stefan Cimbollek (Allergy Department, Virgen del Rocío Universitary Hospital, Seville, Spain), Dr Leonor Cunha (Allergy Department, Porto Hospital Centre, Oporto, Portugal) and Dr Isabel Carrapatoso (Allergy Department, Coimbra University Hospital Centre, Coimbra, Portugal) for the development of the final version of the questionnaire, thank you.

I gratefully acknowledge the help of Professor Jorge Gama (UBI), Dr. Inês Laia-Dias (FCS-UBI), Drs Isabel Skypala (Royal Brompton & Harefield NHS Trust, UK), Ulugbek Nurmatov (Cardiff University, UK), Bright Nwaru (University of Gothenburg, Sweden), Professors Rosa Mª Afonso and Henrique Pereira (UBI), for the development of the systematic review, thank you all.

I would like to thank my friends Nuno Dias, for his support with the design of the figures, Mário and São Vicente for their corrections in Portuguese language grammar, Professors Mafalda Fonseca, Olga Lourenço (FCS-UBI) and Professor Arminda Jorge (FCS-UBI and CHUB), for their invaluable work, support, friendship, advice and patience in hearing my doubts and dismays.

I would like to thank all the study volunteers without whom this project would never have been possible.

And last but by no means not least, a very special thank you to my wife, Alexandra, who besides collaborating in each and every one of the phases of this thesis, sometimes with much greater commitment than myself, put up with me during the days of intensive work, where the only topic of conversation was the thesis, unaware of the reality that surrounded me. You were the one who raised our children, put up with my bad character and looked after me in the most difficult moments, like only a true-life partner can do. Thank you for your company throughout this adventure that is our life.

Thank you all.

Abstract

Background:

Food allergy is an important health problem in western-style countries, and its prevalence has increased in the last three decades. Studies of the prevalence of food allergy in the general population in Portugal are scarce. Thus, the objectives of the present thesis were: a) to design and validate a food allergy study questionnaire for Portuguese adults, b) to determine the prevalence, and clinical characteristics of food allergy in a population of adolescents and adults in Beira Interior, and c) to determine the prevalence, and clinical characteristics of food allergy in the elderly population worldwide by conducting a systematic review of the bibliography and a subsequent meta-analysis of the data.

Methods:

A 17-item questionnaire was developed and applied by phone to a group of food allergy patients and a group of healthy individuals, with subsequent reassessment (re-test). Face and content validity, intelligibility, construct validity, and test-retest reliability (temporal stability) were analysed. This tool, once validated, was applied in two population-based individuals samples (3,168 adolescents; mean age: 14.3±1.1; 51.7% female; 1.436 adults; mean age of 47 years, median age: 45 years, 50.6% female), registered at participating Healthcare cross-sectional studies performed in various healthcare centres and secondary schools from central Portugal. All randomly selected individuals (1702 adolescents; mean age: 14.9±2.1 years; median age: 14 years; 61.9% female; 840 adults; (mean age: 48 years, median age: 46 years, 51.3% female) replied to the food allergy questionnaire by phone (adults) or in a written form (adolescents). Those who reported an adverse food reaction were invited to come to the hospital, where clinical history was taken, skin prick (SPT) and prick-prick skin (SPPT) tests were performed and food allergen-specific IgE levels (sIgE) were determined. An open oral challenge was performed in selected cases. Cases of positive clinical history of immediate (up to 2 hours after ingestion) reaction in association with positive food sIgE levels and/or skin prick tests were classified as IgE-associated probable food allergy. Cases of positive clinical history of delayed (more than 2 hours after ingestion) and negative food sIgE levels independently of positive SPT or SPPT results were classified as non-IgE associated probable food allergy.

A systematic review and meta-analysis on the prevalence and risk factors for food allergy in elderly individuals were conducted. A searched of international electronic databases including MEDLINE, EMBASE, Cochrane Library, CINAHL, AMED and ISI Web of Science, as well as clinical trials databases for published, unpublished and on-going

studies from 1980 to 2019. There were no restrictions on the language or geography of publication. The Critical Appraisal Skills Programme (CASP) quality assessment tool was used to appraise the methodological quality of the included studies. A descriptive summary with data tables was elaborated, and when clinically relevant and statistically adequate, a meta-analysis using random-effects modelling was carried out, given the expected clinical, methodological and statistical heterogeneity of the selected studies. The PRISMA checklist guided the reporting of the systematic review.

Results:

Face and content validity of the questionnaire allowed item reduction from 30 to 17 items with adequate content validity index > 0.78. Construct validity was confirmed in a group of 66 confirmed food allergic patients. Test-Retest Reliability (general temporal stability) of the test had a Spearman correlation coefficient value of 0.845 for the retest. Cohen's Kappa values for the relevant questions were greater than 0.890 for almost all items. No differences were found when sex, age and volunteers' recruitment origin were analysed. An inverse relationship was found between reliability and retest time interval.

The prevalence of probable food allergy in our sample was 1.41% in adolescents and 1% in adults, with fresh fruits and shellfish in adolescents and shellfish and fish in adults as the most frequently implicated foods. IgE-mediated probable food allergy occurred in 1.23% of adolescent and in 0.71% of adult cases, and fresh fruits and shellfish in adolescents and shellfish and peanut in adults were the foodstuffs mainly involved. Cutaneous symptoms were most frequently reported and prevalence values and food types were discrepant between self-reported and probable food allergies in both populations.

The prevalence of food allergy in the elderly was 6.46% for self-report, slightly lower than that of SR + food-specific IgE levels (6.95%) and SR + SPT (1.30%). In addition, it was lower than that in non-elderly adults, but higher than in children assessed by self-report outcomes. Finally, it was lower when compared with the other age groups when self-report symptoms were combined with *in vitro* or *in vivo* outcome assessment. No results were obtained regarding time and geographical trends, predominant foods, risk and prognostic factors, and clinical manifestations of food allergy in the elderly. There was great heterogeneity both in the systematic review and the meta-analysis, which was lowest for shellfish (I^2=0.000%) and highest for fruits (I^2=98.205%).

Conclusions:

Due to the quick and easy implementation, confirmation of face, content and construct validity as well as high temporal reproducibility, the screening questionnaire was a useful study tool for an initial approach to detection of food allergies in adults.

The prevalence of probable food allergies in Portuguese adolescents and adults was low, mostly related to fresh fruits, shellfish, nuts and peanut in the former, and to shellfish, fish, peanut and nuts in the latter. Most cases frequently involved cutaneous symptoms.

The systematic review allowed us to draw up-to-date estimates of the prevalence of adverse food reactions in elderly individuals, worldwide. However, most of the studies were not focused on the population over 60 years of age, which resulted in an evident lack of information and biases that might affect exposure and outcomes. This fact conditioned the knowledge of the clinical characteristics, implicated foods, evolution and diagnosis of food allergy in these individuals, as well as the development of possible preventative measures focused specifically on the elderly population.

Keywords

Adolescents;Adults;AdverseFoodReaction;CutaneousTests;Elderly;Epidemiology;Food allergy;OpenFoodChallenge;Prevalence;Portuguese;Reliability;Reproducibility;ScreeningQuestionnaire;SystematicReview;Validation

Resumo alargado

Introdução:

As reacções adversas alimentares, entre as quais está incluída a alergia alimentar, são um importante problema de saúde pública no Mundo Ocidental, tendo-se registado um aumento da sua prevalência durante os últimos trinta anos. Embora estas reacções não tenham a magnitude de outras doenças alérgicas, é certo que têm uma importante repercussão na qualidade de vida dos doentes, condicionando-lhes certas restrições alimentares, assim como situações de *stress* emocional e dificuldade para a sua integração social. Apesar de existirem vários estudos de base populacional em diferentes regiões do mundo, existem muitos poucos estudos sobre a prevalência populacional de alergia alimentar em Portugal: apenas um estudo em crianças entre os 3 e os 11 anos e outro um inquérito telefónico em uma pequena amostra de adultos. Outras lacunas são de salientar. Em primeiro lugar, é importante realçar que não existe um questionário específico em idioma português para o rastreio deste tipo de patologias. Em segundo lugar, o notável aumento da população idosa, com mais de 60 anos de idade (de acordo com a definição da OMS) a nível mundial, não tem sido acompanhado por estudos focados na alergia alimentar, sendo estes muitos escassos. Quando existem, os dados sobre idosos estão frequentemente englobados dentro dos estudos realizados em adultos, sem diferenciação, o que dificulta o adequado conhecimento do impacto desta patologia nos idosos.

Assim, os objectivos da presente tese são: a) Desenhar e validar um questionário específico para o rastreio de alergia alimentar em adultos, b) determinar a prevalência e as características clínicas da alergia alimentar em uma população de adolescentes e adultos residentes na Beira Interior e c) determinar a prevalência e características clínicas da alergia alimentar na população de idosos a escala mundial, através da realização de uma revisão bibliográfica sistemática e uma posterior meta-análise dos dados.

Métodos:

Para a validação do questionário, foi realizado um estudo multicêntrico transversal em uma amostra randomizada simples de 126 adultos entre 18 e 82 anos (66 deles com diagnóstico prévio confirmado de alergia alimentar por prova de provocação oral e 60 voluntários saudáveis), residentes na região da Beira Interior – Centro de Portugal. A esta amostra foi aplicado telefonicamente um questionário, em idioma português, de 17

questões para o rastreio de alergia alimentar em duas fases (teste e reteste). Foram analisadas a validade aparente (ou facial) e de conteúdo, a inteligibilidade, a validade conceptual e a fiabilidade teste-reteste (estabilidade temporal) desta ferramenta. O questionário foi aplicado após a sua validação a duas amostras populacionais de indivíduos residentes na Beira Interior (3168 adolescentes: média de idade de 14,3±1,1 anos; 51,7% deles raparigas e 1436 adultos: média de idade de 47 anos, mediana de 45 anos, 50,6% mulheres), registados nas escolas secundárias e nos Centros de Saúde participantes.

O questionário foi respondido por 1702 adolescentes (média de idade de 14,9±2,1 anos; mediana de 14 anos; 61,9% raparigas) e 840 adultos (média de idade de 48 anos; mediana de 46 anos, 51,3% mulheres), por via telefónica (adultos), ou por escrito (adolescentes). Os indivíduos que reportaram a existência de uma reacção adversa alimentar foram referenciados para uma unidade hospitalar, onde foi realizada uma história clínica específica, testes cutâneos (por picada - SPT e por dupla picada, com alimentos *in natura* - SPPT) e determinação de IgE específica para alergénios alimentares (sIgE). Nos casos onde existia dúvida diagnóstica foi realizada uma prova de provocação oral aberta com alimento. Os casos com história clínica positiva de uma reacção imediata (até 2 horas após a ingestão do alimento) em associação com resultados positivos de IgE específica para alergénios alimentares e/ou testes cutâneos, foram considerados como alergia alimentar provável, mediada por IgE. Os casos em que existiu uma história clínica positiva de uma reacção retardada (mais de 2 horas após a ingestão do alimento) e resultados negativos de IgE específica para alergénios alimentares, independentemente do resultado dos testes cutâneos, foram considerados como alergia alimentar provável não mediada por IgE.

Para abordar o objectivo de análise da prevalência e factores de risco para alergias alimentares em idosos, foi realizada uma revisão sistemática e uma meta-análise acerca da prevalência e características clínicas da alergia alimentar em indivíduos com mais de 60 anos de idade, a nível mundial, em várias bases de dados electrónicas (MEDLINE, EMBASE, Cochrane Library, CINAHL, AMED e ISI Web of Science), assim como diversas bases de dados de ensaios clínicos publicados, não publicados e em fase de desenvolvimento desde 1980 até 2019. A pesquisa bibliográfica não teve restrição idiomática nem geográfica. Foi utilizado o programa Critical Appraisal Skills Programme (CASP) como ferramenta para a avaliação da qualidade metodológica dos estudos incluídos. Os dados obtidos foram mostrados de maneira sumária em forma de tabelas. Foi realizada uma meta-análise utilizando um modelo de efeitos aleatórios com os dados

clinica e metodologicamente adequados desde o ponto de vista estatístico. A lista de verificação PRISMA dirigiu o processo da revisão sistemática.

Resultados:
A análise da validade aparente e de conteúdo do questionário, conduziram à redução de 30 para 17 itens com um índice de consistência interna superior a 0,78. A validade conceptual foi assegurada num grupo de 66 pacientes com alergia alimentar confirmada. A fiabilidade teste-reteste (estabilidade temporal geral) do teste apresentou um coeficiente de correlação de Spearman do 0,845 para o reteste. Os valores associados ao teste Kappa de Cohen para as questões relevantes foram superiores a 0,890 para quase todos os itens. Não foram encontradas diferenças em função do sexo, idade nem procedência dos voluntários. Contudo, detetou-se uma relação inversa entre a fiabilidade e o intervalo temporal do reteste.

A prevalência de alergia alimentar autorreportada na nossa amostra populacional foi de 11% em adolescentes e de 6% em adultos, sendo os frutos frescos, mariscos e leite os alimentos mais frequentemente implicados nas reacções apresentadas pelos adolescentes, e os mariscos, frutas frescos e peixe nos adultos. Após a finalização do estudo alergológico, a prevalência de alergia alimentar provável na nossa amostra populacional baixou para 1,41% nos adolescentes e para 1,0% nos adultos. Os alimentos mais frequentemente implicados foram os frutos frescos, marisco e frutos secos nos adolescentes, e os mariscos, peixe e amendoim/frutos secos nos adultos. Foi identificado um mecanismo mediado pela IgE em 1,23% dos adolescentes e em 0,71% dos adultos, sendo os frutos frescos e mariscos nos adolescentes, e marisco e amendoim nos adultos, os alimentos mais frequentemente envolvidos nestes casos. A sintomatologia mais frequentemente apresentada foi a cutânea. Foi encontrada uma discrepância em ambas as populações, em termos dos valores da prevalência e tipo de alimentos implicados encontrados durante fase do autorreporte e os obtidos após a finalização do estudo alergológico completo, sendo os valores de prevalência sempre superiores quando baseados no autorreporte.

A prevalência de alergia alimentar autorreportada na população idosa foi de 6,46%, discretamente menor do que quando associada à determinação dos níveis de IgE específica para alergénios alimentares (6,95%), mas superior à observada quando baseada em testes cutâneos (1,30%). Os valores encontrados nos estudos efectuados por autorreporte foram inferiores aos dos adultos não-idosos, mas superiores aos das crianças. Finalmente, a população idosa apresentou, nos estudos que combinaram o

autorreporte com outros métodos de diagnóstico *in vitro* ou *in vivo,* valores da prevalência de alergia alimentar menores do que nos observados nos outros grupos etários.

Não foram identificadas associações entre os tipos de alimentos implicados, sintomatologia relacionada, temporalidade de aparecimento dos sintomas, distribuição geográfica, factores de risco ou de prognóstico na população idosa com alergia alimentar.

Foi observada uma grande heterogeneidade entre os estudos considerados, quer na revisão sistemática, quer na meta-análise. Esta heterogeneidade foi menor nos artigos que estudaram a alergia ao marisco (I^2=0,000%) e maior naqueles que estudaram a alergia aos frutos frescos (I^2=98,205%).

Conclusões:

Como resultado da sua simples e rápida aplicabilidade, confirmação da sua validade aparente, conceptual e de conteúdo, assim como da sua elevada estabilidade temporal, o questionário desenhado demonstrou ser uma eficaz ferramenta numa primeira abordagem para o rastreio e identificação da alergia alimentar em adultos e que pode ser aplicado, com as devidas adaptações relacionadas com a dieta e costumes locais, em outros países de língua oficial portuguesa.

A prevalência da alergia alimentar provável na nossa amostra de adolescentes e adultos portugueses foi baixa, principalmente relacionada com a ingestão de frutos frescos, mariscos, frutos secos e amendoim nos primeiros e com mariscos, peixe e frutos secos nos segundos.

Estes resultados confirmam que os alimentos implicados são similares aos referidos em outros estudos realizados com similar metodologia em outros países da área Mediterrânica, com similar cultura e alimentação. O nosso estudo confirmou a relação inversa entre os valores de prevalência de alergia alimentar e o grau de exigência do diagnóstico alergológico. Por outro lado, foi dos escassos trabalhos a nível mundial que descreveram as características clínicas da alergia alimentar numa determinada população geral, sendo o primeiro destas características em Portugal.

A realização da revisão sistemática permitiu realizar uma estimativa actualizada da prevalência das reacções adversas alimentares na população idosa a nível mundial.

A maior parte dos estudos existentes sobre esta temática não estão focados na população maior de 60 anos de idade, resultando numa evidente falta de informação que enviesa os nossos resultados.

Esta situação condiciona o correto conhecimento das características clínicas, alimentos implicados, evolução e diagnóstico da alergia alimentar nesta faixa etária.

Em termos futuros, para uma determinação mais exacta da prevalência real da alergia alimentar na população portuguesa nas suas várias faixas etárias (adolescentes, adultos e idosos), será fundamental implementar efectuar um estudo multicéntrico mais alargado, que envolva unidades de saúde de todo o País. Mais ainda, será fundamental conseguir-se efectuar o estudo de forma completa, recorrendo, sempre que adequado, a provocações orais duplamente cegas, Esta abordagem, com detecção de números mais alargados de doentes com alergias alimentares, poderá também permitir avaliar a eventual existencia de fenótipos clínicos diferentes de alergias alimentares nos três grupos etários. Mais ainda, implicará a realização do primeiro estudo mundial sobre alergias alimentares em idosos. Por outro lado, a estabilidade de eventuais fenótipos de alergias alimentares poderá será avaliada num estudo longitudinal. Assim, através destas e outras abordagens, poderemos comprender melhor o impacto atual da alergia alimentar e propor uma estratégia diagnóstica, terapêutica e preventiva, se possível, nesta área.

Palavras-chave

Adolescentes;Adultos;AlergiaAlimentar;Fiabilidade;Epidemiologia;Idosos;Portugal;Português;Prevalência;ProvocaçãoOralAberta;QuestionáriodeRastreio;ReaçãoAdversaAlimentar;Reprodutibilidade;RevisãoSistemática;TestesCutâneos;Validação.

Index

List of Figures

List of Tables

List of Abbreviations

AFR	Adverse Food Reactions
APP	Appendix
AU/AE	Acute Urticaria/Angioedema
BAT	Basophil Activation Test
CASP	Critical Appraisal Skills Programme
CHUB	Cova da Beira University Hospital Centre
CI	Confidence Intervals
CLI	Carlos Lozoya Ibáñez
COSMIN	COnsensus-based Standards for the selection of health Measurements Instruments
CRD	Component Resolved Diagnosis
DBPCFC	Double-Blind Placebo-Controlled Food Challenge
EAACI	*European Academy of Allergy and Clinical Immunology*
EuroPrevall	The Prevalence, Cost, and Basis of Food Allergy across Europe
F	Female
FA	Food Allergy
FCS-UBI	Faculty of Health Sciences, University of Beira Interior
GRADE	Grades of Recommendation Assessment, Development and Evaluation
I-CVI	Item Content Validity Index
IgE	Immunoglobulin E

IPCB	Polytechnic Institute of Castelo Branco
ILD	Inês Laia Dias
ISG	Intelligibility study groups
ISRCTN	International Standard Randomised Controller Trial Number
JG	Jorge Gama
LTB	Luís Taborda Barata
M	Male
NIAID	*National Institute of Allergy and Infectious Diseases*
NPV	Negative Predictive Value
OAS	Oral Allergy Syndrome
OFC	Open Food Challenge
OR	Odds Ratio
p	Probability
PPV	Positive Predictive Value
PROSPERO	International Prospective Register of Systematic Reviews
Ref	Reference
s-CVI/Ave	I-CVIs average
sIgE	Specific Immunoglobulin E
SPPT	Skin Prick-by-Prick Test
SPSS	Statistical Package for the Social Sciences
SPT	Skin Prick Tests

SR	Self-Report
UBI	University of Beira Interior
UK	United Kingdom of Great Britain and Northern Ireland
ULSCB	Castelo Branco Local Health Unit
US	United States of America
US$	United States of America Dollar
W.H.O.	World Health Organisation

1. Introduction

1.1 Overview

Adverse food reactions, including food allergy, are a problem of great relevance in countries with a Westernised way of life, where our culture is used to having three meals a day, with an estimated 2-3 tons of food being eaten by an individual during his/her lifetime (1). With this daily contact with such quantities of food, it is not surprising that there is such a high number of situations that are associated with "food allergy". In fact, in recent years there has been a large number of scientific articles where the main theme is "food allergy", and which can be found in books and scientific journals (2,3) as well as in other media, such as magazines, news on television, radio and the internet (1).

Although the prevalence of immune-based adverse food reactions (food allergies) does not have the magnitude of other allergic diseases (estimated at "more than 1-2%, but less than 10% of the population" (4), it is certain that it has an enormous impact on the eating habits and social integration of patients with this problem (5,6) and can even be a significant cause of mortality (2,7). A study carried out in the US showed that about 20% of the adult population had to change their diet due to the appearance of an adverse food reaction or suspected food allergy (8). This situation leads in many cases to very restrictive diets, since the patient fears the appearance of adverse reactions (8), with the subsequent "emotional cost", inherent to the decrease in quality of life (9,10).

In addition to this reality, adverse food reactions (AFR) also represent an important source of expenditure not only for the individual but also for society, as absenteeism in the workplace in the case of adults or at school, in the case of adolescents, is greater in this type of patient (10,11). Lower school performance in patients in this age group may be a consequence of the latter situation (12). In financial terms, a study from 2011 estimated a cost of around US$510 million per year in the US (10) due to this health problem.

The differential diagnosis between a non-allergic adverse food reaction and a food allergy is certainly complex. On the one hand, there is a wide range of symptoms related to adverse food reactions (13), which can include very mild and frequent reactions such as urticaria or Oral Allergy Syndrome (OAS), reactions involving respiratory symptoms and/or abdominal ones, or even potentially deadly reactions such as anaphylaxis. In contrast, the multitude of foods involved, and the difficulty in carrying out a diagnostic study, which is complex, time-consuming and expensive, must be considered. These aspects taken together constitute a challenge for the physician since it is not always easy to reach a

definitive diagnosis. This difficulty limits the knowledge of the real values of food allergy at the population level, as well as its clinical characteristics. Furthermore, different dietary preferences and access to food for each population also conditions the type of food involved in the appearance of adverse food reactions.

Therefore, this challenging field of clinical research, which is always evolving and is so difficult to diagnose, justifies our attention *per se* and which we will develop in the following chapters.

1.2 Diagnosis of food allergy

There is a wide spectrum of food intake-associated manifestations (13), ranging from the more frequent and generally mild cutaneous symptoms (acute urticaria, angioedema), to the most severe and fortunately less frequent ones such as anaphylaxis, but also including other symptoms namely ocular, respiratory (nasal, asthma) or abdominal.. However, only those symptoms observed by the physician or adequately collected in the clinical history, in an objective manner, can be considered “adverse food reactions (AFR)” (13).

Among these, we should only regard as “food allergies” the ones with an impact on health, resulting from a response by the immune system against foodstuffs it is exposed to and which it mistakenly identifies as aggressors. These reactions are mainly, but not exclusively, mediated by immunoglobulin E (IgE), and must be reproducible when the body is exposed to the same food (13). In this way, those reactions in which there is no involvement of an immune mechanism (or where it is not possible to identify one), or in which there another type of organic response (metabolic, toxic, pharmacological or ill-defined) is implicated, are called “food intolerances” (13) and these can simulate reactions typical of an immune mechanism (Figure 1).

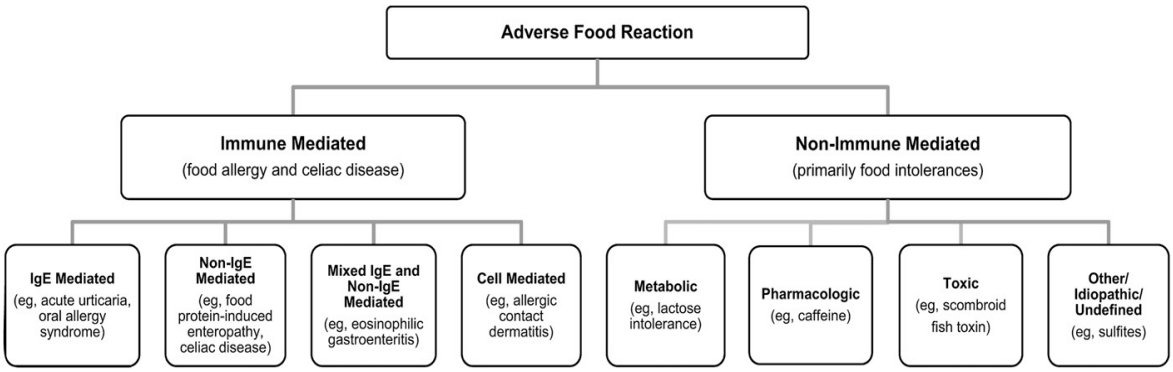


Figure 1: Types of adverse reactions to food (Boyce 2010)(13)

In this context, an immune mechanism has not been demonstrated in reactions caused by some food additives and preservatives, such as tartrazine and sulfites (13). Among these types of reactions, we must also consider symptoms associated with food aversions, which are not reproducible when the involved food is administered through a masking technique (single or double-blind) (13).

In addition, other immune-based diseases such as coeliac disease (mediated by a non-IgE-dependent cellular mechanism), or some immunodeficiencies that cause food intolerances should not be considered true food allergies (13–16).

Independently of the identification of these immune-based reactions for the study of food allergy, the only method that can be considered as a definitive diagnosis is double-blind placebo-controlled food challenge (DBPCFC). This approach was introduced as a protocol by May, in 1977 (17), and has been adopted by the *European Academy of Allergy and Clinical Immunology* (EAACI) since 2004 (18) as the "gold standard" for the definitive diagnosis of food allergy.

However, this method is a lengthy, expensive procedure and needs independent auxiliary staff to prepare the food in order to mask it, as well as experienced medical and nursing staff with specific training in the field namely in addressing and treating potentially serious reactions (anaphylaxis), a context which is not always available in all clinical centres. Therefore, and taking into account the diagnostic recommendations by the *National Institute of Allergy and Infectious Diseases* (NIAID) (13) and the *European Academy of Allergy and Clinical Immunology* (EAACI) (19), we can differentiate different levels of diagnosis, depending on the sensitivity and specificity of the different tests (Table 1).

Table 1: Food allergy diagnostic levels classification according to sensitivity and specificity

Diagnostic Test		**Sensitivity**	**Specificity**
Medical History		Very high	Extremely low
Cutaneous tests (SPT, SPPT)		High	Low
In vitro Tests (Total IgE, Allergen specific serum IgE)		High	Low
Cutaneous Tests + Laboratory tests in combination		Medium	Medium
Oral food challenges	Open Oral Challenge	Low	High
	DBPCFC	Extremely low	Very high

1.2.1 Diagnosis by Medical history

The clinical history to be taken in patients who report an adverse food reaction must be very detailed, incorporating several items of essential information: type of symptoms and treatment given, food involved, amount ingested and type of preparation, time of onset of symptoms, reappearance of symptoms and later tolerance or not, as well as association with other triggers (13).

However, information extracted from the clinical history depends largely on the interviewee's ability to communicate the information, as well as the interviewer's experience and knowledge. Even though, in other fields of Allergology, such as asthma or chronic urticaria (20,21), the existence of protocols facilitates the collection of the clinical history, a “normalised clinical history” of general use is not yet available, although some advances have been made in this area such as Skypala & Venter's proposal to create an information collection protocol for both adults and children (22). We should consider this lack of a “normalised clinical history” as a potential information bias that makes the initial stage of diagnosis notably difficult.

1.2.2 Diagnosis by Cutaneous tests

Skin tests are the first approach to the initial diagnosis of food allergy (19), aiming at identifying reactions mediated by an IgE-dependent mechanism, through the detection of

erythematous weals in skin that was tested with food allergen extracts patients are sensitised to. The most widely used tests are the Skin Prick Test (SPT) and the Skin Prick-by-Prick Test (SPPT), the former being performed with commercial extracts and the latter with fresh or cooked food. Other techniques, such as intradermal and epicutaneous tests, are rarely used, given their lack of standardisation and low evidence of diagnostic effectiveness (13,19).

However, despite the indisputable usefulness of these types of tests (13,19,23) other factors condition the information provided by these diagnostic methods, regardless of the measurement technique used (24). These factors include a lack of standardisation of allergenic extracts by different manufacturers, as well as different proposals for "cut-off" values for positivity, in relation to the diameter of weals used in their measurement, either in general terms or only for certain foods. In general, a larger diameter of weals is associated with greater specificity, although in contrast, it significantly decreases sensitivity (16,25). On the other hand, although Skin Prick Tests (SPT) can be used in patients of any age, reactivity may be lower in children and the elderly (26).

1.2.3 Diagnosis by *In vitro* tests

Like skin tests, *in vitro* tests are a first approach in diagnosing IgE-mediated adverse reactions. In recent years, in addition to the determination of specific IgE levels against native food allergens, there has been an increase in the determination of specific IgE levels against molecular components of each food allergen (Component Resolved Diagnosis – CRD), which is a highly specific, but not very sensitive approach (27). Nevertheless, the latter approach has allowed a better understanding of food sensitisation mechanisms. Thus, CRD is relevant both in the identification of primary sensitisation to food, as well as for the study of co-sensitisations and/or cross-sensitisations (28,29), especially in situations where the clinical history is not clear or there is a suspicion of co-sensitisation to inhalant allergens. However, the high cost, together with low sensitivity of CRD means that diagnosis based on this technique is not commonly used in population prevalence studies (27,28).

Apart from these aspects, the previous, IgE-based diagnostic methods are also useful as biomarkers of the temporal evolution of an individual's degree of sensitivity to the "offending" food, thereby allowing a better understanding of the disease prognosis. On the other hand, although still under investigation, *in vitro* tests may help to determine the severity and risk of subjecting a patient to oral challenge tests, which will minimise the existence of potentially serious reactions resulting from these procedures (29).

However, and similarly to what happens with the use of skin tests, there is no consensus on the cut-off values used as a reference for diagnosis, reaction severity (30) and prognosis of IgE-mediated food allergy, with notable variations in sensitivity and specificity for each food (30,31).

Other diagnostic techniques, such as the Basophil Activation Test (BAT), have been applied to the diagnosis of allergies to various foods, such as peanuts, milk and eggs in children (32–34), as well as to the diagnosis of pollen-food syndromes. BAT has shown greater specificity and positive predictive values than skin tests and the determination of specific IgE, both for native food and molecular components, although its sensitivity is relatively low. However, recent studies report specificities between 75% and 100% and sensitivities between 77% and 98%, depending on the foods and populations investigated (35), and even provide greater specificity than SPT and specific IgE for the diagnosis of food allergy for some nuts (36). On the other hand, BAT it is an expensive technique, which requires specific technical characteristics that not all research centres have (19). However, in the not-too-distant future, it may be a technique that avoids the risks of oral provocation with food, either for the definitive diagnosis of food allergy (35), or to learn about its temporal evolution in these patients (37–39).

Although the specificity of skin tests and *in vitro* tests regarding the diagnosis of food allergy is superior to the information collected from a clinical history, and its use is indisputable (13), these tests must be considered with caution. They should always be used as a complement to the clinical information obtained from clinical history, as these tests only provide information on the possible food sensitisation of the patient, without discriminating between a true "IgE-mediated adverse reaction" and an asymptomatic sensitisation (40,41). On the other hand, these tests do not adequately differentiate cases where there is a cross-reaction between different foods due to the presence of homologous proteins between food groups and pollens (30,41). Finally, in adverse reactions where IgE is not involved, these diagnostic tests do not provide relevant information regarding the underlying mechanism.

1.2.4 Diagnosis using oral challenges

Oral challenges are the diagnostic tests that have the highest diagnostic specificity in food allergy, regardless of the underlying immune mechanism (13,18,42,43). They allow the reproduction of the exposure, in a controlled environment, to the suspected food, in situations in which the conclusion is unclear, and the diagnostic *in vivo* or *in vitro* tests

are inconclusive. Furthermore, oral challenges are useful in research studies on food allergy.

The standard Gold procedure for a "food allergy certainty" diagnosis is a food challenge using the double-blind placebo-controlled method (DBPCFC), which minimises the existence of bias in the interpretation of results either by the patient or by the clinician. However, this procedure is expensive, time-consuming, and not without risk, as there is no clear correlation between the result of *in vivo* and/or *in vitro* tests and the probability of the patient developing a serious reaction (44,45), as also happens with any other oral provocation methods. For this reason, DBPCFC should only be performed in a hospital environment by experienced clinical staff (41) and should be avoided in those cases with a clear history of anaphylaxis.

On the other hand, in cases where a possible negative result is suspected, either due to an unconvincing clinical history or when the complementary diagnostic tests point to an eventual tolerance of the food, other types of oral challenges (open or simple blind, much faster and accessible, although of less specificity) should be performed to confirm, before the patient, the lack of need of an avoidance diet (13).

It should be noted that these oral challenge diagnostic tests should be preceded by an avoidance diet of variable duration (2-8 weeks) (13) and, in the case of DBPCFC, when there is a negative result, this test should be followed by a final open challenge test (13).

1.3. Operational definitions of food allergy for epidemiological studies

There is a plethora of studies on the prevalence of food allergy, estimating values that range between "more than 1-2%, but less than 10% of the population" (4) up to values that vary between 3.5 -35% in adults and 7-40% in children, when based upon self-report (9,46–48). In addition, prevalence values have been shown to range between 2-4% in adults (46,47) and 1-3% in children, when epidemiological studies include other diagnostic tests together with self-report (48–52).

This wide disparity in prevalence values is a consequence of the application of different research methodologies, resulting from the diagnostic methods used (46,47). Thus, we will find several types of work related to the prevalence of food allergy that use different operational definitions of food allergy (46,47,53):

- "Self-reported food allergy", where only a more or less comprehensive questionnaire for adverse food reactions is applied (47); these publications are the most numerous, as many include this method as a preliminary stage for carrying out a more in-depth investigation; in this context, patients with reported symptoms upon food ingestion are regarded as having "Self reported / possible food allergy".
- "Probable food allergy", where in addition to a positive clinical history (questionnaire-based), positive *in vitro* (sIgE – specific Immunoglobulin E) and/or *in vivo* (skin tests: SPT) results are also combined in the definition.
- "Confirmed food allergy", where, in addition to a positive, questionnaire-based clinical history, and positive *in vivo* and/or *in vitro* tests, patients also have positive oral challenges; these cases are regarded as "certain or real, confirmed food allergy" particularly in those few studies in which challenge tests were carried out according to the DBPCFC method.

Thus, if we want to graphically represent the relationship between different types of population studies and the "real" food allergy rate in the form of a pyramid based on sensitivity and magnitude of the diagnostic specificity of "food allergy" (Figure 2), we will find those studies based on self-report, which are very sensitive but of little specificity, at the base of the pyramid. On the other hand, we will find at the top of the pyramid, and for specificity, values obtained after the performance of oral challenge tests (mainly those performed by the DBPCFC method), with intermediate values being those that match the clinical history directed at food allergy in combination with *in vivo* and/or *in vitro* tests. This representation can help us to interpret the reliability of the work carried out in this area of research.

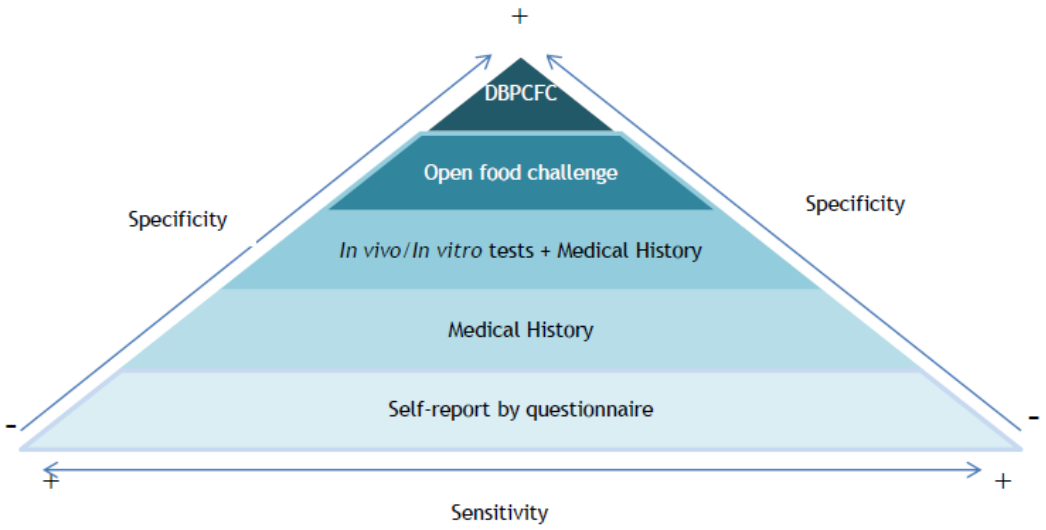


Figure 2: Relation between sensitivity (X-axis) and specificity (Y- axis) in populational food allergy studies.

1.4 Prevalence of food allergy

There are data in the literature indicating that the prevalence of food allergy has increased in the last three decades (41), being more frequent in pediatric ages than in adulthood. However, these findings related to food allergy must be carefully interpreted (16), because, as analysed in the previous sections, the diagnosis of food allergy is remarkably complex, with different levels of sensitivity and specificity depending on the technique used.

If we focus our attention on the most recent systematic review and meta-analysis of the epidemiology of food allergies in the general European population (47) and only take into account the self-reported information, we find that the response rate depends notably on the structure and applicability of the questionnaire, as previously mentioned by Rona (46). This is greater in questionnaires applied in two phases (an initial screening phase, followed later by another, more specific, phase for respondents with a positive answer), than in those with a single response period, since memory bias is more evident in the latter. Apparently, there is no influence from whether the questionnaire is simple (up to 10 questions) or complex (more than 10 items). However, nor does the response seem to depend on the type: face-to-face (face-to-face between interviewer and respondent) or non-face-to-face (telephone, internet or postal application) (Table 2)

Another factor that should be taken into account is that questionnaires are not always validated, and when they are, they are sometimes only applicable to a specific population, where culture and eating habits may not be similar to those of other populations (49,54–57). This great “flexibility” to carry out the type and structure of the questionnaire is conditioned by the lack of standardization of a questionnaire type, a situation previously mentioned. Furthermore, we must also acknowledge the existence of a possible response bias derived from the greater predisposition to respond to the questionnaire by individuals with adverse food reactions or who know people who have them, conditions that often give overestimated prevalence values.

Table 2: Self-report prevalence and questionnaires characteristics in Europe (2000-2016)

Type of questionnaire	Author	Country	Year	Population	Sample	Reply rate	Application	Food allergy Prevalence
Biphasic-Complex	Orhan	Turkey	2009	Children	2739	81%	Face-to-Face	5.7%
Biphasic-Complex	Marklund	Sweden	2004	Adolescents	1488	78%	Face-to-Face	19.0%
Complex	Cafarelli	Italy	2011	Children	900	77%	Face-to-Face	10.5%
Complex	Falcão*	Portugal	2004	Adults	1564	77%	Face-to-Face	4.8%
Complex	Osterballe	Denmark	2009	Adolescents	843	72%	Face-to-Face	26.5%
Complex	Pereira	UK	2005	Children	3144	71%	Face-to-Face	11-12%
Complex	Zuberbier	Germany	2004	Adults & Children	13300	69%	By Post	35%
Simple	Gelincik	Turkey	2008	Adults	11816	67%	By Phone	9.5%
Simple	Rancé	France	2005	Children	3500	55%	Face-to-Face	7.0%
Simple	Venter	UK	2006	Children	1440	48%	Face-to-Face	11.8%
Simple	Silva**	Portugal	2016	Children	2762	42%	Face-to-Face	3.7%
Simple	Pénard-Morand	France	2005	Children	7781	30%	Face-to-Face	2.1%

Adapted from Nwaru (47), *Falcão (58), **Silva (59), Vierk (60).

Similar problems are found in determining the values of the general prevalence of food allergy when other means of diagnosis are used, as mentioned by the meta-analyses by Rona and Nwaru (46,47), which are worldwide and European-wide, respectively. These authors found values between 2-5% and 2.7% -10.1% when SPT or specific IgE are used (subject to the use of different measurement cut-offs). These prevalence values decrease notably when the previous techniques are associated with clinical history (up to 2.7%) (47) or oral challenge tests (open or DBPCFC) (2.6%-2.7%) (46,47), considering the latter the latest reference standard for diagnosing real food allergy.

The same is true with the type of foods involved, as they often vary in type and frequency of appearance within the same population studied, notably depending on the diagnostic procedure applied. However, the only meta-analysis that provides information in this regard did not include studies on fruits, vegetables, seeds, nuts, cereals or meat (46).

Besides, some studies do not include certain symptoms within the spectrum of food allergy, as in the case of Oral Allergy Syndrome (OAS) (57,61,62).

Nonetheless, when we consider the prevalence values according to different age groups, it is agreed that it is higher in pediatric than in adult age (46,47), although we must take into account that there is a greater amount of work published in the former age group, which could be a bias factor.

On the other hand, when we focus our attention on the elderly population, we must notice its evident relative increase worldwide. In fact, recent estimates calculate that the percentage of the elderly population could increase from 13% of the world population over 60 years of age (about 962 million people, being 137 million over 80 years old), to an estimated value of 2.1 billion people, so that 425 million will be over 80 years old (63). However, there are still few studies on the prevalence of food allergy in elderly individuals. Even so, when studies cover this age group, the data is usually inserted in the general adult population (4,46,47,64), and it is not possible to determine whether the values are different from those of the pediatric age or adults in general. However, the data compiled by Nwaru (47) points towards a higher prevalence of food allergy in elderly Europeans, although this conclusion is only a conjecture.

1.5 Prevalence of food allergy in Portugal

Studies of the prevalence of food allergy in the general population in Portugal are scarce. During the last few years, some research in the paediatric area have appeared, one involving a population on an outpatient consultation at a hospital in Lisbon (65) and the other, much more recent, consisting of an epidemiological study carried out in a general paediatric population of 4045 children between the ages of 3 and 11 from Beira Interior (66), where a questionnaire in two phases was applied, with subsequent application of *in vivo* and *in vitro* tests and in some cases, also food challenges. However, there are no current published data regarding the prevalence of food allergies in Portuguese adolescents. In the case of adults, we only have a study in a small population sample (659 participants) in the city of Porto in 2004 (58). This study only consisted of a telephone survey, without a later phase with clinical reevaluation in the hospital or application of other diagnosis tests, but only the results of the self-report are known.

1.6 Objectives of the study

For the reasons listed above, we believe it is important and relevant to perform a study on the prevalence of food allergy in adolescents and adults in a general Portuguese population (located in Beira Interior), applying various diagnostic tools with various levels of sensitivity and specificity, including self-report, application of a clinical history specifically focused on identification of food allergy, and performance of *in vivo* and *in vitro* tests, and, where applicable, open food challenges.

Finally, we also intend to determine the prevalence values, and analyse the implicated foods and clinical characteristics at the population level in the elderly population. For this aspect, and given the small sample size in our population to be studied and the estimated values of food allergy in this age group (47), we decided to carry out a systematic review and the subsequent meta-analysis of the related worldwide bibliography in several databases, without any restriction on language of publication or the origin of the work.

Therefore, the following work objectives were proposed:

- To design and validate a food allergy study questionnaire for Portuguese adults.
- To determine the prevalence, and clinical characteristics of food allergy in a population of adolescents in Beira Interior.
- To determine the prevalence, and clinical characteristics of food allergy in an adult population in Beira Interior.
- To synthesize the evidence on prevalence and clinical characteristics of food allergy in the elderly population worldwide by conducting a systematic review of the bibliography and a subsequent meta-analysis of the data.

These work objectives, as well as their methodology, results and discussion, will be developed throughout this dissertation work.

2. Material and Methods

2.1. Validation of a questionnaire

2.1.1. Setting

This study, including a cross-sectional component (analysis of internal consistency) and a temporal component (analysis of reproducibility), was carried out at three Healthcare centres in the central region of Portugal and at the Allergy outpatient clinics of the Central Hospitals of Castelo Branco Local Health Unit and Cova da Beira University Hospital Centre, serving a population of 180,000 inhabitants who are >15 years old (67). It was carried out between 2012 and 2015. All patients and healthy volunteers gave their written informed consent.

2.1.2. Volunteers and study design

Overall, we studied 174 volunteers, as shown in Figure 3. Initially, we recruited four groups of adult volunteers into two clusters with characteristics similar to those of subjects in whom a future study on food allergy was to be carried out.

The first cluster ("Intelligibility study groups-ISG") was formed by two groups of individuals: a series of 24 healthy volunteers from the general population (recruited at participating healthcare centres and hospitals), and another series of 22 patients with food allergy confirmed by clinical history, specific IgE levels, cutaneous tests and double-blind placebo-controlled food challenges (DBPCFC)(patients with IgE-mediated food allergy), and 2 patients with positive clinical history and DBPCFC but negative specific IgE levels and cutaneous tests (patients with non-IgE-mediated food allergy), belonging to Allergy outpatient clinics of the central hospital of the Castelo Branco Local Health Unit and Cova da Beira University Hospital Centre.

The second cluster (case and control patients) included 66 adult patients with food allergies that were confirmed according to the same protocol used for the ISG patient group. Patients were recruited from the Allergy Outpatient Clinic of the Castelo Branco Local Health Unit and Cova da Beira University Hospital Centre ("Case Group"). Healthy volunteers (n=60) from the general population were also randomly selected from the files of General Practitioners belonging to the participating Healthcare Centers and who were invited to take part in the study ("Control Group").

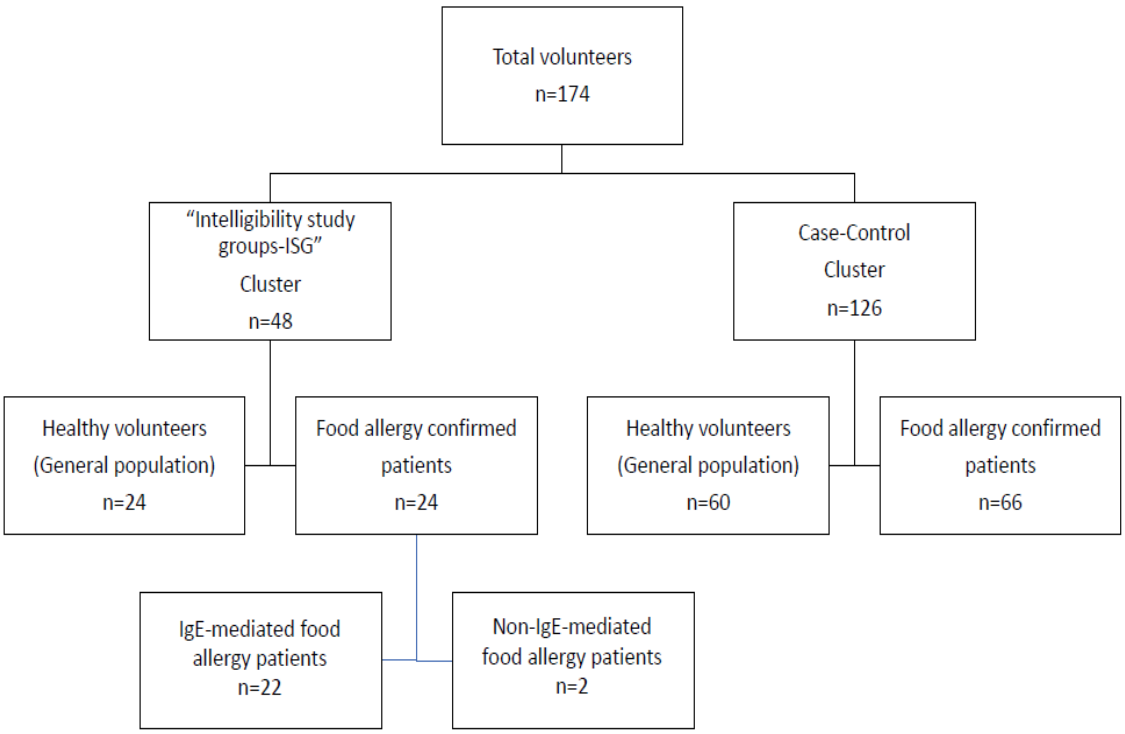


Figure 3: Volunteers and study design flowchart

2.1.3. Development of the clinical screening questionnaire

The initial step consisted of a bibliographical search for published validated questionnaires for screening food allergies in adults and was performed on PubMed using terms such as "questionnaire", "survey", "food allergy", "food hypersensitivity", "history", "tool", "diagnosis". Published reports, namely EuroPrevall studies, did not include full questionnaires or did not mention any validation data. In addition, possible cultural adaptations might be needed.

Although there is international consensus that the allergy-focused history is a key part of the diagnostic approach, there is no agreement regarding the type of questions to be asked, or the typified clinical history, as highlighted by Skypala et al (22).

For these reasons, we decided to develop a clinical history screening questionnaire for our study. Its design was based upon specific principles, as defined by a panel of experts in line with principles previously used in other publications using questionnaires in other fields of (68–70), as well as taking into account Portuguese (71) and European guidelines (19). It was also based upon a questionnaire previously applied to children with food allergies (72), with an adequate sample size calculated in accordance with appropriate recommendations (73,74).

The questionnaire aimed at screening the presence of adverse food reactions and their risk factors. It also included the main clinical manifestations of adverse reactions to foods which are crucial to its diagnosis, as well as demographic data such as age, gender and Healthcare Centre of referral.
The questions were designed in an objective way in seven domains, in a procedure similar to that used in a questionnaire developed and validated by our group, for detecting children with food allergies (75). The first questions focused on the identification of the volunteer (assigning an identification code for data anonymisation, gender and age) and request to answer the questionnaire (questions 1-4).

In addition, item 17 asked volunteers about their willingness to carry out a food allergy study in a specialised center. Domain #1 focused on confirmation of the presence of a previous adverse reaction to food (item 5). We must stress that the questionnaire only proceeded on from this point in case of a positive answer to this question. Domain #2 aimed at identifying the food which triggered the adverse reaction (question 6). Domain #3 focused on characterisation of the reaction to suspect food(s), and included questions 7 and 8. These questions were answered separately for each identified trigger food, and included evaluation of reported symptoms and their severity, as well as definition of the reaction as immediate or delayed. Domain #4 included questions 9 and 10, and asked the need for treatment and procedures followed in response to the reaction. Domain #5 involved questions about previous reactions and how long ago had the previous reaction taken place (items 11 and 12). Domain #6 studied the accessibility to diagnosis of food allergy, focusing as well on medical specialty care versus general practitioner care (questions 13 and 14). Domain #7 included questions 15 and 16, on personal and family history of allergy, as risk factors.

2.1.4. Analysis of theoretical construct: face and content validity

This initial version was analysed by a panel of three medical experts with experience in food allergy, who checked the questionnaire in terms of face validity, bearing in mind food allergy concepts and guidelines (Table 3). Analysis of content validity was performed by submitting the questionnaire for review to a team of nine medical specialists in allergy with well acknowledged clinical and research experience in food allergy, who rated the relevance of each question in terms of current guidelines and knowledge (1-not relevant; 2-somewhat relevant; 3-quite relevant; 4-highly relevant)(76). The Item Content Validity Index (I-CVI) (77,78) was calculated for each question, as the number of experts that gave a rating of 3 or 4, divided by the total number of experts, and I-CVI was regarded as significant if its value was 0.78 or above (79) (Table 3). In addition, experts also suggested

modifications deemed as relevant, proposed the inclusion of new aspects and reviewed semantics as well, in a procedure similar to that previously performed by Lyra et al (72). The questionnaire was then converted into a Google Docs format in order to facilitate collection of data via a phone call (Appendix -App I.1).

2.1.5. Logical (Intelligibility) analysis of the questionnaire

In order to assess its intelligibility, adequacy, logic, and comprehension of the questions and duration, as well as the eventual need to modify some of the terms for the sake of clarity and adequate data collection, a pilot study was performed, with the questionnaire being applied to the two volunteer groups, matched in terms of socioeconomic status and degree of literacy ("Intelligibility study groups-ISG"). In 50% of cases, the questionnaire was applied by phone and in the other 50% it was applied in a written form (App I.1.2). Time taken to complete the questionnaire was measured in both groups. In addition, these volunteers were asked for an opinion about the degree of difficulty and pertinence of the questionnaire items. With the feedback obtained, some of the questions were simplified.
Subsequently, the questionnaire was again sent to a panel of three Allergists with experience in food allergy, who agreed upon the final version of the questionnaire. Thus, literature review, Allergy experts and healthy volunteers as well as patients with DBPCFC-confirmed food allergy contributed to content validity of the questionnaire.

2.1.6. Analysis of empirical construct: construct validity

In order to assess construct validity, the 17-item questionnaire was analysed in terms of known-group validity. This was based on analysis of the agreement between positive replies to its questions and the actual presence of food allergy in patients with previously confirmed food allergy (positive food-specific skin tests, positive food allergen-specific IgE, and positive DBPCFC).

2.1.7. Test-Retest Reliability (Temporal Stability) of the questionnaire

The questionnaire was analysed in terms of reliability, using a test-retest approach. The questionnaire was applied via a phone call by a trained technician under allergist supervision, to the case and control groups as previously defined in the "volunteers" section and re-applied via a phone call to the case and control groups, on a second contact ("test-retest" technique) (73) after the first phone call.

2.1.8. Statistical analysis

Spearman's correlation coefficient (*Spearman's Rho value*) was used for determination of temporal stability, regarding values >0.70 in absolute value as a strong correlation.
Analysis of concordance and reproducibility of the questionnaire was performed using Cohen's Kappa Test for each question. Cohen's Kappa results and their 95% confidence

intervals were accepted as having good concordance if Kappa values were >0.60, and as having almost perfect concordance for levels of Kappa >0.80 (73). Data were studied using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) (74). A level of significance of less than 0.05 was regarded as statistically significant.

Table 3: Initial 30 items screening questionnaire and Item Content Validity Index (I-CVI) average performed by the nine experts medical specialists in allergy.

Question Number	Item	Item CVI
1	Identity Code of volunteer	**1**
3	Gender	**0.888**
3	Age in years	**0.888**
4	Do you want to answer this questionnaire?	**1**
5	*Ethnicity*	0.222
6	*Social grade (occupation)*	0.111
7	*Literacy*	0.111
8	*Do you have any systemic disease?*	0.111
9	Do you have any adverse food reaction?	**1**
10	What kind of food causes your reaction?	**1**
11	*How much food caused the reaction?*	0.333
12	*Was the food that caused the reaction cooked (or not)?*	0.222
13	What kind of reaction did you have?	**1**
14	*Where did you have the reaction?*	0.111
15	How long after food ingestion did the reactions appear?	**0.888**
16	Did you need medical treatment?	**1**
17	If answer was "yes" for item 9, Where did you receive medical treatment?	**0.888**
18	*What kind of treatment did you receive (intravenous, oral)?*	0.333
19	*Did food ingestion occur on an empty stomach?*	0.111
20	*Was food ingestion associated with exercise?*	0.222
21	*Was food ingestion associated with any drug treatment?*	0.111
22	*Did you drink alcohol beverages during food ingestion?*	0.222
23	Have you had any previous episodes with the same food?	**1**
24	How long ago did the previous reaction take place?	**1**
25	*Have you had subsequent episodes with the same food?*	0.333
26	Have you been previously diagnosed with food allergy?	**1**
27	Have you ever been to a specialty appointment by an Allergist doctor?	**1**
28	Do you have any other allergic disease? (personal history of atopy)	**1**
29	Does anybody in your family have an allergic disease?	**0.888**
30	Would you want to be followed up at a specialty clinic?	**1**

Italic: Items deleted in final version.

2.1.9. Ethical aspects

This study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki and all procedures involving subjects/patients were approved by the Ethics Committees of the Amato Lusitano Hospital (Castelo Branco Local Health Unit), the Cova da Beira University Hospital Centre, and the Sub-Regional Health Authorities of Castelo Branco (App II). Written informed consent was obtained from all subjects/patients.

2.1.10. Translation into English

The final questionnaire was translated into English by a professional translator and then this version was back translated into Portuguese by another professional translator who was blinded to the original questionnaire in Portuguese. The original and the back translated versions were then compared. Final adjustments to the English version were then carried out by consensus.

2.2. Self-Report based Prevalence and clinical features of adverse food reactions

2.2.1. Population and samples

For this study, we considered two types of samples: adolescents and adults.

For the sample of adolescents, we took into account the 3168 adolescents aged between 10-23 years old (mean age: 14,3±1.1; 51.7% female) registered in seven secondary schools of the cities of Castelo Branco and Covilhã, in central Portugal.

Regarding the sample of adults, we considered the 76946 adults of both sexes, aged between 18 and 80 years; mean age of 48 years (median age: 46 years, 51.3% female), registered in the files of general practitioners from the six Healthcare Centres belonging to the Local Health Unit of Castelo Branco which accepted to participate in the study (Castelo Branco, Vila Velha de Ródão, Sertã, Proença-a-Nova, Oleiros and Idanha-a-Nova).

Based on an estimated prevalence of 4% (4,46,48,49,80,81), and considering a 95% confidence interval and a margin of error of 2% we calculated that we would need a representative sample of 399 adolescents and 369 adults (STATA Statistical Package®). Considering an expected reply rate of 40%, the sample size was set at 779 adolescents and 923 adults. We therefore decided to contact all adolescent students of the seven previously referred schools and at least 1000 adults proportionally distributed in accordance with the number of individuals registered at each Healthcare Centre and randomly selected to be contacted by telephone.

Data regarding the details of adolescent recruitment per school are shown in Table 4.

Table 4: Adolescents sample size distribution

#Amato Lusitano School only accepted 100 schoolchidren sample

School Center	Adolescent population	Total percentage
João Roiz	259	8.17%
Professor Doutor António Sena Faria Vasconcelos	236	7.45%
Cidade de Castelo Branco	316	9.98%
Nuno Álvares	900	28.41%
Afonso de Paiva	294	9.28%
Amato Lusitano #	100#	3.16%
Covilhã (total of schools)	1063	33.55%
Total schools	3168	100%

The total sample distribution according to age, as well as gender is shown in Figure 4.

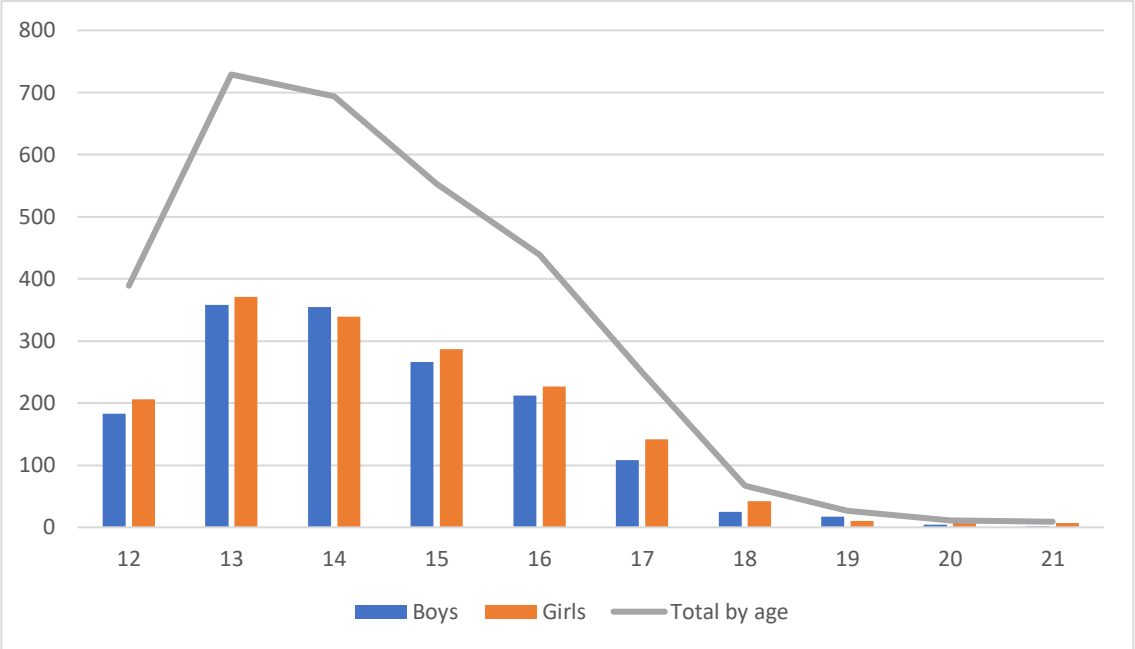


Figure 4: Sample age adolescents' schoolchildren populational distribution

The age distribution of the adult population, with a breakdown according to place of residence, is shown in Figure 5.

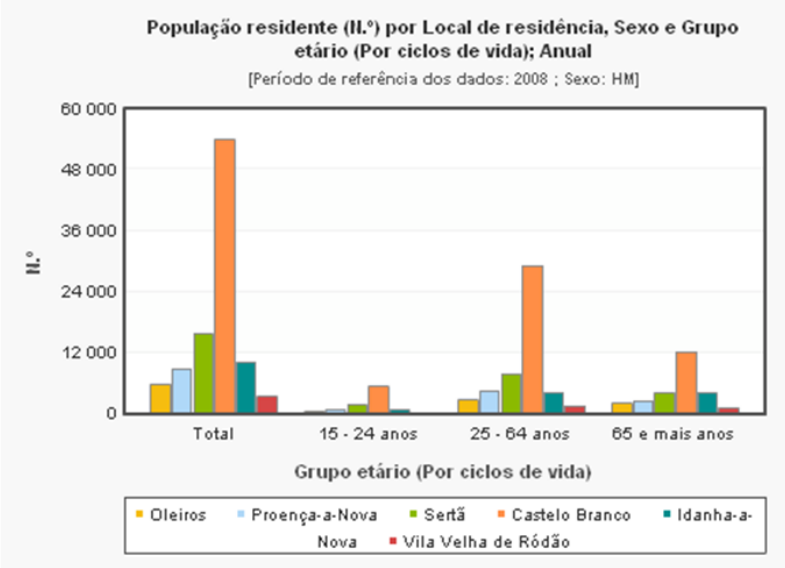


Figure 5: Distribution of adult resident population age clusters, by place of residence (Censos 2004) (67)

The specific calculation of adult sample size according to place of residence is shown in Table 5.

Table 5: Adult sample size distribution

Concelho (Health care area)	Total population >20 years-old	Total percentage	Sample size
Castelo Branco	53,909	55.13%	550
Vila Velha de Ródão	3,450	3.52%	35
Sertã	15,663	16.02%	160
Proença A Nova	8,849	9.05%	91
Oleiros	5,754	5.88%	60
Idanha A Nova	10,147	10.37%	104
Total Concelhos	97,772	100%	1,000

2.2.2. Study design

These were population-based, cross-sectional studies, performed in the two previously described populations during a four year-long period (2011-2012 in adults and 2013-2015 in adolescents). These studies were approved by the Ethics Committees of the Faculty of Health Sciences of the University of Beira Interior, of the Amato Lusitano Hospital and the former Administrative Sub-Region of Health of Castelo Branco (App II.1 and II.2). The study of the adolescent population was also approved by the Ministry of Education (DGIDC, Reg. Nº 0266300001 from January 2012) (App II.3). In order to achieve a higher response rate, the study was publicised in the local media (Press and Radio), before application of the questionnaire (App III). A list of all students in each class of each school was obtained and adolescents were selected by a simple randomisation process. All volunteers, and their legal guardians/parents in the case of individuals under the age of 18 years old, gave written informed consent. The joint flowchart concerning both studies (in adolescents and in adults) is shown in Figure 6.

All 1436 randomly selected adults (mean age: 47 years, median age: 45 years, 50.6% female) registered at participating Healthcare Centres were contacted by telephone and a validated food allergy questionnaire was applied (82). In the case of the 3168 adolescents, questionnaires were given by hand in a written form (App I.2) at participating schools.

Those volunteers (adolescents and adults) who reported a previous adverse food reaction were subsequently contacted by phone by a trained Allergist within the following three months.

Volunteers who again confirmed the previous self-report of an adverse reaction, at the phone contact, were invited to a full allergy screen at the participating hospitals, where a standardised food allergy-related clinical history was taken (52,83), skin prick tests (SPT) and, where applicable, prick-prick skin tests (SPPT) were performed and blood was collected for determination of food allergen-specific IgE levels.
In those cases in which the clinical history was unclear and SPT results as well as specific IgE levels were negative, an open oral challenge was performed. If the latter patients did not exclude the suspected food from the diet, an eviction diet was followed for a minimum of seven days prior to the food challenge.
Patients with a positive clinical history of immediate (up to 2 h after ingestion) reaction in association with positive food sIgE levels and/or skin prick tests (with or without performance of a positive open challenge) were classified as IgE-associated probable food allergy. Cases of positive clinical history or delayed (more than 2 h after ingestion) and negative food sIgE levels independently of positive SPT or SPPT results, were classified as non-IgE associated probable food allergy.

Figure 6: Schematic flow chart of the study design and investigations performed in both populations

2.2.3. Questionnaire

A 17-item, previously validated questionnaire on adverse food reactions (82) with its development being a part of a chapter of this thesis, was applied by phone to all adult volunteers and given by hand in a written form to all adolescent volunteeers, at their schools, in as previously mentioned. This questionnaire included demographic data, questions on the occurrence of previous episodes of adverse reactions to foods, types of foods involved, types of reactions, post-ingestion latency time until appearance of symptoms, date of latest reaction, need for medical assistance, personal or family history of atopic diseases.

2.2.4. Determination of allergen-specific IgE levels

In all individuals who came to the outpatient clinic, 5 ml of peripheral blood were taken for the determination of total serum IgE and aeroallergen-specific screening IgE (Phadiatop inhalant allergens®) levels, as markers of atopy, as well as suspected food-specific IgE levels. A fluorometric (ImunoCAP® 250 Phadia Diagnosis)-based technique was used (Phadia & Thermo Scientific, Uppsala, Sweden). Allergen-specific levels above 0.35 KUA/L were regarded as positive.

2.2.5. Skin Prick Tests

In vivo studies included SPT (LETI Laboratories, Spain; Bial-Aristegui, São Mamede do Coronado, Portugal; Stallergènes, Antony, France) for aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blatella germanica*, *Aspergillus*, *Alternaria*, *Cladosporium*, Latex, Cat dander, Dog dander, *Plantago*, *Olea*, *Pinus*, *Cupressus*, *Quercus ilex*, *Poa*, *Lollium*, *Phleum*, *Salsola*, *Artemisia* and *Parietaria judaica*) and suspected foods. When available, SPPT with native suspect foods were performed, since the sensitivity of the latter test is higher when compared with SPT using commercial extracts (84). Tests were carried out in duplicate on the volar aspect of the forearms. A drop of each commercial extract was placed upon the skin and each drop was pricked through using a metal lancet (Stallergènes, Antony, France). Histamine dihydrochloride and saline solution as positive and negative controls were used respectively. The mean weal diameter was recorded after 15 minutes. Wheals with a mean diameter at least 3 mm greater than that of the negative control were regarded as positive. SPPT tests used the same methodology but fresh foods were used.

2.2.6. Oral Challenge

Open oral challenges were performed both in cases with positive clinical history, SPT and/or SPPT and sIgE levels to suspect foods and also in those cases in which clinical history was unclear and SPT results as well as specific IgE levels were negative or discrepant. Open challenge tests were carried out with suspect food(s)(55), in accordance with published guidelines (9,11,13,18,46,85). In those cases in which individuals did not avoid the suspect foods, in spite of having symptoms, an eviction diet for at least seven days before the oral challenge was carried out and monitored (13,18,42,86,87). Oral challenges were performed at the hospitals, under direct clinical observation for 4 hours post-challenge and further 24 hour-long monitoring, depending upon presence or absence of reported symptoms. No double-blind, placebo-controlled food challenges were carried out.

2.2.7. Statistical analysis

Data were analysed using the Software Package for Social Sciences (SPSS) version 20.0® (SPSS Inc., Chicago, IL, USA). Analysis of normality of distribution of variables was performed using the One Sample Kolmogorov-Smirnov test. Descriptive analysis was used for the characterization of the sample. Chi-Square test or Fischer's Exact Test were used in the case of nominal variables. Comparative analysis of quantitative variables was carried out using Student´s t-test or Mann-Whitney U test depending on distribution of variables. Odds ratio values were calculated for analysis of possible risk factors for adverse for reactions. A p value of less than 0.05 was regarded as significant with all statistical tests.

2.3. Development of a protocol for a sistematic review for the study of food allergy in the elderly

2.3.1. Search strategy

The summary of this systematic review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO)(88), with the following registration number: CRD42018102140.

We have developed a comprehensive search strategy for screening published and unpublished studies. As sources of published studies, we searched the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register), MEDLINE, EMBASE, CINAHL, AMED, ISI Web of Science (Science and Social Science Index).

The bibliographies of all eligible studies were also scrutinised to identify additional possible studies. Unpublished and research in progress were searched in key Internet-based relevant databases: www.clinicaltrials.gov; http://www.isrctn.com/ (ISRCTN Registry); www.anzctr.org.au. In addition, to extend our search for published, unpublished and ongoing studies, we contacted an international panel of experts in this field.

Studies from all over the world were included, when they met the inclusion/exclusion criteria. No language restrictions were imposed; translations were undertaken where necessary. We reported any literature that we were unable to translate. Search dates will be from January 1980 to February 2019. Search terms are detailed in Supplementary Materials chapter (App IV). One change was made to the protocol, and this was registered by submission of an updated version to PROSPERO and was also documented on the final manuscript with the results of the systematic review.

2.3.2. Inclusion criteria for study designs

We included all observational, including cohort, case-control and cross-sectional studies. In addition, systematic reviews and meta-analyses with the same focus were also scrutinised. These study designs were selected to ensure the selection and pooling of the highest possible level of evidence based on the aims of this review.

In terms of population, we selected studies that included (not only exclusively) participants aged 60 years or older, reporting or having a diagnosis of food allergy. This cut-off age was used as a criterion for considering an individual as "elderly" since our systematic review will include studies from all over the world, and the World Health Organisation (W.H.O.) proposed 60 years as a working definition of an "older person" in African countries (89). In addition, although 65 years is recommended by W.H.O. as a cut off level in western countries (90,91), and this is the threshold used in most studies in elderly individuals in those countries, there are some epidemiological studies also performed in such countries which use 60 year cut off age for identifying elderly people (92). This will ensure that our study will be fully inclusive.
The following study designs will be excluded: narrative literature reviews, discussion papers, non-research letters and editorials, case studies and case series, animal studies.

2.3.3. Study selection

Titles and abstracts of included papers were independently checked by two investigators (ILD and CLI) as "include", "exclude" or "unclear". The full text of all potentially eligible studies will be retrieved and independently assessed against the inclusion criteria (see above) by two reviewers. The reviewers decided which of the studies fit the inclusion criteria: any disagreements were resolved by discussion, with a third researcher (LTB) used to arbitrate the process.
To ensure transparency, the process of selection was summarised using a PRISMA flow diagram. (Fig 17, page 54).

2.3.4. Data Extraction

Data from selected articles were extracted independently by two reviewers (ILD and JG), who transferred data from their original presentation to a proper form made in Microsoft Excel© software, adapted to each food subgroup, with each study receiving a reference code (App IV.5). Any discrepancy was resolved by discussion with the third reviewer (LTB). When an article presented results from N different studies, then N different forms were created to collect data. Before using the form, we tested it in a pilot extraction step with a selected sample of studies. This allowed us to check the capacity of the constructed for to capture the relevant information that was to be used for analysis.

Indirect data were also collected from figures and charts, adapting their interpretation from two different authors by consensus, and authors of original articles were also be contacted for further information and retrieval of additional data. In articles in which data from elderly patients were analysed together with those from non-elderly patients, authors

were also contacted in order to clarify or make available data pertaining to the former group, for subgroup analyses.

2.3.5. Data Items

The following information was collected from selected studies involving elderly individuals, using the same approach that was previously used in a systematic review protocol which involved all epidemiological parameters of food allergies in European individuals of various ages but which did not focus on elderly individuals (93): a) Frequency of food allergy (i) by self-report; ii) by clinical symptoms plus positive SPT or IgE to food allergens; iii) by clinical symptoms, positive SPT or IgE to food allergens and also food challenge confirmed; b) Most frequently involved food allergens; c) Most frequently observed symptoms and symptom clusters; d) Timeframe of symptom development upon ingestion of foods; e) Time trends in frequency of food allergy; f) Geographical differences in prevalence of food allergy and related food allergens; g) Risk factors for food allergy.

2.3.6. Outcome assessment

Diverse methods of assessment have been used to define food allergy in different studies. Thus, for estimation of the prevalence (point, period and lifetime prevalence) and incidence (incidence rate, cumulative incidence) of food allergies, we included all methods that were used in previous primary studies, including self-reported assessment, clinician diagnosis, allergic sensitisation (based upon skin prick test results, skin prick-prick test results, food allergen-specific IgE levels, skin atopy patch tests) and food challenges (open, single-blinded, double-blinded). However, analyses took into account each such type of operational definition of food allergy in epidemiological studies.

Regarding the analysis of risk factors and clinical manifestations of adverse food reactions, we only included studies that have studied objectively confirmed food allergic reactions (using food challenges), since this ensured the most robust approach to assessing a potential causal relationship between the studied risk factors and the studied outcome (food allergy as expressed by food-induced symptoms in a food challenge). This approach was also followed by the previously mentioned systematic review by Nwaru et al, which studied the epidemiology of food allergy for all ages, in Europe (47).

2.3.7. Risk of bias assessment strategy

Risk of bias assessment was independently verified by two different reviewers (ILD and JG) for each individual study that was selected, using the Critical Appraisal Skills Programme (CASP) quality assessment tool for the types of included studies, including assessment of internal and external validity (94–96). We assessed heterogeneity, consistency and risk of bias. For each possible answer 0, 1 or 2 points were given to each question/parameter, for the following options "No", "Can't tell" and "Yes", respectively. Quality of evidence and recommendation for the different outcomes was assessed using the GRADE system (97).

All studies and their individual elements were graded in terms of adequacy of the study regarding the research question, risk of selection bias, measurement of exposure, and assessment of outcomes. Disagreements were resolved by a third reviewer (LTB).

2.3.8. Analysis, data synthesis, publication bias and reporting

A narrative synthesis of the data was performed. In addition, a descriptive summary with data tables was elaborated, in order to summarise literature findings (98), and when deemed clinically relevant and statistically adequate, meta-analysis using either fixed-effect or random-effects modelling was carried out (99–101).

A random-effects meta-analysis was performed for the self-reported food allergy to estimate the prevalence of each specific food group (seafood, nuts, peanuts, fruits, milk (included cheese) and others). Also, a pooled prevalence of the self-reported food allergy was estimated using the inverse variance method. The confidence intervals (CI) for each prevalence was taken at 95%. Statistical heterogeneity between studies was assessed by Cochran's Q test and by I^2 index ($p<0.05$ considered statistically significant). Statistical analysis was undertaken using Comprehensive Meta-Analysis, version 3.3.

Forest plot and Funnel plot charts were made, when necessary, to compare results or to identify publication bias, since publication bias leads to funnel plot asymmetry, if 10 or more relevant studies are detected (102). Begs and Egger's methods were used for testing such funnel plot asymmetry (103,104). Heterogeneity between studies was analysed using the the I^2 statistical index (105). Statistical analysis was carried out using Software Package for Social Sciences (SPSS) version 25.0®. Finally, the PRISMA-P statement and checklist were followed for reporting of the systematic review (106,107).

2.3.9. Ethics, dissemination data protection

Ethical approval was not obtained since the data to be collected and analysed cannot be linked to specific individuals. A data management plan was implemented in cases in which data from specific studies can be accessed directly or obtained from article authors. Retrieved data were kept in a database with protected access and was only used by the involved authors.

3. Results

3.1. Validation of the questionnaire

3.1.1. Face and content validity

From the initial 30 questions, only 17 were kept (Tables 6 and 7), with 0.967 being the final average of the I-CVIs for the 17 scale items (s-CVI/Ave). These 17 items were regarded as essential for obtaining adequate information from the patients, and distributed by seven domains.

3.1.2. Demographics of the study volunteers

3.1.2.1 Intelligibility study groups-ISG:

The 24 healthy volunteers included in the "ISG-healthy" group were from the general population (50% females, median age of 45±7 years) and the 24 volunteers with confirmed food allergy (positive clinical history, specific IgE, skin tests, DBPCFC), recruited from the Allergy outpatient clinics belonging to both hospitals (83% females, median age of 36±11 years), were included in the "ISG-patients" group.

3.1.2.2. Case and Controls Groups:

The 66 patients with previously confirmed (clinical history, specific IgE, skin tests, DBPCFC) food allergies were aged between 18 and 74 years (mean=38.27±9.3 years; 73% female). Forty-six of these patients reported symptoms related to one single foodstuff and the other 20 were sensitised to more than one food. Implicated foodstuffs were seafood (32 cases), fresh fruits (26 cases), tree nuts (11 cases), peanut (8 cases), vegetables, chicken and egg (4 cases each) and other foodstuffs (8 cases). The 60 healthy volunteers recruited from the general population were aged between 18 and 82 years (mean=50±14.21 years; 55% female).

3.1.3. Intelligibility and testing of the questionnaire

All volunteers confirmed the intelligibility and adequacy of the 17 questionnaire items. It was estimated that the questionnaire, when applied to volunteers without adverse food reactions (AFR), would take one minute to complete for the written form, and 2 minutes for the phone-applied form. In case of food allergy-confirmed volunteers, it took between 2 and 10 minutes (mean of 4.5±1.5 minutes), for the written form and 2 minutes for the phone-applied form, respectively.

Table 6: Screening questionnaire and references used in its design

Question Number	Item	References
1	Identity Code of volunteer	(55)
3	Gender	(49,55,57,70–72,108–110)
3	Age in years	(49,55–57,70–72,108–110)
4	Do you want to answer this questionnaire?	(49,55)
5	Do you have any adverse food reaction?	(49,55,70–72,108,109,111)
6	What kind of food causes your reaction?	(19,42,49,55,56,70–72,108-111)
7	What kind of reaction did you have?	(13,19,110,42,49,55–57,71,72,109)
8	How long after food ingestion did the reactions appear?	(13,19,42,49,55,57,71,72,108,110)
9	Did you need medical treatment?	(42,49,72,108)
10	If answer was "yes" for item 9, Where did you receive medical treatment?	(49,108)
11	Have you had any previous episodes with the same food?	(19,42,72,110)
12	How long ago did the previous reaction take place?	(19,42,49,72,110)
13	Have you been previously diagnosed with food allergy?	(49,56,108)
14	Have you ever been to a specialty appointment by an Allergist doctor?	(49,56,108)
15	Do you have any other allergic disease? (personal history of atopy)	(19,42,49,55–57,72,108–110,112)
16	Does anybody in your family have an allergic disease?	(13,19,42,49,55,56)
17	Would you want to be followed up at a specialty clinic?	(49,55)

3.1.4. Analysis of empirical construct: construct validity

The 17-item questionnaire was analysed in terms of known-group validity in a group of 66 patients with previously confirmed food allergy (positive food-specific skin tests, positive food allergen-specific IgE, and positive DBPCFC) and in a group of 60 healthy volunteers. Questionnaire items 5 (main), as well as 6-8, consistently identified food-allergic patients with excellent discrimination from healthy controls (sensitivity 100%; specificity 100%). Furthermore, item 8 ("How long after food ingestion did the reactions appear?") also discriminated between patients with confirmed classical IgE-mediated food allergy (all had reactions in less than 2 hours after food ingestion) and patients with non-IgE-mediated food allergy (who had reaction more than 2 hours after food ingestion).

Table 7: Screening questionnaire Portuguese Version

Número da Questão	**Item**
1	Código de Identificação do Voluntário
2	Género
3	Idade em anos
4	Deseja responder a este questionário?
5	Já teve alguma reacção a algum alimento?
6	Qual é o alimento que lhe provocou reacção?
7	Que tipo de reacção teve?
8	Quanto tempo após ter comido surgiram as reacções?
9	Precisou de tratamento médico?
10	Se respondeu "sim" ao item 9, onde recebeu tratamento?
11	Quantos episódios similares já teve com o mesmo alimento?
12	Há quanto tempo teve a última reacção?
13	Já lhe foi diagnosticada alergia alimentar por algum médico?
14	Já foi visto alguma vez em consulta da especialidade de Alergia?
15	Para além das reacções aos alimentos, também sofre de outras alergias? (asma, rinite, conjuntivite, alergia cutânea, outras)
16	Alguém da sua família tem alguma doença alérgica?
17	Deseja continuar o estudo da sua situação numa consulta de Imunoalergologia?

3.1.5. Test-Retest Reliability (Temporal stability)

In the Case Group, mean re-application time value was 8±10 weeks (range: 2 to 38 weeks; median and mode: 2 weeks). In the control group, mean re-application time was 8±7 weeks (range: 2 to 34 weeks; median and mode: 2 weeks), thereby allowing analysis of the variability of replies to each of the items of the questionnaire. Temporal stability was calculated by determining *Spearman's Rho* correlation coefficient for eight items (items number 5, 9, 11-15, 17) which were regarded as indispensable, since they objectively characterised the development of adverse food reactions, and also due to the "yes-no" binary answer type. The set of eight previously mentioned items, both globally and also taking gender, age, time interval between test and retest, as well as the volunteers' source of referral (diagnosed patients and Health Care Centres) into account, are shown in Table 8.

Table 8: Temporal Stability for Relevant questions by sex, age, time interval and local origin.

Parameter	**Parameter classes**	**Rho Spearman´s Values**	***p* value**
Sex	Female	0.913	p< 0.001
	Male	0.873	p< 0.001
Age (years)	<25	0.748	p< 0.001
	25-50	0.921	p< 0.001
	>50	0.752	p< 0.001
Test-retest time interval (weeks)	<8	0.923	p< 0.001
	9-30	0.697	p< 0.010
	>30	0.569	p< 0.050
Volunteers' local of origin	Hospital Patients	0.372	p< 0.100
	Out of Hospital Patients	0.667	p< 0.001
	Community Healthcare Centre #1	0.733	p< 0.010
	Community Healthcare Centre #2	0.450	p< 0.100
	Community Healthcare Centre #3	0.758	p< 0.001

No differences were found in temporal stability when sex, age and volunteer origin were analysed. An inverse relationship was found between reliability and retest time interval. In addition, reproducibility was calculated by determining Cohen´s Kappa values for the globality of the test and in the same items previously referred (Table 9). Except for items 12, 15 and 17, all questions had a high degree of stability.

Table 9: Analysis of Temporal Stability (Test- Re-test Reliability)

Question Number	**Item**	**Cohen´s Kappa Value (Test-Retest reliability: intraclass correlation)**
5	Do you have any adverse food reaction?	0.914
9	Did you have medical treatment?	0.830
11	Have you had any previous episodes with the same food?	0.696
12	How long ago did the previous reaction take place?	0.641
13	Have you been previously diagnosed a food allergy?	0.886
14	Have you ever been to a specialty appointment by an Allergist doctor?	0.892
15	Do you have any other allergic disease?	0.441
17	Would you want to be followed up at specialty clinic?	0.296

3.2 Determination of prevalence and features of self-reported food allergy

3.2.1. Adolescents

Of the 3168 questionnaires that were handed out (Figure 7), 1752 were returned with the written informed consent correctly filled in (57.3% reply rate). The questionnaire was properly completed by 1702 individuals (97.2% of the total of returned questionnaires; mean age: 14.9±2.1 years; median age: 14 years; 61.9% female). Of these, 183 adolescents reported previous adverse reactions (total of 239 episodes) upon ingestion of at least one food (11.01%).

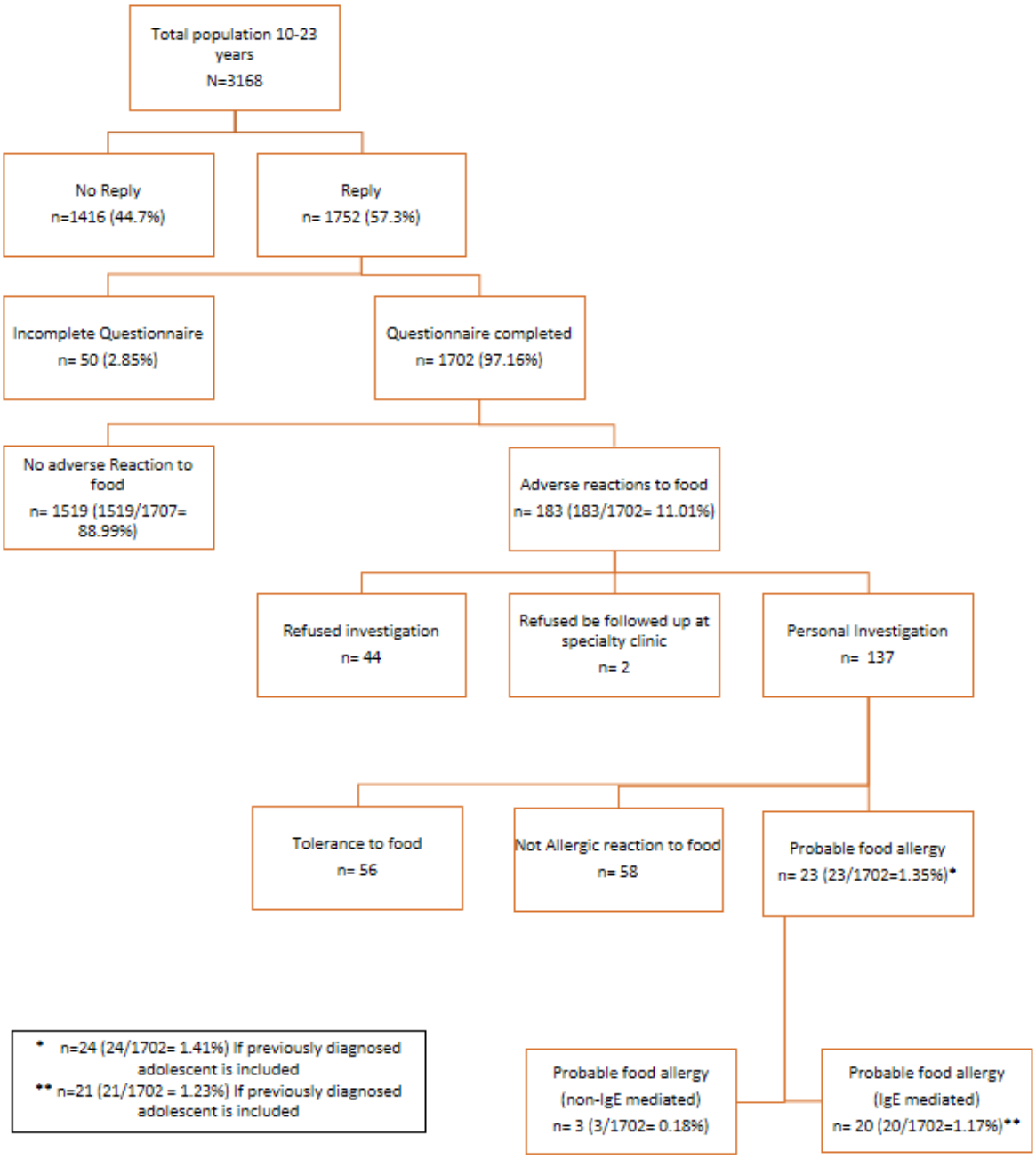


Figure 7: Flow chart of the study design and investigations performed in adolescents

These reactions had most frequently taken place 4 months to 5 years before (42.0% of the cases). Most adolescents reported symptoms with more than one type of food (50.2%; 92/183). Regarding episodes of adverse food reactions, most commonly implicated foods were fresh fruits (59/239 episodes– 24.7%; 73/239 episodes – 30.5% if latex-related fruits were included as well), seafood (32/239 episodes – 13.4%), milk (30/239 episodes – 12.5%) and nuts (15/239 episodes, excluding peanut – 6.3 %) (Figure 8).

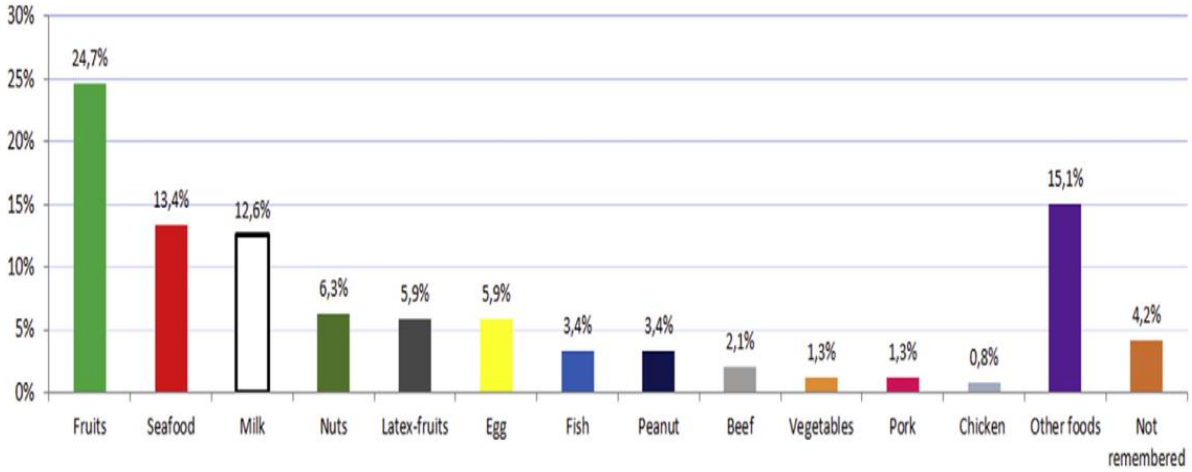


Figure 8: Most frequently implicated foodstuffs (Val. in %) n=239

Most frequently reported symptoms were cutaneous (urticaria/angioedema; 107 episodes – 44.7%), followed by abdominal (34 episodes – 14.2%), respiratory symptoms (18 episodes – 7.53%) or oral allergy syndrome (17 episodes – 7.1%). 49 episodes (20.5%), were difficult to define clinically (Figure 9).

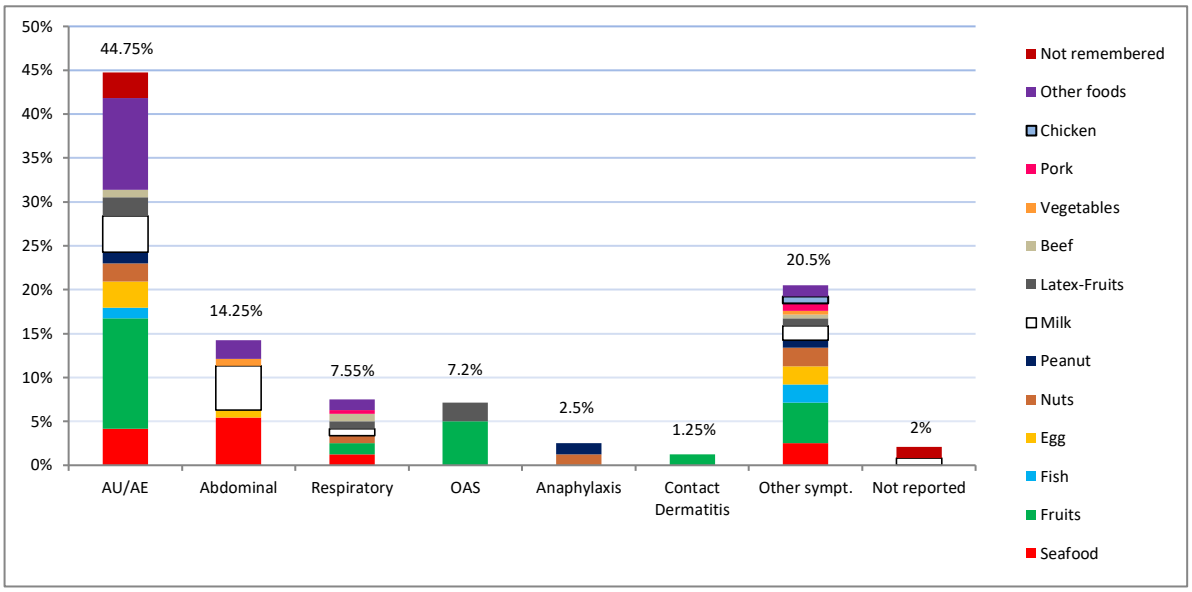


Figure 9: Symptoms by foods (Values in %) n=239

In addition, the ingestion of certain foods was associated with the development of particular symptoms. In this way, fresh fruits, milk and egg were in relation to cutaneous manifestations, shellfish in relation to abdominal symptoms, fresh fruits in connection with OAS, and nuts and peanuts in anaphylaxis.

In most of the reported episodes (43.5%), symptoms developed within 30 minutes upon ingestion and in 30.95% of the cases had a delayed onset (between 2 and 24 hours) (Figure 10).

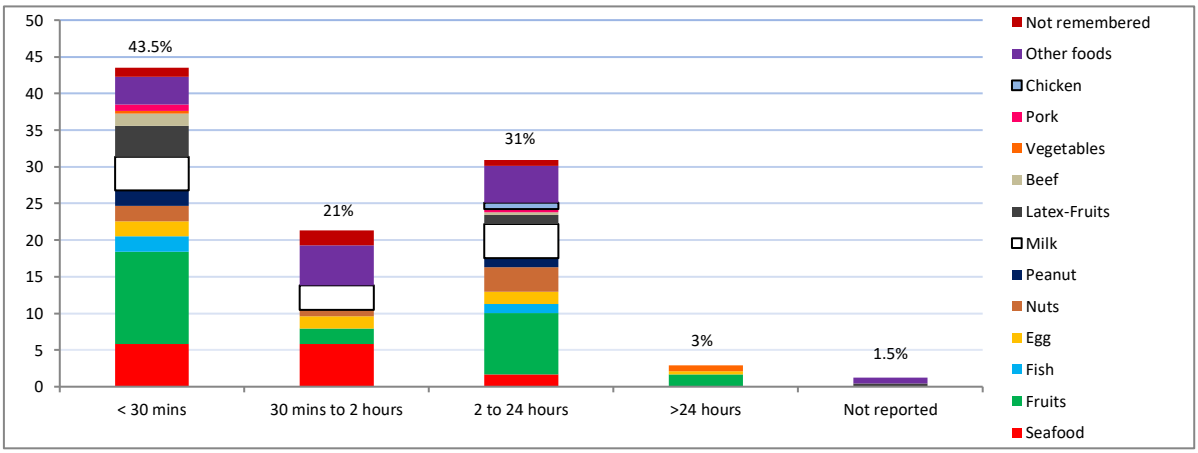


Figure 10: Time until development of symptoms upon food ingestion. (n= 239; Val. in %)

Most of the 183 adolescents who reported a total of 239 episodes of AFR mentioned two to five reactions with the same food (48.6%; 89/183 individuals, reporting 116 episodes), with fresh fruits being the most frequent one in this group (38 out of 116 episodes and in 47 out 116 episodes if latex related fruits were included). No individuals with latex sensitisation were found.

In addition, 35 out of 183 adolescents (19.15%) reported 46 episodes of an adverse food reaction, with seafood being the most frequently associated food in this group (10/46 episodes) (Figure 11).

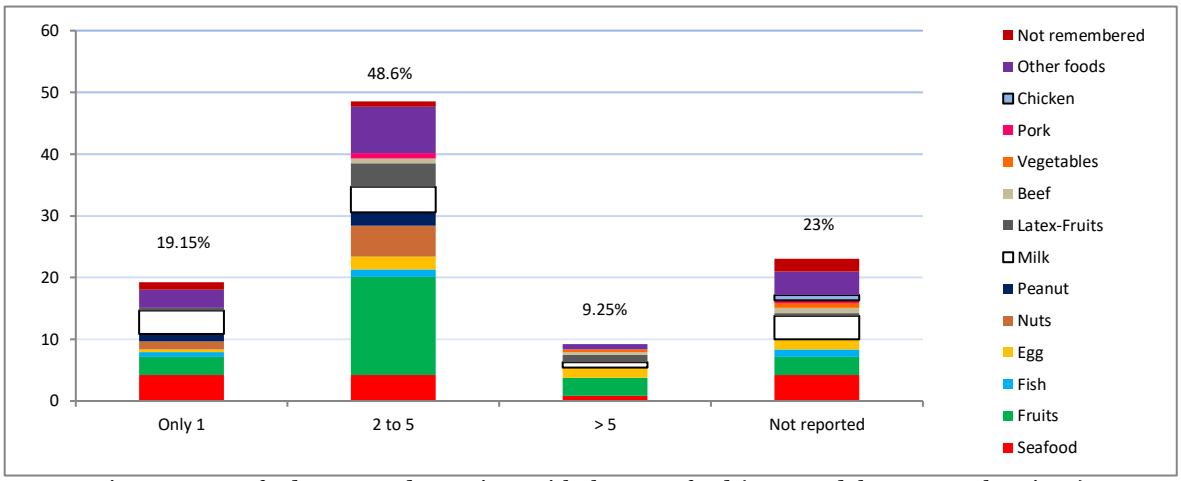


Figure 11: Nr. of Adverse Food Reactions with the same food (n=183 adolescents; Values in %)

About 56% (102/183) of the adolescents needed medical treatment: 67% of them (68 cases) at a Hospital Emergency Department, 12.5% (13 cases) by a General Practitioner, 13.5% (14 cases) by self-medication and 7% (7 cases) by an Allergy specialist.
Most individuals who reported reactions (59%) had not been diagnosed an adverse food reaction and only 30% had been given such a diagnosis by an Allergist.
Having a personal (OR: 3.00; 95% CI: 1.80-5.00) or a family history (OR: 2.60; 95% CI: 1.53-4.32) of atopy were factors significantly associated with an increased risk of having an adverse food reaction.

3.2.2. Adults

Of the 1436 randomly selected individuals, we successfully contacted 965 by telephone (67% reply rate), and the questionnaire was fully completed in 840 cases (58% of the total sample). These individuals had a mean age of 48 years (median age: 46 years), and 51.3% were female. Of these, 52 reported previous adverse reaction upon ingestion of at least one foodstuff (total of 58 episodes), giving an estimated prevalence of 6% (95% CI: 4.4 – 7.6%) (Figure 13). The self-reported reactions had mostly occurred in the 6 months to 5 years previous to the phone contact (n=35; 42% of the cases).

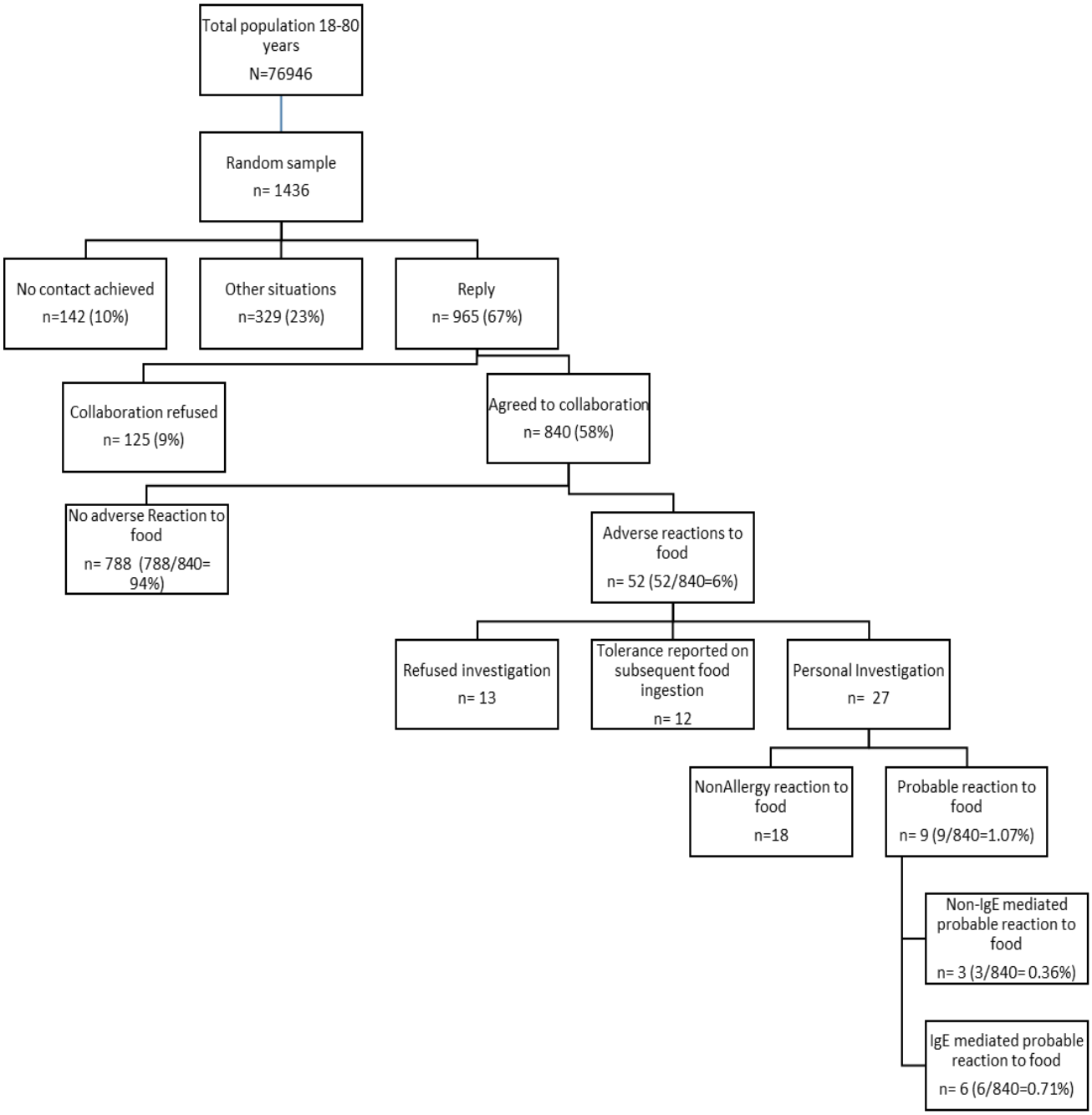


Figure 12: Flow chart of the study design and investigations performed in adults

Most commonly reported foods were seafood (20 episodes - 34.6%), various fresh fruits (12 episodes - 21.1%) and fish (11 episodes - 19.2%) (Figure 13).

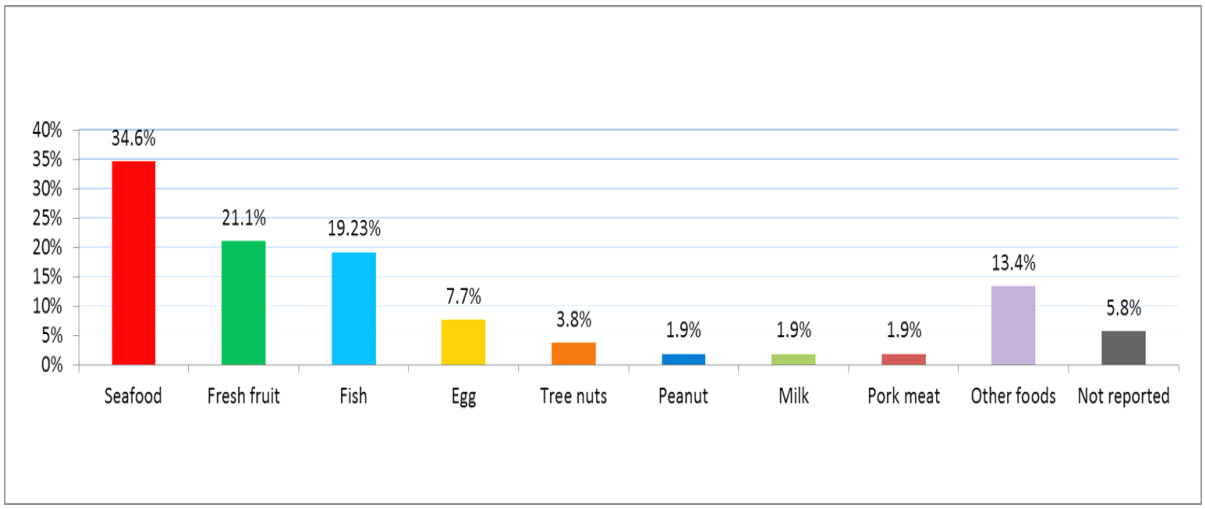


Figure 13: Most frequently implicated foodstuffs (n= 58 episodes)

Since some volunteers reported more than one symptom in relation to food ingestion, the total number of episodes accounted for in this section was 58. Of these, most frequently reported episodes were cutaneous (urticaria/angioedema; 28 episodes - 48.3% of the cases), followed by Oral Allergy Syndrome (OAS) (9 episodes - 16.6%), respiratory (8 episodes - 15%) and gastro-intestinal (4 episodes - 6.6%) symptoms (Figure 14).

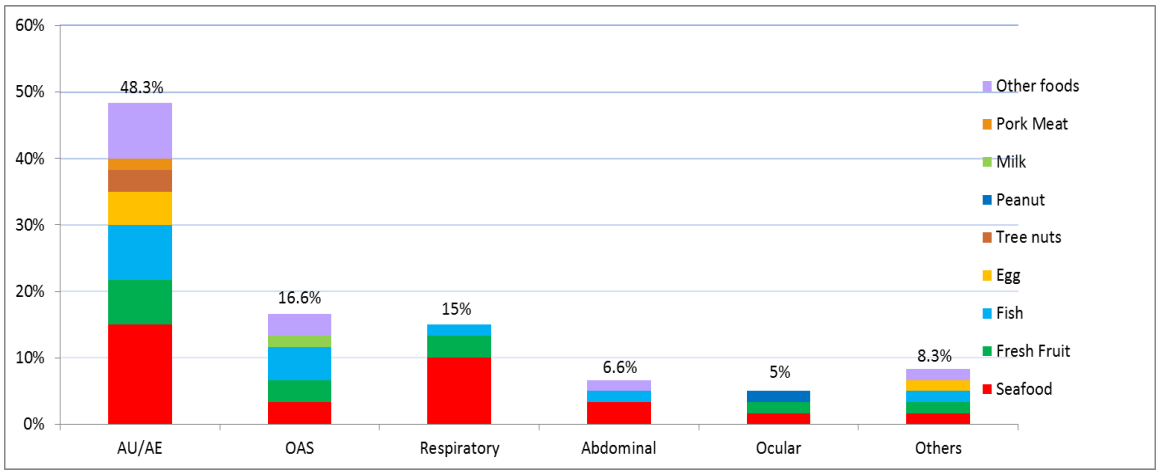


Figure 14: Self-reported symptoms by foodstuffs (n=58 episodes)

In most cases (55%), symptoms developed within 30 minutes upon ingestion and only 26% of the cases had a delayed onset (between 2 and 24 hours) (Figure 15).

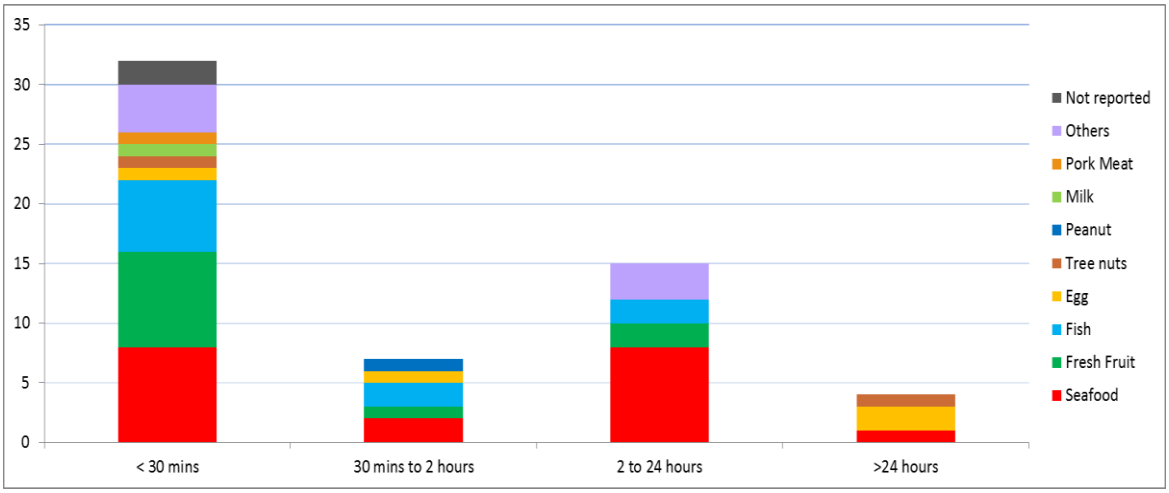


Figure 15: Time for development of symptoms upon food ingestion (number of episodes, n= 58)

Most individuals reported between 2 and 5 episodes with the same food (46.6%, with seafood being the most frequent one). More than 5 episodes were reported in 31% of the cases, with fresh fruits being the food most frequently involved (Figure 16).

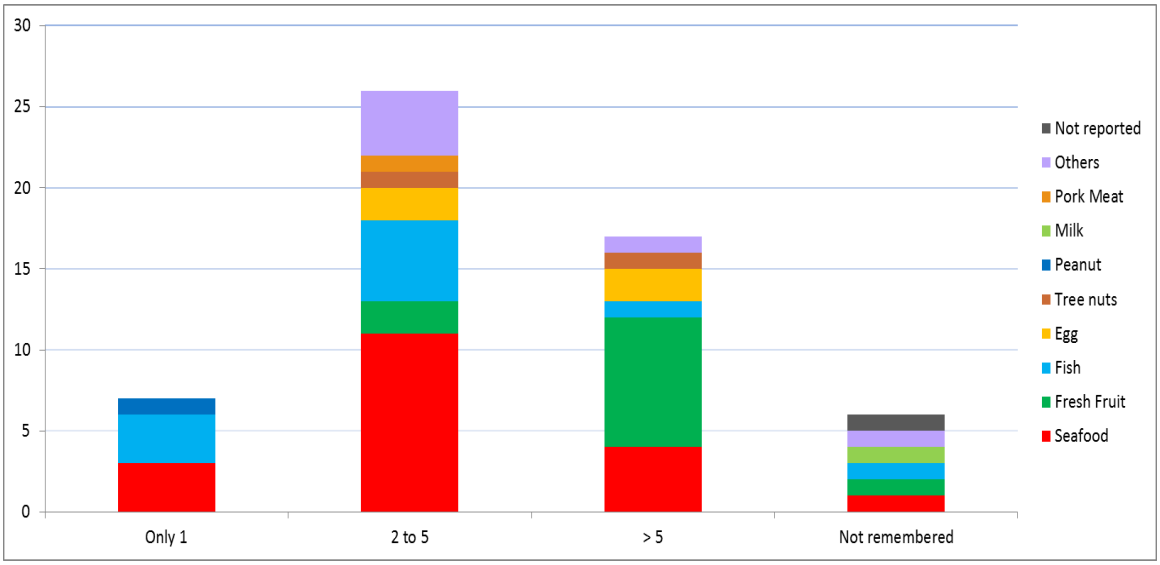


Figure 16: Number of episodes with the same food (number of episodes, n= 58)

Medical treatment had been given in 29/52 (56%) of the individuals. Most of them (27/52; 51%) had never been diagnosed an adverse food reaction, and only 16% (8/52) had been diagnosed a food allergy by an Allergist. Having a personal (OR: 3.72; 95% CI: 2.04-6.77) or a family history (OR: 1.70; 95% CI: 0.90-3.21) of atopy were factors significantly associated with an increased risk of having an adverse food reaction.

3.3. Laboratory and skin prick test-based prevalence of food allergies.

3.3.1. Adolescents

Of the 183 individuals who reported an AFR, 44 (24%) declined to continue the study, and 2 adolescents (1.1%) did not complete the study (one of them had already been thoroughly studied) (Figure 8). The remaining 137 adolescents (74.9% of the total number of AFR cases) were subsequently seen at an allergy hospital appointment. Of these, 56 (40.9%) reported absence of symptoms upon subsequent ingestion of the suspect food in the period between completion of the questionnaire and the hospital appointment, and were therefore not further studied. Thus, the remaining 81 adolescents under study (59.1% of the 137 adolescents seen at the hospitals) completed the full allergy workup (clinical history, SPT/SPPT, food-specific lgE levels, and open oral challenge tests, in some cases, as described in section 3.4.1). We identified two types of AFR response patterns, based on the existence or absence of an IgE-mediated mechanism.

SPT performed with commercial food extracts were positive in 19 foods out of 22 in the group of adolescents with an lgE-associated mechanism and in 3 out of 9 foods tested in the non-IgE associated cases (general test sensitivity of 66.7%, specificity of 100%, PPV: 100%, NPV: 86.4%) No differences between commercial extracts were found. Fresh food SPPT were positive in 13 out of 15 cases in the group of adolescents with an IgE-associated mechanism and only one in the non-IgE associated cases (general test sensitivity of 87.5%; specificity: 100%, PPV: 100%, NPV: 91.7%)(Table 10).

Table 10: Sensitivity, Specificity and predictive values of cutaneous tests in Schoolchildren

	Sensitivity	**Specificity**	**PPV**	**NPV**
Prick-Test	66.6%	100%	100%	86.4%
Prick by prick-Test	87%	100%	100%	91.7%

In the twenty cases in which an IgE-mediated association was newly found, specific lgE levels to implicated foods as well as Phadiatop were positive in all of them, and in addition, the mean total lgE serum levels were higher than compared with the group with non-IgE-mediated reactions (265.78 KUA/L versus 63.93 KUA/L, respectively; $p<0.001$; Mann-Whitney U Test) (Table 11) . Of the three adolescents in whom no IgE-associated mechanism was demonstrated, only two were atopic, one with a positive Phadiatop® test (patient #2) and one with positive SPT to aeroallergens (patient #23).

Table 11: Characteristics of diagnosed Allergy patients (Adolescents)

Patient ID	Age	Sex	IgE levels (KUA/L)	Food Specific IgE	Personal History of atopy	Family History of atopy	SPT aero allergens	Sensitization to more than one foodstuff	Foodstuff	Symptoms	Time for symptom development	Similar episodes with the same food	SPT with Commercial food extracts	Food Prick by Prick skin test	Open Food Challenge	Probable Allergy mechanism
#1	12	M	269	Positive	Yes	No	Positive	No	Other tree nuts	Anaphylaxis	<30 mins	2 to 5	Positive	Positive	Not performed	IgE mediated
#2	12	M	69	Negative	Yes	No	Negative	No	Milk	Other symptoms	> 24 hours	> 5	Negative	Not performed	Positive	Non IgE mediated
#3	12	F	258	Positive	Yes	Yes	Positive	Yes	Peanut, Egg	Urticaria / angioedema	< 30 mins (peanut), 2-24 Hours (Egg)	Only 1	Positive (peanut), Negative (egg)	Positive (peanut), Negative (Egg)	Not performed	IgE mediated (only for peanut)
#4	13	M	529	Positive	Yes	Yes	Positive	No	Fruits	OAS	< 30 mins	> 5	Negative	Positive	Not performed	IgE mediated
#5	15	F	230	Positive	Yes	Yes	Positive	No	Seafood	Urticaria / angioedema	<30 mins	2 to 5	Negative	Positive	Positive	IgE mediated
#6	15	F	92	Positive	Yes	Yes	Positive	No	Other tree nuts	Anaphylaxis	<30 mins	Only 1	Positive	Positive	Not performed	IgE mediated
#7	15	F	86	Positive	Yes	Yes	Positive	No	Fruits	OAS	<30 mins	> 5	Positive	Positive	Not performed	IgE mediated
#8	18	F	114	Positive	No	No	Positive	No	Fruits	Urticaria / angioedema	30 mins to 2 hours	> 5	Positive	Positive	Positive	IgE mediated
#9	19	M	303	Positive	Yes	Yes	Positive	No	Other tree nuts	Urticaria / angioedema	30 mins to 2 hours	Only 1	Positive	Not performed	Not performed	IgE mediated
#10	16	M	164	Positive	Yes	Yes	Positive	No	Fruits	OAS	<30 mins	2 to 5	Positive	Positive	Positive	IgE mediated
#11	16	M	233	Positive	Yes	Yes	Positive	No	Fruits	OAS	<30 mins	2 to 5	Positive	Positive	Positive	IgE mediated
#12	16	M	238	Positive	Yes	No	Positive	No	Fruits	OAS	<30 mins	> 5	Positive	Positive	Positive	IgE mediated
#13	14	F	112	Positive	Yes	Yes	Positive	No	Fruits	OAS	<30 mins	> 5	Positive	Positive	Positive	IgE mediated
#14	17	F	279	Positive	Yes	Yes	Positive	No	Seafood	Anaphylaxis	<30 mins	Only 1	Positive	Positive	Positive	IgE mediated

Table 11 (continuation): Characteristics of diagnosed Allergy patients (Adolescents)

Patient ID	Age	Sex	IgE levels (KUA/L)	Food Specific IgE	Personal History of atopy	Family History of atopy	SPT aero allergens	Sensitization to more than one foodstuff	Foodstuff	Symptoms	Time for symptom development	Similar episodes with the same food	SPT with Commercial food extracts	Food Prick by Prick skin test	Open Food Challenge	Probable Allergy mechanism
#15	16	F	1686	Positive	Yes	Yes	Positive	No	Seafood	Anaphylaxis	<30 mins	Only 1	Positive	Positive	Positive	IgE mediated
#16	16	M	88,5	Positive	Yes	No	Positive	No	Seafood	Urticaria / angioedema	<30 mins	2 to 5	Positive	Positive	Positive	IgE mediated
#17	15	F	112,7	Positive	Yes	Yes	Positive	No	Seafood	Urticaria / angioedema	<30 mins	2 to 5	Positive	Positive	Positive	IgE mediated
#18	17	M	131,2	Positive	Yes	No	Positive	Yes	Peanut, Seafood	Peanut: OAS Seafood: Urticaria / angioedema	<30 mins	2 to 5	Positive (peanut & seafood)	Not performed	Negative (peanut) Positive (seafood)	IgE mediated (only for seafood)
#19	14	F	127,9	Positive	Yes	Yes	Positive	No	Seafood	Urticaria / angioedema, Abdominal	<30 mins	2 to 5	Positive	Positive	Positive	IgE mediated
#20	15	F	34,9	Negative	No	No	Positive	No	Other tree nuts	Respiratory	2 to 24 hours	2 to 5	Positive	Negative	Positive	Non IgE mediated
#21	14	F	114,4	Positive	Yes	Yes	Positive	No	Other tree nuts	Urticaria / angioedema	<30 mins	2 to 5	Positive	Not performed	Positive	IgE mediated
#22	16	M	87,9	Negative	No	No	Negative	No	Other tree nuts	Urticaria / angioedema	2 to 24 hours	2 to 5	Negative	Positive	Positive	Non IgE mediated
#23	15	M	148	Positive	Yes	Yes	Positive	No	Fruits	OAS	<30 mins	> 5	Positive	Not performed	Positive	IgE mediated

3.3.2. Adults

Of the 52 cases who reported AFR, 13 (25%) declined to continue in the study, and 39 were invited to the hospital. We obtained information from all of these individuals (75% of all AFR cases). Of these, 12 (23%) reported that they had tolerated the suspected food after the initial phone call, and 27 individuals (52% of the total of AFR) completed the full study (clinical history, SPT/SPPT and determination of total and allergen-specific IgE levels). As had happened in the adolescent population, two types of AFR response patterns, based on the existence or absence of an IgE-mediated mechanism were identified.

An immunologically-mediated adverse food reaction was diagnosed in 9 patients [9/840; 1% (95% CI: 0.39-1.31%)] of the total of number of individuals (mean age: 45 years, median age: 47 years, 55.6% female). IgE-mediated sensitisation was demonstrated in 6 of them, giving a value of probable food allergy of 0.71% (95% CI: 0.14-1.28%). The details of the patients who were regarded as having immunologically mediated food allergy are shown in Table 12. Most frequently implicated foods were shellfish (50%), fish (20%), peanut and fresh fruits (15% each).
Ingestion of shellfish was implicated in four of the six cases of the IgE-mediated sensitisation, while nuts and peanut were involved in one case each. Two individuals had reactions with more than one food, but IgE-mediated sensitization was only shown in one volunteer who was allergic to peanut and nuts.

Of the six cases in which an IgE-associated mechanism was detected, Phadiatop was positive in five, whereas this test was negative in all cases of food allergy in which IgE-mediated sensitisation was not shown. In addition, total serum IgE values were significantly higher in the group of patients with demonstrated IgE-mediated sensitisation, as compared with the group with non-IgE-mediated reactions (207.33 KUA/L versus 30.66 KUA/L, respectively; $p < 0.001$; Mann-Whitney U test).

SPT performed with commercial food extracts were positive with seven out of nine foods reported in the IgE-mediated group, in comparison with only two out of five foods reported in the non-IgE-mediated group (general sensitivity of test of 64%, specificity of 82%, PPV: 64%, NPV: 82%).

SPPT carried out with fresh foods were positive in eight out of nine cases in the volunteers from the IgE-mediated group and in three out of five volunteers of the non IgE-mediated group (general sensitivity of the test of 89%, specificity: 79%, PPV: 66%, NPV: 94%) (Table 13).

Table 12: Characteristics of diagnosed Allergy patients (Adults)

Patient ID	Age	Sex	IgE levels (KUA/L)	Foodstuff Specific IgE	Personal History of atopy	Family History of atopy	Phadiatop	SPT Aeroalergens	Sensitization to more than 1 foodstuff	Foodstuff	Symptoms	Time for symptom development	SPT with Commercial food extracts	Food Prick by Prick skin test	Open Food Challenge	Allergy mechanism
#1	37	M	114	Positive	Yes	Yes	Positive	Positive	No	Seafood	Asthma	< 30 mins	Positive	Positive	Not performed	IgE mediated
#2	57	M	540	Positive	No	Yes	Positive	Positive	No	Seafood	Anaphylaxis	< 30 mins	Positive	Positive	Not performed	IgE mediated
#3	34	F	255	Positive	Yes	Yes	Positive	Positive	No	Seafood	Urticaria/ angioedema	< 30 mins	Positive	Positive	Not performed	IgE mediated
#4	36	F	128	Negative	Yes	Yes	Positive	Positive	Yes	Fruits, Seafood	OAS	< 30 mins	Positive	Positive (1)	Not performed	IgE mediated
#5	50	M	125	Positive	No	No	Negative	Positive	No	Seafood	Urticaria/ angioedema	30 mins to 2 hours	Positive	Positive	Not performed	IgE mediated
#6	47	M	82	Positive	No	No	Positive	Positive	Yes	Peanut, other tree nuts	Urticaria/ angioedema	30 mins to 2 hours	Positive	Positive	Not performed	IgE mediated
#7	55	F	36	Negative	Yes	Yes	Negative	Negative	No	Fish	Urticaria/ angioedema	2-24 hours	Negative	Positive	Not performed	Non IgE mediated
#8	37	F	26	Negative	No	No	Negative	Negative	No	Seafood	Urticaria/ angioedema	2-24 hours	Positive	Positive	Not performed	Non IgE mediated
#9	60	F	30	Negative	Yes	No	Negative	Negative	Yes	Fish, Seafood	Urticaria/ angioedema	2-24 hours	Negative	Negative	Positive (2)	Non IgE mediated

(1): Positive only to seafood (2): Only performed with fish. Patient refused oral challenge with seafood.

Table 13: Sensitivity, Specificity and predictive values of cutaneous tests in adults

	Sensitivity	**Specificity**	**PPV**	**NPV**
Prick-Test	64%	82%	64%	82%
Prick by prick-Test	89%	79%	66%	94%

3.4. Oral food challenge-based prevalence of food allergies

3.4.1: Adolescents

Thirty-two open oral challenges were performed in twenty-seven volunteers (Table 14), which were clearly positive in seventeen of them: isolated OAS in five cases; OAS in association with diarrhea and colicky abdominal pain in two cases; vomiting and diarrhea in four cases; isolated generalised urticaria in two cases; generalised urticaria and angioedema of lips in one case; generalised urticaria and mild dyspnea in one case. All of these cases occurred 15 to 30 minutes after the onset of the tests; finally, there were two cases of delayed reaction: one involving colicky abdominal pain and diarrhea starting 9-12 hours after the challenge and one consisting of mild urticarial rash and itchy skin which started 12 hours after the test). No cases of delayed anaphylaxis were identified.

Table 14: Results from Open Oral Challenges performed in adolescent volunteers

Results from Oral open Challenge Performed	**N**
Number of Volunteers	27
Total number of Open Oral Challenges	32
Positive Oral challenges	17
Oral Allergic Syndrom (OAS)	5
Vomiting + diarrhea	4
OAS + vomiting + acute andominal pain	2
Acute Urticaria	2
Acute Urticaria + lip angioedema	1
Acute Urticaria + dyspnoea	1
Delayed urticaria	1
Delayed abdominal pain	1

Upon completion of the study, twenty four adolescents (one had already been diagnosed IgE-mediated milk allergy in another hospital) were diagnosed an AFR with an immunological basis (24/1702; 1.41% of the total number of adolescents that filled in the questionnaire; 95% CI=0.90–2.03%; mean age: 15.1 years, median age: 15 years, 54.1% female), and a probable IgE-mediated mechanism was detected in twenty one of them (21/1702; 1.23%; 95% CI: 0.67-1.72%.)(Table 11 shows the results for the newly diagnosed adolescents).

Most frequently implicated foods were fresh fruits (30.8%, mostly belonging to rosaceae family), shellfish (26.9%, mainly crustaceans), nuts (23% walnut, cashew and hazelnut), peanut and milk (7.7% each) and egg (3.8% each) (Table 16).

The most prevalent symptoms in all studied cases were cutaneous (40% of cases), followed by OAS (32%) and anaphylaxis (16%) with the latter being associated with the ingestion of nuts and shellfish (two cases each one). Only in the three cases which were not IgE-associated were the symptoms delayed, appearing more than 2 hours upon ingestion, since in all cases with an IgE-association, symptoms appeared in less than 2 hours upon ingestion (Table 16, page 38).

Of all the adolescents who finished the study at the Hospitals (81 individuals), 65 cases (80.2%) needed treatment for their symptoms, mostly at an Emergency Department. A high proportion of cases diagnosed with food allergy (either IgE- or non-IgE-associated) reported the presence of personal and/or family history of atopy.

3.4.2. Adults

Upon analysis of the clinical history, laboratory data and SPT/SPPT results, an oral challenge test was carried out when there were doubts regarding the presence of a food allergy. Four open oral challenges were performed in two volunteers (Table 15). One of the challenges was clearly positive (angioedema of the face, tongue and lips starting 15 minutes upon the beginning of the challenge) but the remaining challenges were negative. The patient with the positive oral challenge (patient #9) refused a new challenge with the other implicated food (Table 12). This patient was regarding as having non-IgE associated food reaction since she had negative food-specific IgE levels, low total serum IgE levels, negative personal and family history of atopy and her reported reactions upon ingestion of the suspect food were delayed.

Table 15: Positive Open Oral Challenges characteristics performed in adult volunteers

Oral Open Challenge	N
Number of Volunteers	2
Total number of Open Oral Challenges	4
Positive Oral challenges	1
Face, tonge and lips angioedema	1

Most frequently implicated foods in open oral challenges were fish (75%) and shellfish (25%), being positive only in one case (fish).

In terms of symptoms reported in cases diagnosed as probable food allergy (both IgE- and non-IgE-mediated), the most prevalent one was cutaneous (50% of cases), followed by respiratory (22%) and OAS (22%). Delayed symptoms, occurring between 2 and 24 hours upon ingestion, were only reported in three out of nine cases, all of which belonging to the non IgE-mediated group. In the remaining six cases, reactions were immediate, and all occurred in individuals from the IgE-mediated group (Table 15). Of all the 27 individuals observed at the Hospital, about 57% (n=15) reported that they had needed treatment for their food-induced symptoms.

3.4.3. Associated Factors

No significant association factors were found in either age group, between severity of reaction and sex, age, type of food, or time elapsed since the latest reaction. In the same way, we found no significant association between severity of the food-induced reaction and total serum IgE levels.

Table 16: Confirmed probable food allergy by age groups

Age groups	**Total**			**IgE-mediated**				**Non-IgE-mediated**			
	Prevalence of probable food allergy	Foodstuffs	Symptoms	Prevalence	Foodstuffs	Total IgE	Time for development	Prevalence	Foodstuffs	Total IgE	Time for development
Adults	1.07%	Seafood: 50%; Fish: 20%; Peanut, Tree nuts and Fruit: 10% each.	Cutaneous: 50%; Respiratory e OAS: 22% each; Anaphylaxis : 5%	0.71%	Seafood: 66%; Peanut 11%; Tree nuts: 11%	207.33 KUA/L	≤2 hs	0.36%	Fish: 50%; Seafood: 50%	30.66 KUA/L	2-24 Hs
Adolescents	1.41%	Fruits: 30.8%; Seafood: 26.9%, Tree nuts: 23%; Peanut and milk: 7.7% each, Egg: 3.8%.	Cutaneous: 40%; OAS: 32%; Anaphylaxis : 16%; Abdominal, and Respiratory: 4% each.	1.23%	Fruits: 38% Seafood: 33% Tree nuts: 19% Peanut and milk: 5% each	265.78 KUA/L	≤2 hs	0.18%	Tree nuts: 66% Milk: 33%	63.93 KUA/L	>24 Hs.

3.4.4. Final analysis

Finally, we determined populational values of prevalence of adverse food reactions according to diagnostic criteria, foodstuffs and ages (Table 17).

Although the estimated prevalence in individuals who did not reply to the questionnaire (non-responder population) was not calculated, and data shown were only a populational extrapolation of those obtained in our study, they offer interesting information about the differences in prevalence rates we found.

Firstly, we found a remarkable difference in prevalence values between the different phases of the studies, related to the type of methodology used, with higher values in the self-report phase than in the final phase after full allergy work-up.

Secondly, the prevalence of AFR in adolescents was higher than in adults, with any of the methodologies used for diagnosis.

Thirdly, we found that with several of the most frequently involved foodstuffs in the development of AFR in the self-report phase, such as milk and egg, an immune mechanism (mediated or not by IgE) was not confirmed. In those cases in which an immune mechanism was involved, as was the case with fresh fruits, shellfish and fish, the prevalence values were clearly significantly lower than those that were not associated with such a mechanism.

On the other hand, we found a low prevalence of AFR to nuts and peanuts both in self-report and also after full allergy workup.

Globally, we found that population extrapolated prevalence of AFR was less than 5% in the case of the most frequently implicated foods.

Table 17: Population values of prevalence of Food Adverse Reactions
by diagnostic criteria, foodstuffs and ages. (Adults, N= 840; Adolescents, N= 1702)

Diagnostic Criteria		**Total**	**Fruit (Latex-related included**	**Milk**	**Seafood/ Shellfish**	**Egg**	**Tree nuts**	**Peanut**	**Fish**
Self-reported	Adults	6%	1.31%	0.12%	2.14%	0.48%	0.24%	0.12%	1.19%
	Adolescents	11.01%	4.29%	1.76%	1.88%	0.82%	0.88%	0.47%	0.47%
IgE-mediated	Adults	0.71%	0%	0%	0.48%	0%	0.12%	0.12%	0%
	Adolescents	1.23%	0.47%	0%	0.41%	0%	0.23%	0.06%	0%
Non-IgE-mediated	Adults	0.36%	0%	0%	0.24%	0%	0%	0%	0.24%
	Adolescents	0.18%	0%	0.06%	0%	0%	0.12%	0%	0%

3.5. Systematic review of food allergy in the elderly

3.5.1. Study selection and characteristics

This systematic review, based on studies published between January 1980 and February 2019, identified 31,059 articles and an additional set of 2 studies through hand searches and expert suggestions, which yielded a total of 31,061 articles for screening (Figure 17).

After removal of duplicates, 12,869 articles remained for further screening. On the basis of title and abstract reading, and based upon pre-defined exclusion criteria, 12,651 articles were excluded. Most of these papers were not incorporated into the study because they focused on various aspects of gastrointestinal problems, but not on food allergy; the remainder were excluded because they only included children or young adults. Thus, the full texts of 218 articles were examined in greater detail. Of these articles, 140 were excluded for not being population-based, for clearly not including elderly individuals, or for various other reasons, leaving 78 papers. Of these, 68 articles were excluded for various reasons (Figure 17), and 10 papers were included in the narrative synthesis, being all of them primary studies, out of which 9 studies were included in at least one meta-analysis.

The articles reviewed were 10 cross-sectional studies, conducted in five European countries - Finland, Portugal, Poland, Sweden, and the United Kingdom - and one North American country - United States of America. The pooled number of elderly individuals in the twelve included primary studies was 22,340.
A summary of the analysis of the ten articles included in qualitative synthesis is shown in Table 18.

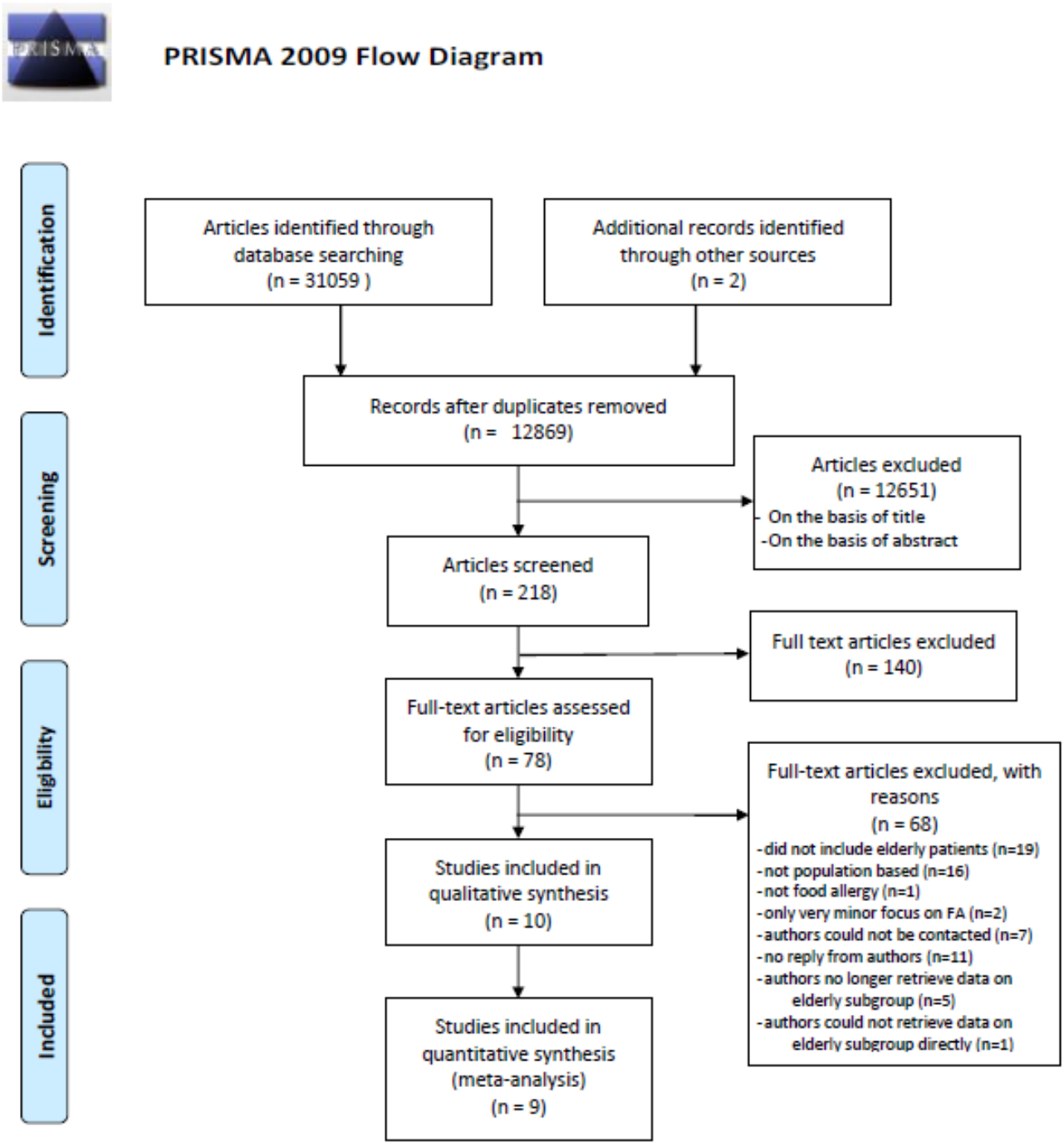


Figure 17. PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for studies on the epidemiology of food allergy in elderly individuals

Table 18. Summary of the characteristics of studies included for qualitative analysis: studies published worldwide until February 2019.

Study name	Country/ Region	Design	Method of outcome assessment	Food groups included	Sampling	Sample size (60+)	Ref
Isolauri, 2004	Finland	Cross-sectional	SR IgE	Milk/ Dairy products	Randomized	100	(113)
Rentzos, 2019	Sweden	Cross-sectional	SR IgE	Milk/ Dairy products Fruit Nuts Seafood Other/Any foods	Randomized	332	(114)
Lozoya, 2016	Portugal	Cross-sectional	SR IgE SPT OFC	Milk/ Dairy products Fruit Nuts Seafood Other/Any foods	Randomized	230	(115)
Emmett, 1999	UK	Cross-sectional	SR	Milk/ Dairy products Fruit Nuts Seafood Other/Any foods	Randomized	2880	(116)
Gupta, 2019	US	Cross-sectional	SR	Milk/ Dairy products Nuts Seafood Other/Any foods	Randomized	10839	(117)
Mossakowska, 2008	Poland	Cross-sectional	SR	Fruit Other/Any foods	Randomized	301	(118)
Sicherer, 2004	US	Cross-sectional	SR	Seafood	Randomized	1876	(119)
Sicherer, 2003	US	Cross-sectional	SR	Nuts	Randomized	1700	(120)
Sicherer, 2010	US	Cross-sectional	SR	Nuts	Randomized	3091	(121)
Vierk, 2007	US	Cross-sectional	SR	FA in total (no specific foods mentioned)	Randomized	991	(60)

3.5.2. Risk of bias assessment

Out of the ten primary studies selected for this systematic review, three were graded as weak, four as moderate and three as strong risk of bias (Table 19).

Table 19. Summary of the characteristics and bias grading of studies included for qualitative analysis: studies published worldwide until February 2019.

Study name	CASP Checklist used	Bias grading
Isolauri, 2004	Cohort study	Weak
Rentzos, 2019	Cohort study	Weak
Lozoya, 2016	Cohort study	Weak
Emmett, 1999	Cohort study	Strong
Gupta, 2019	Cohort study	Moderate
Mossakowska, 2008	Cohort study	Strong
Sicherer, 2004	Cohort study	Moderate
Sicherer, 2003	Cohort study	Moderate
Sicherer, 2010	Cohort study	Moderate
Vierk, 2007	Cohort study	Strong

3.5.3. Overall frequency of food allergy

3.5.3.1 Prevalence by self-reported food allergy

All of the studies evaluated self-reported prevalence of food allergy (Table 20). The overall pooled point prevalence of self-reported food allergy in people over 60 years old was 6.46% (95% CI 5.5-7.54%), which was higher than that in children - 2.50% (95% CI 2.2-2.8%) - but lower than that in adults – 8.25% (95% CI 7.6-8.9%) reported in the same studies (Table 21). Nevertheless, there was significant heterogeneity between the studies, as described later in detail at the end of this chapter.

3.5.3.2. Prevalence by self-reported food allergy plus food-specific IgE levels

Three studies (113–115) also evaluated prevalence of food allergy in elderly individuals, based upon self-report plus food-specific IgE levels (Table 20). These reports further assessed the prevalence of food allergy in adults and children, but Isolauri et al (113) only did so for cow's milk/dairy productss (Table 21).

The overall pooled point prevalence of positive SR plus food-specific IgE levels in people over 60 years old was 6.95% (95% CI 5.23-9.16%), which was lower than that in adults – 10.53% (95% CI 9-12.2%) and in children – 9% (95% CI 4.6-16.4%) reported in the same studies (Table 21).

3.5.3.3. Prevalence by self-reported food allergy plus skin prick test

Only one study (115) analysed the prevalence of food allergy based on self-report plus SPT/SPPT results in adults over 60 years old sub-group (Table 20).

The overall pooled point prevalence of positive SR plus SPT in people over 60 years old was 1.30% (95% CI 0.26-3.94%), which was similar to that in adults – 1% (95% CI 0.4-2.2%)(Table 21) reported in the same studies. This study did not include children and, thus, results cannot be compared with that age range.

3.5.3.4. Prevalence by full allergy workup

Regarding full allergy workup (self-report + SPT/SPPT and/or specific IgE + oral food challenge), only one of the selected studies carried out oral food challenges to measure the prevalence of food allergy in the over 60 years-old sub-group, but not in children (115). Lozoya et al (115) did so in two adult subjects, with 1 positive OFC for fish allergy (0.43% 95% CI: 0.0-2.6), suggesting a prevalence lower than that in adults (1.31% 95% CI: 0.6-2.6).

No studies used double-blind placebo-controlled food-challenge assessments.

Table 20. Summary of the overall pooled point prevalence of food allergy in the elderly.

Study name	Sample size	SR (%)	SR + IgE (%)	SR + SPT (%)
Isolauri, 2004	100	13	7.00	Not reported
Rentzos, 2019	332	19.1	1.8	Not reported
Lozoya, 2016	230	4.35	0.00	1.30
Emmett, 1999	2880	4.20	Not reported	Not reported
Gupta, 2019	10839	8.8	Not reported	Not reported
Mossakowska, 2008	301	3.32	Not reported	Not reported
Sicherer, 2004	1876	5.76	Not reported	Not reported
Sicherer, 2003	1700	1.71	Not reported	Not reported
Sicherer, 2010	3091	1.33	Not reported	Not reported
Vierk, 2007	991	9.59	Not reported	Not reported

Table 21. Prevalence of food allergy (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	6.46	8.25	2.50
SR + IgE	6.95	10.53	9
SR + SPT	1.30	1	Not reported
SR + SPT / IgE + OFC	0.43	1.31	0.00
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

3.5.4. Prevalence of food allergy according to food group

3.5.4.1. Milk and dairy products

The prevalence of allergy to milk/dairy products was presented in 5 studies (113–117) with two different methods of outcome assessment: self-report (114–117) and self-report in addition to milk-specific IgE levels (113). The prevalence of milk allergy in children was only measured in one of the included studies (113).

The point prevalence of milk/ dairy products allergy by self-report was 1.68% (95% CI 1.11-2.5%) in the elderly, similar to that in adults – 1.63% (95% CI 1.28-2.04%) – and lower than that in children - 14.00%.

The point prevalence of milk/dairy products allergy as detected by SR + milk-specific IgE levels was 7.00% in the elderly, comparable to that in children (9.00%) and higher than that in adults (2.50%) reported in the same studies (Table 22).

Table 22. Prevalence of allergy to milk and dairy products (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	1.68	1.63	14.00
SR + IgE	7.00	2.50	9.00
SR + SPT	Not reported	Not reported	Not reported
SR + SPT / IgE + OFC	Not reported	Not reported	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

3.5.4.2 Fruits

Four studies (114–116,118) presented the prevalence of self-reported fruit allergy. One study (115) presented the results of SPT performed after self-reported allergy to fruits.

Two studies specified the reported fruits – strawberries, bananas and oranges (118) and apple, apricot, banana, cherry, dried fruit, kiwi, lingonberry, melon, nectarine, orange, peach, pear, plum, strawberry and avocado (114).

The overall pooled point prevalence of self-reported fruit allergy was 2.00% (95% CI 1.60-2.51%) in the elderly (Table 23). Two studies (114,115) provided data for the comparison with the general adult population, which had an overall pooled self-reported fruit allergy prevalence of 3.08% (95% CI 2.30-4.10%), higher than that in the elderly. No studies presented the prevalence of allergy to fruit in children.

The prevalence of fruit allergy as determined by SR + SPT (115) was 0.43% in the elderly, which was lower than that in adults (0.98%).

Table 23. Prevalence of fruit allergy (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	2.00	3.08	Not reported
SR + IgE	Not reported	Not reported	Not reported
SR + SPT	0.43	0.98	Not reported
SR + SPT / IgE + OFC	Not reported	Not reported	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

3.5.4.3. Nuts and peanut

The self-reported prevalence of allergy to isolated peanuts or other nuts was presented in 6 studies (114–117,120,121) while allergy to both peanuts and other nuts, simultaneously, was presented in 2 studies (120,121). Four studies reported other specific nuts analysed by self-report - tree nut, walnut, almond, hazelnut, pecan, cashew, pistachio, other tree nuts (117); almond, Brazilian nut, chestnut, hazelnut and walnut (114); tree nut (120,121). Only 2 studies (120,121) presented the relevant data in the children sub-group.

The overall pooled point prevalence of allergy to peanuts in the elderly, by self-report, was 0.69% (95% CI 0.39-1.19%), which was lower than that in adults – 1.34% (95% CI 1.07-1.68%) – and similar to that in children – 0.70% (95% CI 0.52-0.96%)(Table 24). The prevalence of self report and peanut-specific IgE (117) in the elderly was 2.71%, lower than that in adults (5.77%).

Table 24. Prevalence of peanut allergy (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	0.69	1.34	0.70
SR + IgE	2.71	5.77	Not reported
SR + SPT	Not reported	Not reported	Not reported
SR + SPT / IgE + OFC	Not reported	Not reported	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

The overall pooled point prevalence of self-reported allergy to other nuts in the elderly was 0.76% (95% CI 0.43-1.27%), lower than that in adults – 1.32% (95% CI 1.05-1.65%) – but slightly higher than that in children – 0.46% (95% CI 0.32-0.68%)(Table 25). The prevalence of self-report and specific-IgE levels to nuts was reported only in 1 study (114) as 8.73% in the elderly, lower than that in adults (21.13%). The prevalence of allergy to other nuts by SR + SPT (115) in the elderly was 0.00%, lower than that in adults (0.33%).

Table 25. Prevalence of other nuts allergy (%I) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	0.76	1.32	0.46
SR + IgE	8.73	21.13	Not reported
SR + SPT	0.00	0.33	Not reported
SR + SPT / IgE + OFC	Not reported	Not reported	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

The overall pooled point prevalence of self-reported allergy to both peanuts and other nuts in the elderly was 0.06% (95% CI 0.01-0.19%), lower than that in adults – 0.22% (95% CI 0.04-0.70%) – and children – 0.34% (95% CI 0.22-0.53%) (Table 26). The prevalence of allergy to both peanuts and other nuts by SR + SPT (115) in the elderly was 0.00%, lower than that in adults (0.16%).

Table 26. Prevalence of both peanut and other nuts allergy (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	0.06	0.22	0.34
SR + IgE	Not reported	Not reported	Not reported
SR + SPT	0.00	0.16	Not reported
SR + SPT / IgE + OFC	Not reported	Not reported	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

3.5.4.4. Seafood (Shellfish and fish)

Four studies (114,115,117,119) presented the prevalence of self-reported shellfish allergy, and one that of SR + SPT (115). Five studies (114–117,119) presented the prevalence of self-reported allergy to fish. Two studies (115,119) presented the prevalence of self-reported allergy to both fish and shellfish, simultaneously, as well as allergy to any/other seafood, as by self-report. One study (115) also reported the prevalence of allergy to fish and shellfish by SR + SPT. The prevalence of seafood in children was only reported in one study (119).

The overall pooled point prevalence of self-reported shellfish allergy in the elderly was 0.47% (95% CI 0.18-0.90%), lower than that in adults – 0.63% (95% CI 0.41-0.92%) – and children – 0.50% (Table 27). The prevalence of allergy to shellfish by SR + SPT in the elderly was 0.00%, lower than in adults (1.64%).

Table 27. Prevalence of shellfish allergy (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	0.47	0.63	0.50
SR + IgE	Not reported	Not reported	Not reported
SR + SPT	0.00	1.64	Not reported
SR + SPT / IgE + OFC	Not reported	Not reported	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

The overall pooled point prevalence of self-reported fish allergy in the elderly was 0.49% (95% CI 0.23-0.59%), lower than that in adults – 0.81% (95% CI 0.61-1.11%) – but higher than that in children – 0.17% (Table 28). The prevalence of fish allergy by SR + SPT in the elderly was 0.43%. The prevalence of fish allergy by SR + SPT + OFC in the elderly was 0.43%, higher than that in adults (0.00%).

Table 28. Prevalence of fish allergy (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	0.49	0.81	0.17
SR + IgE	Not reported	Not reported	Not reported
SR + SPT	0.43	Not reported	Not reported
SR + SPT / IgE + OFC	0.43	0.00	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

The prevalence of self-reported allergy to both fish and shellfish in the elderly was 0.05% (95% CI 0.01-0.26%), lower than that in adults - 0.21% (95% CI 0.13-0.34%) - and children (0.08%) -, and the prevalence of fish and shellfish allergy by SR + SPT in the elderly was 0.43%, higher than in adults (0.33%)(Table 29).

Table 29. Prevalence of both fish and shellfish allergy (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	0-17
Only SR	0.05	0.21	0.08
SR + IgE	Not reported	Not reported	Not reported
SR + SPT	0.43	0.33	Not reported
SR + SPT / IgE + OFC	Not reported	Not reported	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

The prevalence of any/other seafood allergy by self-report in the elderly was 2.52% (95% CI 1.92-3.28%), lower than that in adults - 2.70% (95% CI 2.38-3.07%) - and higher than in children (0.58%).

3.5.4.5. Other foods

Five studies (114–118) analysed the prevalence of self-reported food allergy to other foods. One study (115) also reported the prevalence of food allergy by SR + SPT, and one study (114) by self-report and food-specific IgE levels. The specific foods reported in each study were: eggs, sesame, soy, wheat/flour/gluten, chocolate, pulses and others (116); wheat, soy, sesame and eggs (117); rye, rabbit meat, pig meat, snails, sausages, honey, chocolate, biscuits, eggs and others (115); eggs, pepper, garlic, chamomile and ice cream (118); anise/caraway, bean, beef, chamomile, carrot, cayenne/red pepper, chicken, celery, chilli/tabasco, chocolate, coriander, curry, eggs, flour (non-wheat), flour (wheat), fried/fat food, parsley, pea, poppy seed, pork/pig, potato, red meat, salami, sour milk/yogurt, soy, sunflower seed, sweet pepper, tomato, wine/beer and others (114). The overall pooled point prevalence of self-reported allergy to other foods in the elderly was 3.42 % (95% CI 2.88-4.05%), lower than that in adults – 4.74% (95% CI 3.75-5.92%)(Table 30). The prevalence of allergy to other foods by self-report and food-specific IgE levels in the elderly was 3.61%, higher than that in adults (2.96%), and the prevalence of allergy to other foods by SR + SPT in the elderly was 0.00%, lower than that in adults (0.49%).

Table 30. Prevalence of allergy to other foods (%) for each method of outcome assessment, in each age subgroup.

Method of outcome assessment	**60+**	**18-59**	**0-17**
Only SR	3.42	4.74	Not reported
SR + IgE	3.61	2.96	Not reported
SR + SPT	0.00	0.49	Not reported
SR + SPT / IgE + OFC	Not reported	Not reported	Not reported
SR + SPT / IgE + DBPCFC	Not reported	Not reported	Not reported

3.5.5. Clinical characteristics

Only one study (115) presented the clinical characteristics in the over 60 years of age sub-group (Table 31). Clinical features had the following prevalence in the elderly: acute urticaria/angioedema – 2.17%, by self-report (3.93% in adults) and 0.87%, after SR + SPT (2.95% in adults); abdominal symptoms – 0.43%, by self-report (0.66% in adults) and 0.43%, by SR + SPT (0.33% in adults); respiratory – 0.43%, by self-report (1.31% in adults) and 0.00%, by SR + SPT (0.16% in adults); OAS – 1.30%, by self-report (1.15% in adults) and 0.43%, by SR + SPT (0.33% in adults); ocular – 0.43%, by self-report (0.49% in adults) and 0.00%, by SR + SPT (0.00% in adults); anaphylaxis – 0.00%, by self-report (0.00% in adults) and 0.00%, by SR + SPT (0.16% in adults); other – 0.00%, by self-report (0.82% in adults) and 0.00%, by SR + SPT (0.16% in adults).

Table 31. Clinical characteristics of food allergy (%) for each method of outcome assessment, in each age subgroup.

Clinical characteristics	**Method of outcome assessment**	**60+**	**18-59**
Acute urticaria/angioedema	Only SR	2.17	3.93
	SR + SPT	0.87	2.95
Abdominal symptoms	Only SR	0.43	0.66
	SR + SPT	0.43	0.33
Respiratory	Only SR	0.43	1.31
	SR + SPT	0.00	0.16
OAS	Only SR	1.30	1.15
	SR + SPT	0.43	0.33
Ocular	Only SR	0.43	0.49
	SR + SPT	0.00	0.00
Anaphylaxis	Only SR	0.00	0.00
	SR + SPT	0.00	0.16
Other symptoms	Only SR	0.00	0.82
	SR + SPT	0.00	0.16

3.5.6. Predominant foods associated with food allergy

In spite of the heterogeneity of study methods across reports, we can describe the specific foods predominantly reported or associated with allergic reactions in the elderly. Regarding self-report, the most frequently involved foodstuffs were fresh fruits and milk. Regarding SR + specific IgE, it was nuts and milk. Regarding SPT and OFC, results were only reported in one study (115).

3.5.7. Time trends in the frequency of food allergy

Of all included studies, only two (120,121) allowed inferring time trends in the frequency of food allergy in elderly patients, but only for specific foods (nuts). In this context, the overall prevalence of peanut and tree nut allergy remained relatively the same in the elderly (above 61 years of age) over the course of six years (from 2002 to 2008). Specifically, SR-based prevalence for any nuts was 1.6% in 2002 and 1.3% in 2008; for peanut, it was 0.5% in 2002 and 0.7% in 2008 and for other nuts, it was 0.7% in 2002 and 0.4% in 2008. No other time trends were found in our analysis.

3.5.8. Geographical trends

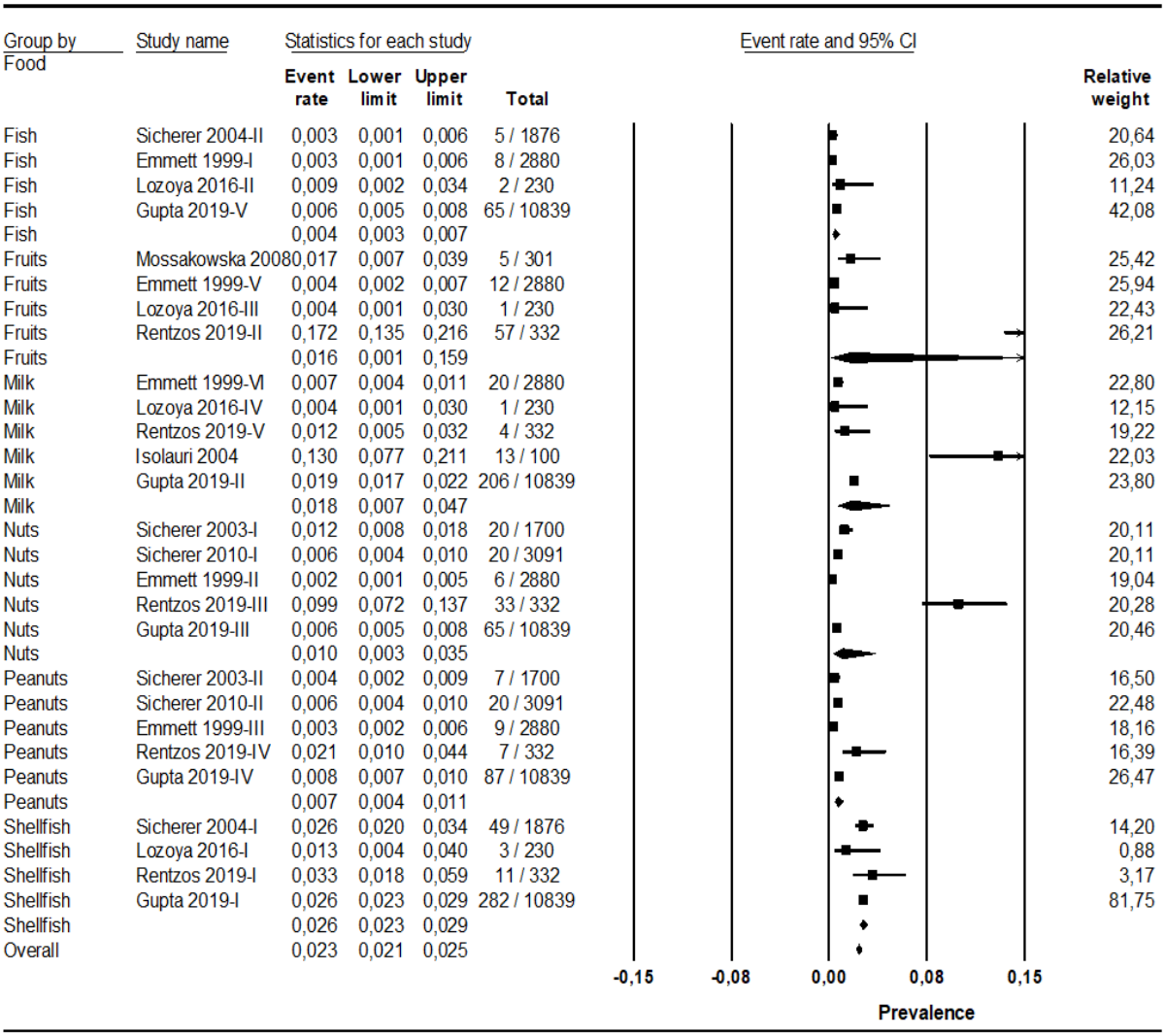
The ten studies included in the systematic review were conducted in five European countries - Finland, Portugal, Poland, Sweden, and the United Kingdom - and one North American country - United States of America. Taking into account only the studies that focused on allergy to any foodstuff, values varied between higher values - 18,98%, in Sweden (114) and in the US (18,77%, in 2019 (117) and 9,59% in 2007 (60)), and lower values - 4,35%, in Portugal (115) and 4,20%, in the UK (116). Lower values were also seen in a Polish study, but this report only focused on centenarians (118). The difference in values observed within the US may have to do with differences in sample size (10,838 elderly individuals in Gupta's study and only 991 elderly individuals in Vierk's study (60,117)), besides having been carried out with a 12 year difference (2019 versus 2007). However, overall, due to the heterogeneity of study methods across reports, we were unable to adequately calculate whether there were significant geographical differences in the prevalence of food allergy in elderly individuals, either in general terms or in terms of specific foods.

3.5.9. Risk and prognostic factors for food allergy

Of the 10 studies included in the systematic review, the data were embedded in the adult sample, and none focused on risk or prognostic factors for food allergy in the elderly, and therefore we were unable to calculate whether such an association can be made for any specific disease, condition or lifestyle.

3.5.10. Meta-analysis

Nine studies were included in the meta-analysis (113–121) with a total of six food groups analyzed – fish, fruits, milk and dairy products (milk), nuts, peanuts and seafood. One study (60) was only used in the systematic review, and not in the meta-analysis, since the available data did not show which foodstuffs were involved in the reactions developed by the elderly individuals. (Figure 18).



Fish: τ^2=0.163, χ^2=7.218, df=3, p=0.065, I^2=58.440%
Fruits: τ^2=5.812, χ^2=167.138, df=3, p<0.001, I^2=98.205%
Milk: τ^2=1.037, χ^2=70.880, df=4, p<0.001, I^2=94.357%
Nuts: τ^2=2.028, χ^2=202.605, df=4, p<0.001, I^2=98.026%
Peanuts: τ^2=0.207, χ^2=17.811, df=4, p=0.001, I^2=77.542%
Shellfish: τ^2=0.000, χ^2=2.125, df=3, p=0.547, I^2=0.000%
Overall: τ^2=1.032, χ^2=825.992, df=25, p<0.001, I^2=96.973%

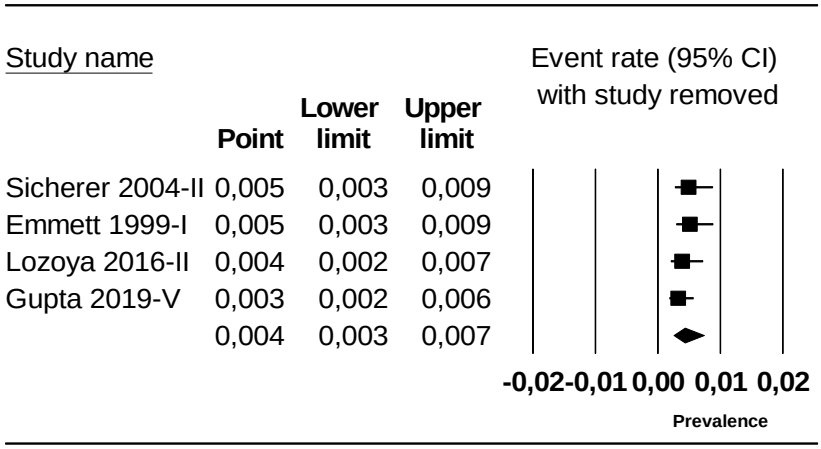
Figure 18. Forest plot for the pooled prevalence of self-reported food allergy for each food type

A random-effects meta-analysis was performed for the self-reported food allergy to estimate the prevalence of each specific food group, as previously mentioned (Table 32). Also, a pooled prevalence of the self-reported food allergy was estimated using the inverse variance method. Confidence intervals (CI) for each prevalence were taken at 95%. Statistical heterogeneity between studies was assessed by Cochran's Q test and by I^2 index ($p<0.05$ considered statistically significant).

Table 32. Self-reported food allergy prevalence. Random-effects meta-analysis

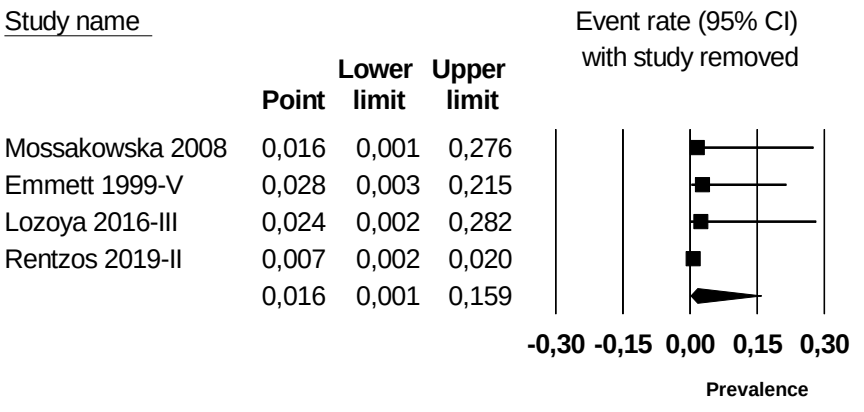
Fish	
Number of studies	4
Number of participants	15825
Prevalence (%) (95% CI)	0.4 (0.3 – 0.7)
Fruits	
Number of studies	4
Number of participants	3743
Prevalence (%) (95% CI)	1.6 (0.1 – 15.9)
Milk	
Number of studies	5
Number of participants	14381
Prevalence (%) (95% CI)	1.8 (0.7 – 4.7)
Nuts	
Number of studies	5
Number of participants	18842
Prevalence (%) (95% CI)	1.0 (0.3 – 3.5)
Peanuts	
Number of studies	5
Number of participants	18842
Prevalence (%) (95% CI)	0.7 (0.4 – 1.1)
Seafood	
Number of studies	4
Number of participants	13277
Prevalence (%) (95% CI)	2.6 (2.3 – 2.9)
Overall	
Number of studies	9
Number of participants	21349
Prevalence (%) (95% CI)	2.3 (2.1 – 2.5)

There was great heterogeneity between studies for each food group, with the lowest values occurring for shellfish (I^2=0.000%) and the highest for fruits (I^2=98.205%). For a better understanding of this clear heterogeneity, a sensitivity analysis was performed for each specific food group, which consisted of removing one study at a time in order to evaluate the sources of heterogeneity (Figures 19-23). Statistical analysis was performed using Comprehensive Meta-Analysis, version 3.3.



Fish (without Gupta 2019 study (117)): τ^2=0.038, χ^2=2.331, df=2, p=0.312, I^2=14.218%

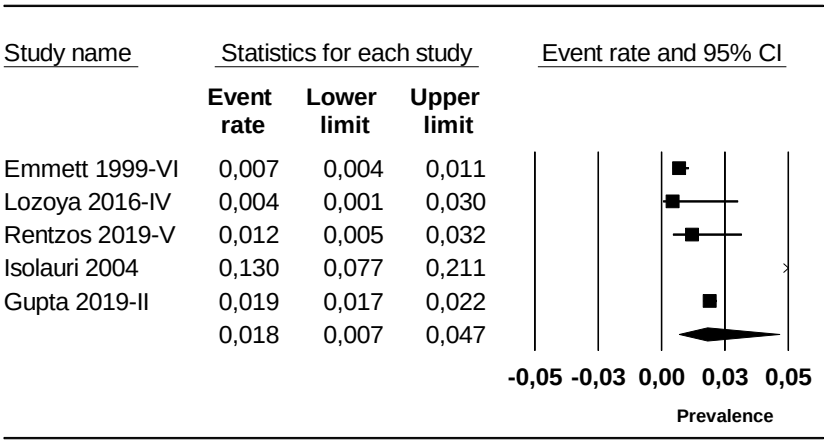
Figure 19. Sensitivity analysis (one study removed) of the random effects' meta-analysis for prevalence of self-reported fish allergy.



Fruits (without Rentzos 2019 study (114)): τ^2=0.580, χ^2=6.909, df=2, p=0.032, I^2=71.052%

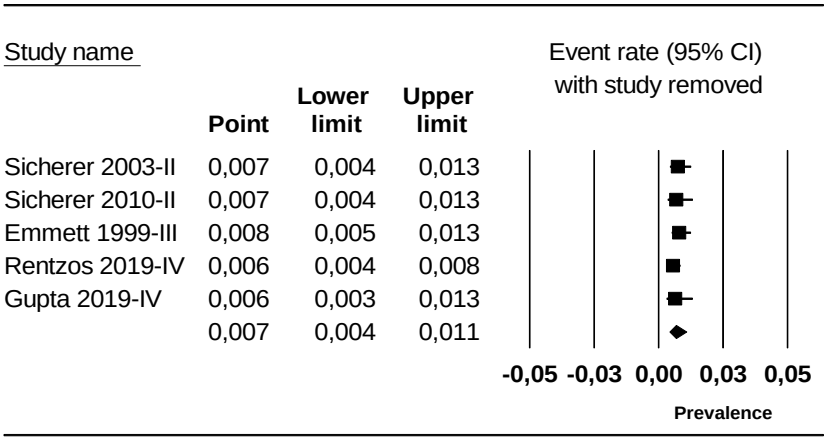
Fruits (without Rentzos 2019 and Mossakowska 2008 studies (114,118)): τ^2=0.000, χ^2=0.002, df=1, p=0.967, I^2=0.000%

Figure 20. Sensitivity analysis (one study removed) of the random effects' meta-analysis for prevalence of self-reported fruit allergy



Milk (without Isolauri 2004 study (113)): τ^2=0.404, χ^2=21.235, df=3, p<0.001, I^2=85.876%
Milk (without Isolauri 2004 and Gupta 2019 studies (113,117)): τ^2=0.000, χ^2=1.322, df=2, p=0.516, I^2=0.000%

Figure 21: Sensitivity analysis (one study removed) of the random effects' meta-analysis for prevalence of self-reported milk allergy.



Peanuts (without Rentzos 2019 study (117)): τ^2=0.117, χ^2=9.638, df=3, p=0.022, I^2=68.873%
Peanuts (without Rentzos 2019 and Gupta 2019 studies (114,117)): τ^2=0.075, χ^2=3.593, df=2, p=0.116, I^2=44.342%

Figure 22: Sensitivity analysis (one study removed) of the random effects' meta-analysis for prevalence of self-reported peanut allergy.

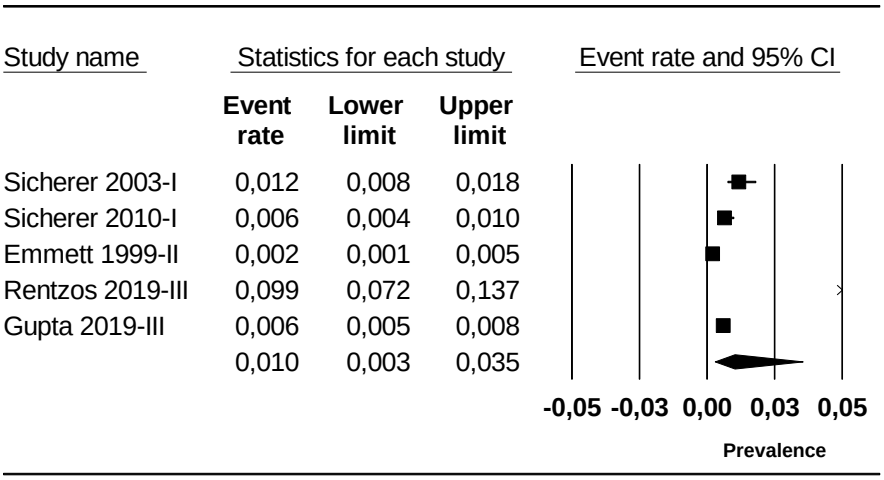


Figure 23: Sensitivity analysis (one study removed) of the random effects' meta-analysis for prevalence of self-reported nut allergy.

After performing sensitivity analysis, we identified several sources of heterogeneity in the data provided by the articles included in the meta-analysis, resulting in an evident dispersion of the results in each foodstuff group. Thus, we identified an author in the fish group (117), two authors in each of the other groups: fruits (114,118), milk (113,117) and peanuts (114,117), as well as all authors in the nut group (114,116,117,120,121).

4. Discussion

4.1. Overall considerations

In the present study, for the first time, we determined and characterised adverse food reactions and food allergy in a population of Portuguese adults and adolescents. For this purpose, we developed a questionnaire as a screening tool, and after its application and subsequent, thorough, study of participating volunteers in a hospital, we were able to determine the prevalence values of adverse food reactions and food allergy in a stepwise manner, based on self-reported history, clinical, laboratory and food challenges.
On the other hand, we also conducted a systematic review on food allergy in elderly individuals, which provided us with better understanding of this pathology in an age group that is under studied. Discussion and contextualisation of our findings will be described next.

4.2. Validation of a questionnaire

We developed and analysed in terms of face, content and construct (know-group) validity and reliability (temporal stability), for the first time in the Portuguese language, a screening questionnaire of adverse food reactions in the general adult population. This questionnaire was rapid and easily applicable, and showed excellent known-group validity, as well as a high degree of temporal stability. On the other hand, there was no variability in results when gender, age and extra-hospital referral source of the volunteers were taken into account. In addition, *Spearman's Rho* correlation coefficient did not show significant differences across Health Care Centres where control, healthy volunteers were recruited.

Although, after the pilot study, we only analysed 126 volunteers (60 randomly selected healthy controls and 66 patients with confirmed food allergies), this number is well within what is accepted as an appropriate sample size for this type of studies. In fact, our ratio of subjects / items (N/p) was 4.5, which is above the minimum requirement of a ratio of 3 (74) and, furthermore, the minimum number of volunteers (n=126) was also above the recommended minimum of 50 (74).

For the assessment of the questionnaire, we studied reproducibility (test-retest stability) of the questionnaire, which was very high in global terms, as expressed in Spearman's Rho

values of 0.80. Furthermore, reproducibility of specific items showed Cohen's Kappa values greater than 0.80 for most items, which is very good given the number of analysed items (73,122). However, again items 12: "time elapsed since the previous episode", 11:"existence previous episodes of food allergy", item 15: "personal history of atopy" and 17: "Would you want to be followed up at specialty clinic?" significantly varied with time, between test and retest. This may have been due to memory bias, as reported by other studies (123), or may have been due to the fact that volunteers might not be aware of the co-existence of other allergic diseases in them or did not report them either during test or re-test phase. In addition, in the case of item 12, discrepancy may arise from the fact that adverse food reactions may develop between test and retest, as a result of accidental exposure (108,124), as actually happened in a minor proportion of the patients, or inversely by development of tolerance (109). In addition, volunteers with food allergies may develop novel reactions to new foodstuffs not mentioned in the first test, as may happen with patients sensitised to various food families (fruits, fish, seafood, egg, milk, etc) (124,125) thereby potentially affecting items 11 and 12, but apparently without a clear relationship with item 15 ("Do you have any other allergic disease?") and 17 ("Would you want to be followed up at specialty clinic?").

Low temporal stability was found for items 15 and 17, ("Do you have any other allergic disease?" and "Would you want to be followed up at specialty clinic?"), with a value for Cohen´s Kappa of 0.441 and 0.296 respectively (Table 9). This may have been due to the fact that a proportion of patients either became aware that they had an allergic disease or had a confirmed diagnosis of allergic disease between test and retest, as was observed in some cases. On the other hand, since patients were already being followed up at a clinic and the remainders of the volunteers were healthy, this may have been associated with confusion regarding the need to be re-evaluated. Finally, the low temporal stability may also have been due to a memory bias as previously referred, since it was not possible to analyse this item separately from the variability between groups (healthy controls versus patients with food allergies) using Spearman's coefficient, given the relatively limited size of the sample. In spite of these aforementioned factors potentially affecting the "8 crucial questions" (items 5,9,11-15,17), six of these questions maintained an optimal degree of temporal stability which afforded the whole of the test a high level of reproducibility.

In our study, although most patients were retested within two weeks of the initial test, there was high amplitude of time intervals, with a few of the patients being retested after 30 weeks. We acknowledge that this may be a limitation of our study since current guidelines for the performance of this type of studies state that the ideal interval should be between 4

weeks and 6 months (ideally between 15 and 45 days) (126–128). Nevertheless, our study followed COSMIN guidelines (129), and allowed the study of reliability (internal consistency and some aspects of reliability).

One important feature of our screening questionnaire is the fact that it is short and quick to apply. This is highly relevant to its application in clinical settings as well as in studies involving large samples, since it has been shown that volunteers' attention time span decreases as the length of a questionnaire increases (130). In addition, our questionnaire adequately discriminated patients with confirmed food allergies from those without food allergies. It also discriminated between patients with IgE-mediated food allergies (n=22) from those with non-IgE-mediated food allergies, on the basis of item 8. However, the latter group only included two patients and this is a limitation of our study.

Our study had other limitations. Firstly, it is a pilot study that needs a larger sample to improve its performance and applicability. Secondly, due to the type of questions being asked, and the format of replies, it was not possible to carry out internal stability procedures. Finally, it needs to be further studied, with a higher sample, in terms of its limits for discriminating between classical IgE-mediated and non-IgE-mediated food allergies.

In spite of the limitations, our study also has new and consistent results. Firstly, our results do suggest that this screening questionnaire is essentially useful for screening of food allergies in cross-sectional studies but may need to be optimized for the follow-up of patients over time. Furthermore, this questionnaire is the first one developed and validated in the Portuguese language for adults with food allergies and we believe it may be applied in all Portuguese speaking countries worldwide (250 million people). In addition, our questionnaire is simple and quickly applicable and is also fully based upon accepted criteria for a sensitive collection of the clinical history of food allergies (13,110). We also believe that it is easily adaptable to other languages, particularly because not many clinical screening questionnaires are available for the study of adverse food reactions as an initial approach to the investigation of food allergy in adults.

4.3. Prevalence of probable food allergy in adults and adolescents

We have shown that the prevalence of probable food allergies in our two populations is low, with cutaneous symptoms being the most frequently ones involved. Otherwise, we found an interesting difference in foodstuffs involved in both populations. Whereas in adolescents, fresh fruit, shellfish and nuts were the most frequently involved foods, in adults, shellfish, fish, peanut and nuts featured more prominently (Table 16).

The initial, written questionnaire, showed that the values of self-reported food allergy (11.01% in adolescents and 6% in adults, phone-called applied) were within values reported in other population-based studies - 3-40% in adolescents (46,47,48,49,51,55,81,109,131,132,133) and 3-19% in adults (46,47,49,53,55,58,60,109). Similarly, the values obtained in our study for the prevalence of probable food allergy in adolescents (1.41%) and adults (1%) were similar to those reported in the US and North America (2,5% in the first case and 1-10% in the second one)(4,85), and in Europe (0.5%-3.5% in adolescents and 0.3-5.6 in adults) (47,51,53,57,109,133), although the latter values were obtained after performance of single or double-blind oral challenge tests (47,48,50,53,109,133,134).

This discrepancy in prevalence results between self-reported and medically confirmed data (using *in vitro* and *in vivo* tests and/or oral challenge) has been described. In fact, previous studies have shown that self-reports tend to overestimate food allergies (46-48,50,51,53,55,57,60,109,133,135). Curiously, in a study carried out in Canadian adults, no significant differences were observed between self-reported symptoms with a set of 5 foods (80) and the subsequent confirmation of food allergies (81), but the methodology used was certainly different.

In any case, most studies have shown that self-reported symptoms tend to overestimate the prevalence of food allergies, and suggest that this may be partly explained by a bias in self perception of symptoms and wrongly ascribing them to food ingestion. Cultural factors, health literacy or accessibility to a medical diagnosis may be involved (51,133), since, in our study, only 16% of adolescents and adults that reported food-associated symptoms had ever seen an Allergist for that reason, in line with values observed by Lyons et al. (53) in other European countries. Nevertheless, prevalence values across different studies are hardly comparable, given the heterogeneity of study designs and the types of population involved. In any case, the overestimation of self-reported food-related adverse food reactions may be

worrying since it is frequently associated with inappropriate restriction diets with subsequent nutritional deficits (5).

The implicated foods, both in self-reported allergies as well as in test-confirmed, probable food allergies, in our study are included in the so-called "big eight allergens" (60) – milk, egg, peanut, tree nuts, wheat, soy, fish and shellfish (83) and are similar to those found in other population-based studies using similar methodology in Europe (9,47,48–50,53,55,57,58,61,136–138), Asia (135,139), the US (13,42,60,80,83,85,132) and in other geographically similar areas (81,133).

With respect to our adult population, most frequently implicated foods (seafood, fresh fruits and fish) were similar to those found in previous studies (49,53,55), but interestingly, in our adolescent population, we observed that fresh fruits were the most frequently implicated foods places our study in line with those performed in western and Mediterranean Europe (49,50,55), but not with those from northern Europe, North America (9,13,47,48,61,80,81,85,140) or, surprisingly, the eastern Mediterranean Europe (133), probably due to differences in study methodology.
In fact, these differences may be partly due to cultural differences in food habits(135) or concurrent pollen sensitisation, although we cannot exclude the posibility that the comparatively smaller size of our sample may have influenced our results.
It is indeed possible that different dietary habits between both age groups, as has been reported in other Mediterranean countries (141–143), may have influenced our findings regarding differences in the most frequently involved foods in triggering symptoms.
Nevertheless, our population values of prevalence of food adverse reactions by diagnostic criteria, foodstuffs and ages, are well within the previously observed ranges reported in systematic reviews and meta-analysed (46,47).

In addition, it is also fundamental to stress that, in contrast with our study, OAS is often not regarded as a symptom of food allergy, since it is frequently associated with pollen-induced respiratory symptoms in the same patient, as happened in our study, and is therefore regarded as a "secondary allergy" by various research groups (61,62,111,134). Nevertheless, recent investigations do not rule out the association between this manifestation and the onset of future episodes of food anaphylaxis (44). Thus, even if only for this reason, the identification of OAS in patients is readily justified.

It is also important to highlight the discrepancy between the panels of implicated foods when we compared self-reported results with those obtained upon completion of the allergy study. Whereas the self-reported panel mainly included fresh fruits, milk and shellfish in

adolescents, and shellfish, fresh fruits and fish in adults, the confirmed (post-tests) panel essentially identified fresh fruit, shellfish and nuts in the first case and shellfish, fish, peanut and nuts in adults (Tables 11, 12 and 16). Other studies also identified similar situations in adolescents in Europe (49,51,55,61,134) and in adults worldwide (49,55,61,111). This fact has additionally been confirmed by various meta-analyses (46,47,62), having such discrepancies been partly ascribed to differences in the concept of adverse food reactions between patients and the immunologically-based "allergy" diagnosed by allergist doctors. This highlights the need for an adequate diagnostic approach to food-associated symptoms, so that subsequent detrimental situations may be averted or better controlled (144). These observations stress the need for an adequate diagnostic approach in order to avoid inadequate diets (5,6), difficulties in the reintroduction of the "culprit" food in case allergy was not confirmed (145), stress and anxiety because of eventual accidental ingestion of suspected foods (6,7,146–150), or even bullying at school (151).

Cutaneous symptoms were the most prevalent ones in the two age group populations of our study, both in self-report and in those volunteers who completed the full allergy workup. as has been previously described by most other groups (13,19,42,47,49,55,58,60,61,80,83,85,111,134,138,152), although that was not the case in a questionnaire-based study in adults in the UK (54) and in other 8 european countries (53). However, in the latter studies, only a limited repertoire of foods was analysed, which may explain the observed discrepancies.

An interesting aspect of our work involved data obtained from self-reported symptoms. In this context, we found several positive associations between the ingestion of certain foods and the development of certain symptoms, with differences being observed between adolescents and adults. In the former, we found that fresh fruits, milk and egg were associated with cutaneous manifestations, shellfish was related to abdominal symptoms, fresh fruits were reported in connection with OAS, and nuts and peanuts were associated with anaphylaxis, associations which, with the exception of the latter two, had not been previously reported (13,44,49). On the other hand, in our adult population, shellfish, fruits and fish were associated with cutaneous manifestations and OAS, and shellfish and fruit were most frequently associated with respiratory and abdominal symptoms. Fish and shellfish were the most frequent triggers of single and more severe episodes (mostly involving respiratory symptoms). Although several studies carried out in different European countries and in the US showed that the most frequent symptoms related to food ingestion were cutaneous (13,42,47,49,55,58,60,61,80,85,111,134,138,153) and gastrointestinal (53), such studies do not discriminate what type of food causes these

symptoms. Thus, our work is the only one where the existence of an association between the developed symptoms related to the ingestion of certain foodstuffs is clearly reported. However, we must consider these data with caution, because it is known that foods may be a trigger for underlying diseases, especially atopic dermatitis, but also rhinoconjunctivitis and asthma, in areas of high prevalence of pollinosis (41), as is the case of our region. This situation could explain the high number of cases that developed cutaneous symptoms and OAS in our work, regardless of the causal foodstuffs that were mainly found as the cause of adverse food reactions in other studies (13,42,47–50,53,55,60,61,80,81,83–85,111,132,133,135–139). Although Sicherer et al. found, in a large sample of about 15,000 participants in a US telephone interview-based study, that gastrointestinal and cutaneous symptoms were the most prevalent self-reported symptoms upon ingestion of seafood and fish (153), such information may have been biased since it was only based on self-diagnosis. Furthermore, self-report makes it difficult ot differentiate between toxin infection and "food allergy", which could explain the relationship between ingestion of shellfish and fish and gastrointestinal symptoms (152). It is also accepted that tree nuts and peanut are the most common causes of food-induced anaphylaxis, due to the higher prevalence of nut allergies, and seafood (fish and shellfish included) is increasely seen as a frequent trigger in adults and adolescents (44,49). In any case, having shown an association between specific foodstuffs and types of symptoms, makes our work much more interesting and novel and warrants further studies, in other populations, to confirm our findings.

Bearing in mind the timeframe for the appearance of symptoms, we found two predominant response patterns, previously identified by Osterballe (61): an immediate type of reaction, arising in less than 30 minutes post-ingestion, mainly associated with fresh fruits and milk in teenagers, and shellfish, fresh fruits and fish in adults; and a more delayed, between 2 and 24 hours post-ingestion, mainly associated with fresh fruits and milk in adolescents and shellfish in adults. The reason underlying this difference is not clear, although it may have been due to discrepant IgE-binding capacity of B cell epitopes on different food allergens (154).

In volunteers with confirmed probable food allergy, we also found an inverse relationship between symptom latency time and severity, and a positive association between latency time and probable mediation by IgE. It should be stressed that the six non-IgE mediated cases (three in each population type), had a latency time between 2 and 24 hours upon ingestion, and one of them, with a latency time greater than 24 hours. Most of the IgE-mediated cases had developed within 30 minutes upon ingestion. In addition, anaphylaxis

cases were all associated with the ingestion of nuts and peanut in adolescents and with seafood in adults. This is in line with tree nuts, peanut and seafood being the most common causes of food-induced anaphylaxis in adults and adolescents (44). On the other hand, the inverse relationship observed between the length of time interval between ingestion of food and the onset and severity of symptoms is thought to be important in clinical practice. Severe reactions tend to occur rapidly after ingestion of the culprit foodstuff (45), although the reason for this phenomenon is not fully clear. Although the role of serum levels of food-specific IgE in severity of reactions is not clear (45), individuals with more severe reactions tend to have an IgE-mediated mechanism (44). In any case, it is widely accepted that acute reactions appear to be due to an IgE-mediated mechanism, while in delayed ones, the causative mechanisms may be different one, and are not yet well defined (152).

We also analysed eventual risk factors associated with the development of food allergies. Multivariate analysis showed that a personal or a family history of atopy were significantly associated with a higher risk of having food allergies, as has been described in previous studies and metanalyses focusing on adults (2,13,155), adolescents and children (2,13,47,48,152,155,156). However, these results should be tanken cautiously since this was a cross-sectional study, and not a prospective, cohort one.

One of the limitations of the present study was the fact that we could not perform double blind, placebo-controlled food challenges, a test which is regarded as the “gold standard” for the final diagnosis of food allergy. In spite of this, the current report is the first population-based study in a Portuguese population, including adolescents and adults. Furthermore, it yields information on probable food allergy in this population, based upon not only a positive clinical history/questionnaire, but also the application of a new, validated questionnaire, on diagnostic tests including SPT, food-specific IgE levels and open oral food challenges, which makes it a very thorough study. In fact, a high proportion of population-based studies on food allergies, performed in other countries, only applied a questionnaire (49,60,61,80,81,134,153), and few others only performed cutaneous tests or determination of food-specific serum IgE in suspect cases of food allergy (50,84,131,135). We only found a multicentre population-based study conducted in eight European countries, where a methodology similar to ours (validated common questionnaire applied, referring cases with adverse food reactions to the hospital centers for subsequent allergenic study, including DBPCFC) was applied (53). This study showed similar self-report and probable food allergy prevalence values as ours, althought it differs in the type of symptoms and implied foodstuffs involved. This discrepancy may be due to such study having used a questionnaire

with fewer questions directly related to food adverse reactions (only 7 out 9 questions). It may also be due to the fact that it only assessed "nine priority foods" in the subsequent phases of the allergy study. Finally, it also had a higher drop-out rate of adult volunteers when compared with our study (57% vs 25%, respectively). Thus, we believe we should consider a higher accuracy of our study, although we did not performance DBPCFC.

Another possible limitation of our study concerns the fact that 25.1% of the adolescents who reported adverse food reactions did not complete the study, which is partly explained by the clear national increase in the "Healthcare service usage" fees, during the implementation of the study (157,158). In addition, an increase in unstable employment during the period of the study limited absences from work by parents accompanying the adolescents in hospital visits (159). Nevertheless, this situation did not occur in the adult population sample, where we were able to obtain information from most (75%) of those individuals who had reported a food allergy, indicating that our study was associated with a relatively low drop out rate in this age group, which might, otherwise, be a limiting factor, as previously referred. A relatively high drop-out rate and low participation is indeed a limiting factor in population-based epidemiological studies, and has been reported in multiple studies, with the reply rate being inversely associated with the magnitude of the study. The reply rate has varied, in various studies, between 40-50% (48,55,61,134) and 61-86% (49,51,131) in children and teenagers, and between 31-67% (55,61,153) in adults when studies are only based upon questionnaires and it is lower (55,134) when a more thorough assessment (skin tests, blood tests, food challenges) is involved. The only exception was a Turkish study in children, which is the only exception we found, and in which the reply rate was very similar both to the questionnaire and in the subsequent investigation phase (89.3% and 80.5%, respectively) (133). Nevertheless, our reply rate was quite acceptable for this type of studies (57.3% in adolescents and 67% in adults). In spite of the relative limitations in our study, the size of our sample and the features of our work reached the predefined values in terms of statistical power, representativity and proportionality for analysis. Relatively low reply rates may also lead to a selection bias, with mainly people who are more concerned about allergy problems being more prone to returning the questionnaire. However, if this were the case, we would expect to find high self-report prevalence rates, in comparison with other studies, and this was not the case.

4.4. Prevalence of probable food allergy in the elderly

To the best of our knowledge, this is the first systematic review specifically focusing on food allergy in elderly individuals (over 60 years old). Overall, very few studies addressing this issue were detected and, in most cases, results were embedded in general results for adults, which forced us to contact the authors, in order to retrieve data from the elderly subgroup.

A wide spectrum of "food allergy" definitions was found throughout many of the published studies, with most simply relying on self-report and only a few, using double-blind placebo-controlled food-challenge (DBPCFC), the "golden standard" for the diagnosis of food allergy.

The use of self-report is, by itself, a confounding factor, because it depends on an information bias from the surveyed person as well and mainly as on the type and methodology used in the applied questionnaire, leading to an under- or, more frequently, an overestimation of food allergy prevalence. On the other hand, in those cases in which complementary data - *in vivo* (SPT) or *in vitro* (food-specific IgE levels) - were used in addition to self-report, data suggesting a "probable" and not a "definitive" food allergy were seldomly provided, because oral food challenges were not carried out in several cases. A study by Rentzos et al (114) only measured positive food-specific IgE levels to estimate the prevalence of food allergy in a general population, but not reporting whether the study volunteers had any symptoms or a medical diagnosis of food allergy. Nevertheless, this method cannot assess food allergy but merely food sensitization (13). In addition, one study, where the elderly population was studied in detail, provided a high prevalence value of food allergy. However, these values were based on positive results of SPT and sIgE of aeroallergens and food allergens together (160). In this study, the authors did not differentiate between both types of allergen sources, thereby resulting in very high, but inaccurate food allergy prevalence values, and, therefore, we did not include this study in the systematic review or meta-analysis. On the other hand, some authors also considered the existence of volunteers with concurrent sensitization to various foods (114,115,117) without clarifying how many sensitizations corresponded to each volunteer, which may have led to an overestimation of prevalence values. In addition, Vierk et al (60), considered that not all cases in which gastrointestinal symptoms appeared were allergic, but only intolerant. In any case, we found an overall strong bias rating in our investigation depending on the methodology used in the different studies.

Overall, we encountered a significant lack of information regarding elderly patients in most studies. For example, five studies (113–117) reporting clinical manifestations and prognostic factors associated with the onset of food allergy in the overall adult population were found, but only one author (115) provided discriminated data about the elderly subjects' results, information that we used for our work. This was a limitation in terms of global assessment of the investigation of these parameters.

In addition, although three previous systematic reviews (4,46,47) carried out a thorough epidemiological study about food allergy, focusing upon differences between children and adults, again these reports failed to analyze results in the elderly subgroup, thereby making it impossible to comparison those results with our own.

In our systematic review, the overall pooled point prevalence of self-reported symptoms found in the elderly was lower than those found in non-elderly adults, but higher than those in children (6.46% Vs 8.25% and 2.50%, respectively). When self-report symptoms were combined with specific food allergy IgE levels these values were lower when compared with the other age groups (6.95% Vs 10.53% and 9%). This differs greatly from the results in a study from Nwaru el al (47), who reported a higher prevalence in the children subgroup in both type of studies, being much higher in those that combined self-report and specific food allergy IgE levels. One explanation for the different results may be the great heterogeneity across studies analysed in our investigation, as well as in the three previously mentioned systematic reviews in adult food allergy (4,46,47), a fact that has been stated by these authors in the discussion of their results in meta-analyses and systematic reviews.

In our work, we studied the heterogeneity of the data contained in the different articles, not only within each article, but also among the different selected articles. Firstly, we noted the existence of differences in the selection of the subject samples, the operational definition of food allergy as previously referred, specific foods that were analysed and the methods of outcome assessment. Even in studies in which the same foods were analysed, or the same method of outcome assessment was used, such as self-report, for instance, not all questionnaires were validated by a group of specialists in the diagnosis of food allergies (118), and therefore not all questionnaires asked the same questions or focused on the same aspects. Additionally, some studies went beyond questionnaires and underwent sequential steps for the confirmation of probable food allergy (113–115) such as the measurement of food-specific IgE levels or SPT, although none used DBPCFC, the gold-standard for definitive diagnosis.

Secondly, during the meta-analysis procedure in self-report studies, we showed that, in addition to the reasons listed above, some articles were in themselves, causes of data spreading due to their heterogeneity within each foodstuff group. This fact made it difficult to compare the different prevalence values.

We must take into consideration that most of the publications reviewed merely relied on self-report, some used self-report toghether with *in vivo* and/or *in vitro* tests (food-specific IgE levels or SPT) and only a few reported challenge tests, more frequently oral food challenge and rarely DBPCFC (the gold standard for food allergy diagnosis). In any case, we found an important agreement between our results and several conclusions from the three previously mentioned reviews (4,46,47).

While in our work we found that food allergy prevalence outlined in studies based only on self-report was lower than that in those combining self-report and *in vivo* or *in vitro* tests (food-specific IgE levels or SPT), this is in disagreement with Nwaru et al (47), who observed a lower prevalence in those studies which used only self-report (5.9%) than those combining self-report with food specific IgE levels (2.7%) or SPT (1.5%). This interesting and unexpected disparity should be interpreted with caution. When we compare all studies where prevalence was only determined by self-report with those that were methodologically more thorough, we can see that the pooled sample size of individuals of the former – 21,678, with mean ranging from 301 to 10,839 (60,116–118,120,121,153) – was much higher than that of the latter – pooled size of 662 elderly individuals, mean of 220 individuals; range from 100 to 332 (113–115) -. Thus, the relative weight of prevalence values of the former studies is higher than that of the latter ones, which may have biased the results.
In addition, calculation of prevalence of food allergy value based upon self-report took into account all ten selected studies, whereas determination of prevalence in reports that also used *in vitro* or *in vivo* tests could only be based on fewer studies, thereby resulting a drastic decrease in sample size.

However, it is very important to state that, in the three studies that performed a thorough allergy workup (113–115), the expected decrease in prevalence values can be seen as diagnostic rigour increases (ie. just self-report; self-report plus SPT/SPPT and/or specific IgE; self-report plus SPT/SPPT and/or specific IgE plus oral food challenge) as was described in adults and children (4,46,47,55,57,60).

We must highlight several strengths in our work, mainly the novelty of the study of food allergy prevalence in the elderly population worldwide, based on a systematic review and subsequent meta-analysis, which, to the best of our knowledge, is the first systematic review of this type on food allergy in this age range.

In addition, several measures and steps were undertaken regarding the comprehensive search strategy, selection of electronic databases, absence of language restrictions and the overall abstract and full-text selection process, in order to ensure that no relevant studies went unseen and also to minimise selection bias. Unlike that of Nwaru et al (47), our systematic review did not have any limitations regarding the geographical origin of the selected articles, nor their language or date of publication. Additionally, while two previous systematic reviews only searched three (46,47) or four (4) electronic databases, we extended our research to a total of twelve electronic databases and added a manual search of any relevant studies within the references of all articles found.

However, our work has some limitations. There was a significant level of difficulty in accessing all relevant data within the final selected studies, either because of the way data were presented in the articles (with or without confidence intervals and p-values, randomised or not), incomplete reports and missing results or because of the ambiguity with which data regarding people over 60 years of age were reported (age range not mentioned or absence of sample size). Most studies focused solely on the general adult population with the inclusion of people over 60 in the total sample of adults. Where this happened, the authors were contacted, but very few replied or were able to provide the necessary data, which kept us from using possibly relevant studies in our systematic review and, with it, reaching more significant conclusions with regard to food allergy in the elderly. When contacted authors did reply, a back and forth chain of communication was kept in order to maximize the shared data.

Furthermore, specific foods studied also varied greatly across studies, thus making it harder to assess their actual predominance in food allergy in the elderly. Some studies (120,121,153) limited their assessed foods to specific food groups (seafood or nuts, for instance) and therefore may have missed subjects with food allergies other than those they were looking for. On the other hand, we did not take into account cultural differences in food habits (135) or food availability inherent to our worldwide study that may have influenced our results.

Finally, due to the low number of studies involving elderly individuals, as well as the difficulty in obtaining results from certain authors and the nature of the selected studies, we were unable to calculate other aspects that we had initially proposed to address: time trends in prevalence of food allergy and related food allergens; predominant foods associated with food allergy; most frequent food-induced symptoms; geographical variations; food-specific induction of symptoms or risk factors for food allergy; or risk and prognostic factors associated with food allergy in the elderly. Most studies either did not have the necessary data in their scope of results or, if present, the data did not allow their analysis with regards to the elderly, even after contacting the authors.

5. Conclusions

5.1. Validation of the questionnaire

We developed, for the first time in the Portuguese language, a screening questionnaire for the study of adverse food reactions in adults, which showed high reproducibility and good potential to be a useful screening test in potentially different settings.

5.2. Prevalence of probable food allergy in adults and adolescents

The prevalence of probable food allergy in our sample of Portuguese population was low (1.41% in adolescents e about 1% in adults). Fresh fruits, shellfish, nuts and peanut were the main implicated foods in adolescents, and shellfish and fish in adults.

IgE-mediated probable food allergy occurred in 1.23% of the cases in adolescents and 0.71% in adults. The foods mainly involved were fresh fruits, shellfish and nuts in adolescents, and shellfish, peanut and nuts in adults.
Our study confirmed that the foodstuffs spectrum involved are similar to those referred in other studies, carried out with similar methodology, in other countries of the Mediterranean area, with similar culture and dietary pattern.

The most frequently reported symptoms were cutaneous. There was a clear discrepancy between self-reported and probable food allergy, both in terms of prevalence and of the implicated foods. This study is the first step towards a thorough study of food allergies and their repercussions in our country and may contribute towards a global characterization of food allergies in theses ages groups in other western countries.

5.3. Prevalence of probable food allergy in elderly individuals

In terms of prevalence of food allergy in the elderly, that of self-report (6.46%) was slightly lower than that of SR + food-specific IgE levels (6.95% and SR + SPT (1.30%). The overall prevalence of food allergy in the elderly was lower than that in non-elderly adults but higher than in children for self-report outcome assessment, and lower when compared with the other age groups when self-report symptoms were combined with *in vitro* or *in vivo* outcome assesment, when data were available.

Regarding the prevalence of allergy to specific foods in the elderly, in comparison with non-elderly adults, the former had a higher prevalence of allergy to milk (both SR and IgE), fish (only in SR + SPT and SR + OFC) and other foods (SR + IgE). These prevalence values were lower to fruits (both SR and SR + SPT), peanuts (both SR and SR + IgE), other nuts (SR + IgE and SR + SPT), shellfish (both SR and SPT), fish (only in SR) and other foods (only in SR + SPT). When compared with children, the elderly had similar prevalence values of allergy to peanuts (SR) and shellfish (SR), higher to other nuts (SR) and fish (SR) and lower to milk (both SR and SR + IgE).

Finally, we must point out that there is a significant number of populational studies on prevalence of food allergy, worldwide. However, most of them are not focused on individuals over 60 years of age, which results in an evident lack of information about elderly individuals, who are an increasingly abundant segment of the population. This may condition the knowledge of the clinical characteristics, diagnosis, implicated foods, and progression of food allergy in these individuals, as well as the development of possible preventative measures specifically focused on the elderly population.

6. Future plans

Our prevalence study aims to be the basis for a future application of the methodology in our country, by implementing the participation of several reference centres at a national level. This will increase human and economic resources, thereby overcoming the shortcomings that we identified in our work. Furthermore, the questionnaire we used may also be applied in other Portuguese speaking countries, even if with some cultural adaptations. Collaborative studies are currently underway between Portugal and Brazil in this context.

However, during the development of the present study, new methods of laboratory-based diagnosis have been incorporated into the study of food allergies. These essentially include the determination of IgE levels against food allergen molecular components (Component-Resolve Diagnosis) and basophil activation tests (BAT), resources we did not have access to, due to lack of funding and which, in a future, more comprehensive study, may also be incorporated into the study design, particularly CRD.

Similarly, the design of a multi-centre study, with the inclusion of more experienced and prestigious centres, will facilitate the performance of double-blind placebo-controlled food-challenge, thereby overcoming one of the weaknesses of our study. Such an approach will also potentially provide values on food allergy that are closer to reality. In addition, we highly recommend that future studies on food allergies use the double-blind placebo-controlled food-challenge as their definition of food allergy or, if not feasible, food-specific IgE levels and skin prick tests, instead of simply using a self-report.

During the systematic review and subsequent meta-analysis, we only found a small number of studies dedicated to the investigation of food allergy in the elderly, in contrast to those dedicated to the general adult and paediatric populations. This situation makes it difficult to have a clear idea of the special characteristics of food allergies in elderly individuals, an age group which is becoming increasingly larger not only in developed but also developing countries. This problem, far from being an important limitation, opens up a wide range of possibilities for research in this area. In fact, an international, multi-centre study on the prevalence of food allergy in the elderly is currently being designed, with the active participation of our team.

With these approaches we will be able to determine with greater accuracy the real prevalence of food allergy in the Portuguese population in its various age groups (adolescents, adults and the elderly), and compare it, as well as the clinical and sensitisation

features of affected individuals, with the rest of the countries in our surroundings, especially those belonging to the Mediterranean region, given its similar climatic, food and cultural characteristics. Furthermore, the proposed studies may allow us to be in a better position to understand the current impact of food allergy in various populations, and propose a diagnostic, therapeutic and preventive strategy, if possible, in this field.

7. References

1. Sampson HA. Food allergy. Part 1: Immunopathogenesis and clinical disorders. J Allergy Clin Immunol. 1999;103(5):717–28.
2. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol. 2011 Mar;127(3):594–602.
3. Open database: Search (“food hypersensitivity”[MeSH Terms] OR (“food”[All Fields] AND “hypersensitivity”[All Fields]) OR “food hypersensitivity”[All Fields] OR (“food”[All Fields] AND “allergy”[All Fields]) OR “food allergy”[All Fields]) AND (“2000/01/25”[PDat] : “2020/01/25”[PDat]) [internet]. US National Library of Medicine. National Institues of Health. [accesed 2020 Jan 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed.
4. Chafen JJS, Newberry S, Riedl M, Bravata D, Maglione M, Suttorp M, et al. Diagnosing and Managing Common Food Allergies. A Systematic Review. JAMA. 2015;303(18):1848–56.
5. 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(2):159–67.
6. Lau GY, Patel N, Umasunthar T, Gore C, Warner JO, Hanna H, et al. Anxiety and stress in mothers of food-allergic children. Pediatr Allergy Immunol. 2014;25(3):236–42.
7. Namork E, Fæste CK, Stensby BA, Egaas E, Løvik M. Severe allergic reactions to food in Norway: A ten year survey of cases reported to the Food Allergy Register. Int J Environ Res Public Health. 2011;8(8):3144–55.
8. Sicherer SH, Sampson HA. 9. Food allergy. J Allergy Clin Immunol. 2006;
9. Marklund B, Ahlstedt S, Nordström G. Health-related quality of life among adolescents with allergy-like conditions - With emphasis on food hypersensitivity. Heal Qual Life Outcomes. 2004;2:1–12.
10. Patel DA, Holdford DA, Edwards E, Carroll N V. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. J Allergy Clin Immunol. 2011;128(1):110-115.e5.
11. Flabbee J, Petit N, Jay N, Guénard L, Codreanu F, Mazeyrat R, et al. The economic costs of severe anaphylaxis in France: An inquiry carried out by the Allergy Vigilance Network. Allergy. 2008;63(3):360–5.

12. Calsbeek H, Rijken M, Bekkers MJTM, Dekker J, Van Berge Henegouwen GP. School and leisure activities in adolescents and young adults with chronic digestive disorders: Impact of burden of disease. Int J Behav Med. 2006;13(2):121–30.
13. Boyce JA, Jones SM, Rock L, Sampson HA, Cooper SF, Boyce S, 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(6 SUPPL.):S1–58.
14. Johansson SGO, Hourihane JOB, 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(9):813–24.
15. Sampson HA. Update on food allergy. J Allergy Clin Immunol. 2004;113(5):805–19.
16. Sampson HA. Food allergy: Past, present and future. Allergol Int. 2016;65(4):363–9.
17. May C. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. J Allergy Clin Immunol . 1976;58(4):500–15.
18. Bindslev-Jensen C, Ballmer-Welser 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(7):690–7.
19. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI Food Allergy and Anaphylaxis Guidelines: Diagnosis and management of food allergy. Allergy. 2014;69(8):1008–25.
20. Global initiative for asthma: Asthma management and prevention, 2019. Pract Nurse. 2019;49(5).
21. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73(7):1393–414.
22. Skypala IJ, Venter C, Meyer R, Dejong NW, Fox AT, Groetch M, et al. The development of a standardised diet history tool to support the diagnosis of food allergy. Clin Transl Allergy. 2015 Feb 19;5(1):1–9.
23. Urisu A, Ebisawa M, Ito K, Aihara Y, Ito S, Mayumi M, et al. Japanese guideline for food allergy 2014. Allergol Int. 2014;63(3):399–419.

24. Van Der Valk JPM, Gerth Van Wijk R, Hoorn E, Groenendijk L, Groenendijk IM, De Jong NW. Measurement and interpretation of skin prick test results. Clin Transl Allergy. 2016;6(1):1–6.
25. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clin Exp Allergy. 2000;30(11):1541–6.
26. Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, et al. GA2LEN skin test study I: GALEN harmonization of skin prick testing: Novel sensitization patterns for inhalant allergens in Europe. Allergy. 2009;64(10):1498–506.
27. Flores Kim J, McCleary N, Nwaru BI, Stoddart A, Sheikh A. Diagnostic accuracy, risk assessment, and cost-effectiveness of component-resolved diagnostics for food allergy: A systematic review. Allergy. 2018;73(8):1609–21.
28. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, et al. EAACI Molecular Allergology User's Guide. Pediatr Allergy Immunol. 2016;27:1–250.
29. Borres MP, Maruyama N, Sato S, Ebisawa M. Recent advances in component resolved diagnosis in food allergy. Allergol Int. 2016;65(4):378–87.
30. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291-307.e5.
31. García Figueroa BE, Gamboa PM, Asturias JA, López-Hoyos M, Sanz ML. Guidelines on the clinical usefulness of determination of specific immunoglobulin E to foods. J Investig Allergol Clin Immunol. 2009;19(6):423–32.
32. Santos AF, Douiri A, Bécares N, Wu SY, Stephens A, Radulovic S, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. J Allergy Clin Immunol. 2014 Sep 1;134(3):645–52.
33. Ocmant A, Mulier S, Hanssens L, Goldman M, Casimir G, Mascart F, et al. Basophil activation tests for the diagnosis of food allergy in children. Clin Exp Allergy. 2009 Aug;39(8):1234–45.
34. 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.

35. Hemmings O, Kwok M, McKendry R, Santos AF. Basophil Activation Test: Old and New Applications in Allergy. Curr Allergy Asthma Rep. 2018 Dec 1;18(77):1–12.
36. Elizur A, Appel MY, Nachshon L, Levy MB, Epstein-Rigbi N, Golobov K, et al. NUT Co Reactivity - ACquiring Knowledge for Elimination Recommendations (NUT CRACKER) study. Allergy. 2018 Mar 1;73(3):593–601.
37. Santos AF, Du Toit G, Douiri A, Radulovic S, Stephens A, Turcanu V, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. J Allergy Clin Immunol. 2015 Jan 1;135(1):179–86.
38. Song Y, Wang J, Leung N, Wang LX, Lisann L, Sicherer SH, et al. Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges. Ann Allergy, Asthma Immunol. 2015 Apr 1;114(4):319–26.
39. Chinthrajah RS, Purington N, Andorf S, Rosa JS, Mukai K, Hamilton R, et al. Development of a tool predicting severity of allergic reaction during peanut challenge. Ann Allergy, Asthma Immunol. 2018;121(1):69-76.e2.
40. 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(1):76–86.
41. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41–58.
42. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: Food allergy. J Allergy Clin Immunol. 2012;129(4):906–20.
43. Niggemann B. When is an oral food challenge positive? Allergy. 2010;65(1):2–6.
44. Turner PJ, Baumert JL, Beyer K, Boyle RJ, Chan CH, Clark AT, et al. Can we identify patients at risk of life-threatening allergic reactions to food? Allergy. 2016;71(9):1241–55.
45. Pettersson ME, Koppelman GH, Flokstra-de Blok BMJ, Kollen BJ, Dubois AEJ. Prediction of the severity of allergic reactions to foods. Allergy. 2018;73(7):1532–40.
46. 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(3):638–46.

47. 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(1):62–75.
48. 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(4):884–92.
49. 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(1):133–40.
50. Pénard-Morand C, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Charpin D, et al. Prevalence of food allergy and its relationship to asthma and allergic rhinitis in schoolchildren. Allergy. 2005;60(9):1165–71.
51. Kavaliunas A, Šurkiene G, Dubakiene R, Stukas R, Žagminas K, Šaulyte J, et al. Europrevall survey on prevalence and pattern of self-reported adverse reactions to food and food allergies among primary schoolchildren in Vilnius, Lithuania. Med. 2012;48(5):265–71.
52. 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(4):505–10.
53. Lyons SA, Burney PGJ, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L, Clausen M, et al. Food Allergy in Adults: Substantial Variation in Prevalence and Causative Foods Across Europe. J Allergy Clin Immunol Pr. 2019;7(6):1920-1928.e11.
54. Young E, Stoneham MD, Petruckevitch A, Barton J, Rona R. A population study of food intolerance. Lancet. 1994;343(8906):1127–30.
55. 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(3):338–45.
56. 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(7):1023–9.
57. Osterballe M, Mortz CG, Hansen TK, Andersen KE, Bindslev-Jensen C. The prevalence of food hypersensitivity in young adults. Pediatr Allergy Immunol. 2009;20(7):686–92.
58. Falcão H, Lunet N, Lopes C, Barros H. Food hypersensitivity in Portuguese adults. Eur J Clin Nutr. 2004;58(12):1621–5.

59. Silva, P; Vieira, C; Santos N. Alergia alimentar na população do ensino público pré-escolar e 1.º ciclo do concelho de Portimão. In: Rev Port Imunoalergologia. 2016. p. 32.
60. Vierk KA, Koehler KM, Fein SB, Street DA. Prevalence of self-reported food allergy in American adults and use of food labels. J Allergy Clin Immunol. 2007;119(6):1504–10.
61. Osterballe M, Hansen TK, Mortz CG, Høst A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. Pediatr Allergy Immunol. 2005;16(7):567–73.
62. 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(5):1210–8.
63. United Nations, Department of Economic and Social Affairs PD (2017). World Population Prospects: The 2017 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP/248. 2017.
64. Jensen-Jarolim E, Jensen SAF. Food allergies in the elderly: Collecting the evidence. Ann Allergy, Asthma Immunol. 2016 Nov 1;117(5):472–5.
65. Bento ML, Armando F, Cesar-Ramos3 JM. Epidemiology of Food Allergy in Portugal. Pediatr Pulmonology, Suppl. 2001;23:38–40.
66. Jorge A, Soares E, Sarinho E, Lorente F, Gama J, Taborda-Barata L. Prevalence and clinical features of adverse food reactions in Portuguese children. Allergy, Asthma Clin Immunol. 2017;13(40):1–10.
67. Portugal I (Censos 2011). http://censos.ine.pt/xportal/xmain?xpid=CENSOS&xpgid=ine_censos_publicacao_det&contexto=pu&PUBLICACOESpub_boui=156644135&PUBLICACOESmodo=2&selTab=tab1&pcensos=61969554. Accessed 1 January 2019.
68. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. Allergy Eur J Allergy Clin Immunol. 2010;65(8):1042–8.
69. Van Der Velde JL, Flokstra-De Blok BMJ, Vlieg-Boerstra BJ, Oude Elberink JNG, Dunngalvin A, Hourihane JO, et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy. 2010 May;65(5):630–5.

70. 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(5):404–11.
71. Prates S. Colheita da História Clínica. Rev Port Immunoalergol. 2009;17(Suppl I):6–10.
72. Lyra NRS, Motta MEFA, Rocha LAR, Solé D, Peixoto DM, Rizzo JA, et al. Adverse Reactions to Foods and Food Allergy: Development and Reproducibility of a Questionnaire for Clinical Diagnosis. J Allergy. 2013;2013:1–7.
73. Fortin M, Côté J, Filion F. Fundamentos e etapas do processo de investigação. 1st Ed. Fortin M, Côté J, Filion F, editors. Loures: Lusodidacta; 2009.
74. Rouquette A, Falissard B. Sample size requirements for the internal validation of psychiatric scales. Int J Methods Psychiatr Res. 2011 Dec;20(4):235–49.
75. Jorge A, Santos Silva M, Lozoya-Ibánez C, Lorente F, Sarinho E, Afonso RM, et al. Development of a tool for screening adverse food reactions and food allergy in Portuguese children. Allergol Immunopathol (Madr). 2019;47(4):342–9.
76. Davis LL. Instrument Review: Getting the Most From a Panel of Experts. Appl Nurs Res. 1992;5(4):194–7.
77. Polit DF, Beck CT. The content validity index: Are you sure you know what's being reported? Critique and recommendations. Res Nurs Heal. 2006;29(5):489–97.
78. Sangoseni O, Hellman M, Hill C. Development and Validation of a Questionnaire to Assess the Effect of Online Learning on Behaviors, Attitudes, and Clinical Practices of Physical Therapists in the United States Regarding Evidenced-based Clinical Practice. Internet J Allied Heal Sci Pract. 2013;11(2):1–7.
79. Lynn M. Determination and quantification of content validity. Nurs Res. 1986;35(6):382–6.
80. Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. J Allergy Clin Immunol. 2010;125(6):1327–35.
81. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, Pierre YS, et al. Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol. 2012;130(4):986–8.

82. Lozoya-Ibáñez C, Macedo A, Rodrigues A, Silva L, Rodrigues E, Pimenta M, et al. Validation of a questionnaire for the study of food allergies in Portuguese adults. Allergy. 2011;66(Suppl):S395 (Abstract).
83. McClain S, Bowman C, Fernández-Rivas M, Ladics GS, Van Ree R. Allergic sensitization: Food- And protein-related factors. Clin Transl Allergy. 2014;4(1):1–9.
84. Burney PGJ, Potts J, Kummeling I, Mills ENC, Clausen M, Dubakiene R, et al. The prevalence and distribution of food sensitization in European adults. Allergy. 2014;69(3):365–71.
85. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: Results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol. 2010;126(4):798-806.e14.
86. Lieberman JA, Sicherer SH. Diagnosis of food allergy: Epicutaneous skin tests, in vitro tests, and oral food challenge. Curr Allergy Asthma Rep. 2011;11(1):58–64.
87. Fleischer DM, Bock SA, Spears GC, Wilson CG, Miyazawa NK, Gleason MC, et al. Oral food challenges in children with a diagnosis of food allergy. J Pediatr. 2011;158(4):578-583.e1.
88. Taborda-Barata L, Laia-Dias I, Lozoya-Ibanez C, Gama J, Skypala I, Nurmatov U. PROSPERO International prospective register of systematic reviews Prevalence and risk factors for food allergy in elderly individuals: protocol for a systematic review [Internet]. Available from: www.ClinicalTrials.gov;
89. W.H.O. Health Statistics and Information Systems. Proposed working definition of an older person in Africa for the MDS Project. [Internet]. 2002 [cited 2019 Jan 7]. [Internet]. 2002. Available from: https://www.who.int/healthinfo/survey/ageingdefnolder/en/
90. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of “elderly.” Geriatr Gerontol Int. 2006 Sep;6(3):149–58.
91. World Health Organisation. Definition of an older or elderly person. Geneva: Switzerland: WHO, 2010. http://www. who. int/ healthinfo/ survey/ ageingdefnolder/ en/ index. html. 2010.
92. Verrill L, Bruns R, Luccioli S. Prevalence of self-reported food allergy in U.S. adults: 2001, 2006, and 2010. Allergy Asthma Proc. 2015 Nov 1;36(6):458–67.

93. 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(1):1–5.
94. CASP. checklist for case–control studies. Available: https://www. casp- uk. net/ wp- content/ uploads/2018/03/ CASP- Case- Control- Checklist- 2018_ fillable_ form. pdf [Accessed 22nd Dec 2018]. 2018.
95. CASP. checklist for cohort studies. Available: https://www. casp- uk. net/ wp-content/ uploads/2018/03/ CASP- Cohort- Checklist- 2018_ fillable_ form. pdf [Accessed 22nd Dec 2018]. 218AD.
96. CASP. checklist for systematic reviews. Available: https://www. caspuk. net/ wp-content/ uploads/2018/03/ CASP- Systematic- Review- Checklist- 2018_ fillable-form. pdf [Accessed 22nd Dec 2018]. 2018.
97. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–6.
98. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
99. Agresti A, Coull BA. Approximate is better than “Exact” for interval estimation of binomial proportions. Am Stat. 1998;52(2):119–26.
100. Borenstein M, Hedges L V., Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Meth. 2010;1:97–111.
101. Rice K, Higgins JPT, Lumley T. A re-evaluation of fixed effect(s) meta-analysis. J R Stat Soc Ser A Stat Soc. 2018;181(1):205–27.
102. Sterne JAC, Harbord RM. Funnel plots in meta-analysis. Stata J. 2004;4(2):127–41.
103. Begg CB, Mazumdar M. Operating Characteristics of a Rank Correlation Test for Publication Bias. 1994;50(4):1088–101.
104. Egger M, Smith GD, Schneider M, Minder C. Papers Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;(315):629–34.
105. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses Testing for heterogeneity. BMJ. 2003;327:557–60.
106. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med. 2009;(7):1–28.

107. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ. 2015 Jan 2;349:1–25.
108. 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(6):746–50.
109. Osterballe M, Hansen TK, Mortz CG, Høst A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. Pediatr Allergy Immunol. 2005;16(7):567–73.
110. Sampson HA. Food allergy - Accurately identifying clinical reactivity. Allergy Eur J Allergy Clin Immunol Suppl. 2005;60(79):19–24.
111. Osterballe M, Mortz CG, Hansen TK, Andersen KE, Bindslev-Jensen C. The prevalence of food hypersensitivity in young adults. Pediatr Allergy Immunol. 2009;20(7):686–92.
112. 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(5):404–11.
113. Isolauri E, Huurre A, Salminen S, Impivaara O. The allergy epidemic extends beyond the past few decades. Clin Exp Allergy. 2004;34(7):1007–10.
114. Rentzos G, Johanson L, Goksör E, Telemo E, Lundbäck B, Ekerljung L. Prevalence of food hypersensitivity in relation to IgE sensitisation to common food allergens among the general adult population in West Sweden. Clin Transl Allergy. 2019;9(22):1–10.
115. Lozoya-Ibáñez C, Morgado-Nunes S, Rodrigues A, Lobo C, Taborda-Barata L. Prevalence and clinical features of adverse food reactions in Portuguese adults. Allergy, Asthma Clin Immunol. 2016;12(36):1–10.
116. Emmett S, Angus F, Fry J LP. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. Allergy. 1999;54(4):380–5.
117. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and Severity of Food Allergies Among US Adults. JAMA Netw open. 2019;2(1):1–14.
118. Mossakowska M, Pawlinska-Chmara R, Broczek KM. Asthma, allergy, and respiratory symptoms in centenarians living in Poland. J Physiol Farmacol. 2008;59(suppl 6):483–9.

119. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. J Allergy Clin Immunol. 2004;114(1):159–65.
120. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: A 5-year follow-up study. J Allergy Clin Immunol. 2003;112(6):1203–7.
121. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol. 2010;125(6):1322–6.
122. Carmo H, Malheiro-Ferreira M. Metodologia da Investigação. Guia para autoaprendizagem. 2nd Ed. Carmo H, Malheiro-Ferreira M, editors. Lisboa: Universidade Aberta; 2008.
123. 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(5):393–402.
124. Sousa F, Antunes J, Paes M, Chambel M, Prates S, Leiria-Pinto P. Exposições acidentais na alergia alimentar. Rev Port Imunoalergol. 2001;9(2):93–100.
125. 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;57:449–53.
126. Cade J, Thompson R, Burley V, Warm D. Development, validation and utilisation of food-frequency questionnaires – a review. Public Heal Nutr. 2002;5(4):567–87.
127. Cade JE, Burley VJ, Warm DL, Thompson RL, Margetts BM. Food-frequency questionnaires: a review of their design, validation and utilisation. Nutr Res Rev. 2004;17(1):5–22.
128. Slater B, Leite de Lima F. Validade e reprodutibilidade dos métodos de inquérito alimentar. In: Fisberg R, Slater B, Lobo Marchioni D, Araújo Martini L, editors. Inquéritos Alimentares: Métodos e Bases Científicos. 1 st Ed. Tamboré: Editora Manole Ltda; 2005. p. 108–31.
129. Mokkink LB, Terwee CB, Knol DL, Stratford PW, Alonso J, Patrick DL, et al. Protocol of the COSMIN study: COnsensus-based Standards for the selection of health Measurement INstruments. BMC Med Res Methodol. 2006;6(2):1–7.

130. Mccoll E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, et al. Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients Methodology. HTA Heal Technol Assess NHS R&D HTA Program Heal Technol Assess. 2001;5(31):81–92.
131. Marklund B, Ahlstedt S, Nordström G. Health-related quality of life in food hypersensitive schoolchildren and their families: Parents' perceptions. Heal Qual Life Outcomes. 2006;4(48):1–12.
132. McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010. J Allergy Clin Immunol. 2013;132(5).
133. Kaya A, Erkoçoğlu M, Civelek E, Çakir B, Kocabaş CN. Prevalence of confirmed IgE-mediated food allergy among adolescents in Turkey. Pediatr Allergy Immunol. 2013;24(5):456–62.
134. 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(10):1534–41.
135. Mahesh PA, Wong GWK, Ogorodova L, Potts J, Leung TF, Fedorova O, et al. Prevalence of food sensitization and probable food allergy among adults in India: The EuroPrevall INCO study. Allergy. 2016;71(7):1010–9.
136. Kummeling I, Mills ENC, Clausen M, Dubakiene R, Pérez CF, Fernández-Rivas M, et al. The EuroPrevall surveys on the prevalence of food allergies in children and adults: Background and study methodology. Allergy. 2009;64(10):1493–7.
137. Fernández-Rivas M, Barreales L, Mackie AR, Fritsche P, Vázquez-Cortés S, Jedrzejczak-Czechowicz M, et al. The EuroPrevall outpatient clinic study on food allergy: Background and methodology. Allergy. 2015;70(5):576–84.
138. Kalogeromitros D, Makris MP, Chliva C, Sergentanis TN, Church MK, Maurer M, et al. An internet survey on self-reported food allergy in Greece: Clinical aspects and lack of appropriate medical consultation. J Eur Acad Dermatology Venereol. 2013;27(5):558–64.
139. Wong GWK, Mahesh PA, Ogorodova L, Leung TF, Fedorova O, Holla AD, et al. The EuroPrevall-INCO surveys on the prevalence of food allergies in children from China, India and Russia: The study methodology. Allergy. 2010;65(3):385–90.
140. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011;128(1):e8–18.

141. Rosi A, Paolella G, Biasini B, Scazzina F, Alicante P, De Blasio F, et al. Dietary habits of adolescents living in North America, Europe or Oceania: A review on fruit, vegetable and legume consumption, sodium intake, and adherence to the Mediterranean Diet. Nutr Metab Cardiovasc Dis. 2019;29(6):544–60.
142. Varela-Moreiras G, Ávila JM, Cuadrado C, del Pozo S, Ruiz E, Moreiras O. Evaluation of food consumption and dietary patterns in Spain by the Food Consumption Survey: Updated information. Eur J Clin Nutr. 2010;64:S37–43.
143. Đorđić V, Božić P, Milanović I, Radisavljević S, Batez M, Jorga J, et al. Guidelines-driven educational intervention promotes healthy lifestyle among adolescents and adults: A serbian national longitudinal study. Med. 2019 Feb 4;55(2):1–11.
144. Crevel RRW, Ronsmans S, Marsaux CFM, Bánáti D. ILSI Europe's food allergy task force: From defining the hazard to assessing the risk from food allergens. J AOAC Int. 2018;101(1):91–5.
145. Eigenmann PA, Caubet JC, Zamora SA. Continuing food-avoidance diets after negative food challenges. Pediatr Allergy Immunol. 2006;17(8):601–5.
146. Bock SA, Muoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 2001;107(1):191–3.
147. 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(5):449–53.
148. 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(3):271–7.
149. Le TM, Zijlstra WT, van Opstal EY, Knol MJ, L'Hoir MP, Knulst AC, et al. Food avoidance in children with adverse food reactions: Influence of anxiety and clinical parameters. Pediatr Allergy Immunol. 2013;24(7):650–5.
150. Namork E, Fæste CK, Stensby BA, Egaas E, Løvik M. Severe allergic reactions to food in Norway: A ten year survey of cases reported to the Food Allergy Register. IntJ Environ Res Public Heal. 2011;8(8):3144–55.
151. 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(1):e10.

152. 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: Summary of the NIAID-Sponsored Expert Panel Report. J Am Diet Assoc. 2011;111(1):17–27.
153. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. J Allergy Clin Immunol. 2004;114(1):159–65.
154. Hartz C, Lauer I, Del Mar San Miguel Moncin M, Cistero-Bahima A, Foetisch K, Lidholm J, et al. Comparison of IgE-binding capacity, cross-reactivity and biological potency of allergenic non-specific lipid transfer proteins from peach, cherry and hazelnut. Int Arch Allergy Immuno. 2010;153(4):335–46.
155. Lack G. Epidemiologic risks for food allergy. J Allergy Clin Immunol. 2008 Jun;121(6):1331–6.
156. Mcbride D, Keil T, Grabenhenrich L, Dubakiene R, Drasutiene G, Fiocchi A, et al. The EuroPrevall birth cohort study on food allergy: Baseline characteristics of 12,000 newborns and their families from nine European countries. Pediatr Allergy Immunol. 2012;23(3):230–9.
157. Portugal. Portaria n.º 1320/2010. Ministérios das Finanças e da Saúde. Diário da República, 1.ª série; N.º 250, 28 de Dezembro de 2010. Diário da República. 2010;1ª Série(250):5964–7.
158. Portugal. Portaria n.º 306-A/2011. Ministérios das Finanças e da Saúde. Diário da República . 2011;1.ª série(242):5348(2-4).
159. Portugal. Taxa de desemprego (Série 2011 - %) por Sexo, Grupo etário e Nível de escolaridade mais elevado completo; Trimestral - INE, Inquérito ao emprego [Internet]. [cited 2020 Mar 7]. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&contecto=pi&indOcorrCod=0005599&selTab=tab0
160. 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(7):1036–44.

8. Appendix

Appendix I. Questionnaire layouts

I.1 Questionnaire layout in Google Docs format

alergia alimentaria

*Obligatorio

Centro de Saúde *

- CBR
- IDN
- PNV
- OLE
- SRT
- VVR

Número de Orden *

Introduzir Código do CS + nº do paciente da listagem

Sexo *

Masculino

Idade em anos *

Deseja responder ao questionário? *

- ○ Sim
- ○ Não
- ○ Não atendeu
- ○ Outro: Faleceu/ Número não atribuido/ Mudou de residência

Já teve alguma reacção alérgica a algum alimento?

- ☐ Sim
- ☐ Não

Se responde "Não" passar para as questões marcadas com * e finalizar

Qual é o alimento que lhe provoca reacção?

- ☐ Leite e Derivados
- ☐ Ovo
- ☐ Peixe
- ☐ Mariscos
- ☐ Amendoim
- ☐ Outros frutos secos
- ☐ Fruta
- ☐ Legumes
- ☐ Leguminosas
- ☐ Carne de Frango
- ☐ Carne de Porco
- ☐ Carne de Vaca
- ☐ Outros
- ☐ Não Recorda

Se respondeu "Outros" especificar

Que tipo de reacção teve 1ª Parte (marcar os sintomas por alimentos)

Introduzir a sintomatologia mais grave

	Urticaria/Angioedema	Dermatite de contacto	SAO	Ocular	Nasal
Leite e derivados	○	○	○	○	○
Ovo	○	○	○	○	○
Peixe	○	○	○	○	○
Mariscos	○	○	○	○	○
Amendoim	○	○	○	○	○
Outros frutos secos	○	○	○	○	○
fruta	○	○	○	○	○
Legumes	○	○	○	○	○
Leguminosas (grão, feijão, lentilhas)	○	○	○	○	○
Carne de frango	○	○	○	○	○
Carne de porco	○	○	○	○	○
Carne de vaca	○	○	○	○	○
Grupo do látex (kiwi, banana, manga, papaia)	○	○	○	○	○
Outros	○	○	○	○	○
Não recorda/não sabe	○	○	○	○	○

Qué tipo de reacção teve 2ª parte (marcar os sintomas por alimentos)

Introduzir a sintomatologia mais grave

	Respiratória	Abdominal	Anafilaxia	Outra
Leite e derivados	○	○	○	○
Ovo	○	○	○	○
Peixe	○	○	○	○
Mariscos	○	○	○	○
Amendoim	○	○	○	○
Outros frutos secos	○	○	○	○
Fruta	○	○	○	○
Legumes	○	○	○	○
Leguminosas (grão, feijão, lentilhas)	○	○	○	○
Carne de frango	○	○	○	○
Carne de porco	○	○	○	○
Carne de vaca	○	○	○	○
Grupo do látex (Kiwi, banana, manga, papaia)	○	○	○	○
Outros	○	○	○	○
Não recorda/não sabe	○	○	○	○

Quanto tempo após ter comido surgiram as reacções?

- ☐ Menos de 30 min
- ☐ De 30 min a 2 horas
- ☐ De 2 horas a 24 horas
- ☐ Superior a 24 horas

Precisou de tratamento médico?

- ☐ Sim
- ☐ Não

Se respondeu afirmativamente, onde recebeu tratamento?

- ☐ SU de um Hospital
- ☐ INEM
- ☐ Centro de Saúde nas primeiras 24 horas
- ☐ Médico de família depois de 24 horas
- ☐ Avaliação pelo médico especialista

Quantos episódios similares já teve com o mesmo alimento?

- ☐ Só 1
- ☐ Entre 2 e 5
- ☐ Mais de 5
- ☐ Não recorda

Há quanto tempo teve a última reacção?

- ☐ Há menos de 1 mês
- ☐ Entre 2 e 6 meses
- ☐ Entre 6 meses e um ano
- ☐ Entre 1 e 5 anos
- ☐ Há mais de 5 anos
- ☐ Não recorda

Já foi visto alguma vez na consulta da especialidade de alergia?

- [ ] Sim
- [ ] Não

Para além das reacções aos alimentos também sofre de problemas com ácaros ou pólens?

- [ ] Asma
- [ ] Rinite
- [ ] Conjuntivite
- [ ] Alergia cutânea
- [ ] Não
- [ ] Outras

*

Alguém da sua família tem alguma doença alérgica?

- [ ] Pai ou mãe
- [ ] irmão ou irmã
- [ ] Avos
- [ ] Tios

*

Desejaria continuar o estudo numa consulta diferenciada de Imunoalergologia no hospital de referência?

- [ ] Sim
- [ ] Não

I.2. Questionnaire layout in printed paper sheet format

INQUÉRITO A ADOLESCENTES DAS ESCOLAS SECUNDÁRIAS DE CASTELO BRANCO

Estudo da prevalência e das características clínicas, serológicas e genéticas da alergia alimentar em crianças e adultos Portugueses

Instruções: Marcar com um círculo apenas a resposta escolhida (ou respostas no caso de resposta múltipla: RM).

1. Código de Centro (não preencher)
2. Identificação do voluntário/a (não preencher)
3. Deseja responder ao questionário? 3.Sim Não
4. Idade (em anos):
5. Já teve alguma "reacção alérgica" a algum alimento? 5 Sim Não
   (Se a resposta tiver sido "NÃO", avançar até às questões nº 15 e 16)
6. Que alimento ou alimentos provoca(m) a reacção (Resposta múltipla RM)?
   a. Leite e derivados b. Ovo c. Peixe d. Mariscos e. Amendoim f. Outros frutos secos g. Fruta h. legumes (batata, cenoura, couve, etc.) i. Leguminosas (feijão, grão, ervilhas, etc.) j. Carne de frango k. Carne de porco l. Carne de vaca m. Látex (Kiwi, banana, manga, papaia, figo, tomate). n. Outros não incluídos nos grupos anteriores. (especificar) o. Não recordo.
7. Que tipo de reacção teve? (descrever os sintomas com o alimento(s) implicado(s). Se não recordar, escrever "não recordo").
8. Quanto tempo após ter comido o alimento surgiram as reacções?
   a. Menos de 30 minutos b. De 30 mins a 2 horas c. De 2 a 24 Horas d. Mais de 24 horas
9. Precisou de tratamento médico? 9. Sim Não
10. Se respondeu afirmativamente à questão 9, onde recebeu tratamento?
    a. Urgência dum Hospital b. INEM c. Centro de Saúde nas primeiras 24 horas
    d. Médico de Família depois de 24 horas e. Avaliação pelo Médico Especialista. f. Automedicação
11. Quantos episódios similares já teve com o mesmo alimento?
    a. Só 1 b. Entre 2 e 5 c. Mais de 5 d. Não recordo
12. Há quanto tempo foi a última reacção?
    a. Há menos de 1 mês b. Entre 2 e 6 meses c. Entre 6 meses e 1 ano d. Entre 1 e 5 anos
    e. Há mais de 5 anos. f. Não recordo.
13. Já foi diagnosticada alergia alimentar por algum médico? 13.Sim Não
14. Já foi visto alguma vez na consulta da especialidade de Alergia? 14.Sim Não
15. Sofre algum tipo de doença alérgica? (Resposta múltipla-RM)
    a. Asma (tosse, pieira, falta de ar). b. Rinite (Espirros, corrimento e comichão nasal)
    c. Conjuntivite (lacrimejo, comichão e vermelhidão ocular) d. Alergia cutânea (eczema, comichão, descamação ou babas na pele) e. Outras (indicar). f. Não.
16. Alguém da sua família tem alguma doença alérgica? (Resposta múltipla-RM)
    a. Pai ou mãe b. Irmão ou irmã c. Avós d. Tios e. Outros (indicar) f. Não
17. Caso de ser possível, desejaria continuar o estudo numa consulta de Imunoalergologia no Hospital de referência? 17.Sim Não

Muito obrigado pela sua colaboração!
A equipa de Investigação

Appendix II. Deliberations of the studies approval

II.1. Study approval by the Ethical Committee of the Amato Lusitano Hospital

MINISTÉRIO DA SAÚDE
ADMINISTRAÇÃO REGIONAL DO CENTRO

HOSPITAL
AMATO LUSITANO

Ofício: Dr. Carlos Lozoya - Responsável do Serviço de Imunoalergologia do HAL
Assunto: Pedido de autorização para realização do projecto "Estudo da prevalência e das características clínicas de alergias alimentares em crianças e adultos portugueses"
Requerente: Prof. Drº. Luís Taborda Barata – Departamento de Ciências Médicas
Titulo: "Estudo da prevalência e das características clínicas de alergias alimentares em crianças e adultos portugueses"
Serviço onde decorre o Trabalho: Serviço de Imunoalergologia do Hospital Amato Lusitano
Investigador Principal: Dr. Carlos Lozoya
Data do pedido: Ofício datado no HAL em 29 de Janeiro de 2009

A Comissão de Ética do HAL comunica ter deliberado emitir parecer favorável ao projecto de investigação "Estudo da prevalência e das características clínicas de alergias alimentares em crianças e adultos portugueses" a realizar no HAL, depois de ter verificado que o referido projecto, estava em conformidade com os parâmetros éticos.

HAL, 10 de Julho de 2009

A Comissão de Ética

MINISTÉRIO DA SAÚDE
ADMINISTRAÇÃO REGIONAL DO CENTRO

HOSPITAL
AMATO LUSITANO

De: Presidente do Conselho de Administração

Para: Ex.mo Sr. Dr. Carlos Lozoya

Data: 25 de Agosto de 2009

Assunto: *Estudo da prevalência e das características clínicas de alergias alimentares em crianças e adultos portugueses*

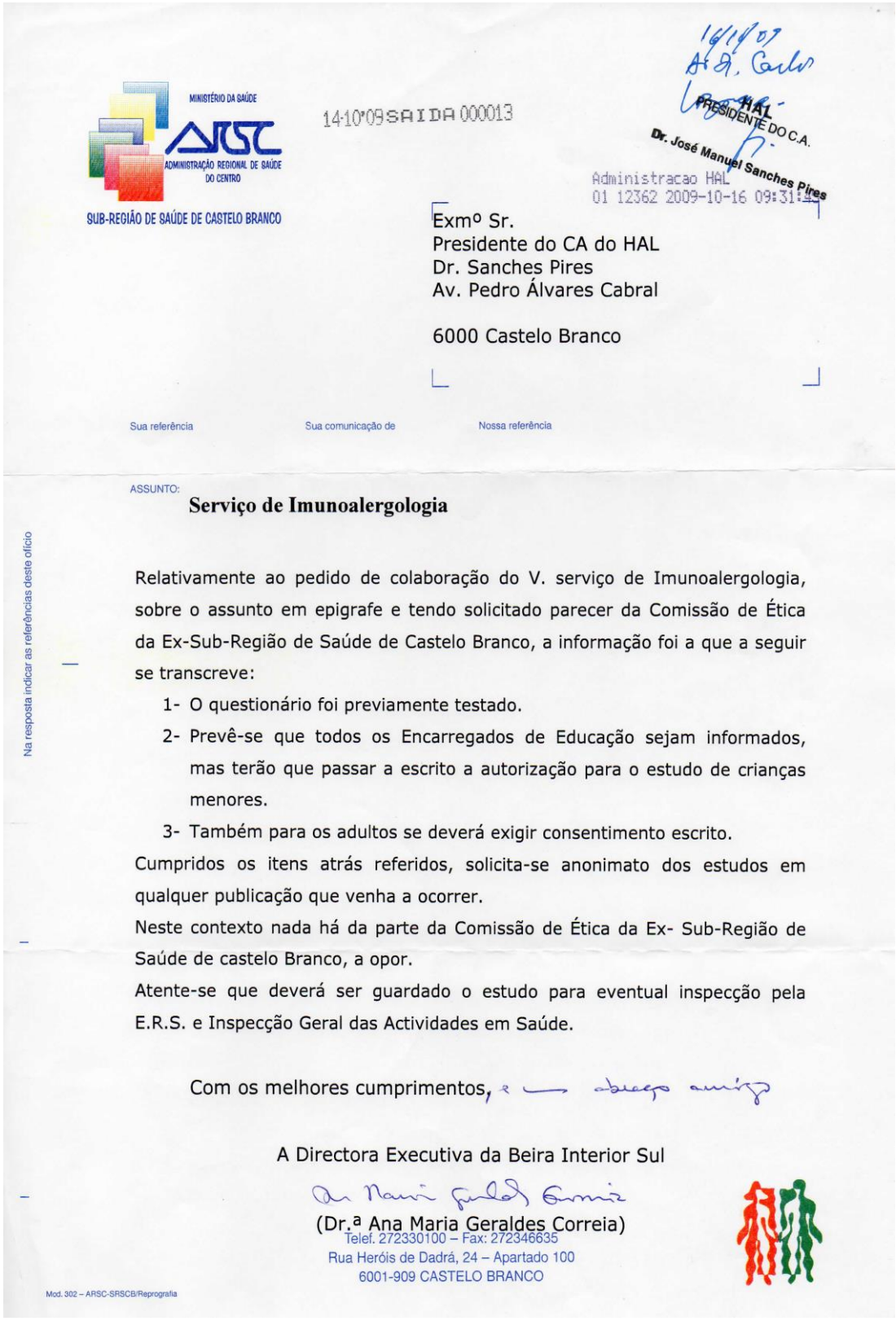
Relativamente ao assunto em epígrafe, informa-se V. Ex.a que a Comissão de Ética emitiu parecer favorável ao pedido de autorização para realização do estudo referido, com o qual o Conselho de Administração deliberou concordar, em 20/08/2009.

O Presidente do Conselho de Administração

Dr. José Manuel Sanches Pires

Administracao HAL
17 10337 2009-08-28 17:32:15

II.2. Study approval by the Ethical Committee of the former Administrative Sub-Region of Health of Castelo Branco



MINISTÉRIO DA SAÚDE
ADMINISTRAÇÃO REGIONAL DE SAÚDE DO CENTRO
SUB-REGIÃO DE SAÚDE DE CASTELO BRANCO

14-10-09 SAIDA 000013

16/10/09
HAL
PRESIDENTE DO C.A.
Dr. José Manuel Sanches Pires
Administracao HAL
01 12362 2009-10-16 09:31:44

Exmº Sr.
Presidente do CA do HAL
Dr. Sanches Pires
Av. Pedro Álvares Cabral

6000 Castelo Branco

Sua referência | Sua comunicação de | Nossa referência

ASSUNTO:
Serviço de Imunoalergologia

Na resposta indicar as referências deste ofício

Relativamente ao pedido de colaboração do V. serviço de Imunoalergologia, sobre o assunto em epigrafe e tendo solicitado parecer da Comissão de Ética da Ex-Sub-Região de Saúde de Castelo Branco, a informação foi a que a seguir se transcreve:

1- O questionário foi previamente testado.
2- Prevê-se que todos os Encarregados de Educação sejam informados, mas terão que passar a escrito a autorização para o estudo de crianças menores.
3- Também para os adultos se deverá exigir consentimento escrito.

Cumpridos os itens atrás referidos, solicita-se anonimato dos estudos em qualquer publicação que venha a ocorrer.

Neste contexto nada há da parte da Comissão de Ética da Ex- Sub-Região de Saúde de castelo Branco, a opor.

Atente-se que deverá ser guardado o estudo para eventual inspecção pela E.R.S. e Inspecção Geral das Actividades em Saúde.

Com os melhores cumprimentos, e abraço amigo

A Directora Executiva da Beira Interior Sul

(Dr.ª Ana Maria Geraldes Correia)
Telef. 272330100 – Fax: 272346635
Rua Heróis de Dadrá, 24 – Apartado 100
6001-909 CASTELO BRANCO

Mod. 302 – ARSC-SRSCB/Reprografia

II.3. Study approval by the Ministry of Education

Carlos Lozoya Ibáñez <clozoya@fcsaude.ubi.pt>
Para:lozoyaib@yahoo.com
20 ene. 2012 a las 17:39

---------- Forwarded message ----------
From: <mime-noreply@gepe.min-edu.pt>
Date: 2012/1/20
Subject: Monotorização de Inquéritos em Meio Escolar: Inquérito nº 0266300001
To: clozoya@fcsaude.ubi.pt

Exmo(a)s. Sr(a)s.

O pedido de autorização do inquérito n.º 0266300001, com a designação *Estudo da prevalência de alergias alimentares em adolescentes dos 12 aos 17 anos de idade*, registado em 26-11-2011, foi aprovado.

Avaliação do inquérito:

> Exmo(a) Senhor(a) Dr(a). Carlos Lozoya Ibáñez
> Venho por este meio informar que o pedido de realização de inquérito em meio escolar é autorizado uma vez que, submetido a análise, cumpre os requisitos de qualidade técnica e metodológica para tal devendo, no entanto, ter em atenção as observações aduzidas.
> Com os melhores cumprimentos
> Isabel Oliveira
> Directora de Serviços de Inovação Educativa
> DGIDC

Observações:

> 1. É nosso entender que o 1º questionário deverá ser preenchido pelos alunos com os EE/pais, pois as questões são muito técnicas e de difícil identificação para uma criança/jovem adolescente;
> 2. Para garantir a rapidez de acesso aos cuidados de saúde, seria bom efetuar um protocolo específico com a USF de Castelo Branco, que assegure este atendimento rápido.
> 3. Quanto á questão do anonimato, os que afirmam desejar continuar o tratamento, deixam de ser anónimos necessariamente e, necessariamente, carecem de autorização dos pais (este tipo de consultas é pago…).
> 4. Deverá ser obtida a autorização dos encarregados de educação dos alunos a inquirir.

Pode consultar na Internet toda a informação referente a este pedido no endereço http://mime.gepe.min-edu.pt. Para tal terá de se autenticar fornecendo os dados de acesso da entidade.

Appendix III. Publicizing of the studies in local media

III.1. Jornal Reconquista, 4 March 2010

ECOMARCHE
Alcains
5,98 € BORREGO inteiro/metades Kg
3,98 € PATO inteiro c/ miúdos Kg
Aproveite Combustíveis a preço Mosquiteiros

reconquista
Ano LXV - Nº. 3338 4 de Março de 2010
DIRECTOR - Agostinho Gonçalves Dias
www.reconquista.pt E-MAIL: reconquista@reconquista.pt
Preço: 0,60 euros
PUBLICAÇÕES PERIÓDICAS Castelo Branco TAXA PAGA
Semanário Regionalista Baixa

Médico do Amato Lusitano realiza estudo pioneiro
Quando a comida provoca alergia
Os alimentos podem provocar alergias em determinadas pessoas. Este é um problema que ainda não é muito conhecido, mas Carlos Lozoya, imunoalergologista em Castelo Branco, está a preparar um estudo nesta área, o primeiro feito em Portugal. Pág. 4

Realizador de cinema com raízes na região
Joaquim Leitão dá aula em Penamacor
Com raízes em Pedrógão de São Pedro, o realizador Joaquim Leitão esteve em Penamacor para dar uma aula de cinema. De seguida falou ao Reconquista sobre o que é isto de ser realizador. Pág. 19

Castelo Branco
Assembleia unânime em defesa do IC31
Pág. 7

Carros furtados
GNR e PSP perseguem larápios
Pág. 9

Educação
Futuro das escolas passa pelas câmaras
Pág. 6

Vila Velha Ródão
Pesqueiras vai entrar em obras
Pág. 29

Penamacor
Gestora do Proder esclarece munícipes
Pág. 27

Fase final
Agora é que o distrital vai piar fino
Pág. 36

Castelo Branco
Dinossauros chegam dia 14
Pág. 5

Obras estão quase prontas
Novo Museu Cargaleiro inaugurado em Junho
Pág. 11

Obra a concurso
Avenida da Europa perde rotunda
Pág. 6

Dentbril
Clínica Médica e Dentária, Lda
• Prótese Fixa e Removível • Implantologia • Ortodontia
Sofia Lourenço Psicologia Clínica
Sandra Paulo Medicina Dentária
Manuela Micaelo Reumatologia
Liliana Moura Nutrição Clínica
Rua Conselheiro Albuquerque, 13 R/c Esq. CASTELO BRANCO
272 323 842 • 964 706 618 • dentbril@clix.pt

albicasa
Av. General H. Delgado, 80 1º piso Escritório A
6000-081 CASTELO BRANCO
www.albicasa.pt

PREÇOS INACREDITÁVEIS.
100€
19€
instituoptico

Pré-escolar avança em Setembro

Ana's e Bebés alarga ao Pré-escolar

A creche Ana's e Bebés, situada junto à residência de Estudantes, em Castelo Branco, vai alargar a sua actividade à educação Pré-escolar já a partir do mês de Setembro. As inscrições começam em Abril. A nova estrutura vai chamar-se Ana's Academy, fica nas imediações da creche e terá capacidade para 45 crianças, dos três aos seis anos.

Além das actividades curriculares, a Ana's Academy irá ter actividades ao nível do Inglês, Expressão Musical e Informática. Dado o interesse das crianças e dos pais que já frequentam a creche, serão ainda organizadas aulas de aprendizagem de um instrumento e uma classe de dança, associada com actividades de Psicomotricidade.

"Vamos ter duas salas de grande dimensão, bem como espaços para desenvolver cada uma das actividades, todos eles equipados com computadores e equipamento de vídeo. Teremos ainda um ginásio e um parque exterior com cerca de 180 metros quadrados" referem as responsáveis da creche, que esperam começar as obras de adaptação em breve.

O avanço para a Educação Pré-escolar implicará a contratação de mais duas educadoras de infância e de duas auxiliares, além de pessoal de apoio. Além disso serão adquiridos novos equipamentos, financiados apenas com verbas privadas. Um esforço que as duas responsáveis fazem a título privado, tal como aconteceu com a creche, que abriu portas em Maio de 2007.

Protecção Civil

Oleiros tem Plano em consulta pública

O Plano Municipal de Emergência de Protecção Civil de Oleiros encontra-se em consulta pública. O documento constitui a linha orientadora de como se deve agir em situações de emergência.

O documento foi publicado, no dia 25 Fevereiro, em Diário da República, dando assim cumprimento à deliberação da Câmara de Oleiros. O Plano pode ser consultado, durante 30 dias, sendo composto por quatro capítulos, a saber: "Enquadramento geral do Plano" "Organização da resposta" "Áreas de intervenção" e "Informação complementar"

O documento pode ser consultado no seguinte endereço electrónico http://www.cm-oleiros.pt e no Gabinete Técnico Florestal do Município de Oleiros, devendo quaisquer sugestões ser remetidas por escrito ao Presidente da Câmara Municipal ou por e-mail para gflorestal@cm-oleiros.pt

Médico da ULS de Castelo Branco com estudo pioneiro

Quando o comer... provoca alergia

As alergias de base imunológica provocam desde uma simples comichão até à morte. É preciso diagnosticar e tratar as verdadeiras causas, mas algumas não estão devidamente exploradas, como por exemplo, as que advêm dos alimentos.

Muitos alimentos vulgares e que fazem parte da nossa dieta habitual podem provocar reacções adversas, ou até mesmo alergias alimentares, os conceitos e os sintomas podem ser parecidos, mas as causas e efeitos são diferentes e importa distingui-los.

As alergias, de base imunológica, podem provocar desde uma simples comichão até à morte. Daí ser necessário diagnosticar e tratar as verdadeiras causas, mas algumas não estão ainda devidamente exploradas, como por exemplo, as das alergias alimentares.

Neste sentido, na sua tese de doutoramento, Carlos Lozoya Ibañez, médico do Serviço de Imunoalergologia do Hospital Amato Lusitano, que frequenta a Faculdade de Ciências da Saúde da Universidade da Beira Interior, vai realizar um estudo sobre "Prevalência e características clínicas e genéticas das alergias alimentares em adultos da Beira Interior" orientado pelo professor Taborda Barata. Esta é uma análise pioneira a nível nacional e a realizar na área abrangida pela Unidade Local de Saúde de Castelo Branco (com excepção dos centros de saúde de Vila de Rei e Mação, devido à distância, e de Penamacor, que não aceitou entrar no estudo).

O estudo consiste na elaboração de um questionário, via telefone, a uma amostra da população da região, neste caso, cerca de mil utentes dos diversos centros de saúde que integram a ULS de Castelo Branco, propostos a partir dos ficheiros dos clínicos gerais.

Carlos Lozoya explica que "ter uma reacção adversa a um determinado alimento é diferente de ter uma alergia alimentar", pois "se a primeira acontece pontualmente, até pelo estado de conservação desse alimento nessa altura, podendo não se repetir, na alergia alimentar prevalece o sintoma, repetindo-se sempre que a pessoa ingere aquele determinado alimento"

Na América há muitos estudos sobre as alergias alimentares, mas na Europa são menos frequentes. Em Portugal é este o primeiro, podendo ser este também o início de um caminho que depois se pode alargar a outras zonas do país, conduzindo a que, dentro de alguns anos, possa haver uma visão global nacional em termos desta problemática. Quando há uma alergia alimentar a maneira mais fácil de a tratar é deixar de comer o alimento que a causa, mas, para isso, é preciso saber qual é realmente.

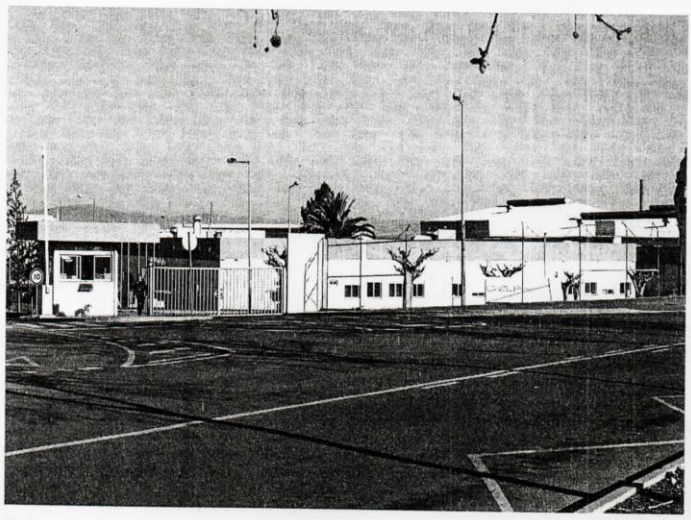
Este estudo já está desenhado há alguns anos, mas "as burocracias inerentes à sua aprovação, como conseguir os pareceres da Comissão de Ética de HAL, da ex-Sub-Região de Saúde de Castelo Branco e agora esta transição para a ULS, levou um ano até que tudo estivesse pronto para avançar"

Os inquéritos devem começar a ser feitos já este mês de Março e os primeiros resultados deverão surgir dentro de 14 a 15 meses. "Um estudo bem feito pode evitar muitos problemas, porque identificam-se as causas e podem arranjar-se soluções mais facilmente", reitera o médico, adiantando que "o estudo vai identificar quem são os utentes que apresentam reacções adversa a alimentos, depois, numa outra fase, quais são mesmo alérgicas, finalizando-se com uma série de estudos laboratoriais"

Nos adultos é mais fácil de identificar a prevalência das alergias alimentares do que nas crianças, mas, depois deste, pode surgir um outro estudo dirigido à população entre os 12 e os 18 anos. "Estes estudos podem servir de base comparativa para outros que depois se venham a fazer, porque a população também é diferente no Interior e no Litoral e nem todas respondem da mesma forma perante estas situações" conclui.

Lídia Barata

III.2. Jornal Reconquista, 15 March 2012



Fábrica de Castelo Branco bate recorde

Delphi chega aos 1300 trabalhadores

A Delphi Castelo Branco atingiu o número recorde de 1300 trabalhadores, assumindo-se como uma das principais empregadoras do distrito. No último ano teve um volume de negócios superior a 2010. Para este ano vai avançar um novo projeto para a Nissan.

A fábrica de componentes elétricos para a indústria automóvel Delphi, em Castelo Branco apresentou, em 2011, um volume de negócios superior a 2010 e atingiu o número recorde de 1300 funcionários. A empresa produz equipamentos para a Ferrari, Maserati, Land Rover e Jonh Deere.

A Delphi de Castelo Branco surge em contraciclo com a crise económica que o país e a europa atravessam. Num ano em que o desemprego subiu em Portugal de forma exponencial, a fábrica albicastrense tem mantido um nível de emprego acima dos números habituais, assumindo-se como a principal empregadora do concelho e como uma das responsáveis pelo desenvolvimento económico da cidade.

Os dados apurados pelo Reconquista estão relacionados com o bom momento de vendas que a Ferrari, Maserati, Land Rover e Jonh Deere têm registado. Ou seja ao contrário de outras marcas que estão a sofrer com a crise, aquelas têm tido vendas superiores ao que seria esperado. Isto também permitiu à Delphi pagar mais horas extraordinárias do que alguma vez aconteceu.

A diversidade e a complexidade dos componentes produzidos em Castelo Branco têm constituído outro trunfo importante, num mercado inconstante como é o setor automóvel.

Outro aspeto importante neste aumento do número de funcionários e no volume de negócios está relacionado com o encerramento da fábrica da Guarda e a transferência da produção de componentes para a Ferrari e Maserati para Castelo Branco.

Hoje a Delphi tem duas unidades fabris em Castelo Branco e funciona 24 horas por dia no setor do corte, e 16 horas na montagem. Estes dados revelam que a fábrica em Castelo Branco atravessa um dos seus melhores momentos de sempre. Se o mercado o exigir a produção pode ser aumentada, já que o setor da montagem também poderá funcionar 24 horas por dia.

Os próprios índices de produtividade das unidades de Castelo Branco estão acima dos da média das fábricas do grupo. Ainda este ano a Nissan junta-se ao portefólio da Delphi albicastrense, num projeto de elevada complexidade.

Os dados referentes ao último ano são bastante animadores num mercado que é bastante volátil e que depende muito das vendas do sector automóvel. Por isso, existe uma grande expetativa em saber como se vão comportar os mercados no segundo semestre de 2012. Isto porque há economistas que defendem que a recessão europeia se vai sentir mais no 2º semestre. E há quem defenda que vão surgir sinais de retoma nesse período.

De referir que 90 por cento dos componentes produzidos em Castelo Branco são exportados para a Europa e 10% para o Brasil e Estados Unidos.

Até ao fecho da nossa edição o Reconquista tentou contatar Jorge Santos, responsável da Delphi para o sul da Europa, mas tal não foi possível.

João Carrega

Reação aos alimentos

Alergias estudadas dos três aos 90 anos

As alèrgias, de base imunológica, podem provocar desde uma simples comichão até à morte. Daí ser necessário diagnosticar e tratar as verdadeiras causas, mas algumas não estão ainda devidamente exploradas, como por exemplo, as das alergias alimentares.

Era desta forma que há um ano Reconquista noticiava o tema da tese de doutoramento de Carlos Lozoya Ibañez, médico do Serviço de Imunoalergologia do Hospital Amato Lusitano, está a realizar na Faculdade de Ciências da Saúde da Universidade da Beira Interior, um estudo sobre "Prevalência e características clínicas e genéticas das alergias alimentares em adultos da Beira Interior", orientado pelo professor Taborda Barata.

Este estudo distingue-se porque, pela primeira vez, é estudada uma faixa da população tão alargada, dos 3 aos 90 anos, algo que as entidades oficiais que se dedicam ao estudo e tratamento das alergias defenderem já que "o modelo deve ser replicado a nível nacional"

Recorde-se que esta é uma análise pioneira a nível nacional e a realizar na área abrangida pela Unidade Local de Saúde de Castelo Branco (com exceção dos centros de saúde de Vila de Rei e Mação, devido à distância, e de Penamacor, que não aceitou entrar no estudo). Carlos Lozoya, na primeira parte do trabalho, inquiriu 1500 pessoas, por telefone, com idades entre os 18 e os 90 anos, sendo que destas, 50 confirmaram ter reações a alguns alimentos e deste grupo, cerca de 30 aceitaram participar na etapa seguinte, das consultas. Mas os resultados são ainda preliminares, contudo, uma conclusão pode já ser avançada, "os portugueses desta região não têm reações diferentes do resto dos cidadãos europeus, onde já foi feito esse registo"

Nesta segunda fase, que está agora em curso, "vão ser inquiridos os adolescentes e jovens, dos 13 aos 17 anos, seguindo os mesmos trâmites que foram colocados aos adultos" se bem que, o médico espera mais dificuldades em termos de adesão às etapas das consultas, "pois agora as taxas moderadoras são mais caras, além de que para os jovens pode ser complicado faltar às aulas para vir a uma consulta"

Mas o estudo final, que deverá ser defendido e publicado em finais de 2013, será ainda complementado com o trabalho realizado pela médica Arminda Jorge, que incide sobre a população dos 3 aos 12 anos.

"É isto que torna este estudo inédito e único, pois nunca se estudou uma faixa tão abrangente da população nesta área" afirma Carlos Lozoya, acrescentando que "por isso já haver quem defenda que tem de ser replicado a nível nacional" para que "dentro de alguns anos, possa haver uma visão global nacional em termos desta problemática"

Sublinhe-se ainda que "um estudo bem feito pode evitar muitos problemas, porque identificam-se as causas e podem arranjar-se soluções mais facilmente"

Lídia Barata

Carlos Lozoya

Appendix IV. Search Strategy

IV.1. Search Strategy I - Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Search Strategy:

---

1. exp Food Hypersensitivity/
2. food hypersensitivit*.mp.
3. food allerg*.mp.
4. allergy, food.mp.
5. exp Fruit/
6. (apple or peach or nectarine peach or apricot or cherry or pear or plum or banana or melon or watermelon or kiwi or citrus or orange or fruit juice or olive oil or wine or honey).mp.
7. Exp Vegetables/
8. (onion or potato or carrot or tomato or celery or soybean or sunflower seeds or cucumber or zucchini or chamomile).mp.
9. Peanut Hypersensitivity/
10. Arachis/ or (Peanut*or PArachis hypogaea or Ara h).mp.
11. Soybeans/ or (Soy* bean or Glycine max or Gly m).mp.
12. Nuts/ or Nut Hypersensitivity/
13. Corylus/ or (Hazelnut* or Corylus avellana or Cor a).mp.
14. Juglans/ or (Walnut* or Juglans regia or Jug r).mp.
15. Anacardium/ or (Cashew* or Anacardium occidentale or Ana o).mp.
16. Bertholletia/ or (Brazil Nut* or Bertholletia excelsa or Ber e).mp.
17. Pistacia/ or (Pistachio* or Pistacia vera or Pis v).mp.
18. Prunus dulcis/ or (Almond*or Prunus dulcis or Pru du).mp.
19. Wheat Hypersensitivity/
20. Triticum/ or (Wheat or Triticum aestivum or Tri a).mp.
21. Egg Hypersensitivity/
22. exp Eggs/ or Hen* egg*.mp.
23. Chickens/ or (Chicken* or Gallus domesticus or Gal d).mp.
24. Milk Hypersensitivity/
25. Milk/ or exp Milk Proteins/ or Milk, Human/
26. Cattle/ or (Cow* or Cow* milk or Bos domesticus or Bos d).mp.
27. Exp Seafood/
28. exp Fishes/ or exp Fish Proteins/ or Parvalbumins/ or Fish allergen*.mp.
29. Penaeidae/ or (Shrimp*or Penaeus aztecus or Pen a or Tropomyosin).mp.
30. exp Gadiformes/ or (Cod or Gadus morhua or Gad c or Gad m).mp.
31. exp Carps/ or (Carp or Cyprinus carpio or Cyp c).mp.
32. Or/1-31

AND “prevalence”
OR “incidence”
OR “risk factor”
OR “prevalence”
AND “adult”

IV.2. Search Strategy II - Database: Embase Classic+Embase

1	exp Food Hypersensitivity/
2	food allerg*.mp.
3	food hypersensitivity.mp.
4	food hypersensitivities.mp.
5	allergy, food.mp.
6	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal$).ti. (1587180)
7	exp animals/ not humans.sh.
8	6 or 7
9	exp Epinephrine/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy]
10	exp "Cause of Death"/
11	((adrenaline or epinephrine) adj3 (dispens$ or prescrib$)).tw. (150)
12	*Prevalence/
13	*Incidence/
14	(incidence or prevalence or epidemiol$).ti.
15	*Epidemiology/
16	*cohort studies/
17	*case control study/
18	food allergy/ep [Epidemiology]
19	exp nutritional intolerance/ep [Epidemiology]
20	exp hospital admission/
21	*mortality/
22	or/9-21
23	or/1-5
24	22 and 23
25	24 not 8
26	limit 25 to yr="1990 - 2018"

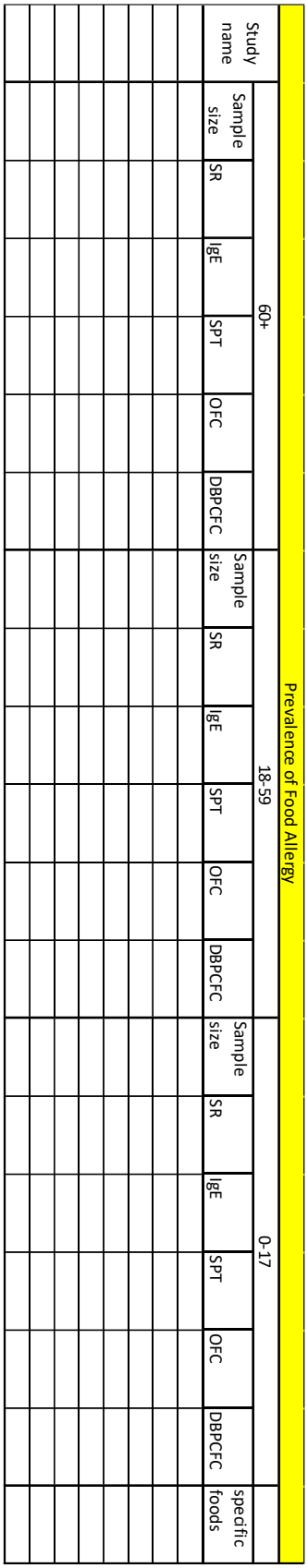
IV.3. Search strategy III – Database: CINAHL

S21	S9 and S20
S20	S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19
S19	(MM "Prevalence")
S18	(MH "Incidence")
S17	(MH "Prescribing Patterns")
S16	"Epinephrine prescription"
S15	"Epinephrine dispensing"
S14	(MH "Epinephrine/AD/SD")
S13	(MH "Epinephrine")
S12	(MM "Hospitalization")
S11	(MM "Disease Surveillance")
S10	(MH "Epidemiology") OR (MH "Epidemiological Research")
S9	S1 or S8
S8	S6 and S7
S7	S4 or S5
S6	S2 or S3
S5	AB allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S4	TI allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S3	AB food or nutrient
S2	TI food or nutrient
S1	(MM "Food Hypersensitivity")

IV.4. Search strategy IV - Database: ISI Web of Science: Science Citation Index, Conference Proceedings Citation

# 2	Topic=((food or nutrient) AND (allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)) AND Topic=((epidemiol* or incidence or prevalance or surveillance or death or mortality or survival or prescrib* or prescript*)) Refined by: Web of Science Categories=(NUTRITION DIETETICS OR FOOD SCIENCE TECHNOLOGY OR ALLERGY) *Databases=CPCI-S Timespan=All Years* *Lemmatization=On*
# 1	Topic=((food or nutrient) AND (allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)) AND Topic=((epidemiol* or incidence or prevalance or surveillance or death or mortality or survival or prescrib* or prescript*)) *Databases=CPCI-S Timespan=All Years* *Lemmatization=On*

IV.5 – Data extraction form



Appendix V. Scientific Production

V.1. Fist Author Scientific Articles

V.1.1 Allergy, Asthma & Clinical Immunology 2016

Lozoya-Ibáñez *et al.*
Allergy Asthma Clin Immunol (2016) 12:36
DOI 10.1186/s13223-016-0139-8

Allergy, Asthma & Clinical Immunology

RESEARCH Open Access

Prevalence and clinical features of adverse food reactions in Portuguese adults

Carlos Lozoya-Ibáñez[1,2], Sara Morgado-Nunes[3], Alexandra Rodrigues[4], Cláudia Lobo[2,5] and Luis Taborda-Barata[2,6*]

Abstract

Background: Only one previous study, via telephone call, on the prevalence of self-reported food allergies has been performed in Portugal, in a small sample of adults. The objective of this study was to determine the prevalence of self-reported and probable food allergy, analyze the clinical features and involved foods in Portuguese adults.

Methods: Population-based, cross-sectional study performed in various healthcare centres from central Portugal. All 1436 randomly selected individuals (median age: 45 years, 50.6 % female) replied to a validated food allergy questionnaire by phone. Those who reported an adverse food reaction were invited to come to the hospital, where clinical history was taken, skin prick (SPT) and prick-prick skin (SPPT) tests were performed and food allergen-specific IgE levels (sIgE) were determined. An open oral challenge was performed in selected cases. Cases of positive clinical history of immediate (up to 2 h after ingestion) reaction in association with positive food sIgE levels and/or skin prick tests were classified as IgE-associated probable food allergy. Cases of positive clinical history of delayed (more than 2 h after ingestion) and negative food sIgE levels independently of positive SPT or SPPT results were classified as non-IgE associated probable food allergy.

Results: The prevalence of probable food allergy in our sample was 1 %, with shellfish and fish as the most frequently implicated foods. IgE-mediated probable food allergy occurred in 0.71 % of cases, with shellfish, peanut and nuts mainly involved. Cutaneous symptoms were most frequently reported. Prevalence values and food types were discrepant between self-reported and probable food allergies.

Conclusions: The prevalence of probable food allergies in Portuguese adults is low, is mostly related to shellfish, peanut and nuts and most frequently involves cutaneous symptoms.

Keywords: Adverse food reaction, Food allergy, Adults, Prevalence, Cutaneous tests, Open food challenge

Background

Food allergy is an important health problem in western-style countries, as the high number of publications (around 21,000 in the past 10 years) on this issue seems to indicate [1, 2]. Although the prevalence of food allergies is not as high as that of other allergic diseases, its repercussions on dietary habits and social integration of food allergic patients is quite relevant [3, 4]. In this regard, a study from the US has shown that about 20 % of the American population changes their diet due to an adverse food reaction, namely food allergy [5]. Furthermore, the economic impact of food allergies, namely in terms of work absentism, is quite high and has been estimated to average around 510 million US$ per year in the US [6].

However, not all adverse reactions to foods are regarded as having an immunologically mediated "food allergy" [1, 7–9]. It is, in fact, necessary to go through a complicated diagnostic process, involving a thorough and detailed clinical history as well as specific tests, among which oral challenges are included [7, 9, 10]. If the diagnostic process is not completed to a great extent, or is

*Correspondence: tabordabarata@fcsaude.ubi.pt
[2] Faculty of Health Sciences, CICS-Health Sciences Research Centre, University of Beira Interior, Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal
Full list of author information is available at the end of the article

somehow incorrect, it may lead to unnecessary or inappropriate dietary eviction measures.

Partly for this reason, the prevalence values of food allergies in the general adult population are not well known. Various meta-analyses [11, 12] have estimated the prevalence of food allergies to any food between 3.5 and 35 % when only self-reported values are analysed and between 2 and 4 % when studies include diagnostic tests. However, these values seem to vary according to the country of reference and the methodology used. Thus, in the US, a recent study based upon a detailed review of various studies that analysed self-reported symptoms as well as confirmed food allergies [13], estimated that food allergies affect "more than 1–2 % but less than 10 %" of the population. In Europe, two population-based studies based upon questionnaires applied via telephone call and followed by clinical assessment, skin prick tests and oral challenge tests, clearly showed discrepant results between the prevalence values of self-reported and confirmed food allergy in adults in Germany (34.9 % self-reported and 3.7 % confirmed food allergy) [14], and in Denmark (19.6 % self-reported and 1.7 % confirmed food allergy) [15], values which are relatively similar to those obtained in the US. As far as we know, no population-based studies on the prevalence of food allergies have been carried out in Portugal, with the exception of one study on self reported food allergy, via telephone call, in a small sample of adults from the city of Oporto [16]. Thus, the objective of our study was to determine the prevalence of both self-reported and probable food allergy, as well as to analyze the clinical features and involved foods in a general population of Portuguese adults.

Methods

Population

For this study, we took into account the fact that 76,946 adults of both sexes, aged between 18 and 80 years, are registered in the files of general practitioners from the six Healthcare Centres belonging to the Local Health Unit of Castelo Branco which accepted to participate in the study (Castelo Branco, Vila Velha de Ródão, Sertã, Proença-a-Nova, Oleiros and Idanha-a-Nova). This is representative of a sample of the general population, since all Portuguese citizens are covered by the National Health Service/Care, and are thus registered at a Healthcare Centre, where they are assigned to a specific general practitioner.

Based on an estimated prevalence of 4 % [12, 14, 16], and considering a 95 % confidence interval and a margin of error of 2 % we calculated that we would need a representative sample of 369 adults. Considering an expected reply rate of 40 %, the sample size was set at 923 adults. We therefore decided to contact at least 1000 adults (about 1.3 % of total population) proportionally distributed in accordance with the number of individuals registered at each Healthcare Centre, located in both rural and urban areas, and randomly selected to be contacted by telephone.

Study design

Population-based, cross-sectional study, performed in a 2 year-long period (2013–2014). It was approved by the Ethics Committees of the Amato Lusitano Hospital and the former Administrative Sub-Region of Health of Castelo Branco. All patients gave written informed consent. All 1436 randomly selected individuals (mean age: 47 years, median age: 45 years, 50.6 % female) registered at participating Healthcare Centres were contacted by telephone and a validated food allergy questionnaire was applied [17]. More specifically, a code number was given to each adult individual registered at each Healthcare centre. Randomization was carried out using a specific randomizer programme (http://www.socialpsychology.org/randomizer.htm), following the principles of simple random sampling. All individuals were contacted by phone in up to three attempts and would not be included in the study if these attempts failed. Those who reported a previous adverse food reaction were invited to participate in the rest of the study (Fig. 1). These volunteers were subsequently contacted by a specialist doctor, and those who again confirmed the persistence of an adverse food reaction were invited for an appointment at the Outpatient Allergy Clinic of the Amato Lusitano Hospital, where a standardized food allergy-related clinical history was taken [18], skin prick tests (SPT) and, where applicable, prick-prick skin tests (SPPT) were performed and blood was collected for determination of food allergen-specific IgE levels. In those cases in which the clinical history was not clear and SPT results as well as specific IgE levels were negative, an open oral challenge was performed. If these patients did not exclude the suspected food from the diet, an eviction diet was followed for a minimum of 7 days prior to the food challenge. Patients with a positive clinical history of immediate (up to 2 h after ingestion) reaction in association with positive food sIgE levels and/or skin prick tests were classified as IgE-associated probable food allergy. Patients with a positive clinical history of delayed (more than 2 h after ingestion) and negative food sIgE levels independently of positive SPT or SPPT results were classified as non-IgE associated probable food allergy.

Questionnaire

A 17-item, previously validated questionnaire on adverse food reactions [17] (Additional file 1) was applied by phone to all volunteers. This questionnaire included demographic data, questions on the occurrence of

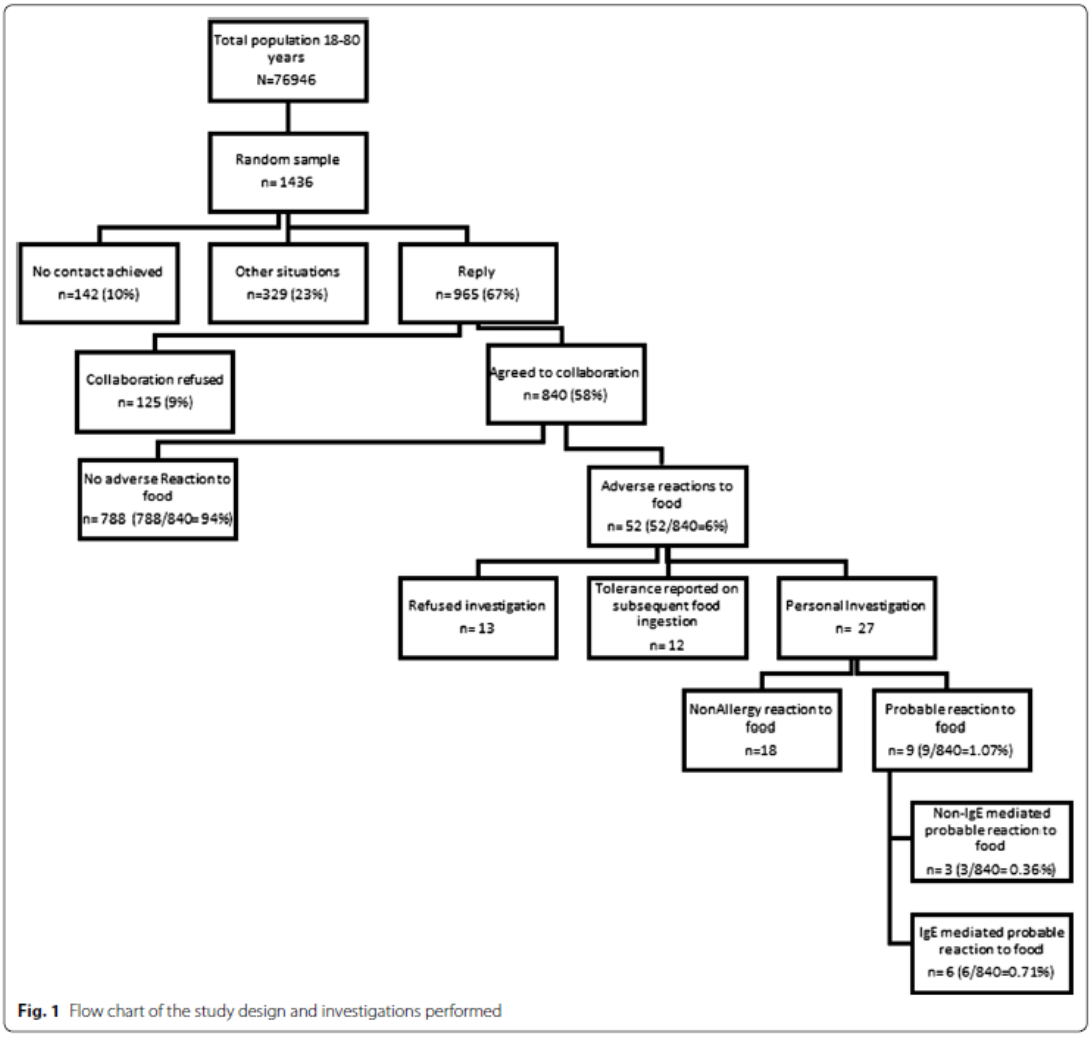


Fig. 1 Flow chart of the study design and investigations performed

previous episodes of adverse reactions to foods, types of foods causing such episodes, types of reactions, post-ingestion latency time for appearance of symptoms, date of latest reaction, need for medical assistance, personal or family history of atopic diseases.

Determination of levels of allergen-specific IgE

In all individuals who came to the outpatient clinic, 5 ml of peripheral blood was taken for the determination of the levels of total serum IgE, aeroallergen-specific screening IgE (Phadiatop inhalant allergens®), as a marker of atopy and suspected food-specific IgE. A fluorometric (ImunoCAP® 250 Phadia Diagnosis)-based technique was used (Phadia and Thermo Scientific, Uppsala, Sweden). Allergen-specific levels above 0.35 KU_A/L were regarded as positive.

Skin Prick Tests

In vivo studies included SPT (LETI Laboratories, Spain; Bial-Aristegui, São Mamede do Coronado, Portugal; Stallergènes, Antony, France) for aeroallergens (house dust mites, cockroach, fungi, latex, cat and dog dander, weeds, tree and grass pollens) and suspected foods and/or SPPT with the suspected foods. Tests were carried out

in duplicate on the volar aspect of the forearms. A drop of each commercial extract was placed upon the skin and each drop was pricked through using a metal lancet (Stallergènes, Antony, France). The mean weal diameter was recorded after 15 min. Wheals with a mean diameter at least 3 mm greater than that of the negative control were regarded as positive. SPPT tests used the same methodology.

Oral challenge

Oral challenges were performed in all cases with unclear clinical history independently of positive or negative SPT [7, 9, 10]. In those cases in which individuals did not avoid the foodstuffs, in spite of having symptoms, an eviction diet for at least 7 days before the oral challenge was carried out and monitored. Oral challenge was performed in an open manner, at the hospital, under direct clinical observation for 4 h post-challenge and further 24 h-long monitoring, depending upon presence or absence of reported symptoms. No double-blind, placebo-controlled food challenges were carried out.

Statistical analysis

Data was analysed using the Software Package for Social Sciences (SPSS) version 20.0® (SPSS Inc., Chicago, IL, USA). Analysis of normality of distribution of variables was performed using the One Sample Kolmogorov–Smirnov test. Descriptive analysis was used for the characterization of the sample. Chi Square test or Fischer's Exact Test were used in the case of nominal variables. Comparative analysis of quantitative variables was carried out using Student's t test or Mann–Whitney U test depending on distribution of variables. Odds ratio values were calculated for analysis of possible risk factors for adverse for reactions. A p value of less than 0.05 was regarded as significant with all statistical tests.

Results

Determination of prevalence and features of self-reported food allergy

Of the 1436 randomly selected individuals, we successfully contacted 965 by telephone (67 % reply rate), and the questionnaire was fully completed in 840 cases (58 % of the total sample). These individuals had a mean age of 48 years (median age: 46 years), and 51.3 % were female. Most individuals belonged to Graffar scale classes III and IV, without significant differences in comparison with individuals who declined to participate in the study (data not shown). Furthermore, participants and those who declined to participate were similar in terms of mean age and gender.

Of these, 52 reported previous adverse reaction upon ingestion of at least one foodstuff, giving an estimated prevalence of 6 % (95 % CI 4.4–7.6 %) (Fig. 1). The self reported reactions had mostly occurred in the 6 months to 5 years previous to the phone contact (n = 35; 42 % of the cases).

Most commonly reported foods were seafood (34.6 %), various fresh fruits (21.1 %) and fish (19.2 %).

Most frequently reported symptoms were cutaneous—urticarial and/or angioedema (48.3 % of the cases), followed by oral allergy syndrome (OAS) (16.6 %), respiratory (15 %) and gastro-intestinal/abdominal—dyspepsia, abdominal pain, diarrhea and/or vomiting (6.6 %) symptoms (Fig. 2). In most cases (55 %), symptoms developed within 30 min upon ingestion and only 26 % of the cases had a delayed onset (between 2 and 24 h) (Fig. 3). The different types of reactions observed, in relation to the timeframe of their development upon ingestion of food (immediate versus delayed), are shown in Fig. 4.

Most individuals reported between two and five episodes with the same food (46.6 %, with seafood being the most frequent one). More than five episodes were reported in 31 % of the cases, with fresh fruits being the food most frequently involved (Fig. 5).

Medical treatment had been given in 29/52 (56 %) of the cases. Most individuals (27/52; 51 %) had never been diagnosed an adverse food reaction, and only 16 % (8/51) had been diagnosed a food allergy by an Allergist.

Having a personal (OR 3.72; 95 % CI 2.04–6.77) or a family history (OR 1.70; 95 % CI 0.90–3.21) of atopy were factors significantly associated with an increased risk of having an adverse food reaction.

Determination of prevalence and features of probable food allergy

Of the 52 cases who reported AFR, 13 (25 %) declined to continue in the study, and 39 were invited to the hospital. We obtained information from all of these individuals (75 % of all AFR cases). Of these, 18 (35 %) reported that they had tolerated the suspected food after the initial phone call, and 21 individuals (40 % of the total of AFR) completed the full study (clinical history, SPT/SPPT and determination of total and allergen-specific IgE levels).

Upon analysis of the clinical history, laboratory data and SPT/SPPT results, an oral challenge test was carried out when there were doubts regarding the presence of a food allergy. Four open oral challenges were performed in two volunteers. One of the challenges was clearly positive (angioedema of the face, tongue and lips starting 15 min upon the beginning of the challenge) but the remaining challenges were negative. The patient with the positive oral challenge (patient #9) refused a new challenge with the other implicated food (Table 1). This patient was regarding as having non-IgE associated food reaction since she had negative food-specific IgE levels, low total

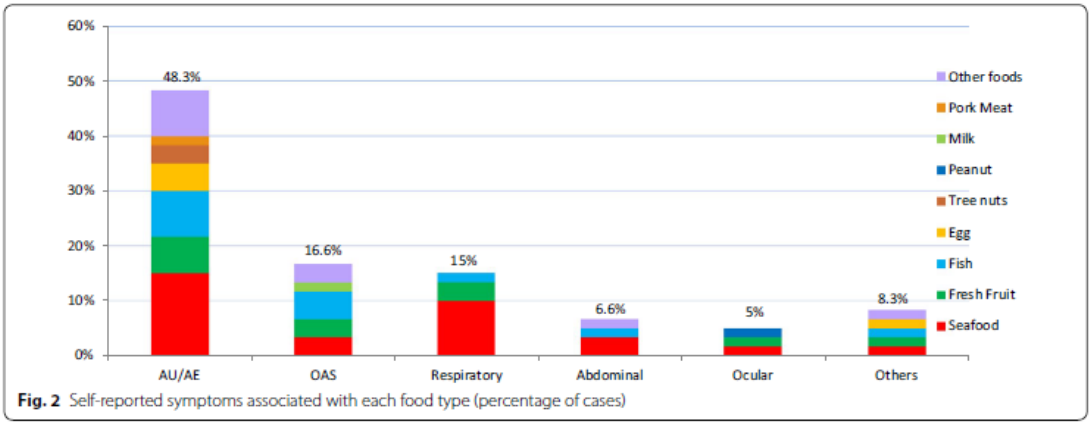


Fig. 2 Self-reported symptoms associated with each food type (percentage of cases)

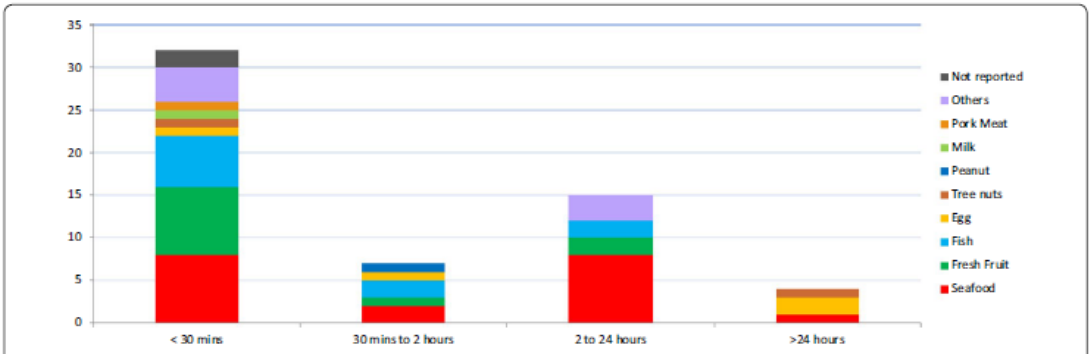


Fig. 3 Time for development of symptoms upon food ingestion (number of cases)

serum IgE levels, negative personal and family history of atopy and her reported reactions upon ingestion of the suspect food were delayed.

An immunologically-mediated adverse food reaction was diagnosed in 9 patients [9/840; 1 % (95 % CI 0.39–1.31 %)] of the total of number of individuals (mean age: 45 years, median age: 47 years, 55.6 % female). IgE-mediated sensitization was demonstrated in 6 of them, giving a value of probable food allergy of 0.71 % (95 % CI 0.14–1.28 %). The details of the patients who were regarded as having immunologically mediated food allergy are shown in Table 1. Most frequently implicated foods were shellfish (50 %) and fish (20 %). IgE-mediated sensitization was only detected in four of the six cases, in association with the ingestion of shellfish and in 1 case, with the ingestion of nuts and peanut. Two individuals had reactions with more than one food, but IgE-mediated sensitization was only shown in one volunteer who was allergic to peanut and nuts.

Of the six cases in which an IgE-associated mechanism was detected, Phadiatop was positive in five, whereas this test was negative in all cases of food allergy in which IgE-mediated sensitization was not shown. In addition, the values of total serum IgE were significantly higher in the group of patients with demonstrated IgE-mediated sensitisation, as compared with the group with non-IgE-mediated reactions (207.33 KUA versus 30.66 KUA, respectively; $p < 0.001$; Mann–Whitney U test).

SPT performed with food commercial extracts were positive with seven out of nine foods reported in the IgE-mediated group, in comparison with only two out of five foods reported in the non-IgE-mediated group (general sensitivity of test of 64 %, specificity of 82 %, PPV: 64 %, NPV: 82 %).

SPPT carried out with fresh foods were positive in eight out of nine cases in the volunteers from the IgE-mediated group and in three out of five volunteers of the

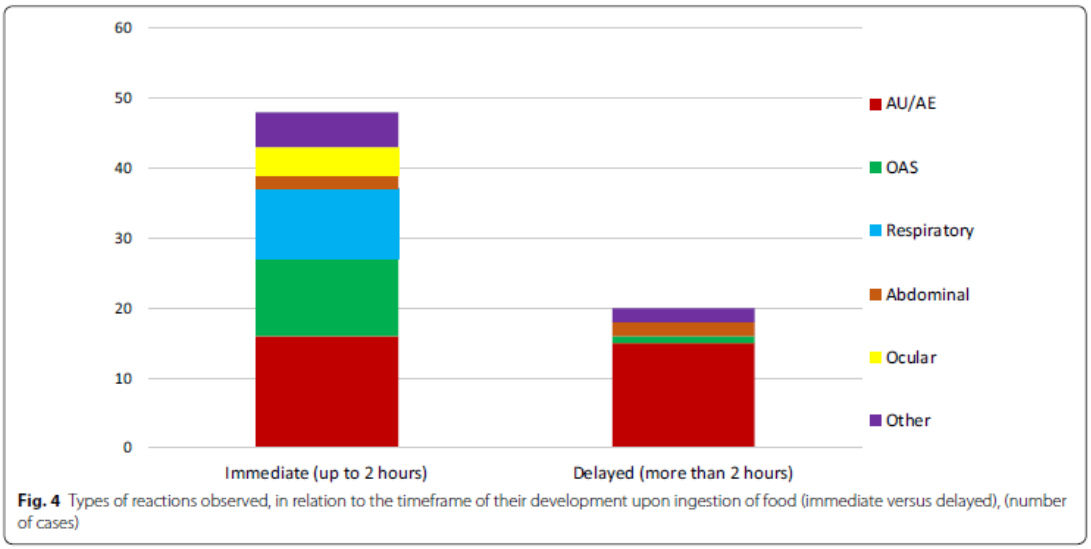


Fig. 4 Types of reactions observed, in relation to the timeframe of their development upon ingestion of food (immediate versus delayed), (number of cases)

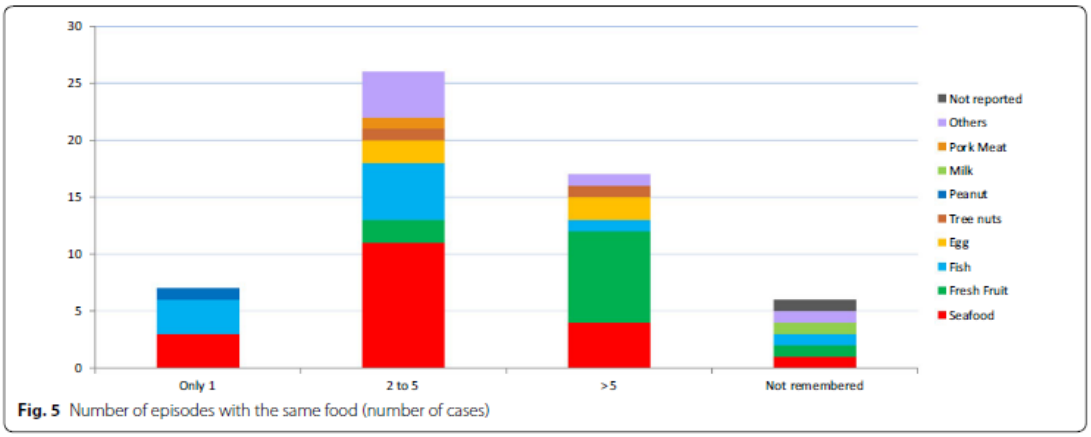


Fig. 5 Number of episodes with the same food (number of cases)

non IgE-mediated group (general sensitivity of the test of 89 %, specificity: 79 %, PPV: 66 %, NPV: 94 %).

In terms of symptoms reported in cases diagnosed as probable food allergy (both IgE- and non-IgE-mediated), the most prevalent one was cutaneous (50 % of cases), followed by respiratory (22 %) and OAS (22 %). Delayed symptoms, occurring between 2 and 24 h upon ingestion, were only reported in three out of nine cases, all of which belonging to the non IgE-mediated group. In the remaining six cases, reactions were immediate, and all occurred in individuals from the IgE-mediated group. Of all the 27 individuals observed at the Hospital, about 57 % reported that they had needed treatment for their food-induced symptoms.

Discussion

The objective of our work was to determine, for the first time in Portugal, the prevalence of probable food allergy, the type of implicated foods, types of symptoms and other associated factors in a general adult population. We have shown that the prevalence of probable food allergies in this population is low, is mostly related to shellfish, peanut and nuts and most frequently involves cutaneous symptoms.

Table 1 Characteristics of diagnosed food allergic patients

Patient ID	#1	#2	#3	#4	#5	#6	#7	#8	#9
Age	37	57	34	36	50	47	55	37	58
Gender	M	M	F	F	M	M	F	F	F
IgE levels (KU_A/L)	114	540	255	128	125	82	36	26	30
Food-specific IgE	Pos	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Neg
Personal history of atopy	Yes	No	Yes	Yes	No	No	Yes	No	Yes
Family history of atopy	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Phadiatop	Pos	Pos	Pos	Pos	Neg	Pos	Neg	Neg	Neg
SPT aeroallergens	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Neg	Neg
Sensitization to >1 food	No	No	No	Yes	No	Yes	No	No	No
Foods	Shellfish	Shellfish	Shellfish	Fruits, seafood	Shellfish	Peanut, tree nuts	Fish	Shellfish	Fish
Manifestations	Asthma	Anaphylaxis	AU/AE	OAS	AU/AE	AU/AE	AU/AE	AU/AE	AU/AE
Time until symptom development	<30 min	<30 min	<30 min	<30 min	30 min–2 h	30 min–2 h	2–24 h	2–24 h	2–24 h
SPT with commercial food extracts	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Pos	Neg
Prick by Prick food skin test	Pos	Pos	Pos	Pos[a]	Pos	Pos	Pos	Pos	Neg
Open food challenge	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Pos
Probable allergy mechanism	IgE-mediated	IgE-mediated	IgE-mediated	IgE-mediated	IgE-mediated	IgE-mediated	Non IgE-mediated	Non IgE-mediated	Non IgE-mediated

M male; *F* female; *Pos* positive; *Neg* negative; *AU* acute urticaria; *AE* angioedema; *OAS* oral allergy syndrome

[a] Positive only to seafood

The utilization of a questionnaire by phone call showed that the prevalence of self-reported food allergy in our study (6 %) was within values reported in other population-based studies namely in Europe, the US and Canada (between 3 and 19 %) [11, 12, 14, 16, 19–23]. On the other hand, the prevalence of probable food allergy in our study (1 %), based upon a positive clinical history, positive skin prick tests and/or food-specific IgE levels and, in some cases, also on a single-blinded food challenge was lower than that observed in North American adults (between 1 and 10 %) [13], but fell within the range of results of various European studies (between 0.8 and 1.1 %) [12, 15, 20].

The discrepancy in prevalence data between self-reported symptoms and symptoms confirmed by medical evidence (in vitro and in vivo tests and/or oral challenges) has been reported by various groups [11, 12, 14, 15, 20, 21]. Curiously, in a study carried out in Canada, no significant differences were observed between self-reported symptoms with a set of five foods [22] and the subsequent confirmation of food allergies [23], but the methodology was different. Thus, most studies have shown that self-reported symptoms tend to overestimate the prevalence of food allergies, and suggest that this may be partly explained by a bias in self perception of symptoms and wrongly ascribing them to the ingestion of foods.

Cultural or health literacy factors, or low accessibility to medical services may also be involved, since, in our study, only 16 % of those individuals who were contacted had previously consulted a specialist doctor because of their symptoms. Nevertheless, differences in prevalence values across studies are hardly comparable, given the heterogeneity of methodologies followed and adult populations included.

The types of foods most frequently implicated in our study, both in self-reported and in probable allergy cases, are included in the so-called "big eight allergens"—milk, egg, peanut, tree nuts, wheat, soy, fish and shellfish [24] and are similar to those found in studies using similar methodologies in Europe [12, 14, 15, 19, 20], namely in Southern Europe [16, 25, 26], the US [7, 9, 21, 27] and Canada [22]. However, the individual prevalence of each food type was different in our study, which may be due to cultural differences in food habits, although we cannot exclude the possibility that the lower size of our sample in comparison with some of the other studies may have influenced the results. In addition, in contrast with our study, the OAS is not always regarded as a symptom of food allergy since it is frequently associated with pollinosis and is regarded as a "secondary allergy" [15, 20, 28].

We also detected discrepancies in implicated foods between the self-reported results (shellfish, fresh fruits and fish) and those obtained upon allergological testing (shellfish, fish, peanut and nuts), as has been previously reported [14, 15, 19, 20]. Furthermore, various meta-analyses [11, 12, 28] have also identified such a discrepancy, and ascribe it to differences in concepts between adverse food reactions perceived by the individual and the immunologically-based "allergy" diagnosed by an allergist. These observations stress the need for an adequate diagnostic approach in order to avoid unnecessary diets [3, 4]. Furthermore, a confirmed diagnosis of food allergy may also increase awareness for prevention of accidental contacts with allergenic foods [29–32].

Cutaneous (urticarial and/or angioedema) manifestations were the most prevalent clinical manifestations both in self-reported and in confirmed, probable food allergy-related cases, as has been previously described [7, 9, 12, 14–16, 19–22, 25, 27], although that was not the case in a questionnaire-based study in the UK [33]. However, in this study, only a limited repertoire of foods was analysed, which may explain this discrepancy.

Analysis of self-reported symptoms found associations between ingestion of certain foods and the development of symptoms. Shellfish, fruits and fish were associated with cutaneous manifestations and OAS, and shellfish and fruit were most frequently associated with respiratory and abdominal symptoms. Fish and shellfish were most frequently triggers of single and more severe episodes (mostly involving respiratory symptoms).

In addition, we also found two different, time-related predominant response patterns, previously identified by Osterballe [20]: an immediate type, developing in up to 30 min post-ingestion, mainly associated with shellfish, fresh fruits and fish, and a delayed type, occurring between 2 and 24 h upon ingestion, with shellfish as the principal implicated food type. The reason underlying this difference is not clear, although it may have been due to discrepant IgE-binding capacity of B cell epitopes on different food allergens [34].

In patients with confirmed probable food allergy, we observed an inverse association between symptom development latency time and their severity. We did not find any case with a latency time greater than 24 h, independently of the pathophysiological mechanism involved, as previously reported [20].

We also performed multivariate analysis of the association between various risk factors and the development of food allergies. Although the relatively small size of our simple may have biased the analysis, personal and family history of allergies were significantly associated with food allergies, which is in agreement with previous studies [1, 7, 12, 35].

Although we performed open food challenges in some of the patients, it was not possible to perform double blind, placebo-controlled food challenges, which are regarded as the "gold standard" for the final diagnosis of food allergies. This was a weakness of our methodology. In spite of this limitation, our approach included not only a standardized clinical history, but also the application of a validated questionnaire, SPT/SPPT, determination of food-specific IgE levels and open oral challenges in certain cases, which makes it a thorough study. In fact, many of the various population studies on food allergies performed in other countries only applied a questionnaire [8, 19, 21–23], and a few others only added skin tests and/or determination of food-specific IgE levels in cases with suspected food allergy [26, 36].

One of the strengths of our study is that we were able to obtain information from most (75 %) of those individuals who had reported a food allergy, indicating that our study was associated with a relatively low drop out rate, which might, otherwise, be a limiting factor. In fact, it has been described that participation rate seems to be inversely related to the thoroughness of a study, averaging between 31–67 % [8, 14, 20] when only questionnaires are involved but dropping to around 40 % [14] when volunteers are requested to undergo a more thorough assessment. In view of this, having had a drop out rate of 25 % in our study allowed us to meet the necessary

calculated requirements for representativeness and statistical proportionality.

Conclusions

The prevalence of probable food allergy in Portuguese adults was low, around 1 %, with shellfish and fish as the most frequently implicated foods. IgE-mediated probable food allergy occurred in 0.71 % of the cases, with shellfish, peanut and nuts mainly involved. Cutaneous symptoms were most frequently reported. There was a discrepancy between self-reported and probable food allergies, both in terms of prevalence values but also in terms of implicated foods.

Our study significantly contributes towards the study of food allergies in Portugal, and it may also be a useful tool for comparison with other studies carried out in other countries.

Additional file

Additional file 1. Validated questionnaire used for assessing adverse food reactions in Portuguese adults.

Abbreviations

AFR: adverse food reaction; AU/AE: acute urticaria/angioedema; CI: confidence interval; IgE: immunoglobulin E; NPV: negative predictive value; OAS: oral allergy syndrome; OR: odds ratio; PPV: positive predictive value; SPPT: skin prick by prick test; SPT: skin prick test.

Authors' contributions

CLI and LTB conceived and coordinated the study and participated in its design. CLI prepared the first draft and carried out the clinical work. LTB helped with writing, reviewed and translated the draft of the manuscript. SMN performed the statistical analysis. AR collaborated in vivo and food oral challenges tests. CL performed in vitro tests. All authors read and approved the final manuscript.

Author details

[1] Castelo Branco Local Health Unit, Allergy Department, Castelo Branco, Portugal. [2] Faculty of Health Sciences, CICS-Health Sciences Research Centre, University of Beira Interior, Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal. [3] Polytechnic Institute of Castelo Branco, Escola Superior de Gestão, Castelo Branco, Portugal. [4] Castelo Branco Local Health Unit, Outpatient Department, Castelo Branco, Portugal. [5] Castelo Branco Local Health Unit, Clinical Pathology Department, Castelo Branco, Portugal. [6] Department of Allergy and Clinical Immunology, Cova da Beira Hospital Centre, Covilhã, Portugal.

Acknowledgements

We thank Nuno Dias for his support with the design of the figures.

Competing interests

The authors declare that they have no competing interests.

Received: 21 March 2016 Accepted: 13 July 2016
Published online: 05 August 2016

References

1. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol. 2011;127:594–602.
2. US National Library of Medicine. National Institues of Health, 2015. Search ("food hypersensitivity" [MeSH terms] or ("food" [all fields] and "hypersensitivity" [all fields]) or "food hypersensitivity" [all fields] or ("food" [all fields] and "allergy" [all fields]) or "food allergy" [all fields]) and ("2004/11/08" [PDat]: "2014/11/05" [PDat]). http://www.ncbi.nlm.nih.gov/pubmed. Accessed 4 Nov 2015.
3. 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;69:159–67.
4. Lau GY, Patel N, Umasunthar T, Gore C, Warner JO, Hanna H, et al. Anxiety and stress in mothers of food-allergic children. Pediatr Allergy Immunol. 2014;25:236–42.
5. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol. 2006;117(Suppl 2):S470–5.
6. Patel DA, Holdford DA, Edwards E, Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. J Allergy Clin Immunol. 2011;128:110–5.
7. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, 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(Suppl 6):S1–58.
8. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. J Allergy Clin Immunol. 2004;114:159–65.
9. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA. ICON: food allergy. J Allergy Clin Immunol. 2012;129:906–20.
10. 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;59:690–7.
11. 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;120:638–46.
12. 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.
13. 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;303:1848–56.
14. 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;59:338–45.
15. Osterballe M, Mortz CG, Hansen TK, Andersen KE, Bindslev-Jensen C. The prevalence of food hypersensitivity in young adults. Pediatr Allergy Immunol. 2009;20:686–92.
16. Falcão H, Lunet N, Lopes C, Barros H. Food hypersensitivity in Portuguese adults. Eur J Clin Nutr. 2004;58:1621–5.
17. Lozoya-Ibáñez C, Macedo A, Rodrigues A, Silva L, Rodrigues E, Pimenta M, et al. Validation of a questionnaire for the study of food allergies in Portuguese adults. Allergy. 2011;66:S395 **(abstract)**.
18. Prates S. Colheita da História Clínica. Rev Port Imunoalergol. 2009;17(Supl I):6–10.
19. 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;108:133–40.
20. Osterballe M, Hansen TK, Mortz CG, Høst A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. Pediatr Allergy Immunol. 2005;16:567–73.
21. Vierk KA, Koehler KM, Fein SB, Street DA. Prevalence of self-reported food allergy in American adults and use of food labels. J Allergy Clin Immunol. 2007;119:1504–10.
22. Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. J Allergy Clin Immunol. 2010;125:1327–35.
23. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol. 2012;130:986–8.

V.1.2. BMJ Open 2019

Open access Protocol

BMJ Open

Prevalence and risk factors for food allergy in older people: protocol for a systematic review

Inês Laia-Dias,[1] Carlos Lozoya-Ibáñez,[2] Isabel Skypala,[3] Jorge M R Gama,[4] Ulugbek Nurmatov,[5] Olga Lourenço,[1,6] Luís Taborda-Barata[6,7]

To cite: Laia-Dias I, Lozoya-Ibáñez C, Skypala I, *et al*. Prevalence and risk factors for food allergy in older people: protocol for a systematic review. *BMJ Open* 2019;**9**:e029633. doi:10.1136/bmjopen-2019-029633

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-029633).

IL-D and CL-I are joint first authors.

Received 02 February 2019
Revised 09 July 2019
Accepted 10 July 2019

For numbered affiliations see end of article.

Correspondence to
Professor Luís Taborda-Barata; tabordabarata@fcsaude.ubi.pt

ABSTRACT

Introduction Studies suggest that the prevalence of food allergy may be increasing worldwide. Results regarding the prevalence and features of adverse food reactions older people have, however, scarcely been analysed in the literature. Thus, the objective of the present systematic review will be to describe the prevalence of food allergy in older individuals, its risk factors, clinical features, as well as the most frequently and commonly involved foods.

Methods and analysis We will conduct a systematic review and meta-analysis of the incidence, prevalence and risk factors for food allergy in older individuals. We will search international electronic databases including MEDLINE, EMBASE, Cochrane Library, CINAHL, AMED and ISI Web of Science for published, unpublished and ongoing studies from 1980 toJanuary 2019. There will be no restriction on the language or geography of publication. We will use the critical appraisal skills programme quality assessment tool to appraise the methodological quality of included studies. A descriptive summary with data tables will be elaborated, and if deemed clinically relevant and statistically adequate, meta-analysis using random-effects modelling will be carried out, given the expected clinical, methodological and statistical heterogeneity of studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist will guide reporting of the systematic review.

Ethics and dissemination Since this systematic review will be solely based on published and retrievable literature, no ethics approval will be obtained. This study will allow us to draw up-to-date estimates of the prevalence of adverse food reactions in older individuals, worldwide, besides allowing the identification of its major risk factors, clinical manifestations and predominant foods responsible for such reactions. A multidisciplinary team has been assembled for this systematic review and will participate in relevant dissemination activities, namely reports, publications and presentations.

PROSPERO registration number CRD42018102140

Strengths and limitations of this study

- ► Food allergy is a growing problem worldwide namely in older individuals.
- ► This is the first systematic review which will specifically address issues related to food allergy in older people, which may have clinical implications.
- ► A thorough and highly sensitive search strategy in leading databases, with no geographical or language restrictions, will be conducted by a multidisciplinary team with expertise in the field.
- ► Study heterogeneity in terms of operational definitions of food allergy may hinder a meta-analysis.

BACKGROUND

The prevalence of food allergies in the general adult population is less well known than in children, since there are fewer studies in the former. Nevertheless, meta-analyses have estimated the prevalence of food allergy in adults to vary between 3.5% and 35% when only based on self-report, and between 2% and 4% when studies include more stringent additional criteria such as positive skin prick tests (SPT) and/or food-specific IgE levels or the gold standard of double-blind placebo-controlled food challenge.[1–3] In addition, the prevalence of food allergy may be increasing worldwide, not only in western countries but also in other countries which have adopted a westernised living style.[1 4]

However, it should be borne in mind that epidemiological studies of food allergies most frequently focus on children and young adults, and reports that specifically include older individuals are scarce.[1–3 5] In fact, most epidemiological results of food allergy involving older people are included in studies that addressed this issue in global populations of adults. Overall, it is not clear whether the prevalence of food allergy is similar, lower or higher in older individuals than in young adults or in children. In this context, a previous meta-analysis has shown that it may be higher in older Europeans,[1] although a second, previous meta-analysis, which screened studies from European and non-European countries showed that the prevalence of food allergy was lower in adults than in children[2]; however, the latter study only used aggregated data, and did not

specifically analyse older adults. Thus, further studies are necessary to clarify this issue. Nevertheless, the prevalence of food allergy may also be increasing in older individuals. For example, the analysis of the US Food and Drug Administration Food Safety Surveys study, which are cross-sectional, telephone surveys of adult American consumers conducted every 3–5 years since 1988 showed that the prevalence of self-reported food allergy increased between 2001 and 2010 in older individuals, although this was only significant in the 60-year-old to 69-year-old group (an increase from 7.7% to 11.7%; p<0.002), but not in the >70-year-old group (increase from 8.7% to 10.6% but p=0.337).[6]

It should also be taken into account that the numbers and relative percentage of older people are increasing worldwide. According to the United Nations,[7] in 2017, 13% of the world population was aged 60 years or over and 2% was aged 80 years or over. In comparison with 2017, by 2050, the population aged 60 years and over is expected to increase twofold (962 million to 2.1 billion), and the population aged 80 years and over may threefold (137 million to 425 million).

The ageing process is accompanied by immunophysiological and biochemical changes that may make food allergies manifest differently in older people, a situation which may be further compounded by concurrent medications and comorbidities, as well as lack of awareness of the problem.[5 8 9] These factors may lead to underdiagnosis and undertreatment of food allergies in older individuals.[5 8] Furthermore, these changes might be reflected not only in clinical manifestations of food allergy but also in positivity of skin test results or levels of food-specific IgE antibodies, which may result in differences in detectable prevalence and risk factors, as well as in predominant foods associated with food allergy in older people. All of these points may demand a different approach regarding its diagnosis and management in comparison with younger adults.[5] However, to the best of our knowledge, no previous systematic review has been published on epidemiological aspects of food allergies specifically in older individuals.

Thus, the objectives of this systematic review will be: (1) to describe the worldwide prevalence, and time trends of food allergy in older people, (2) to describe clinical manifestations and predominant foods associated with food allergy in older people; (3) to analyse risk and prognostic factors associated with food allergy in older individuals.

METHODS AND ANALYSIS

Search strategy

The summary of this systematic review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO)[10].

We have developed a comprehensive search strategy for screening published and unpublished studies. As sources of published studies, we will search the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register), MEDLINE, EMBASE, CINAHL, AMED and ISI Web of Science (Science and Social Science Index).

The bibliographies of all eligible studies will also be scrutinised to identify additional possible studies. Unpublished and research in progress will be searched in key internet-based relevant databases—www.clinicaltrials.gov; http://www.isrctn.com/ (ISRCTN Registry); www.anzctr.org.au. In addition, to extend our search for published, unpublished and ongoing studies, we will contact an international panel of experts in this field.

Studies from all over the world will be included, if they meet the inclusion/exclusion criteria. No language restrictions will be imposed; translations will be undertaken where necessary. We will report any literature that we are unable to translate. Search dates will be from 1980 untilJanuary 2019. Search terms are detailed in online supplementary appendix 1. If any changes are made to the protocol, these will be registered by submission of an updated version to PROSPERO, and will also be documented on the final manuscript with the results of the systematic review.

Inclusion criteria for study designs

We will include all observational, including cohort, case–control and cross-sectional studies. In addition, systematic reviews and meta-analyses with the same focus will be scrutinised. These study designs were selected to ensure the selection and pooling of the highest possible level of evidence based on the aims of this review.

In terms of population, we will select studies that include (not only exclusively) participants aged 60 years or older, reporting or having a diagnosis of food allergy. This cut-off age will used as a criterion for considering an individual as 'older adult' since our systematic review will include studies from all over the world, and the WHO proposed 60 years as a working definition of an 'older person' in African countries.[11] In addition, although 65 years is recommended by WHO as a cut-off level in western countries,[12 13] and this is the threshold used in most studies in older individuals in those countries, there are some epidemiological studies also performed in such countries which use 60-year cut-off age for identifying older people.[6] Thus, we will include data from all individuals who are 60 years or older, in order to ensure that our study will be fully inclusive.

The following study designs will be excluded: narrative literature reviews, discussion papers, non-research letters and editorials, case studies and case series, animal studies.

Study selection

Titles and abstracts of included papers will be independently checked by two investigators. The full text of all potentially eligible studies will be retrieved and independently assessed against the inclusion criteria (see above) by two reviewers. The reviewers will decide which of the studies fit the inclusion criteria: any disagreements

will be resolved by discussion, with a third researcher brought in to arbitrate if needed.

To ensure transparency, the process of selection will be summarised using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Data extraction

Data from selected articles will be extracted independently by two reviewers who will transfer data from their original presentation to a proper form made in Microsoft Excel software, with each study receiving a reference code. Any discrepancy will be resolved by discussion with the third reviewer. If an article presents results from N different studies, then, N different forms will be created to collect data. Before using the form, we will test it in a pilot extraction step with a selected sample of studies. This will allow us to check the capacity of the constructed for to capture the relevant information that will be used for analysis.

If necessary, we will collect indirect data from figures and charts, adapting their interpretation from two different authors by consensus, and authors of original articles will also be contacted for further information and data. In articles in which data from older patients were analysed together with those from younger patients, authors will be contacted in order to clarify or make available data pertaining to the former group, for subgroup analyses.

Data items

The following information will be collected from selected studies involving older individuals, using the same approach that was previously used in a systematic review protocol which involved all epidemiological parameters of food allergies in European individuals of various ages but which did not focus on older individuals[14]: (1) frequency of food allergy (i) by self-report; (ii) by clinical symptoms plus positive SPT or IgE to food allergens; (iii) by clinical symptoms, positive SPT or IgE to food allergens and also food challenge confirmed; (2) most frequently involved food allergens; (3) most frequently observed symptoms and symptom clusters; (4) timeframe of symptom development on ingestion of foods; (5) time trends in frequency of food allergy; (6) geographical differences in prevalence of food allergy and related food allergens; (7) risk factors for food allergy.

Outcome assessment

Diverse methods of assessment have been used to define food allergy in different studies. Thus, for estimation of the prevalence (point, period and lifetime prevalence) and incidence (incidence rate, cumulative incidence) of food allergies, we will include all methods that were used in previous primary studies, including self-reported assessment, clinician diagnosis, allergic sensitisation (based on SPT results, skin prick–prick test results, food allergen-specific IgE levels, skin atopy patch tests) and food challenges (open, single-blinded, double-blinded). However, analyses will take into account each such type of operational definition of food allergy in epidemiological studies.

Regarding the analysis of risk factors and clinical manifestations of adverse food reactions, we will only include studies that have studied objectively confirmed food allergic reactions (using food challenges), since this will ensure the most robust approach to assessing a potential causal relationship between the studied risk factors and the studied outcome (food allergy as expressed by food-induced symptoms in a food challenge). This approach was also followed by the previously mentioned systematic review by Nwaru *et al*, which studied the epidemiology of food allergy for all ages, in Europe.[1]

Risk of bias assessment strategy

Risk of bias assessment will be independently verified by two different reviewers for each individual study that will be selected, using the critical appraisal skills programme quality assessment tool for the types of included studies, including assessment of internal and external validity.[15–17] We will assess heterogeneity, consistency and risk of bias. Quality of evidence and recommendation for the different outcomes will be assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.[18]

All studies and their individual elements will be graded in terms of adequacy of the study regarding the research question, risk of selection bias, measurement of exposure and assessment of outcomes. Disagreements will be resolved by a third reviewer.

Analysis, data synthesis, publication bias and reporting

A narrative synthesis of the data will be performed. In addition, a descriptive summary with data tables will be elaborated, in order to summarise literature findings,[19] and if deemed clinically relevant and statistically adequate, meta-analysis using random-effects modelling will be carried out.[20–22] Forest plot and Funnel plot charts will be made, if necessary, to compare results or to identify publication bias, since publication bias leads to funnel plot asymmetry, if 10 or more relevant studies are detected.[23] Begs and Egger's methods will be used for testing such funnel plot asymmetry.[24 25] Heterogeneity between studies will be analysed using the the I^2 statistical index.[26] Subgroup analysis may eventually be carried out using the following age groups: 60–65, 66–80 and >80 years, if appropriate and if such data can be retrieved from the literature of after contacting authors. Statistical analysis will be carried out using SPSS V.25.0. Finally, the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement and checklist will be followed for reporting of the systematic review.[27 28]

Ethics, dissemination data protection

Ethical approval was not obtained since the data to be collected and analysed cannot be linked to specific individuals. A data management plan will be implemented in

cases in which data from specific studies can be accessed directly or obtained from article authors. Retrieved data will be kept in a database that will have protected access and will only be used by the involved authors.

Patient and public involvement

Since this will be a systematic review, there will be no direct patient or public involvement.

Ethics and dissemination

This systematic review, based on studies published between 1980 and January 2019, will allow us to make assessments and estimates considering the appropriateness of the study design regarding the questions, methods used and risk of selection bias.

More specifically, one strength of the review is that it is novel in that we will provide estimates on the following aspects of food allergy with a focus on older individuals: (1) worldwide prevalence of food allergy in this subgroup of adults; (2) geographical differences in prevalence of food allergy and related food allergens; (3) time trends in prevalence of food allergy and related food allergens; (4) predominant foods associated with food allergy; (5) most frequent symptoms/ symptom clusters, as well as their severity, associated with food allergy; (6) most frequent symptoms associated with specific foods; (7) timeframe of symptom development on ingestion of foods; (8) need for treatment of episodes of food allergy; (9) risk factors associated with food allergy; (10) quality of life due to food allergy (if enough data are available).

Our results will potentially allow drawing conclusions about general and specific aspects of food allergies in older people. This information may be crucial to analysing similarities and differences regarding food allergies between older and younger individuals and eventually defining preventive or diagnostic approaches specifically tailored to the former age group.

Our dissemination strategy will involve presentation at scientific meetings, as well as publication of article(s) in international, peer-reviewed, open-access journals. However, given the increasing relative percentage of older people in the population, the relative lack of awareness of food allergy in this age group, as well as the inherent difficulties in diagnosing food allergies in older individuals, we also plan to organise meetings with general practitioners and other healthcare providers, to analyse and discuss our findings and their potential implications.

Author affiliations
[1]Faculty of Health Sciences, Universidade da Beira Interior, Covilhã, Portugal
[2]Department of Allergy and Clinical Immunology, Hospital Amato Lusitano, Castelo Branco Local Health Unit, Castelo Branco, Portugal
[3]Royal Brompton Hospital, Royal Brompton & Harefield NHS Trust, London, UK
[4]Centre of Mathematics and Applications, Faculty of Sciences, Universidade da Beira Interior, Covilhã, Portugal
[5]Division of Population Medicine, School of Medicine, Cardiff University, Wales, UK
[6]CICS – Health Sciences Research Centre, NuESA – Environment and Health Study Group, Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal
[7]Department of Allergy and Clinical Immunology, Cova da Beira University Hospital Centre, Covilhã, Portugal

Acknowledgements The authors would like to acknowledge Dr Rosa Saraiva, main librarian at the Cova da Beira University Hospital Centre, and Head of the Research and Innovation Department of this institution, for invaluable input in terms of discussion of this manuscript. In addition, the authors would also like to thank Dr Bright Nwaru, Group Leader at the Institute of Medicine, University of Gothenburg, Sweden, for his precious comments regarding the initial steps of designing the search strategy.

Contributors IL-D and CL-I are equal contributors to the design and conceptualisation of this review, and drafted the protocol with primary support from UN (review guarantor) and LT-B. UN, IS and OL were involved in checking various steps of the search strategy, including keywords, as well as the final version of the protocol. JMRG was involved in the statistical strategy for data analysis. IL-D, CL-I and LT-B were involved in establishing eligibility criteria and data extraction forms. All authors provided feedback on the manuscript, at all stages.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Nwaru BI, Hickstein L, Panesar SS, *et al*. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014;69:62–75.
2. Rona RJ, Keil T, Summers C, *et al*. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638–46.
3. Chafen JJ, Newberry SJ, Riedl MA, *et al*. Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;303:1848–56.
4. Tang MLK, Mullins RJ. Food allergy: is prevalence increasing? *Intern Med J* 2017;47:256–61.
5. Jensem-Jarolim E, Jensen SAF. Food allergies in the elderly. Collecting the evidence. *Ann Allergy Asthma Immunol* 2016;117:472–5.
6. Verrill L, Bruns R, Luccioli S. Prevalence of self-reported food allergy in U.S. adults: 2001, 2006, and 2010. *Allergy Asthma Proc* 2015;36:458–67.
7. United Nations,, Department of Economic and Social Affairs,, Population Division. World population prospects: the 2017 revision, key findings and advance tables. Working paper No. ESA/P/WP/ 2017;248.
8. Diesner SC, Untersmayr E, Pietschmann P, *et al*. Food allergy: only a pediatric disease? *Gerontology* 2011;57:28–32.
9. Montanaro A. Allergic disease management in the elderly: a wakeup call for the allergy community. *Ann Allergy Asthma Immunol* 2000;85:85–6.
10. Laia-Dias I, Lozoya-Ibáñez C, Skypala I, *et al*. Prevalence and risk factors for food allergy in elderly individuals: protocol for a systematic review. Prospero 2018: CRD42018102140. Available: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018102140
11. W.H.O. Health Statistics and Information Systems.. Proposed working definition of an older person in Africa for the MDS project. Available: https://www.who.int/healthinfo/survey/ageingdefnolder/en/ [Accessed 7th Jan 2019].
12. World Health Organisation. *Definition of an older or elderly person*. Geneva: Switzerland: WHO, 2010. http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html
13. Orimo H, Ito H, Suzuki T, *et al*. Reviewing the definition of "elderly". *Geriatr Gerontol Int* 2006;6:149–58.
14. Nwaru BI, Panesar SS, Hickstein L, *et al*. The epidemiology of food allergy in Europe: protocol for a systematic review. *Clin Transl Allergy* 2013;3:13.
15. CASP checklist for systematic reviews. Available: https://www.casp-uk.net/wp-content/ uploads/2018/03/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf [Accessed 22nd Dec 2018].

V.1.3 World Allergy Organ. J. 2020

Lozoya-Ibáñez et al. World Allergy Organization Journal (2020) 13:100453
http://doi.org/10.1016/j.waojou.2020.100453

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Prevalence and clinical features of adverse food reactions in Portuguese adolescents

Carlos Lozoya-Ibáñez[a,b,c], Sara Morgado-Nunes[c,d], Alexandra Rodrigues[c,e], Patrícia Fernandes[c,f], Olga Lourenço[b,c], Ana Mafalda Fonseca[b,c] and Luis Taborda-Barata[b,c,g*]

ABSTRACT

Background & aims: The objective of the present study was to determine, for the first time, the prevalence and clinical features of food allergy in Portuguese adolescents.

Methods: Cross-sectional study performed in various secondary schools in central Portugal. Randomly selected adolescents replied to a validated food allergy questionnaire. Those who reported an adverse food reaction were seen at participating hospitals, where clinical history was taken, skin prick (SPT) and prick-prick skin (SPPT) tests were performed, and food allergen-specific IgE levels (sIgE) were determined. An open oral challenge was performed in selected cases. Cases of positive clinical history of immediate (up to 2 h after ingestion) reaction in association with positive food sIgE levels and/or SPT were classified as IgE-associated probable food allergy and as confirmed IgE-mediated food allergy if food challenges were positive. Cases of positive clinical history of delayed (more than 2 h after ingestion) and negative food sIgE levels independently of positive SPT or SPPT results, were classified as non-IgE associated probable food allergy.

Results: The prevalence of probable food allergy in Portuguese adolescents was 1.41% (95% CI: 0.90–2.03%), with fresh fruits, shellfish, nuts, and peanut as the most frequently implicated foods. IgE-mediated probable food allergy occurred in 1.23% (95% CI: 0.67–1.72%) of cases, with fresh fruits, shellfish, and nuts mainly involved. Cutaneous symptoms were most frequently reported.

Conclusions: The prevalence of probable food allergies in Portuguese adolescents is low, is mostly related to fresh fruits, shellfish, nuts, and peanut, and most frequently involves cutaneous symptoms.

Keywords: Adolescents, Adverse food reaction, Food allergy, Prevalence, Cutaneous tests, Open food challenge

INTRODUCTION

Food allergy is a relevant health problem which is associated with considerable morbidity, a non-negligible level of mortality (in cases of food-associated anaphylaxis), and lower quality of life.[1,2] In fact, the impact of food allergies on dietary habits and social integration of food allergic patients is obvious,[3,4] with many affected individuals having to undergo changes in their diet, including, in some cases, very restrictive

[a]Allergy Department, Castelo Branco Local Health Unit, Portugal
*Corresponding author. CICS - Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Avenida Infante D. Henrique, 6200-506, Covilhã, Portugal. E-mail: tabordabarata@fcsaude.ubi.pt
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2020.100453

Received 21 December 2019; Received in revised from 10 June 2020; Accepted 24 July 2020
Online publication date xxx
1939-4551/

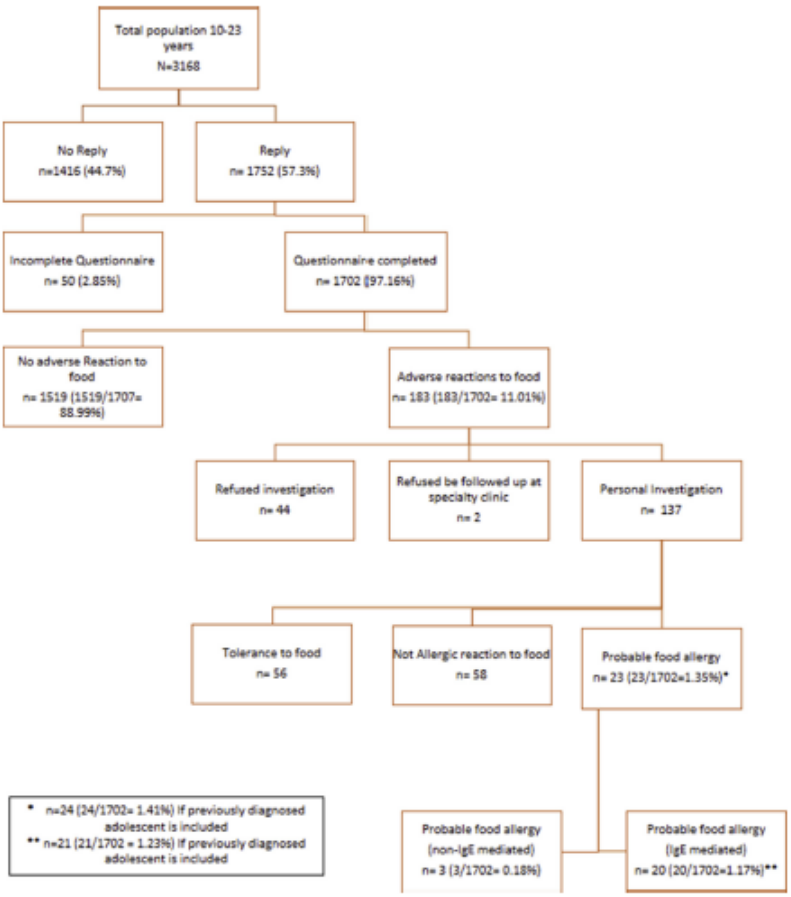


Fig. 1 Flowchart of the study design and investigations

diets, due to an adverse food reaction.[5] In addition, food allergies are also a clear economic burden, namely regarding work or school absenteeism,[6,7] with impact upon school performance[8] and quality of life.[9]

However, not all adverse reactions to foods are regarded as being an immunologically mediated "food allergy".[1,10,11] Partly for this reason, the prevalence values of food allergies in the general adolescent population are not well known. Various meta-analyses have estimated the prevalence of food allergies to any food in schoolchildren to be between 7% and 40% when only self-reported values are analysed,[9,12-15] and between 1% and 3% when studies include diagnostic tests.[14-18] As far as we know, besides a single study in children attending an allergy outpatient clinic,[19] the only actual population-based studies on the prevalence of food allergies carried out in Portugal were performed by our group in children[20] and adults,[21] but no studies in adolescents have been published. Thus, the objective of our study was to determine the prevalence of both self-reported and probable

food allergy, as well as to analyse the clinical features, involved foods, and associated factors in a general population of Portuguese adolescents.

METHODS

Population and sample

For this study, we took into account the fact that 3168 adolescents aged between 1023 years old (mean age: 14.3 ± 1.1; 51.7% female) were registered in 7 secondary schools of the cities of Castelo Branco, and Covilhã, in central Portugal. Based on an estimated prevalence of 4%,[13,22,23] and considering a 95% confidence interval and a margin of error of 2%, we calculated that we would need a representative sample of 399 adolescents (STATA Statistical Package®). Considering an expected reply rate of 40%, we reset the sample size to 779 adolescents.

Study design

This was a cross-sectional study performed in 2013-2015. A list of all students in each class of each school was obtained, and adolescents were selected by a simple randomisation process. A standardised screening questionnaire was given to each volunteer, and those who reported a previous adverse food reaction which was subsequently confirmed by telephone, were invited to an appointment at the outpatient allergy clinics of the participating hospitals, where a standardised food allergy-related clinical history was taken,[24] skin prick tests (SPT) and, when food was available, prick-prick skin tests (SPPT) were performed with a standardised technique, and blood was collected for determination of food allergen-specific IgE levels. In selected cases, an open oral challenge was performed. In these cases, if the patients did not exclude the suspected food from the diet, an elimination diet was followed for a minimum of 7 days prior to the food challenge. Patients with a positive clinical history of immediate (up to 2 h after ingestion) reaction in association with positive food sIgE levels and/or skin prick tests (with or without performance of a positive open challenge) were classified as IgE-associated probable food allergy. Cases of positive clinical history or delayed (more than 2 h after ingestion) and negative food sIgE levels independently of positive SPT or SPPT results, were classified as non-IgE associated probable food allergy.

Questionnaire

A 17-item, previously validated questionnaire on adverse food reactions[25] was given by hand to all volunteers. This questionnaire included demographic data, questions on the occurrence of previous episodes of adverse reactions to foods, types of foods involved, types of reactions, post-ingestion latency time until appearance of symptoms, date of latest reaction, need for medical assistance, and personal or family history of atopic diseases. Those adolescents who reported an adverse food reaction were subsequently contacted by phone by a trained allergist within the following 3 months (Fig. 1). Those who confirmed the previous self-report of an adverse reaction were invited to a full allergy screen at the participating hospitals.

Determination of allergen-specific IgE serum levels

In all individuals seen at the outpatient clinics, 5 ml of peripheral blood were taken for the determination of the levels of total serum IgE, aeroallergen-specific screening IgE (Phadiatop inhalant allergens®), and suspected food-specific IgE levels. No recombinant allergens or pan-allergens were used. A fluorometric (ImmunoCAP® 250 Phadia Diagnosis)-based technique was used (Phadia & Thermo Scientific, Uppsala, Sweden). Allergen-specific levels above 0.35 KU_A/L were regarded as positive.

Skin prick tests

In vivo studies included SPT (LETI Laboratories, Spain; Bial-Aristegui, São Mamede do Coronado, Portugal; Stallergènes, Antony, France) for aeroallergens (house dust mites; cockroach; *fungi*; latex; cat and dog dander; weeds, tree, and grass pollens) and suspected foods and, when available, SPPT with native suspect foods, since the sensitivity of the latter test is higher when compared with SPT using commercial extracts.[26] Tests were carried out in duplicate on the volar aspect of the forearms. A drop of each commercial extract was placed upon the skin, and each drop was pricked through using a metal lancet (Stallergènes, Antony, France). Histamine dihydrochloride as

positive and saline solution as negative controls were used respectively. The mean weal diameter was recorded after 15 min. Weals with a mean diameter at least 3 mm greater than that of the negative control were regarded as positive. SPPT tests used the same methodology, but fresh foods were used.

Oral challenge

Open oral challenges were performed in cases with positive clinical history, SPT and/or SPPT, and sIgE levels to suspect foods, and also in those cases in which clinical history was unclear and SPT results, as well as specific IgE levels, were negative or discrepant. Open challenge tests were carried out with suspect food,[22] in accordance with published guidelines.[10,11,27] In those cases in which individuals did not avoid the suspect foods, in spite of having symptoms, an elimination diet for at least 7 days before the oral challenge was carried out and monitored.[10,11,27-29] Oral challenges were performed at the hospitals, under direct clinical observation for 4 h after challenge. In all cases, volunteers were contacted by phone by the responsible allergist in the following 24 h. Volunteers who reported any symptoms were reassessed at hospital allergy services.

Statistical analysis

Data were analysed using the Software Package for Social Sciences (SPSS) version 20.0® (SPSS Inc., Chicago, IL, USA). Analysis of normality of distribution of variables was performed using the One Sample Kolmogorov-Smirnov test. Descriptive analysis was used for the characterization of the sample. Chi-Square test or Fischer's Exact Test were used in the case of nominal variables. Comparative analysis of quantitative variables was carried out using Student's *t*-test or Mann-Whitney *U* test depending on distribution of variables. Odds ratio values were calculated for analysis of possible risk factors for adverse for reactions. A *p* value of less than 0.05 was regarded as significant with all statistical tests.

RESULTS

Determination of prevalence and clinical features of self-reported food allergy

Of the 3168 questionnaires that were handed out (Fig. 1), 1752 were returned correctly filled in and with the written informed consent (57.3% reply rate). The questionnaire was properly completed by 1702 individuals (97.2% of the total of returned questionnaires; mean age: 14.9 ± 2.1 years; median age: 14 years; 61.9% female). Of these, 183 adolescents reported previous adverse reactions (total of 239 episodes) upon ingestion of at least 1 food (11.01%). These reactions had most frequently taken place 4 months to 5 years before (42.0% of the cases). Most adolescents reported symptoms with more than 1 type of food (50.2%; 92/183). Regarding episodes of adverse food reaction, most commonly implicated foods were fresh fruits (59/239 episodes- 24.7%; 73/239 episodes - 30.5% if latex-related fruits were included as well), seafood (32/239 episodes - 13.4%), milk (30/239 episodes - 12.5%), and nuts (15/239 episodes, excluding peanut - 6.3%) (Fig. 2).

Most frequently reported symptoms were cutaneous (urticaria/angioedema; 107 episodes - 44.7%), followed by abdominal (34 episodes - 14.2%), respiratory symptoms (18 episodes - 7.53%), or oral allergy syndrome (17 episodes - 7.1%). 49 episodes (20.5%), were difficult to define clinically (Fig. 3).

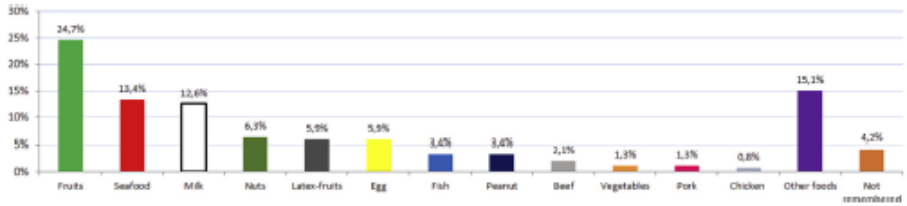


Fig. 2 Most frequently implicated foods by self-report (Values in %); number of episodes = 239

In most of the reported episodes (43.5%), symptoms developed up to 30 min after ingestion, and in 30.95% of the cases had a delayed onset (2–24 h) (Fig. 4).

Most of the 183 adolescents who reported a total of 239 episodes of AFR mentioned 2 to 5 reactions with the same food (48.6%; 89/183 individuals, reporting 116 episodes), with fresh fruits being the most frequent food in this group (38 out of 116 episodes, and in 47 out of 116 episodes if latex related fruits were included). No individuals with latex sensitisation were found.

In addition, 35 out of 183 adolescents (19.15%) reported 46 episodes of an AFR, with seafood being the most frequently associated food in this group (10/46 episodes) (Fig. 5).

About 56% (102/183) of the adolescents needed medical treatment: 67% of them (68 cases) at a hospital emergency department, 12.5% (13 cases) by a general practitioner, 13.5% (14 cases) by self-medication, and 7% (7 cases) by an allergy specialist.

Most individuals who reported reactions (59%) had not been diagnosed an adverse food reaction, and only 30% had been given such a diagnosis by an allergist.

Having a personal (OR: 3.00; 95% CI: 1.80–5.00) or family history (OR: 2.60; 95% CI: 1.53–4.32) of atopy were factors significantly associated with an increased risk of having an adverse food reaction.

Determination of prevalence and clinical features of probable food allergy

Of the 183 individuals who reported an AFR, 44 (24%) declined to continue the study, and 2 adolescents (1.1%) did not complete the study (1 of them had been studied thoroughly already) (Fig. 1). The remaining 137 adolescents (74.9% of the total number of AFR cases) were subsequently seen at an allergy hospital appointment. Of these, 56 (40.9%) reported absence of symptoms upon subsequent ingestion of the suspect food in the period between completion of the questionnaire and the hospital appointment, and were therefore not further studied. Thus, the remaining 81 adolescents under study (59.1% of the 137 adolescents seen at the hospitals) completed the full allergy study (clinical history, SPT/SPPT, food-specific IgE levels, and open oral challenge tests, in some cases). We performed 32 open oral challenges in 27 volunteers, which were clearly positive in 17 of them: isolated OAS in 5 cases; OAS in association with diarrhoea and colicky abdominal pain in 2 cases; vomiting and diarrhoea in 4 cases; isolated generalised urticaria in 2 cases; generalised urticaria and angioedema of lips in 1 case; generalised urticaria and mild dyspnea in 1 case. All of these cases occurred 15–30 min after the onset of the tests; finally, there were 2 cases of delayed reaction: 1 involving colicky abdominal pain and diarrhoea starting 9–12 h after the challenge, and 1 consisting of mild urticarial rash and itchy skin

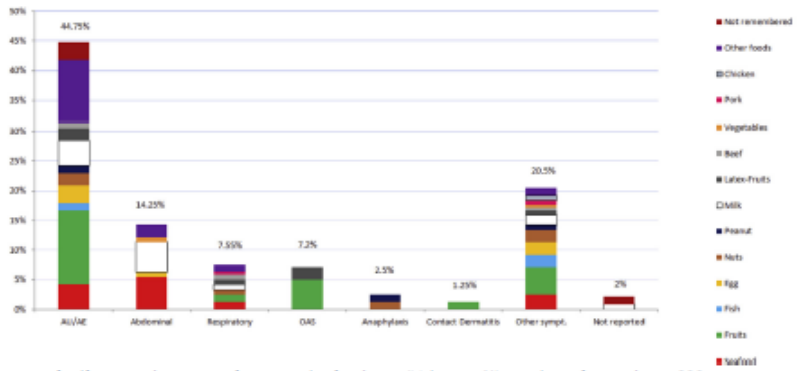


Fig. 3 Distribution of self-reported symptom frequency by food type (Values in %); number of episodes = 239

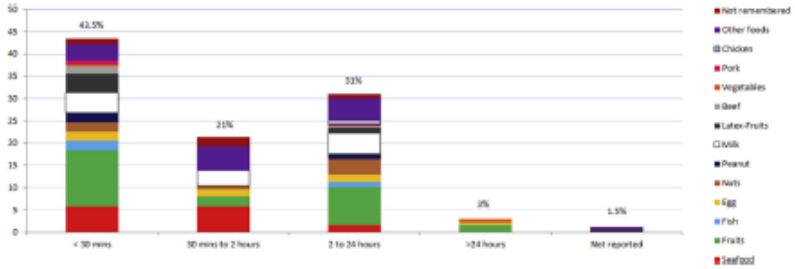


Fig. 4 Self-reported time until development of symptoms upon food ingestion (Values in %); number of episodes = 239

which started 12 h after the test. No cases of delayed anaphylaxis were identified.

Upon completion of the study, 24 adolescents (1 had already been diagnosed IgE-mediated milk allergy in another hospital) were diagnosed an AFR with an immunological basis (24/1702; 1.41% of the total number of adolescents that filled in the questionnaire; 95% CI = 0.90-2.03%; mean age: 15.1 years, median age: 15 years, 54.1% female), and a probable IgE-mediated mechanism was detected in 21 of them (21/1702; I.23%; 95% CI: 0.67–1.72%.) (Table 1 shows the results for the newly diagnosed adolescents).

Most frequently implicated foods were fresh fruits (30.8%). Most of these belonged to the *Rosaceae* family (80% of cases) – apple, pear, strawberry, and/or plum. Banana (*Musaceae*) and/or melon (*Cucurbitaceae*) were involved in 10% of cases, and orange and/or tangerines (*Rutaceae*) in 8% of cases; in the remaining cases, patients reported multiple sensitisations to these fruits. Other reported foods mostly included shellfish (26.9%, mainly crustaceans), nuts (23% walnut, cashew and hazelnut), peanut and milk (7.7% each), and egg (3.8% each). In the 20 cases in which an IgE-mediated association was newly found, specific IgE levels to implicated foods as well as Phadiatop were positive in all of them, and in addition, the mean total IgE serum levels were higher than compared with the group with non-IgE-mediated reactions (265.78 KU_A/L versus 63.93 KU_A/L, respectively; $p < 0.001$; Mann-Whitney *U* Test), Of the 3 adolescents in whom no IgE-associated mechanism was demonstrated, only 2 were atopic, 1 with a positive Phadiatop® test and 1 with positive SPT to aeroallergens. SPT performed with commercial food extracts were positive in 19 foods out of 22 in the group of adolescents with an IgE-associated mechanism and in 3 out of 9 foods tested in the non-IgE associated cases (general test sensitivity of 66.7%, specificity

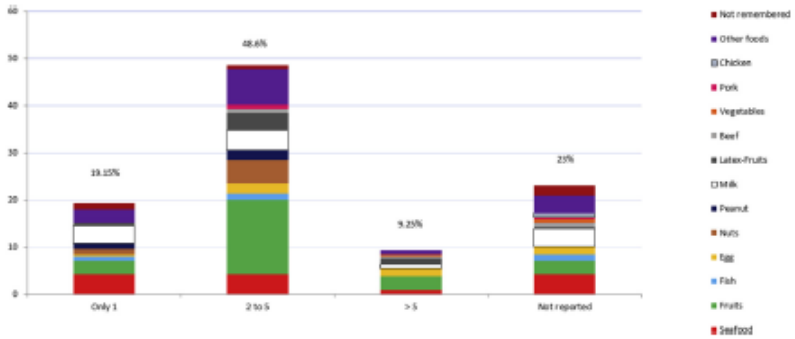


Fig. 5 Self-reported number of episodes induced by the same food (Values in %); number of adolescents (cases) = 183

Patient ID	Age	Sex	IgE levels (KUA)	Food Specific IgE	Personal History of atopy	Family History of atopy	SPT aero allergens	Sensitisation to more than one foodstuff	Foodstuff	Symptoms	Time to symptom development	Similar episodes with the same food	SPT with Commercial food extracts	Food Prick by Prick skin test	Open Food Challenge	Allergy mechanism
#1	12	M	269	POS	Yes	No	POS	No	Other tree nuts	Anaphylaxis	<30 mins	2 to 5	POS	POS	Not performed	IgE mediated
#2	12	M	69	Negative	Yes	No	Negative	No	Milk	Other symptoms	>24 h	>5	Negative	Not performed	POS	Non IgE mediated
#3	12	F	258	POS	Yes	Yes	POS	Yes	Peanut, Egg	UA/AE	<30 mins (peanut),	Only 1	POS (peanut), Negative (egg)	POS (peanut)	Not performed	IgE mediated (only for peanut)
											2-24 h (Egg)			Negative (Egg)		
#4	13	M	529	POS	Yes	Yes	POS	No	Fruits	OAS	<30 mins	>5	Negative	POS	Not performed	IgE mediated
#5	15	F	230	POS	Yes	Yes	POS	No	Seafood	UA/AE	<30 mins	2 to 5	Negative	POS	POS	IgE mediated
#6	15	F	92	POS	Yes	Yes	POS	No	Other tree nuts	Anaphylaxis	<30 mins	Only 1	POS	POS	Not performed	IgE mediated
#7	15	F	86	POS	Yes	Yes	POS	No	Fruits	OAS	<30 mins	>5	POS	POS	Not performed	IgE mediated
#8	18	F	114	POS	No	No	POS	No	Fruits	UA/AE	30 mins to 2 h	>5	POS	POS	POS	IgE mediated
#9	19	M	303	POS	Yes	Yes	POS	No	Other tree nuts	UA/AE	30 mins to 2 h	Only 1	POS	Not performed	Not performed	IgE mediated
#10	16	M	164	POS	Yes	Yes	POS	No	Fruits	OAS	<30 mins	2 to 5	POS	POS	POS	IgE mediated
#11	16	M	233	POS	Yes	Yes	POS	No	Fruits	OAS	<30 mins	2 to 5	POS	POS	POS	IgE mediated
#12	16	M	238	POS	Yes	No	POS	No	Fruits	OAS	<30 mins	>5	POS	POS	POS	IgE mediated
#13	14	F	112	POS	Yes	Yes	POS	No	Fruits	OAS	<30 mins	>5	POS	POS	POS	IgE mediated
#14	17	F	279	POS	Yes	Yes	POS	No	Seafood	Anaphylaxis	<30 mins	Only 1	POS	POS	POS	IgE mediated
#15	16	F	1686	POS	Yes	Yes	POS	No	Seafood	Anaphylaxis	<30 mins	Only 1	POS	POS	POS	IgE mediated

(continued)

Patient ID	Age	Sex	IgE levels (KUA)	Food Specific IgE	Personal History of atopy	Family History of atopy	SPT aero allergens	Sensitisation to more than one foodstuff	Foodstuff	Symptoms	Time to symptom development	Similar episodes with the same food	SPT with Commercial food extracts	Food Prick by Prick skin test	Open Food Challenge	Allergy mechanism
#16	16	M	88,5	POS	Yes	No	POS	No	Seafood	UA/AE	<30 mins	2 to 5	POS	POS	POS	IgE mediated
#17	15	F	112,7	POS	Yes	Yes	POS	No	Seafood	UA/AE	<30 mins	2 to 5	POS	POS	POS	IgE mediated
#18	17	M	131,2	POS	Yes	No	POS	Yes	Peanut, Seafood	Peanut: OAS Seafood: UA/AE	<30 mins	2 to 5	POS (peanut & seafood)	Not performed	POS (seafood) Negative (peanut)	IgE mediated (only for seafood)
#19	14	F	127,9	POS	Yes	Yes	POS	No	Seafood	UA/AE, Abdominal	<30 mins	2 to 5	POS	POS	POS	IgE mediated
#20	15	F	34,9	Negative	No	No	POS	No	Other tree nuts	Respiratory	2-24 h	2 to 5	POS	Negative	POS	Non IgE mediated
#21	14	F	114,4	POS	Yes	Yes	POS	No	Other tree nuts	UA/AE	<30 mins	2 to 5	POS	Not performed	POS	IgE mediated
#22	16	M	87,9	Negative	No	No	Negative	No	Other tree nuts	UA/AE	2-24 h	2 to 5	Negative	POS	POS	Non IgE mediated
#23	15	M	148	POS	Yes	Yes	POS	No	Fruits	OAS	<30 mins	>5	POS	Not performed	POS	IgE mediated

Table 1. (Continued) Characteristics of newly diagnosed Food Allergic patients

of 100%, PPV: 100%, NPV: 86.4%). No differences between commercial extracts were found. Fresh food SPPT were positive in 13 out of 15 cases in the group of adolescents with an IgE-associated mechanism and only 1 in the non-IgE associated cases (general test sensitivity of 87.5%; specificity: 100%, PPV: 100%, NPV: 91.7%).

The most prevalent symptoms in all studied cases were cutaneous (40% of cases), followed by OAS (32%) and anaphylaxis (16%), with the latter being associated with the ingestion of nuts and shellfish (2 cases each). Only in the 3 cases which were not IgE-associated were the symptoms delayed, appearing more than 2 h after ingestion, since in all cases with an IgE-association, symptoms appeared in less than 2 h upon ingestion.

Of all the adolescents who finished the study at the hospitals (81 individuals), 65 cases (80.2%) needed treatment for their symptoms, mostly at an emergency department. However, only 6 individuals with a diagnosis of probable food allergy (4 with anaphylaxis, 1 with respiratory symptoms, and 1 with cutaneous symptoms) sought medical attention. A high proportion of cases diagnosed with food allergy (either IgE- or non-IgE-associated) reported the presence of personal and/or family history of atopy.

No significant association factors were seen between sex, age, locality of origin (rural vs urban areas), type of food, and time elapsed since the latest reaction. In the same way, we found no significant association between severity of the food-induced reaction and total serum IgE levels.

DISCUSSION

Our study determined, for the first time in Portugal, the prevalence of probable food allergy, the type of implicated foods, types of symptoms, and other associated factors in an adolescent population. We have shown that the prevalence of probable food allergies in this population is low, is mostly related to fresh fruits and nuts, and most frequently involves cutaneous symptoms.

The initial, written questionnaire showed that the values of self-reported food allergy (11.01%) were within the range described in other population-based studies (3–40%).[9,12-16,22,30-33] Similarly, the value obtained in our study for the prevalence of probable food allergy (1.41%) is similar to that reported for adolescents in the United States (2,5%)[23,34] and Europe (0.5%–3.5%),[15,33] although the latter values were obtained after performance of single or double-blind oral challenge tests.[13,14,17,30,33,35]

This discrepancy in prevalence results between self-reported and medically confirmed data (using *in vitro* and *in vivo* tests and/or oral challenge) has been described. Previous studies have shown that self-reports tend to overestimate food allergies.[12-15,17,22,30,33,36-38] This discrepancy may be partly due to an information bias based upon an enhanced self-perception of symptoms which are wrongly ascribed to food ingestion. Cultural factors, health literacy, or accessibility to a medical diagnosis may be involved[15,33] (in our study, only 16% of the adolescents that reported food-associated symptoms had ever seen an allergist for that reason). Nevertheless, prevalence values across different studies are hardly comparable, given the heterogeneity of study designs and the types of population involved. In any case, the overestimation of self-reported food-related adverse food reactions may be worrying since it is frequently associated with inappropriate restriction diets with subsequent nutritional deficits.[3]

The implicated foods, both in self-reported allergies as well as in test-confirmed, probable food allergies, in our study are included in the so-called "big eight allergens"[37] and are similar to those found in other population-based studies using similar methodology in Europe,[9,13,14,16,17,22,30,39,40] Asia,[38,41] and the United States.[10,23,31,32,42,43] However, fresh fruits being the most frequently implicated foods, places our study in line with those performed in western and Mediterranean Europe,[16,17,22] but not with those from northern Europe, North America[9,10,13,14,23,30,31,43,44] or, surprisingly, the eastern Mediterranean Europe,[33] probably due to differences in study methodology. In fact, these differences may be partly due to different food habits[38] or concurrent pollen sensitisation, although we cannot exclude the possibility that the comparatively smaller size of our sample may have influenced our results. On the other hand, it is also fundamental to stress that, in contrast with

our study, OAS is often not regarded as a symptom of food allergy, since it is frequently associated with pollen-induced respiratory symptoms in the same patient, as happened in our study, and is therefore regarded as a "secondary allergy" by various research groups.[30,35,45]

It is also important to highlight the discrepancy between the panels of implicated foods when we compared self-reported results with those obtained upon completion of the allergy study. Whereas the self-reported panel mainly included fresh fruits, milk, and shellfish, the confirmed (post-tests) panel essentially identified fresh fruit and nuts. Other studies have also identified similar situations in adolescents in Europe[15,16,22,30,35] and this has been confirmed by meta-analyses,[12,13,45] having such discrepancies partly ascribed to differences in the concept of adverse food reactions between patients and specialist doctors. This highlights the need for an adequate diagnostic approach to food-associated symptoms, so that subsequent detrimental situations may be averted or better controlled.[46] These include inadequate diets,[3] difficulties in the reintroduction of the "culprit" food in case allergy was not confirmed,[47] stress and anxiety because of eventual accidental ingestion of suspected foods,[2,4,48] or even bullying at school.[49]

Cutaneous symptoms were the most prevalent ones in our study, both in self-report and in those adolescents who completed the full allergy workup. This is in agreement with results from most other groups.[10,11,13,16,22,23,30,35,37,43]

An interesting aspect of our work was the analysis of data obtained from the self-reported symptoms. We found several possible associations between the ingestion of certain foods and the development of certain symptoms (fresh fruits, milk, and egg in relation to cutaneous manifestations, shellfish in relation to abdominal symptoms, fresh fruits in connection with OAS, and nuts and peanuts in anaphylaxis), associations which, except for the latter 2, had not been previously reported. On the other hand, bearing in mind the timeframe for the appearance of symptoms, we found 2 predominant response patterns, previously identified by Osterballe:[30] an immediate type of reaction, arising in less than 30 min post-ingestion, and a more delayed, between 2 and 24 h post-ingestion, mainly associated with fresh fruits and milk, in both cases.

As far as adolescents with probable allergy are concerned, we also found an inverse relationship between symptom latency time and symptom severity. In addition, anaphylaxis cases were all associated with the ingestion of nuts and peanut. It should be stressed that the 3 non-IgE mediated cases had a latency time longer than 2 h and most IgE-mediated cases had developed within 30 min upon ingestion.

We also analysed eventual risk factors associated with food allergies. Multivariate analysis showed that a personal or a family history of atopy were significantly associated with a higher risk of having food allergies, as has been described in previous studies and metanalyses focusing on adolescents and children.[1,10,13,14,50]

One of the limitations of the present study was the fact that we could not perform double-blind, placebo-controlled food challenges, a test which is regarded as the "gold standard" for the final diagnosis of food allergy. In spite of this, the current report is the first population-based study in Portuguese adolescents. Furthermore, it yields information on probable food allergy in this population, based upon not only a positive clinical history/questionnaire, but also on diagnostic tests including SPT, food-specific IgE levels, and open oral food challenges (particularly in cases that were clinically less clear or in which there were diagnostic doubts), which makes it a very thorough study. In fact, a high proportion of population-based studies on food allergies performed in other countries only applied a questionnaire,[16,30,35,37,43] and others only performed SPT or determination of food-specific serum IgE in suspect cases of food allergy.[9,17,38]

Another possible limitation of our study concerns the fact that 25.1% of the adolescents who reported adverse food reactions did not complete the study, which is partly explained by the clear national increase in the "Healthcare service usage" fees, during the implementation of the study. In addition, an increase in unstable employment during the period of the study limited absences from work by parents accompanying the adolescents in hospital visits. A relatively high drop-out rate and low participation are indeed limiting

factors in population-based epidemiological studies, and this has been reported in multiple studies, with the reply rate being inversely associated with the magnitude of the study. The reply rate has varied between 40-50%[14,22,30,35] and 61-86%[9,15,16] when studies are only based upon questionnaires, and lower[22,35] when a more thorough assessment (skin tests, blood tests, food challenges) is involved, with a Turkish study being the only exception we found.[33] Nevertheless, our reply rate was quite acceptable for this type of study (57.3%). In spite of the relative limitations in our study, the size of our sample and the features of our work reached the predefined values in terms of statistical power, representativity, and proportionality for analysis. Relatively low reply rates may also lead to a selection bias, mainly with people who are more concerned about allergy problems and more prone to returning the questionnaire. However, if this were the case, we would expect to find high self-report prevalence rates, in comparison with other studies, and this was not the case. Finally, in order to more firmly extrapolate our results to other regions of Portugal, further studies carried out in other regions of the country, as well as a nationwide, multicentre study, are warranted.

CONCLUSIONS

The prevalence of probable food allergy in our sample of Portuguese adolescents was low. Fresh fruits, shellfish, nuts, and peanut were the main implicated foods, and the most frequently reported symptoms were cutaneous. There was a clear discrepancy between self-reported and probable food allergy, both in terms of prevalence and of the implicated foods.

This study is the first step towards a thorough study of food allergies and their repercussions in Portugal and may contribute towards a global characterization of food allergies in adolescents in Europe.

Abbreviations

AFR: Adverse Food Reactions; CI: Confidence Interval; IgE: Immunoglobulin E; NPV: Negative Predictive Value; OAS: Oral Allergy Syndrome; OR: Odds ratio; PPV: Positive Predictive Value; SPT: Skin prick test; SPPT: Skin prick-prick test

Consent for publication

All authors gave their written consent for publication.

Author' contributions

CLI and LTB conceived and coordinated the study and participated in its design. CLI prepared the first draft and performed the clinical approach. LTB helped, reviewed and translated to draft the manuscript. SMN performed the statistical analysis. AR and LTB performed *in vivo* and food oral challenges tests. PF performed *in vitro* tests. OL and AMF applied the questionnaires. All authors read and approved the final version of this manuscript.

Availability of data and materials

Please contact corresponding author for primary data requests.

Funding

This project did not receive any specific funding from any agency, commercial or not not-for-profit sectors.

Ethical aspects

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committees of the Amato Lusitano Hospital, the Administrative Sub-Region of Health of Castelo Branco and the University of Beira Interior. It was also approved by the Ministry of Education (DGIDC, Reg. Nº 0266300001 from January 2012). All volunteers and their legal guardians/ parents gave their written informed consent.

Declaration of Competing Interests

The authors declare no conflicts of interest.

Acknowledgments

We would like to thank Nuno Dias for his support for the graphics design and Marisa Padilha, Ana Martins and Mónica Lopes (Faculty of Health Sciences of the University of Beira Interior) for their collaboration in the application of the questionnaire.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2020.100453.

Author details

[a]Allergy Department, Castelo Branco Local Health Unit, Portugal. [b]CICS-Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal. [c]CACB - Clinical Academic Center of Beiras, Portugal. [d]Polytechnic Institute of Castelo Branco, Escola Superior de Gestão, Castelo Branco, Portugal. [e]Outpatient Clinic Department, Castelo Branco Local Health Unit, Portugal. [f]Clinical Pathology Department, Castelo Branco Local Health Unit, Portugal. [g]Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre, Covilhã, Portugal.

REFERENCES

1. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*. 2011;127:594–602.
2. Namork E, Fæste CK, Stensby BA, Egaas E, Løvik M. Severe allergic reactions to food in Norway: a ten year survey of cases reported to the food allergy register. *Int J Environ Res Publ Health*. 2011;8:3144–3155.
3. de Silva D, Geromi M, Panesar SS, et al. On behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group. Acute and long-term management of food allergy: systematic review. *Allergy*. 2014;69:159–167.
4. Lau GY, Patel N, Umasunthar T, et al. Anxiety and stress in mothers of food-allergic children. *Pediatr Allergy Immunol*. 2014;25:236–242.
5. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol*. 2006;117(2 Suppl):S470–S475.
6. Patel DA, Holdford DA, Edwards E, Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. *J Allergy Clin Immunol*. 2011;128:110–115.
7. Flabbee J, Petit N, Jay N, et al. The economic costs of severe anaphylaxis in France: an inquiry carried out by the Allergy Vigilance Network. *Allergy*. 2008;63:360–365.
8. Calsbeek H, Rijken M, Bekkers MJ, Dekker J, van Berge Henegouwen GP. School and leisure activities in adolescents and young adults with chronic digestive disorders: impact of burden of disease. *Int J Behav Med*. 2006;13:121–130.
9. Marklund B, Ahlstedt S, Nordström G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. *Health Qual Life Outcome*. 2006;4:48.
10. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, 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(6 Suppl):S1–S58.
11. Burks AW, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol*. 2012;129:906–920.
12. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007;120:638–646.
13. Nwaru BI, Hickstein L, Panesar SS, 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.
14. Pereira B, Venter C, Grundy J, Clayton B, Arshad H, 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.
15. Kavaliunas A, Surkiene G, Dubakiene R, et al. Europrevall survey on prevalence and pattern of self-reported adverse reactions to food and food allergies among primary schoolchildren in Vilnius, Lithuania. *Medicina*. 2012;48:265–271.
16. 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.
17. Pénard-Morand C, Raherison C, Kopferschmitt C, et al. Prevalence of food allergy and its relationship to asthma and allergic rhinitis in schoolchildren. *Allergy*. 2005;60:1165–1171.
18. Caffarelli C, Coscia A, Ridolo E, et al. Parent's estimate of food allergy prevalence and management in Italian shool-aged children. *Pediatr Int*. 2011;53:505–510.
19. Bento ML, Armando F, Cesar-Ramos JM. Epidemiology of food allergy in Portugal. *Pediatr Pulmonol*. 2001;(Supplement 23):38–40.
20. Jorge A, Soares E, Sarinho E, Lorente F, Gama J, Taborda-Barata L. Prevalence and clinical features of adverse food reactions in Portuguese children. *Allergy Asthma Clin Immunol*. 2017;13:40. https://doi.org/10.1186/s13223-017-0212-y.
21. Lozoya-Ibáñez C, Morgado-Nunes S, Rodrigues A, Lobo C, Taborda-Barata L. Prevalence and clinical features of adverse food reactions in Portuguese adults. *Allergy Asthma Clin Immunol*. 2016;12:36. https://doi.org/10.1186/s13223-016-0139-8.
22. Zuberbier T, Edenharter G, Worm M, et al. Prevalence of adverse reactions to food in Germany-a population study. *Allergy*. 2004;59:338–345.
23. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol*. 2010;126:798–806.
24. Prates S. Colheita da História Clínica. *Rev Port Imunoalergol*. 2009;17(supl I):6–10.
25. Lozoya-Ibáñez C, Macedo A, Rodrigues A, et al. Validation of a questionnaire for the study of food allergies in Portuguese adults. *Allergy*. 2011;66:S395 (Abstract).
26. Romano A, Di Fonso M, Giuffreda F, et al. Food-dependent exercise-induced anaphylaxis: clinical and laboratory findings in 54 subjects. *Int Arch Allergy Immunol*. 2001;125:264–272.
27. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, 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.
28. Liebermann JA, Sicherer SH. Diagnosis of food allergy: epicutaneous skin tests, in vitro tests, and oral food challenge. *Curr Allergy Asthma Rep*. 2011;11:58–64.
29. Fleischer DM, Bock SA, Spears GC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr*. 2011;158:578–583.
30. Osterballe M, Hansen TK, Mortz CG, Høst A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol*. 2005;16:567–573.
31. Soller L, Ben-Shoshan M, Harrington DW, et al. Overall prevalence of self-reported food allergy in Canada. *J Allergy Clin Immunol*. 2012;130:986–988 (letter).
32. McGowan EC, Keet CA. Prevalence of self-reported food allergy in the national health and nutrition examination survey (NHANES) 2007-2010. *J Allergy Clin Immunol*. 2013;132:1216–1219. e5 (letter).
33. Kaya A, Erkoçoglu M, Civelek E, Çakir B, Kocabas CN. Prevalence of confirmed IgE-mediated food allergy among adolescents in Turkey. *Pediatr Allergy Immunol*. 2013;24:456–462.

34. JJS Chafen, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. *J Am Med Assoc*. 2010;303:1848-1856.
35. Roehr CC, Edenharter G, Reimann S, et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. *Clin Exp Allergy*. 2004;34:1534-1541.
36. 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.
37. Vierk KA, Khoeler KM, Fein SB, Street DA. Prevalence of self-reported food allergy in American adults and use of food labels. *J Allergy Clin Immunol*. 2007;119:1504-1510.
38. Mahesh PA, Wong GWK, Ogorodova L, et al. Prevalence of food sensitization and probable food allergy among adults in India: the EuroPrevall INCO study. *Allergy*. 2016;71:1010-1019.
39. Kummeling I, Mills ENC, Clausen M, et al. The EuroPrevall surveys on the prevalence of food allergies in children and adults: background and study methodology. *Allergy*. 2009;64, 1493-1467.
40. Fernández-Rivas M, Barreales L, Mackie AR, et al. The EuroPrevall outpatient clinic study on food allergy: background and methodology. *Allergy*. 2015;70:576-584.
41. Wong GWK, Mahesh PA, Ogorodova L, et al. The EuroPrevall-INCO surveys on the prevalence of food allergies in children from China, India and Russia: the study methodology. *Allergy*. 2010;65:385-390.
42. McClain S, Bowman C, Fernández-Rivas M, Ladics GS, Van Ree R. Allergic sensitization: food- and protein-realted factors. *Clin Transl Allergy*. 2014;4:11.
43. Ben-Shoshan M, Harrington DW, Soller L, et al. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. *J Allergy Clin Immunol*. 2010;125:1327-1335.
44. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9-17.
45. Zuidmeer L, Goldhahn K, Rona RJ, et al. The prevalence of plant food allergies: a systematic review. *J Allergy Clin Immunol*. 2008;121:1210-1218.
46. Crevel R, Ronsmans S, Marsaux C, Bánáti D. ILSI Europe's food allergy task force: from defining the hazrd to assessing the risk from food allergens. *J AOAC Int*. 2018;101:91-95.
47. Eigenmann PA, Caubet J-C, Zamora SA. Continuing food-avoidance diets after negative food challenges. *Pediatr Allergy Immunol*. 2006;17:601-605.
48. Le TM, Zijlstra WT, van Opstal EY, et al. Food avoidance in children with adverse food reactions: influence of anxiety and clinical parameters. *Pediatr Allergy Immunol*. 2013;24:650-655.
49. Shemesh E, Annunziato RA, Ambrose MA, et al. Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics*. 2013;131:e10.
50. McBride D, Keil T, Grabenhenrich L, et al. The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr Allergy Immunol*. 2012;23:230-239.

Lozoya-Ibáñez et al. World Allergy Organization Journal (2020) 13:100456
http://doi.org/10.1016/j.waojou.2020.100456

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Development of a screening questionnaire for the study of food allergy in adults

Carlos Lozoya-Ibáñez[a,b,c], João Belo[c,d], Rosa M. Afonso[c,e], Henrique Pereira[c,e], Alexandra Rodrigues[c,f] and Luís Taborda-Barata[b,c,g*]

ABSTRACT

Background & aims: As far as we know, no screening questionnaire has been developed and validated for identification of adverse food reactions in Portuguese-speaking adults, as an initial approach towards the investigation of cases of possible food allergy. Thus, the objective of this study was to develop and validate a screening questionnaire of food allergy in adult Portuguese-speaking patients.

Methods: This was a multicentre, cross-sectional study using a simple random sample of 186 adults between 18 and 82 years old from various parts of the centre of Portugal. Intelligibility of the questionnaire was first assessed in 24 patients with confirmed IgE- or non-IgE-mediated food allergy, and in 24 volunteers without food allergies. The 17-item questionnaire was subsequently applied by phone to 78 food allergic patients (66 IgE-mediated and 12 non-IgE mediated) and to 60 non-food allergic volunteers, with subsequent reassessment (re-test). Face and content validity, intelligibility, construct validity, and test-retest reliability (temporal stability) were analysed.

Results: Face and content validity allowed item reduction from 30 to 17 items with adequate content validity index >0.78. Construct validity was confirmed in the 66 confirmed IgE-mediated food allergic patients, 12 non-IgE-mediated food allergic patients, and 60 non-allergic patients. Test-Retest Reliability (general temporal stability) of the test had a Spearman correlation coefficient value of 0.845 for the retest. Cohen's Kappa values for the relevant questions were greater than 0.890 for almost all items. No differences were found when sex, age, and volunteers' recruitment origin were analysed. An inverse relationship was found between reliability and retest time interval.

Conclusions: Due to the quick and easy implementation, confirmation of face, content and construct validity as well as high temporal reproducibility, this screening questionnaire may be a useful study tool for an initial approach to detection of food allergies in adults.

Keywords: Adults, Adverse food reactions, Food allergy, Questionnaire, Validation

[a]Allergy Department, Castelo Branco Local Health Unit, Castelo Branco, Portugal
*Corresponding author. Faculty of Health Sciences, University of Beira Interior, Avenida Infante D. Henrique, 6200-506, Covilhã, Portugal. E-mail: tabordabarata@fcsaude.ubi.pt
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2020.100456

Received 20 December 2019; Received in revised from 14 May 2020; Accepted 5 August 2020
Online publication date xxx

INTRODUCTION

Food allergy is an important health problem in western countries as reflected in the appearance of numerous publications in this field over the past years.[1] For instance, in the United States, up to 20% of the population has been shown to change their diet due to the development of food allergy or other type of adverse reaction to food.[2] Nevertheless, the values for the prevalence of food allergy in the general population, particularly in adults, are not well known. In fact, various meta-analyses[3-5] and other recent studies[6,7] estimate that the prevalence of food allergy may vary according to the methodology used: 6–13% of adults and 6–38% of children when based upon self-reports, and 1–3% at all ages when oral food challenges are performed. Independently of using or not other diagnostic tests, namely oral provocation procedures, most studies on the prevalence of food allergies in the general population have been based upon an initial step involving the application of a questionnaire, which must be validated in order to be useful in terms of analysis.[8-12]

Thus far, only one study on the prevalence of food allergies in the general population has been performed in Portugal, limited to a sample of 659 adult participants older than 39 years old, where the authors performed a large, health and nutrition questionnaire, including questions not only related with food allergy, but also to demographic characteristics and social dietary habits.[13] Furthermore, as far as we know, no validated questionnaires, or clinical history screening questionnaires for epidemiological studies of adverse food reactions (AFR) as an initial approach to the study of food allergies in adults have been developed in Portuguese speaking countries. In fact, there is a lack of validated questionnaires or other clinical screening tools for the study of food allergies in adults, worldwide. Therefore, this is a pilot study, aimed at developing a clinical history screening questionnaire to be specifically applied in adults and studying its validity and reliability.

MATERIALS AND METHODS

Setting

This study was carried out at 3 healthcare centres in the central region of Portugal and at the allergy outpatient clinics of the central hospitals of Castelo Branco Local Health Unit and Cova da Beira University Hospital Centre, serving a population of 180,000 inhabitants older than 15 years old.[14] It was carried out between 2012 and 2015.

Volunteers and study design

Overall, we studied 186 volunteers, as shown in the Fig. 1 flowchart. Initially, we recruited 4 groups of adult volunteers into 2 clusters with characteristics similar to those of subjects in whom a future study on food allergy will be carried out. The first cluster ("Intelligibility study groups-ISG") was formed by 2 groups of individuals: a series of 24 non-food allergic volunteers from the general population (randomly recruited from general practicioners' files of participating healthcare centres and other hospital clinical services doctors files), and another series of 24 randomly recruited patients with food allergy confirmed by clinical history, specific IgE levels, cutaneous tests, and double-blind placebo-controlled food challenges (DBPCFC) (patients with IgE-mediated food allergy), with 2 of them being patients with positive clinical history and DBPCFC but negative specific IgE levels and cutaneous tests (patients with non-IgE-mediated food allergy), belonging to a database of food allergic patients, prepared from the medical records of the allergy outpatient clinics of the central hospital of the Castelo Branco Local Health Unit and Cova da Beira University Hospital Centre. This intelligibility study group was used for piloting purposes.

The second cluster of volunteers (case patients and control individuals) was different from the ISG groups, and was used for validity testing, namely test-re-testing, and included a total of 138 volunteers. This cluster included 66 randomly recruited adult patients with IgE-mediated food allergies, not previously selected for the first cluster, confirmed according to the same protocol used for the ISG patient group (clinical history, specific IgE levels, cutaneous tests and DBPCFC). Patients were randomly recruited from the previously mentioned database of food allergic patients of the Allergy Outpatient Clinic of the Castelo Branco Local Health Unit and Cova da Beira University Hospital Centre ("Case Group-IgE"). An extra group of 12 patients with positive DBPCFC but

Fig. 1 Flowchart of study methodology steps

negative food-specific IgE and SPT were also recruited from the same database, and these patients constituted a non-IgE-mediated food allergy group. Non-food allergic volunteers (n = 60) from the general population were also randomly selected from the files of general practitioners belonging to the participating healthcare centres and who were invited to take part in the study ("Control Group").

Development of the clinical screening questionnaire

The initial step consisted of a bibliographical search for published validated questionnaires for screening food allergies in adults and was performed on PubMed using terms such as "questionnaire", "survey", "food allergy", "food hypersensitivity", "history", "tool", and "diagnosis". Published reports, namely EuroPrevall studies, did not include full questionnaires or did not mention any validation data. In addition, possible cultural adaptations might be needed. Although international consensus agrees that the allergy-focused history is a key part of the diagnostic pathway, there is no agreement regarding the type of questions to be asked, or the typified clinical history, as highlighted by Skypala et al.[15] For these reasons, we decided to develop a clinical history screening questionnaire for our study. Its design was based upon specific principles, as defined by a panel of experts in line with principles previously used in other publications using questionnaires in other fields of study,[16–18] as well as taking into account Portuguese[19] and European guidelines.[20] It was also based upon a questionnaire previously applied to children with food allergies,[21] with an adequate sample size calculated in accordance with appropriate recommendations.[22,23] The questionnaire aimed at screening for the presence of adverse food reactions and their risk factors. It also included the main clinical manifestations of adverse reactions to foods which are crucial to its diagnosis, as well as demographic data such as age, gender, and healthcare centre of referral. The questions were designed in an objective way in 7 domains, in a procedure similar to that used in a questionnaire developed and validated by our group, for detecting children with food allergies.[24] The first questions focused on the identification of the volunteer (assigning an identification code for data anonymisation, gender, and age) and request to answer the questionnaire (questions 1–4). In addition, item 17, asked volunteers about willingness to carry out a food allergy study in a specialized centre. Domain #1 focused on confirmation of the

presence of a previous adverse reaction to food (item 5). We must stress that the questionnaire only proceeded on from this point in case of a positive answer to this question. Domain #2 aimed at identifying the food which triggered the adverse reaction (question 6). Domain #3 focused on characterisation of the reaction to suspect food(s), and included questions 7 and 8. These questions were answered separately for each identified trigger food, and they included evaluation of reported symptoms and their severity, as well as definition of the reaction as immediate or delayed. Domain #4 included questions 9 and 10 and asked the need for treatment and procedures followed in response to the reaction. Domain #5 involved questions about previous reactions and how long ago the last reaction had taken place (items 11 and 12). Domain #6 studied the accessibility to diagnosis of food allergy, focusing as well on medical specialty care versus general practitioner care (questions 13 and 14). Domain #7 included questions 15 and 16, on personal and family history of allergy, as risk factors.

Analysis of theoretical construct: face and content validity

This initial version was analysed by a panel of 3 medical experts with experience in food allergy, who checked the questionnaire in terms of face validity, bearing in mind food allergy concepts and guidelines (Table 1). Analysis of content validity was performed by submitting the questionnaire for review to a team of nine medical specialists in allergy with recognized clinical and research experience in food allergy, who rated the relevance of each question in terms of current guidelines and knowledge (1-not relevant; 2-somewhat relevant; 3-quite relevant; 4-highly relevant).[25] The Item Content Validity Index (I-CVI) was calculated for each question, as the number of experts that gave a rating of 3 or 4, divided by the total number of experts, and I-CVI was regarded as significant if its value was 0.78 or above [26](Table 1). In addition, the experts also suggested modifications deemed as relevant, proposed the inclusion of new aspects and reviewed semantics as well, in a procedure similar to that previously performed by Lyra et al.[21] The questionnaire was then converted into a Google Docs format in order to facilitate collection of data via a phone call.

Logical (intelligibility) analysis of the questionnaire

In order to assess its intelligibility, adequacy, logic, and comprehension of the questions and duration, as well as the eventual need to modify some of the terms for the sake of clarity and adequate data collection, a pilot study was performed, with the questionnaire being applied to the 2 volunteer groups, matched in terms of socioeconomic status and degree of literacy ("Intelligibility study groups-ISG"). In 50% of cases, the questionnaire was applied by phone, and in the other 50% it was applied in a written form. Time taken to complete the questionnaire was measured in both groups. In addition, these volunteers were asked for an opinion about the degree of difficulty and pertinence of the questionnaire items. With the feedback obtained, some of the questions were simplified.

Subsequently, the questionnaire was again sent to a panel of 3 allergists with experience in food allergy, who agreed upon the final version of the questionnaire. Thus, literature review, allergy experts, and non-food allergic volunteers as well as patients with DBPCFC-confirmed food allergy contributed to content validity of the questionnaire.

Analysis of empirical construct: construct validity

In order to assess construct validity, the 17-item questionnaire was analysed in terms of known-group validity. We specifically wanted to test our hypotheses that the test would discriminate between: a) food allergic patients and non-food allergic individuals; b) IgE-mediated and non-IgE-mediated food allergic patients. Known-group validity analysis was based on analysis of the agreement between positive replies to its questions and the actual presence of food allergy in patients with previously confirmed food allergy (positive food-specific skin tests, positive food allergen-specific IgE, and positive DBPCFC), as well as differences in replies between patients with IgE-mediated and non-IgE-mediated food allergy.[22]

Question number	Item	Item CVI
1	Identity Code of volunteer	**1**
3	Gender	**0.888**
3	Age in years	**0.888**
4	Do you want to answer this questionnaire?	**1**
5	*Ethnicity*	0.222
6	*Social grade (occupation)*	0.111
7	*Literacy*	0.111
8	*Do you have any systemic disease?*	0.111
9	Do you have any adverse food reaction?	**1**
10	What kind of food causes your reaction?	**1**
11	*How much food caused the reaction?*	0.333
12	*Was the food that caused the reaction cooked (or not)?*	0.222
13	What kind of reaction did you have?	**1**
14	*Where did you have the reaction?*	0.111
15	How long after food ingestion did the reactions appear?	**0.888**
16	Did you need medical treatment?	**1**
17	If answer was "yes" for item 9, Where did you receive medical treatment?	**0.888**
18	*What kind of treatment did you receive (intravenous, oral)?*	0.333
19	*Did food ingestion occur on an empty stomach?*	0.111
20	*Was food ingestion associated with exercise?*	0.222
21	*Was food ingestion associated with any drug treatment?*	0.111
22	*Did you drink alcohol beverages during food ingestion?*	0.222
23	Have you had any previous episodes with the same food?	**1**
24	How long ago did the previous reaction take place?	**1**
25	*Have you had subsequent episodes with the same food?*	0.333
26	Have you been previously diagnosed with food allergy?	**1**

(continued)

Question number	Item	Item CVI
27	Have you ever been to a specialty appointment by an Allergist doctor?	**1**
28	Do you have any other allergic disease? (personal history of atopy)	**1**
29	Does anybody in your family have an allergic disease?	**0.888**
30	Would you want to be followed up at a specialty clinic?	**1**

Table 1. (Continued) Initial 30 items screening questionnaire and Item Content Validity Index (I-CVI) average performed by the nine experts medical specialists in allergy. *Italic: Items deleted in final versionItems highlighted in bold had a high I-CVI score (high level of concordance among experts).*

Test-retest reliability (temporal stability) of the questionnaire

The questionnaire was analysed in terms of reliability, using a test-retest approach. The questionnaire was applied via a phone call by a trained technician under allergist supervision, to the case and control groups as previously defined in the "volunteers" section and re-applied via a phone call to the case and control groups, on a second contact ("test-retest" technique)[22] after the first phone call.

Statistical analysis

Spearman's correlation coefficient (*Spearman's Rho value*) was used for determination of temporal stability, regarding values > 0.70 in absolute value as a strong correlation.

Analysis of concordance and reproducibility of the questionnaire was performed using Cohen's Kappa Test for each question. Cohen's Kappa results and their 95% confidence intervals were accepted as having good concordance if Kappa values were >0.60, and as having almost perfect concordance for levels of Kappa >0.80.[22] Data were studied using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).[27] A level of significance of less than 0.05 was regarded as statistically significant.

Ethical aspects

This study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki, and all procedures involving subjects/patients were approved by the Ethics Committees of the Amato Lusitano Hospital (Castelo Branco Local Health Unit), the Cova da Beira University Hospital Centre, and the Sub-Regional Health Authorities of Castelo Branco. Written informed consent was obtained from all subjects/patients.

RESULTS

Face and content validity

From the initial 30 questions, only 17 were kept (Table 2), with 0.967 being the final mean of the I-CVIs for the 17 scale items (mean I-CVI). These 17 items were regarded as essential for obtaining adequate information from the patients (Supplementary Material 1), and distributed by 7 domains.

Demographics of the study volunteers

Intelligibility study groups-ISG (pilot testing)

The 24 non-food allergic volunteers included in the "ISG-NFA" group were randomly recruited from the medical files of general population registed at participating primary care centres (50% females, median age of 45 ± 7 years). The 24 volunteers with confirmed food allergy (positive clinical history, specific IgE, skin tests, DBPCFC), randomly recruited from the Allergy outpatient clinics belonging to both hospitals (83% females, median age of 36 ± 11 years), were included in the "ISG-FA" group. These 2 groups were matched in terms of age, gender, Graffar scale, and degree of literacy.

Case and controls groups (validation testing)

The 66 patients with previously confirmed (positive clinical history, specific IgE, skin tests, and

Question number	Item	References
1	Identity Code of volunteer	19
3	Gender	9,10,12,18,19,21,31,32,39
3	Age in years	9-12,18,19,21,31,32,39
4	Do you want to answer this questionnaire?	9,10
5	Do you have any adverse food reaction?	9,10,12,18,19,21,31,32
6	What kind of food causes your reaction?	9,10-12,18-21,31,32,39,41
7	What kind of reaction did you have?	9-12,19-21,31,32,39-41
8	How long after food ingestion did the reactions appear?	9,10,12,19-21,31,39-41
9	Did you need medical treatment?	10,21,31,41
10	If answer was "yes" for item 9, Where did you receive medical treatment?	10,31
11	Have you had any previous episodes with the same food?	20,21,39,41
12	How long ago did the previous reaction take place?	10,20,21,39,41
13	Have you been previously diagnosed with food allergy?	10,11,31
14	Have you ever been to a specialty appointment by an Allergist doctor?	10,11,31
15	Do you have any other allergic disease? (personal history of atopy)	9-12,18,20,21,31,39,41
16	Does anybody in your family have an allergic disease?	9,10,11,20,40,41
17	Would you want to be followed up at a specialty clinic?	9,10

Table 2. Screening questionnaire and references used in its design

DBPCFC) food allergies were aged between 18 and 74 years (mean = 38.27 ± 9.3 years; 73% female). Forty-six of these patients reported symptoms related to one single foodstuff, and the other 20 were sensitised to more than one food. Implicated foodstuffs were seafood (32 cases), fresh fruits (26 cases), tree nuts (11 cases), peanut (8 cases), vegetables, chicken and egg (4 cases each), and other foodstuffs (8 cases). The 12 patients with previously confirmed (positive clinical history and DBPCFC, but negative specific IgE and skin tests) non-IgE mediated food allergies were aged between 27 and 68 years (mean = 46.58 ± 11.5 years; 67% female). Seventy-five percent of these patients reported symptoms related to one single foodstuff, and the other 25% were sensitised to more than one food. Implicated foodstuffs were seafood (11 cases), fresh fruits (2 cases), and other foodstuffs (8 cases). The 60 non-food allergic volunteers recruited from the general population were aged between 18 and 82 years (mean = 50 ± 14.21 years; 55% female). These 3 groups were matched in terms of age, gender, Graffar scale, and degree of literacy.

Intelligibility and testing of the questionnaire

All volunteers in the ISG-NFA and ISG-FA groups confirmed the intelligibility and adequacy of the 17 questionnaire items. It was estimated that the questionnaire, when applied to volunteers without AFR, would take 1 min to complete for the written form, and 2 min for the phone-applied form. In case of food allergy-confirmed volunteers, it took between 2 and 10 min (mean of

4.5 ± 1.5 min), for the written form and 2 min for the phone-applied form, respectively.

Analysis of empirical construct: construct validity

The 17-item questionnaire was analysed in terms of known-group validity in 3 different groups: a) a group of 66 patients with previously confirmed IgE-mediated food allergy, b) a group of 12 patients with previously confirmed non IgE-mediated food allergy, and c) a group of 60 non-food allergic volunteers.

Questionnaire items 5 (main), as well as 6-8, consistently identified food-allergic patients (both IgE-mediated and non-IgE-mediated) with excellent discrimination from non-food allergic controls (sensitivity 100%; specificity 100%), and being a "percentage of agreement" indicator. Furthermore, item 8 ("How long after food ingestion did the reactions appear?") also discriminated between patients with confirmed classical IgE-mediated food allergy (all had reactions in less than 2 h after food ingestion) and patients with non-IgE-mediated food allergy (who had reaction more than 2 h after food ingestion) with high sensitivity (100%) and specificity (100%).

Test-retest reliability (temporal stability)

In the case-control validation cluster groups (IgE- and non-IgE-mediated analysed together), mean re-application time value was 7 ± 9 weeks (range: 2-38 weeks; median and mode: 2 weeks). In the control group, mean re-application time was 8 ± 7 weeks (range: 2-34 weeks; median and mode: 2 weeks), thereby allowing analysis of the variability of replies to each of the items of the questionnaire. Temporal stability was calculated by determining *Spearman's Rho* correlation coefficient for 8 items (items number 5, 9, 11-15, 17) which were regarded as indispensable, since they objectively characterized the development of adverse food reactions, and due to the "yes-no" binary answer type. The set of 8 previously mentioned items, both globally and also taking gender, age, time interval between test and retest, as well as the volunteers' source of referral (diagnosed patients and Health Care Centres) into account are shown in Table 3. Five patients had new reactions between test and re-test phases, by

Parameter	Parameter classes	Rho spearman's values	*p* value (*)
Sex	Female	0.927	$p < 0.001$
	Male	0.898	$p < 0.001$
Age (years)	<25	0.724	$p < 0.001$
	25-50	0.986	$p < 0.001$
	>50	0.713	$p < 0.001$
Test-retest time interval (weeks)	<8	0.947	$p < 0.001$
	9-30	0.614	$p < 0.010$
	>30	0.500	$p < 0.050$
Volunteers' local of origin	Hospital Patients	0.489	$p < 0.100$
	Out of Hospital Patients	0.667	$p < 0.001$
	Community Healthcare Centre #1	0.733	$p < 0.010$
	Community Healthcare Centre #2	0.450	$p < 0.100$
	Community Healthcare Centre #3	0.758	$p < 0.001$

Table 3. Temporal Stability for Relevant questions by sex, age, time interval and local origin. *(*) p value indicates statistical significance of Spearman's Rho for each different subgroup*

inadvertent ingestion of suspect foods or ingestion by self-initiative to see whether they could tolerate the foods. No differences were found in temporal stability when sex, age, and volunteer origin were analysed. An inverse relationship was found between reliability and retest time interval.

DISCUSSION

In the present study, we developed and analysed in terms of face, content and construct (known-group) validity and reliability (temporal stability), for the first time in the Portuguese language, a screening questionnaire of adverse food reactions in the general adult population. This questionnaire was rapid and easily applicable, and showed excellent known-group validity, as well as a high degree of temporal stability. On the other hand, there was no variability in results when gender, age, and extra-hospital referral source of the volunteers were taken into account. In addition, *Spearman's Rho* correlation coefficient did not show significant differences across health care centres where control, non-food allergic volunteers were recruited.

Although, after the pilot study, we only analysed 138 volunteers (60 randomly selected non-food allergic controls, 64 patients with confirmed IgE-mediated food allergies, and 12 patients with confirmed non-IgE-mediated food allergies), this number is well within what is accepted as an appropriate sample size for this type of studies.[23]

For the assessment of the questionnaire, we studied reproducibility (test-retest stability) of the questionnaire, which was very high in global terms, as expressed in Spearman's Rho values of 0.80. Furthermore, reproducibility of specific items showed Cohen's Kappa values greater than 0.80 for most items, which is very good given the number of analysed items.[22,28] However, again items 12: "time elapsed since the previous episode", 11:"existence previous episodes of food allergy", item 15: "personal history of atopy" and 17: "Would you want to be followed up at specialty clinic?" significantly varied with time, between test and retest. This may have been due to memory bias, as reported by other studies,[29] or may have been due to the fact that volunteers might not be aware of the co-existence of other allergic diseases in them or did not report them either during test or re-test phase. In addition, in the case of item 12, discrepancy may arise from the fact that adverse food reactions may develop between test and retest, as a result of accidental exposure[30,31] or as self-initiative to test a minor portion of food, as actually happened in a small proportion of the patients (n = 5) in our study, or inversely by development of tolerance, which was unlikely in our study, given the short period of time between test and re-test.[32] In addition, volunteers with food allergies may develop novel reactions to new foodstuffs not mentioned in the first test, as may happen with patients sensitised to various food families (fruits, fish, seafood, egg, milk, etc)[30,33] thereby potentially affecting items 11 and 12.

Low temporal stability was found for items 15 and 17, ("Do you have any other allergic disease?" and "Would you want to be followed up at specialty clinic?"), with a value for Cohen's Kappa of 0.441 and 0.296 respectively (Table 4). This may have been due to the fact that a proportion of patients either became aware that they had an allergic disease or had a confirmed diagnosis of allergic disease between test and retest, as was observed in some cases. On the other hand, since food allergic patients were already being followed up at a clinic and the remainder of the volunteers were non-food allergic, this may have been associated with confusion regarding the need to be re-evaluated. In fact, non-food allergic volunteers who changed their answers between test and re-test, had mild symptoms they interpreted as possible rhinitis, conjunctivitis or dermatitis, which waxed and waned, which may have been associated with such changes in answers to item 17. Finally, the low temporal stability may also have been due to a memory bias as previously referred, since it was not possible to analyse this item separately from the variability between groups (non-food allergic controls versus patients with food allergies) using Spearman's coefficient, given the relatively limited size of the sample. In spite of these aforementioned factors potentially affecting the "8 crucial questions" (items 5,9,11–15,17), 6 of these questions maintained an optimal degree of temporal stability which afforded the whole of the test a high level of reproducibility.

Question number	Item	Cohen's Kappa Value (Test-ReTest reliability: intraclass correlation)
5	Do you have any adverse food reaction?	0.914
9	Did you have medical treatment?	0.830
11	Have you had any previous episodes with the same food?	0.696
12	How long ago did the previous reaction take place?	0.641
13	Have you been previously diagnosed a food allergy?	0.886
14	Have you ever been to a specialty appointment by an Allergist doctor?	0.892
15	Do you have any other allergic disease?	0.441
17	Would you want to be followed up at specialty clinic?	0.296

Table 4. Analysis of temporal stability (test- Re-test reliability). *$p < 0.05$ for all values*

In our study, although most patients were retested within 2 weeks of the initial test, there was high amplitude of time intervals, with a few of the patients being retested after 30 weeks. We acknowledge that this may be a limitation of our study since current guidelines for the performance of this type of study state that the ideal interval should be between 4 weeks and 6 months (ideally between 15 and 45 days).[34-36] Nevertheless, our study followed COSMIN guidelines,[37] and allowed the study of reliability (internal consistency and some aspects of reliability).

One important feature of our screening questionnaire is the fact that it is short and quick to apply. This is highly relevant to its application in clinical settings as well as in studies involving large samples, since it has been shown that volunteers' attention time span decreases as the length of a questionnaire increases.[38] In addition, our questionnaire adequately discriminated patients with confirmed food allergies from those without food allergies. It also discriminated between patients with IgE-mediated food allergies (n = 22, for the intelligility phase and n = 66 for the other validity assessment phases) from those with non-IgE-mediated food allergies (n = 12), on the basis of item 8, regarding timing of development of reactions upon food ingestion. However, the latter group only included 12 patients, which is a limitation of our study, and we are also aware that some patients with non-IgE-mediated food allergies may also have early onset symptoms.

Our study had other limitations. Firstly, it is a pilot study that needs a larger sample to improve its performance, applicability, and generalizability. Although, based on the sociodemographic features of our samples of patients and controls, we believe that these were representative of the Portuguese population for the age range in question, we still have to adequately study its generalizability to other Portuguese speaking countries. Secondly, although we used the acknowledge known-groups validity with 2 groups of food-allergic patients (IgE- and non-IgE-mediated) and 1 group of non-food allergic individuals to assess construct validity, due to the type of questions being asked, and the format of replies, it was not possible to carry out factor analysis or internal stability procedures. In addition, our questionnaire needs to be further studied with a higher sample, in terms of its limits for discriminating between classical IgE-mediated and non-IgE-mediated food allergies.

In spite of the limitations, our study also has new and consistent results. Firstly, our results do suggest that this screening questionnaire is essentially useful for screening of food allergies in cross-sectional studies but may need to be optimized for the

follow-up of patients over time. Furthermore, this questionnaire is the first one developed and validated in the Portuguese language for adults with food allergies, and we believe it may be applied in all Portuguese speaking countries worldwide (250 million people). In addition, our questionnaire is simple and quickly applicable and also fully based upon accepted criteria for a sensitive collection of the clinical history of food allergies.[39,40] We also believe that it is easily adaptable to other languages, particularly because not many clinical screening questionnaires are available for the study of adverse food reactions as an initial approach to the investigation of food allergy in adults. Our study was an alternative to the validation, in Portuguese, of the clinical history section of the EuroPrevall questionnaires and one of our future projects will be to assess the validity of our questionnaire in comparison with such EuroPrevall approach, regarded as a quality reference.

In conclusion, we developed, for the first time in the Portuguese language, a screening questionnaire for the study of adverse food reactions in adults, which showed high reproducibility and good potential to be a useful screening test in potentially different settings.

Consent for publication
All authors gave their written consent for publication.

Authors' contributions
CLI participated in the study design, data collection and analysis; AR participated in data collection; JB carried out the statistical analyses; LTB, RMA and HP supervised the whole project and participated in study design and data analysis. All authors participated in writing the manuscript.

Availability of data and materials
Please contact corresponding author for primary data requests.

Funding
This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of competing interest
The authors declare no conflict of interests.

Acknowledgments
We would like to thank the help of Dr. Joana Belo and Dr. Arminda Jorge (Departments of Immunoallergology, and Paediatrics, respectively, of Cova da Beira University Hospital Centre, Covilhã, Portugal), Dr María Luisa Somoza and Prof. Francisco Javier Ruano (Allergy Department, Infanta Leonor Hospital, Madrid, Spain), Dr Stefan Cimbollek (Allergy Department, Virgen del Rocío Universitary Hospital, Seville, Spain), Dr Leonor Cunha (Allergy Department, Porto Hospital Centre, Oporto, Portugal) and Dr Isabel Carrapatoso (Allergy Department, Coimbra University Hospital Centre, Coimbra, Portugal) for the development of the final version of the questionnaire.

Appendix ASupplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2020.100456.

Author details
[a]Allergy Department, Castelo Branco Local Health Unit, Castelo,Branco, Portugal. [b]CICS-Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal. [c]CACB-Clinical Academic Center of Beiras, Portugal. [d]Polytechnic Institute of Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias, Castelo Branco, Portugal. [e]Psychology and Education Department, University of Beira Interior, Covilhã, Portugal. [f]Outpatient Clinic Department, Castelo Branco Local Health Unit, Portugal. [g]Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre, Covilhã, Portugal.

REFERENCES

1. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*. 2011;127:594-602. https://doi.org/10.1016/j.jaci.2010.11.044.
2. Sicherer SH, Sampson H. Food allergy. *J Allergy Clin Immunol*. 2006;117:S470-S475. https://doi.org/10.1016/j.jaci.2005.05.048.
3. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analisys. *J Allergy Clin Immunol*. 2007;120:638-646. https://doi.org/10.1016/j.jaci.2007.05.026.
4. Soares-Weiser K, Takwoingi Y, Panesar SS, et al. The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy*. 2014;69:76-86. https://doi.org/10.1111/all.12333.
5. Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:62-75. https://doi.org/10.1111/all.12305.
6. Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw open*. 2019;2(1):1-14. https://doi.org/10.1001/jamanetworkopen.2018.5630.
7. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018;141(1):41-58. https://doi.org/10.1016/j.jaci.2017.11.003.
8. Young E, Stoneham MD, Petruckevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet*. 1994;343:1127-1130. https://doi.org/10.1016/S0140-6736(94)90234-8.
9. Zuberbier T, Edenharter G, Worm M, et al. Prevalence of adverse reactions to food in Germany-a population study.

Allergy. 2004;59:338-345. https://doi.org/10.1046/j.1398-9995.2003.00403.x.

10. 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. https://doi.org/10.1067/mai.2001.116427.
11. Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. Food allergy and food sensitization in early childhood: results from the DARC cohort. *Allergy*. 2009;64:1023-1029. https://doi.org/10.1111/j.1398-9995.01952.x.
12. 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. https://doi.org/10.1111/j.1399-3038.2008.00842.x.
13. Falcão H, Lunet N, Lopes C, Barros H. Food hypersensitivity in Portuguese adults. *Eur J Clin Nutr*. 2004;58:1621-1625. https://doi.org/10.1038/sj.ejcn.1602017.
14. Portugal, INE (censos 2011) http://censos.ine.pt/xportal/xmain?xpid=CENSOS&xpgid=ine_censos_publicacao_det&contexto=pu&PUBLICACOESpub_boui=156644135&PUBLICACOESmodo=2&selTab=tab1&pcensos=61969554. Accessed 1 January 2019.
15. Skypala I, Venter C, Meyer R, et al. The development of a standardised diet history tool to support the diagnosis of food allergy. *Clin Transl Allergy*. 2015;5:7. https://doi.org/10.1186/s13601-015-0050-2.
16. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. *Allergy*. 2010;65:1042-1048. https://doi.org/10.1111/j.1398-9995.2009.02310.x.
17. Van der Velde JL, Flokstra-de Blok BMJ, Vlieg-Boerstra BJ, et al. Development, validity and reliability of the food allergy independent measure (FAIM). *Allergy*. 2010;65:630-635. https://doi.org/10.1111/j.1398-9995.2009.02216.x.
18. 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. https://doi.org/10.1111/j.1399-3038.2012.01302.x.
19. Prates S. Colheita da História Clínica. *Rev Port Immunoalergol*. 2009;17(Suppl I):6-10.
20. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines. Diagnosis and management of food allergy. *Allergy*. 2014;69:1008-1025. https://doi.org/10.1111/all.12429.
21. Lyra NRS, Motta MEFA, Rocha LAR, et al. Adverse reactions to foods and food allergy: development and reproducibility of a questionnaire for clinical diagnosis. *J Allergy*. 2013;2013:920679. https://doi.org/10.1155/2013/920679.
22. Fortin MF, Côté J, Filion F. *Fundamentos e etapas do processo de investigação*. 1st ed. Loures: Lusodidacta; 2009. ISBN 978-989-8075-18-5.
23. Rouquette A, Falissard B. Sample size requirements for the internal validation of psychiatric scales. *Int J Methods Psychiatr Res*. 2011;20:235-249. https://doi.org/10.1002/mpr.352.
24. Jorge A, Santos-Silva M, Lozoya-Ibáñez C, et al. Development of a tool for screening adverse food reactions and food allergy in Portuguese children. *Allergol Immunopathol*. 2018. https://doi.org/10.1016/j.aller.2018.09.008. Pii: S0301-0546(18)30143-30145.
25. Davis LL. Instrument review: getting the most from your panel of experts. *Appl Nurs Res*. 1992;5:194-197.
26. Lynn MR. Determination and quantification of content validity. *Nurs Res*. 1986;35:382-385.
27. Maroco J. *Análise Estatística com utilização do SPSS*. 3rd ed. Lisboa: Sílabo; 2010. ISBN 978-972-618-452-2.
28. Carmo H, Malheiro-Ferreira M. *Metodologia da Investigação. Guia para autoaprendizagem*. 2nd ed. Lisboa: Universidade Aberta; 2008. ISBN 978-972-674-512-9.
29. 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. https://doi.org/10.1034/j.1398-9995.2001.056005393.x.
30. Sousa F, Antunes J, Paes MJ, Chambel M, Prates S, Leiria-Pinto P. Exposições acidentais na alergia alimentary. *Rev Port Imunoalergol*. 2001;19:93-100.
31. Uguz A, Lack G, Pumphrey R, et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy*. 2005;35:746-750. https://doi.org/10.1111/j.1365-2222.2005.02257.x.
32. 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. https://doi.org/10.1111/j.1399-3038.2005.00251.x.
33. 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. https://doi.org/10.1034/j.1398-9995.2002.13494.x.
34. Cade J, Thompson R, Burley V, Warm D. Development, validation and utilisation of food-frequency questionnaires – a review. *Publ Health Nutr*. 2002;5:567-587. https://doi.org/10.1079/PHN2001318.
35. Cade JE, Burley VJ, Warm RL, Thompson RL, Margetts BM. Food-frequency questionnaires: a review of their design, validation and utilization. *Nutr Res Rev*. 2004;17:5-22. https://doi.org/10.1079/NRR200370.
36. Slater B, Leite de Lima FE. Validade e reprodutibilidade dos métodos de inquérito alimentar. In: Fisberg RM, Slater B, Lobo Marchioni DM, Araújo Martini L, eds. *Inquéritos Alimentares: Métodos e Bases Científicos*. 1st ed. Tamboré: Editora Manole Ltda; 2005:108-131. ISBN 852-041-638-1.
37. Mokkink LB, Terwee CB, Knol DL, et al. Protocol of the COSMIN study: consensus-based Standards for the selection of health measurement instruments. *BMC Med Res Methodol*. 2006;6:2. https://doi.org/10.1186/1471-2288-6-2.
38. McColl E, Jacoby A, Thomas L, et al. Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients. *Health Technol Assess*. 2001;5:81-92. https://doi.org/10.3310/hta5310.
39. Sampson HA. Food allergy – accurately identifying clinical reactivity. *Allergy*. 2005;60(Suppl. 79):19-24. https://doi.org/10.1111/j.1398-9995.2005.00853.x.
40. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, 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(6 Suppl):S1-S58. https://doi.org/10.1016/j.jaci.2010.10.007.

41. Burks W, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol*. 2012;129:906-920. https://doi.org/10.1016/j.jaci.2012.02.001.

Abbreviations

AFR
Adverse Food ReactionsCOSMIN
Consensus-based Standards for the selection of health Measurement INstrumentsDBPCFC
Double-Blind Placebo-Controlled Food ChallengeI-CVI
Item Content Validity IndexIgE
Immunoglobulin EISG
Intelligibility Study GroupsISG-FA
Intelligibility Study Groups-Food AllergicISG-NFA
Intelligibility Study Groups-Non Food Allergic

V.2 Co-Author Scientific Articles

V.2.1 Allergologia et Immunopathologia 2019

Allergol Immunopathol (Madr). 2019;47(4):342-349

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

Development of a tool for screening adverse food reactions and food allergy in Portuguese children

A. Jorge[a,b], M. Santos Silva[c], C. Lozoya-Ibánez[a,d], F. Lorente[e], E. Sarinho[f], R.M. Afonso[g], H. Pereira[g], L. Taborda-Barata[a,h,*]

[a] CICS – Health Sciences Research Centre, University of Beira Interior, Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal
[b] Department of Paediatrics, Cova da Beira Hospital Centre, Covilhã, Portugal
[c] Quality Management Unit, Cova da Beira Hospital Centre, Covilhã, Portugal
[d] Allergy Department, Castelo Branco Local Health Unit, Castelo Branco, Portugal
[e] Department of Pediatrics, Salamanca University Hospital, Spain
[f] Center for Research in Allergy and Clinical Immunology (HC/UFPE), Federal University of Pernambuco, Recife, Brazil
[g] Psychology and Education Department, University of Beira Interior, Covilhã, Portugal
[h] Department of Allergy & Clinical Immunology, Cova da Beira Hospital Centre, Covilhã, Portugal

Received 20 July 2018; accepted 4 September 2018
Available online 30 November 2018

KEYWORDS
Adverse food reaction;
Children;
Consistency;
Food allergy;
Questionnaire;
Reproducibility;
Temporal stability

Abstract
Introduction and objectives: A standardised questionnaire may be an excellent tool for epidemiological studies aiming at screening children with suspected food allergies. Thus, the aim of the present study was to develop a screening questionnaire for assessing children with suspected food allergy and to analyse its reproducibility.
Materials and methods: A questionnaire of adverse food reactions was developed by literary review of similar questionnaires validated in other countries as well as less well defined, non-validated Portuguese questionnaires. Peer review of the questionnaire by a panel of specialists and subsequent exploratory analysis was carried out by applying the questionnaire in children with confirmed food allergy. Test–retest analysis was performed by giving a face-to-face questionnaire to 159 children with suspected adverse food reactions, aged between three and 11 years. Temporal stability using Spearman Rho correlation test and reproducibility was studied using Cohen's Kappa index.
Results: 115 children confirmed adverse food reactions that occurred with one or more foods. Retest was given about three weeks after the test, to 50 of these children who were randomly selected. The questionnaire showed good temporal stability (Spearman correlation coefficient of 0.834), and good reproducibility (only two of the 27 items had a Kappa index <0.60).
Conclusions: This questionnaire showed good temporal stability and reproducibility. Its validation for screening children with suspected food allergy will allow a standardised approach to diagnosis and comparison of results obtained in different centres.

* Corresponding author.
E-mail address: tabordabarata@fcsaude.ubi.pt (L. Taborda-Barata).

https://doi.org/10.1016/j.aller.2018.09.008

Introduction

Food allergy involves reactions to foods in which an immunological mechanism can be demonstrated and which includes IgE-mediated reactions.[1,2] However, other mechanisms may be implicated in adverse reactions to foods, namely non-toxic mechanisms such as intolerance.[3] Clinical manifestations of food allergy are diverse, but most frequently include mucocutaneous reactions, although anaphylaxis may also occur,[4–6] with children and adolescents having a higher risk.[7] A final diagnosis of food allergy requires confirmation by in vivo and in vitro tests (''probable'' food allergy), as well as oral provocation procedures (gold standard; ''confirmed'' food allergy), in specific situations.[8] However, clinical suspicion may be based on a clear history of reproducible specific food-associated symptoms with resolution upon eviction[4] in association with predictive thresholds for food-specific IgE levels.[8] This is helpful for the characterisation of the suspect food, clinical features and their severity, thereby allowing the appropriate clinical management of the situation, avoiding too restrictive or unnecessary diets.[9] It may also allow clarification regarding which foods must be avoided to prevent serious reactions on contact with suspect foods.[6] In accordance with international guidelines,[4,10] skin prick tests (SPT) and determination of food-specific IgE levels should be focused on specific foods, guided by clinical history and food-specific IgE levels.[8]

The prevalence of food allergy may be increasing, at least for certain foods,[11] and is highest in children and then declines with age.[6,12–14] If assessment of the prevalence of food allergy is based on self-report (''perceived/possible'' food allergy), the values show a broad variation (3–47%), depending upon factors such as age, geographical area, operational definition of ''food allergy'', ''food hypersensitivity'' or ''adverse food reaction'' used, and the questionnaire methodology applied (by telephone, self-administered, interviewer-driven, etc.).[10,15–18] In this context, a standardised, reliable, easily completed and available questionnaire may be an excellent tool for epidemiological studies focusing on detecting children with suspected food allergies. Although it is possible to translate questionnaires validated in other languages, it is not always feasible to adapt such questionnaires for use with populations that are culturally different, which may compromise the validity of the data obtained.[19] Furthermore, most epidemiological studies provide scant information on the questionnaires that were used,[14–18,20] even those that used the EuroPrevall questionnaire.[21,22] In this context, a previously developed questionnaire in Brazil underwent preliminary studies by some members of our team, in terms of reproducibility and was shown to have a high number of questions with a good Kappa index ($\geq$0.6).[23]

In Portugal, a couple of studies carried out in children at Allergy clinics used non-validated questionnaires.[24,25] Thus, the objective of the present report was to analyse internal consistency and reproducibility of this questionnaire for the study of adverse food reactions and food allergy in Portuguese children.

Methods

Development of the questionnaire

The first step consisted in a bibliographical search for validated questionnaires for application in children with suspected food allergies. We found no validated questionnaires for the Portuguese population. Questionnaires used in prevalence studies in other countries did not mention validation data[26–28] and EuroPrevall studies did not include readily available questionnaires.

We then built a preliminary version of our questionnaire, based upon the most frequent clinical manifestations of food allergy reported in other studies[10,27,29–31] and upon the questionnaire previously tested for reproducibility and temporal stability in Brazilian children.[23] Guidelines from Portuguese[9] and European[32] scientific societies were taken into account. Our questionnaire included more questions (deemed clinically relevant) than the one used in Brazil, and was a confirmatory, second phase questionnaire, as seen in other studies.[20,21,31]

Clinical data that are crucial for the diagnosis[32,33] were reflected in our questionnaire: nature of the suspect food, time lag between ingestion and development of symptoms, whether ingestion of the suspect food induced similar symptoms on other occasions; other triggers such as physical exercise, and when the previous reaction took place[32] were also analysed. Questions on reproducibility of symptoms were also included.

Pre-test, logical and content validity

A pilot study was then performed with the questionnaire in twenty-four children from the paediatric outpatient Allergy Clinic of Cova da Beira Hospital Centre, with clinical, laboratory and double-blind, placebo-controlled challenge-confirmed (DBPCFC) food allergy (14 males and 10 females; mean age of 7.4 years, SD $\pm$ 3.4). This stage aimed at assessing the applicability of the questionnaire, logic, comprehension and adequacy of the questions from the point of view of the target population. It also allowed us to perform a first evaluation of the consistency of the questions. The time it took parents to fill in the questionnaire was timed and doubts reported by children and their parents were recorded. The questionnaire was regarded as thorough by the children and parents but with simple and easily understandable questions and adequately timed (duration of 7–12 minutes).

With the feedback obtained with this pilot study, we made some changes, namely in the sequence of the questions. We also simplified some of the questions and defined the parameters better, in order to turn open questions into closed ones.

Once completed, the questionnaire was sent to a panel of three Allergists with experience in food allergy, and comments obtained were used for analysis of logical or apparent validity, and content validity of the questionnaire. Thus,

content validity was confirmed with a panel of children and their parents, Allergy experts and literature review.

The final questionnaire was also read by a specialist in Portuguese linguistics, to correct language errors.

Description of the questionnaire

In addition to questions regarding demographics, the questionnaire included 17 questions (Table 1), in seven domains. Domain 1 focused on confirmation of the presence of a previous adverse reaction to food. Domain 2 aimed at identifying the food which triggered the adverse reaction. The questionnaire only proceeded on from this point in the event that at least one trigger food had been selected. Domain 3 focused on the characterisation of the first reaction to suspect food(s), and included questions 3–9. These questions were answered separately for each identified trigger food, and included evaluation of reported symptoms and their severity, definition of the reaction as immediate or delayed, identification of eventual triggers, how the food induced the reaction, and identification of new foods that might have been neglected. Domain 4 included questions 10 and 11 and focused on procedures followed in response to the reaction. Domain 5 involved questions about the stability of reactions upon a new contact. Questions included how long ago the last reaction had taken place (item 12), subsequent ingestion of the suspect food and eventual reactions (item 13), changes in severity or tolerance to the food on subsequent contact (item 14), and the number of new episodes (item 15). Finally, Domain 6 included questions 16 and 17, on personal and family history of allergy, as risk factors.

Initial study

A shortened form of the final questionnaire consisting only of questions on demographics and two questions (questions 1 and 2) regarding the previous occurrence of food reactions and identification of the suspect foods was sent to all children from public Pre-Schools and Primary Schools of the region of Beira Interior (Belmonte, Covilhã and Fundão), Portugal. Of the 2474 children whose parents replied to this simplified questionnaire (Questionnaire 1), 176 children were detected as having possible, self-reported food allergy. The parents of 159 of these children then replied to the complete questionnaire (Questionnaire 2) (Supplementary materials 1 and 2) and 115 confirmed a suspicion of adverse reaction to at least one food (Fig. 1).

Test–retest

Reliability of the screening questionnaire was studied for intra-observer reliability (test–retest). From the group of 115 children with suspected food allergy, we randomly selected 50 children for test–retest analysis, who again had to fill in the same questionnaire. The retest was applied by the same researcher, 1–12 weeks (mean five, median three weeks) after the first application of the questionnaire. For the calculation of the retest results, the food associated with the most severe reaction was selected, if there were reactions to more than one food.

Statistical analysis

Spearman's Rho correlation coefficient (with a level of significance of $p < 0.01$) was used to analyse temporal stability, regarding values >0.70 in the absolute value as a strong correlation. Analysis of concordance and reproducibility of the questionnaire was performed using Cohen's Kappa test for each question. Cohen's Kappa results and their 95% confidence intervals were interpreted for levels of concordance: 0.00 – poor; 0.01–0.20 – slight; 0.21–0.40 – fair; 0.41–0.60 – moderate; 0.61–0.80 – substantial; >0.80 – almost perfect.[34] Data were analysed using the Software Package for Social Sciences (SPSS) version 20.0®. A p value of less than 0.05 was regarded as significant with all tests.

Ethical considerations

This study was approved by the Ethics Committees of the Faculty of Health Sciences of the University of Beira Interior and Cova da Beira Hospital Centre. All parents/guardians signed a written informed consent. The questionnaire was approved by the General Board for Curricular Innovation and Development (Direcção-Geral de Inovação e de Desenvolvimento Curricular – DGIDC).

Results

Demographic data

The 50 children who were randomly selected in order to perform the test–retest had a mean age of 8.7 ± 2.4 years and 58% were male. Most of the children (69%) lived in an urban environment, 37 (74%) were atopic and 31 (62%) had family history of atopic diseases. The most frequently reported reactions to foods occurred with fresh fruits ($n = 16$); fish ($n = 9$); and eggs ($n = 8$).

Temporal stability

Analysis of temporal stability using the sum of the most relevant test/re-test replies to questions 4, 5, 10, 11 (which allowed characterisation of clinical manifestations and their severity) and 16, showed a Spearman's Rho correlation coefficient of 0.834.

Analysis of concordance and reproducibility of the questionnaire

Kappa Cohen's test was used for analysis of reproducibility (intra-observer reliability) of the test–retest for each question (Table 1). For the 17 questions, 27 analyses of concordance were performed. One of the questions (9) showed perfect concordance for one category, nine items showed an almost perfect concordance (Kappa between 0.81–1), fifteen items had a good or very good Kappa value (>0.6) and two (items 5 and 12) showed a moderate Kappa value (0.48 and 0.56, respectively).

Table 1 Assessment of reproducibility of a screening questionnaire for the detection of adverse food reactions and food allergy.

Questions		Relative concordance			Kappa (CI 95%)
		n		%	
Domain 1 – Confirmation of allergic reaction					
1	Does your child have any health problem or reaction with any food or drink?	50	50	100	1.0 (1.00–1.00)
Domain 2 – Identification of suspect food					
2	Which food or drink triggers a reaction?	47	50	–	–
	Milk	49	50	98	0.91 (0.74–1.08)
	Egg	50	50	100	1.0 (1.00–1.00)
	Fish	49	50	98	0.94 (0.82–1.06)
	Soy bean	48	50	96	0.89 (0.74–1.04)
	Peanut	50	50	100	0.75 (0.57–0.92)
	Meat	50	50	100	0.83 (0.55–1.10)
	Fresh fruits	50	50	100	1.0 (1.00–1.00)
	Fresh legumes	48	50	96	0.6 (0.24–0.96)
	Other	49	50	98	0.92 (0.82–1.03)
Domain 3 – Characterisation of the first reaction and associated features					
3	When your child had the reaction, was that the first time that he/she ate/drank that food?	43	50	86	0.77 (0.62–0.93)
4	How long after having eaten the food did the reaction occur?	49	50	98	0.88 (0.74–1.01)
5	What type of reaction did your child have after having eaten/drunk that food/drink?	–	–	–	–
	Respiratory symptoms	47	50	94	0.82 (0.62–1.02)
	Gastrointestinal symptoms	45	50	90	0.77 (0.57–0.96)
	Mucocutaneous symptoms	49	50	98	0.94 (0.83–1.05)
	Cardiovascular symptoms	48	50	96	0.48 (−0.14 to 1.10)
6	How was the reaction triggered by the food/drink?	50	50	100	1.0 (1.00–1.00)
7	If your child smells that food or it touches his/her skin, does he/she have any reaction?	48	50	96	0.85 (0.66–1.04)
8	Were factors such as physical exercise, ingestion of medication or any other associated with the reaction to the foods?	50	50	100	–
9	Did your child ever have itchy, swollen or tingling lips, mouth or throat after having eaten any other food?	50	50	100	1.0 (1.00–1.00)
Domain 4 – Procedure followed after reaction					
10	Was your child taken to hospital when he/she had the reaction to food/drink?	47	50	94	0.83 (0.68–0.99)
11	Did your child have to be given any medication when he/she had the reaction	46	50	92	0.87 (0.74–0.99)
Domain 5 – Stability of reaction upon new contact					
12	How long ago did the last reaction take place?	40	50	80	0.56 (0.36–0.76)

Table 1 (*Continued*)

Questions		Relative concordance			Kappa (CI 95%)
		n		%	
13	After the first reaction, did your child eat the same suspect food again? Please describe the reaction, in the event that there was one.	49	50	98	0.88 (0.65–1.11)
14	If your child ate the food more than once, have reactions to it changed in severity over time, to the same food?	47	50	94	0.85 (0.69–1.01)
15	In total, how many episodes of adverse reactions to the same food did your child have?	47	50	94	0.89 (0.77–1.01)
Domain 6 – Risk factors					
16	Does your child have any other allergies?	40	50	80	0.64 (0.46–0.82)
17	Does anyone in the child's family have any allergies?	43	50	86	0.79 (0.65–0.93)

CI: confidence interval.

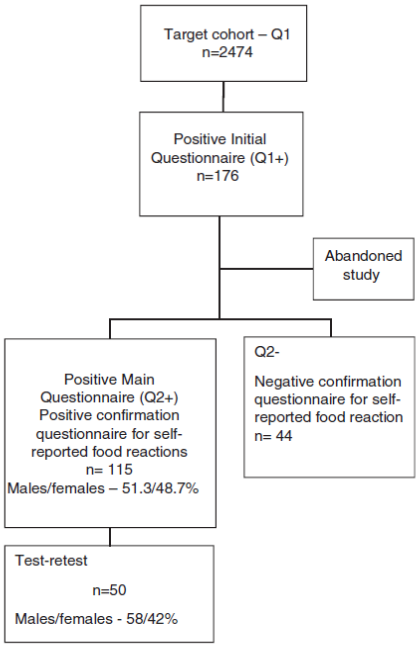


Figure 1 Flow chart of the study design for analysis of reproducibility and temporal stability in Portuguese schoolchildren.

The item related to identification of suspect food (item 2) showed a good or very good Kappa value (≥0.75) for all foods, except for fresh legumes (0.60).

Although most parents did not know whether the first reaction coincided or not with the first ingestion (item 3), we found a good concordance in replies to this question as well as in terms of the number of episodes (item 15) (0.77 and 0.89, respectively).

In terms of questions aiming at characterising the reactions, question 4, whose objective was to discriminate between early and delayed reactions, showed a relative concordance of 98% and a Kappa value of 0.88. Questions related to clinical features of the reactions were grouped into mucocutaneous, respiratory, digestive or cardiovascular manifestations (item 5) and showed good temporal consistency (≥0.77) except for cardiovascular symptoms (Kappa of 0.48). Item 6 aimed at identifying the contact route with the food (inhalation, cutaneous contact or ingestion), and showed a concordance of 100% and a Kappa value of 1. Item 13, which aimed at assessing the reproducibility of the reaction, showed a 98% concordance and a Kappa value of 0.88.

Questions regarding food episode-associated hospital visits (item 10) and medication prescribed (item 11) also showed an almost perfect concordance value (0.83 and 0.87, respectively), and aimed at assessing severity of the reaction.

In terms of the question regarding triggers/co-triggers such as physical exercise or drugs (item 8) all answers were ''I do not know''.

Questions 16 and 17 aimed at assessing possible risk factors for the reactions and showed a Kappa value of 0.64 for other allergic symptoms in the children, and of 0.79 for allergic disease in children's families.

Discussion

In the present study, we developed and studied feasibility, reliability (test–retest reproducibility), face and content validity of a questionnaire for screening adverse food reactions in children. The questionnaire was shown to be simple to apply, to have good temporal stability, as well as good or very good reproducibility of most questions,[19,35] thereby suggesting its adequacy for screening children with adverse food reactions.

The questionnaire was called ''Questionnaire 2 (Q2)'' and was intended to be applied to children with suspected food allergies who had reported food-related symptoms in a preliminary, two question-long questionnaire (''Q1''). This means that we intended to follow a two-step approach for epidemiological studies, also used in EuroPrevall[21] and other studies.[20,31] Nevertheless, our Q2 screening questionnaire was designed to be applied without the need for the initial Q1 questionnaire. Our full questionnaire involves a semi-structured interview, which makes it more powerful than a simple checklist, and its construction followed a theoretical model, based upon a robust theoretical review of the literature. In addition, it also continued the work of a previously published questionnaire in Brazil,[23] with the addition of questions deemed to be clinically relevant.

With its two initial questions, this questionnaire allows the identification of children with adverse food reactions who may be at risk of developing further reactions. Question 1 aimed at detecting the presence of self-reported adverse reactions to foods and question 2 aimed at identifying the trigger foods. Although these questions are not specific enough to exclude non-allergy related situations, they are potentially highly sensitive, thereby allowing the inclusion of all cases of adverse food reactions which will be more specifically studied by the subsequent items in the questionnaire. In fact, most previously used questionnaires,[18,20,22] namely those used in EuroPrevall[21] and the Brazilian studies[23] included two similar initial questions.

As far as reliability is concerned, our questionnaire was assessed for intra-observer stability. In this context, temporal stability demonstrated high and significant Spearman Rho correlation values ($r = 0.834$; $p < 0.01$), thereby suggesting that it has good enough temporal stability (value close to 1) for it to be applied in our target population.

Kappa index has been studied in various studies in children, to assess concordance among various observers[34] but also for analysis of intra-observer reliability.[36,37] Our study used Kappa index for assessment of the reproducibility of the different questions and eventually proposing their modification or exclusion. All domains showed high levels of concordance, with only two questions in Domain 3 (characterisation of the first reaction) showing a fair concordance Kappa value (question 4, for cardiovascular symptoms; and question 12, regarding how long ago had the previous reaction taken place). Thus, all the remaining 15 questions demonstrated a substantial concordance (Kappa value > 0.6), and nine questions showed an almost perfect concordance (Kappa between 0.81 and 1). It is difficult to compare these parameters since we could not find any published validation of similar screening questionnaires for food allergies in the literature, apart from the Brazilian study.[23] The Brazilian study showed almost perfect concordance in two questions (''Has your child had any reaction when this food only touched his/her skin?'' and ''Did your child feel itching, swelling, or numbness in his/her mouth after eating fruit or raw vegetable?'') and this was in agreement with our study.

Our study showed that there was a good concordance in the identification of suspect foods except for fresh legumes, which may be due to the fact that in our population there is a low prevalence of adverse reactions to fresh legumes,[24,25,38] as has also been reported in other countries.[20,22] In fact, allergy to legumes is not regarded as a common food allergy.[11] Furthermore, whenever reactions to fresh legumes were reported in our study, these were mild or mostly based upon a single episode of symptoms, which may make it more difficult for the reaction to be remembered, as was demonstrated in a previous study on cow's milk allergy/intolerance.[39]

In terms of characterisation of the first reaction (Domain 3), although most parents did not know whether it coincided with the first ingestion of the suspect food (question 3), we still found a good concordance in replies to this question (0.77), with values that were higher than those reported in the Brazilian questionnaire (0.55).[23]

Still in Domain 3, answers concerning clinical characterisation of the reaction showed substantial concordance ($\geq$0.77) except for cardiovascular symptoms (0.48), which may have been due to the fact that these symptoms were very seldomly reported in our sample. In terms of triggers such as physical exercise or medication (question 8), all answers were ''I do not know'' which, in spite of full concordance, did not allow us to further study this aspect. Thus, although these triggers are regarded as relevant in other studies,[29] we could not demonstrate that in our patients.

In Domain 4 (procedure followed after reaction), questions regarding going to hospital as well as medication given, are useful for assessing the severity of the reaction, and showed an almost perfect level of concordance (0.83 and 0.87, respectively), thereby suggesting that there may be a sharper memory of issues of greater frequency or severity.[39] These high levels of concordance were higher than those found in Brazilian children, in similar questions,[23] possibly because the reactions involved were of lower magnitude.

In Domain 5 (stability of reactions upon new contact), concordance was also almost perfect (Kappa value of 0.88) for answers about the number of adverse food reaction episodes. This is possibly because we narrowed parent choice by allowing them to choose from a range of numbers of episode rather than by asking them to fill in a single absolute number of episodes.

Still in Domain 5, in terms of time elapsed since the previous reaction (question 12), we only found a moderate concordance value (Kappa of 0.56), which was, nevertheless, higher than that observed in the Brazilian children (Kappa of 0.28).[23] Questions that deal with elapsed time and age of occurrence may show a low degree of concordance, due to memory bias. In fact, memory of the previous episode may depend upon the severity of the event and time elapsed ever since.[26,39] Another reason may be that these reactions may include both food-induced allergies as well as non-allergic adverse food reactions with different degrees

of severity. In addition, after the initial interview, parents may have attempted to remember the episodes in order to give a more precise reply on retest. Finally, children may have developed tolerance to foods between test and retest as was demonstrated in similar studies in children.[39,40]

In Domain 6 (assessment of risk factors), questions 16 and 17, which aimed at assessing risk factors, only showed good Kappa values (0.64 for other allergic symptoms, and 0.79 for history of allergies in the family). This may be partially explained by the fact the parents of some children may have become more aware that their children had an allergic disease or had a confirmed diagnosis of allergic disease between test and retest, as happened in some cases. In addition, low temporal stability may also have been due to a memory bias, as has been previously reported.[38,40]

Our study has some limitations. Firstly, content validity was only assessed in twenty-four children with food allergies, which is a relatively low number of individuals. Nevertheless, a similar analysis was also performed in 50 children with suspected food allergies. Thus, we believe that the sample size used for this study may have been adequate according to item analysis recommendations[41] Secondly, although most questions had very good consistency and reproducibility, some of the questions had low consistency and will need to be reformulated or removed by multiplex reduction analysis. Thirdly, reliability analysis of the questionnaire using alfa Cronbach's test was not carried out because the intrinsic nature of the items of the instrument did not allow it.[37] Fourthly, the time lag between test–retest was moderately outside the ideal time range (two weeks), although the median in our study was only three weeks, and the mean was five weeks, which is similar to other reports. Nevertheless, this time lag may have been associated with memory bias. In addition, our questionnaire will subsequently have to be validated regarding its sensitivity and specificity by comparing it to the gold standard technique of DBPCFC. Although our 24 children with DBPCFC-confirmed food allergy filled in the questionnaire, we did not perform such an analysis at this stage. Finally, although our questionnaire is simple and was used for screening children for adverse food reactions and food allergies, it may still be further improved by introducing Likert-type questions to increase its robustness for detecting specific food allergy profiles. Further studies are warranted, namely in collaboration with the Brazilian questionnaire.[23]

Nevertheless, our questionnaire has the advantage of being simple to use, easily available, and follows criteria for diagnosis of food allergy.[4,10,21] This is particularly relevant in terms of its application for a rapid and simple diagnosis of possible food allergy in children, a population in which such a problem is highly relevant.[7,11]

Thus, we believe our questionnaire may subsequently be applied in all Portuguese-speaking countries (250 million people) and has features that allow its application worldwide, given its availability, ease of application, global consistency and temporal stability.

Conclusions

We have developed the first questionnaire in Portugal for screening food allergies in children, which has very good internal consistency and reproducibility and can be easily applied. It holds good potential as a useful screening test for food allergies.

Funding

This study did not have any external funding. Costs regarding questionnaires and laboratory tests were paid for by internal investigator funds (Faculty of Health sciences and Cova da Beira Hospital).

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

We would like to thank the Departments of Paediatrics of Cova da Beira Hospital and all nursing staff that helped with skin prick tests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.aller.2018.09.008.

References

1. Johansson JG, 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;113:832–6.
2. Sicherer SH, Sampson H. Food allergy. J Allergy Clin Immunol. 2006;117:S470–5.
3. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol. 2011;127:594–602.
4. Boyce JA, Assáad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126:S1–58.
5. Santos AF, Lack G. Food allergy and anaphylaxis in pediatrics: update 2010–2012. Pediatr Allergy Immunol. 2012;23:698–706.
6. Niggemann B. Special aspects of food allergy in children. Hautarzt. 2012;63:288–93.
7. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 1992;327:380–4.
8. Eigenmann PA. Do we still need oral food challenges for the diagnosis of food allergy? Pediatr Allergy Immunol. 2018;29:239–42, http://dx.doi.org/10.1111/pai.12845.
9. Carrapatoso I, Falcão H, Cunha L, Jordão F, Sampaio G, Costa AC, et al. Alergia alimentar. Rev Port Imunoalergol. 2009;17 Suppl. 1:5–40.
10. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69:1008–25.
11. 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.

12. Mills EN, Mackie AR, Burney P. The prevalence, cost and basis of food allergy across Europe. Allergy. 2007;62:717–22.
13. Keil T. Epidemiology of food allergy: what's new? A critical appraisal of recent population-based studies. Curr Opin Allergy Clin Immunol. 2007;7:259–63.
14. Nissen SP, Kjaer HF, Høst A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. Pediatr Allergy Immunol. 2013;24:549–55.
15. 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;120:638–46.
16. Pereira B, Venter C, Grundy G, 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;116:884–92.
17. Shu SA, Chang C, Leung PS. Common methodologies in the evaluation of food allergy: pitfalls and prospects of food allergy prevalence studies. Clin Rev Allergy Immunol. 2014;46:198–210.
18. Hoyos-Bachiloglu R, Ivanovic-Zuvic D, Álvarez J, Linn K, Thöne N, de los Ángeles Paul M, Borzutzky A. Prevalence of parent-reported immediate hypersensitivity food allergy in Chilean school-aged children. Allergol Immunopathol. 2014;42:527–32.
19. Farias Júnior JC, Lopes AS, Mota J, Santos MP, Ribeiro JC, Halla PC. Validade e reprodutibilidade de um questionário para medida de atividade física em adolescentes. Rev Bras Epidemiol. 2012;15:198–210.
20. 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;39:1027–35.
21. Kummeling I, Mills ENC, Clausen M, Dubakiene R, Fernández Pérez C, Fernández-Rivas M, et al. The EuroPrevall surveys on the prevalence of food allergies in children and adults: background and study methodology. Allergy. 2009;64:1493–7.
22. Kavaliunas A, Surkienė G, Dubakienė R, Stukas R, Zagminas K, Saulitė J, et al. EuroPrevall Survey on prevalence and patterns of self-reported adverse reactions to food and food allergies among primary schoolchildren in Vilnius, Lithuania. Medicina (Kaunas). 2012;48:265–71.
23. Lyra NRS, Motta MEFA, Rocha LAR, Solé D, Peixoto DM, Rizo JA, et al. Adverse reactions to foods and food allergy: development and reproducibility of a questionnaire for clinical diagnosis. J Allergy. 2013;2013:1–7.
24. Morais-Almeida M, Prates S, Pargana S, Arêde C, Godinho N, Tavares C, et al. Alergia alimentar em crianças numa consulta de imunoalergologia. Rev Port Imunoalergol. 1999;7:167–71.
25. Bento ML, Armando F, Cesar-Ramos JM. Epidemiology of food allergy in Portugal. Pediatr Pulmonol. 2001; Suppl. 23:38–40.
26. Rancé F, Grandmottet X, Granjean H. Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. Clin Exp Allergy. 2005;35:167–72.
27. 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;17:356–63.
28. 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;59:338–45.
29. 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;65:630–5.
30. Kanny G, Moneret-Vautrim DA, Flabbee J, Beaudoin E, Morisset M, Thevenin F. Population study of food allergy in France. J Allergy Clin Immunol. 2001;108:133–40.
31. Sandin A, Annus T, Björkstén B, Nilsson L, Riikjärv M-A, 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.
32. Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111:1601–8.
33. Sampson HA. Food allergy – accurately identifying clinical reactivity. Allergy. 2005;60 Suppl. 79:19–24.
34. Cerda J, Villarroel L. Evaluación de la concordancia interobservador en investigación pediátrica: Coeficiente de Kappa. Rev Chil Pediatr. 2008;79:54–8.
35. Watson PF, Petrie A. Method agreement analysis: a review of correct methodology. Theriogenology. 2010;73:1167–79.
36. Prous MJGY, Salvanés FR, Ortells LC. Validation of questionnaires. Reumatol Clin. 2009;5:171–7.
37. Rodriguez MC, Maeda Y. Meta-analysis of coefficient alpha. Psychol Methods. 2006;11:306–22.
38. Lozoya-Ibáñez C, Morgado-Nunes S, Rodrigues A, Lobo C, Taborda-Barata L. Prevalence and clinical features of adverse food reactions in Portuguese adults. Allergy Asthma Clin Immunol. 2016;12:36, http://dx.doi.org/10.1186/s13223-016-0139-8.
39. 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.
40. Van Zyl Z, Maslin K, Dean T, Blaauw R, Venter C. The accuracy of dietary recall of infant feeding and food allergen data. J Hum Nutr Diet. 2016;29:777–85, http://dx.doi.org/10.1111/jhn.12384.
41. Rouquette A, Falissard B. Sample size requirements for the internal validation of psychiatric scales. Int J Methods Psychiatr Res. 2011;20:235–49.

V.3. International scientific congress
V.3.1. EAACI Annual Meetings
V.3.1.1 Istanbul 2011

This is to certify that the abstract

1027 – Validation of a questionnaire for the study of food allergies in Portuguese adults

was presented as poster by

Carlos Lozoya-Ibáñez

at the 30th Congress of the European Academy of Allergy and Clinical Immunology in Istanbul, Turkey
11-15 June 2011

Ömer Kalaycı
Congress President

Jan Lötvall
President of EAACI

1024
Persistence of peanut allergen in the environment

Watson, W[1]; Woodrow, A[2]; Stadnyk, A[3]; James, H[4]
[1]Dalhousie University, Department of Pediatrics, Division of Allergy, IWK Health Centre, Halifax, Canada; [2]IWK Health Centre, Division of Allergy, Halifax, Canada; [3]Dalhousie University, Department of Pediatrics, Division of Immunology, IWK Health Centre, Halifax, Canada; [4]IWK Health Centre, Division of Immunology, Halifax, Canada

Background: Peanut allergy has a major impact on quality of life. Exposures to small amounts can trigger serious reactions. Previous studies have shown that cleaning table surfaces with common cleaning agents is effective in removing peanut allergen (Perry et al, J Allergy Clin Immunol 2004;113:973–6). We sought to determine the persistence of peanut allergen on a typical table surface if no cleaning occurred.
Method: 5 ml of peanut was smeared on a 12 inch by 12 inch square on a table surface. Five squares were used. Samples for measurement of Ara h 1 were taken prior to peanut application and at regular intervals for 110 days, from different areas of the table surface contaminated with the peanut butter. Samples were analysed for Ara h 1 using a monoclonal-based ELISA.
Result: There was no detectable peanut allergen on the table surface prior to the application of peanut butter. At each time point for 110 days there was significant Ara h 1 on the table surface, at a level that was comparable to baseline, immediately post application. A standard cleaning agent (a mild bleach spray) promptly removed the allergen on surfaces after 110 days, and Ara h 1 was below the level of detection.
Conclusion: Peanut is a very robust food and the proteins appear to be very durable over time. Ara h 1 does not degrade over time, at least over 110 days. Active cleaning of contaminated areas appears to be the only way of removing the allergen.

1025
Cluster analysis revealed four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms

Nomura, I[1]; Morita, H[2]; Fukuie, T[1]; Shoda, T[1]; Ohtsuka, Y[3]; Hosokawa, S[3]; Watanabe, M[3]; Terada, A[3]; Hoshina, H[3]; Takamasu, T[3]; Arai, K[4]; Ohya, Y[1]; Saito, H[2]; Matsumoto, K[2]
[1]National Center for Child Health and Development, Allergy, Tokyo, Japan; [2]National Center for Child Health and Development, Allergy and Immunology, Tokyo, Japan; [3]Japanese Research Group for Neonatal, Infantile Allergic Disorders, Tokyo; [4]National Center for Child Health and Development, Gastroenterology, Tokyo, Japan

Background: Non-IgE-mediated gastrointestinal food allergies in neonates and infants, involving already established entities; Food Protein-Induced Enterocolitis Syndrome, Food Protein-Induced Proctocolitis Syndrome, Food Protein-Induced Enteropathy Syndrome and Allergic Eosinophilic Gastrointestinal Disorders, are now increasing their prevalence. Because there are patients showing different concepts from these entities, we intended to analyze whole patients with GI allergy to find more useful classification of those disorders.
Method: Total 176 patients' data was submitted to headquarter. Forty-six patients were performed food challenge test. About these 46 diagnosis-confirmed patients, cluster analysis was done by using five variables (birth weight, onset day, vomiting, bloody stool, milk-specific IgE antibody).
Result: Four clusters (Cluster 1~4) were generated by cluster analysis and vomiting and bloody stool were found to be the strongest discriminatory variables. Cluster 1 had both vomiting and bloody stool. Cluster 2 had vomiting. Cluster 3 showed none of those. Cluster 4 showed bloody stool. Food challenge test provoked almost same symptom as in the onset of disease. Cluster 3 showed significantly lower birth weight and the highest eosinophil counts. Although each Cluster might be assigned to already-established cell-mediated food allergies, several differences were existed.
Conclusion: Classification of the patients by initial symptoms is very useful in making diagnosis and treating patients. Each cluster had distinct clinical features and may have different pathogenetic mechanisms. Comparison of patients by an international research setting is also necessary.

1026
The incidence and risk factors of immediate type food allergy during the first year of life in Korean infants: a birth cohort study

Kim, J; Chang, E; Han, Y; Ahn, K; Lee, S
Samsung Medical Center, Sungkyunkwan University School of Medicine, Department of Pediatrics, Seoul, Republic of Korea

Background: Food allergies (FA) occur frequently during infancy and cow's milk, eggs, and peanuts are known common food allergens. However, risk factors pertaining to FA in infants are not well understood. We conducted this study to determine the incidence of FA in Korean infants and identify the risk factors of FAs during the first year of life in a birth cohort study.
Method: Pregnant women ≥ 34 weeks of gestation were enrolled in this study. Participants were asked to complete questionnaires describing basic demographic information including family history of allergic diseases. Since birth, all the babies were regularly followed up for FA symptoms through telephone interviews at 4, 8, and 12 months of age. When the parents reported any suspicious allergic symptoms, the infants were brought to the outpatient clinic and examined by an allergy specialist. FA was defined as a repetitive convincing history of immediate allergic reactions following the ingestion of offending food.
Result: A total of 1 177 infants (601 boys and 576 girls) and their parents completed this study. The prevalence of FA was 5.3% in infants. The three leading causes of FA were hen's eggs (33/62), cow's milk (20/62) and peanut/nuts (8/62). Sixty (96.8%) children showed cutaneous manifestations. Children with a history of maternal atopic dermatitis showed a significantly higher prevalence of FA ($P = 0.012$) [aRR = 3.17]. In addition, children who were born in autumn had a higher prevalence than those born during spring ($P = 0.005$) [aRR = 3.48]. We also observed a higher prevalence of FAs in children with a history of paternal FA than those without this history, although these differences were not definitely significant ($P = 0.063$). Gender, duration of exclusive breastfeeding, age at the introduction to solid foods, maternal education levels, maternal FA, maternal allergic rhinitis, maternal asthma, paternal atopic dermatitis, paternal allergic rhinitis, and paternal asthma were not found to be related to the development of FA in infancy.
Conclusion: We identified several characteristics that may influence the development of FA in the next generation, including maternal atopic dermatitis and autumn birth.

1027
Validation of a questionnaire for the study of food allergies in Portuguese adults

Lozoya-Ibáñez, C[1]; Macedo, A[2]; Rodrigues, A[3]; Silva, L[4]; Rodrigues, E[5]; Pimenta, M[6]; Mendes, T[7]; Taborda-Barata, L[8]
[1]Allergy Service, Unidade Local de Saúde de Castelo Branco, EPE, CICS, Centro de Investigação em Ciências da Saúde, University of Beira Interior, Castelo Branco, Portugal; [2]University of Beira Interior, CICS, Centro de Investigação em Ciências da Saúde, Covilhã, Portugal; [3]Unidade Local de Saúde de Castelo Branco, EPE, Emergency Service, Castelo Branco, Portugal; [4]Instituto Politécnico de Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias, Castelo Branco, Portugal; [5]Unidade Local de Saúde de Castelo Branco, EPE, Idanha A Nova Community Health Center, Castelo Branco, Portugal; [6]Unidade Local de Saúde de Castelo Branco, EPE, Vila Velha de Ródão Community Health Center, Castelo Branco, Portugal; [7]Unidade Local de Saúde de Castelo Branco, EPE, Sertã Community Health Center, Castelo Branco, Portugal; [8]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, CICS, Centro de Investigação em Ciências da Saúde, University of Beira Interior, Covilhã, Portugal

Background: One of the most important tools for the study of food allergies is a

standardized and validated questionnaire. As far as we know, no such questionnaire has been applied in adults in Portugal. Therefore, the aim of the present study was to validate a questionnaire for food allergies in a sample of adult Portuguese patients.
Method: This was a multicentre, cross-sectional study using a simple random sample of 50 adults aged between 18 and 80 years from various parts of the centre of Portugal. In addition, the questionnaire was also applied to 25 patients diagnosed with food allergy. A 17 question questionnaire was applied by phone to both groups, with subsequent reassessment (re-test) with a time interval ranging between 2 weeks and 10 months (median of 1.5 months). Eight closed questions were analyzed for internal consistency and temporal stability using SPSS 17.0.
Results: A Cronbach alpa value of 0.961 (excellent) was determined for internal consistency. The following parameters were considered as obligatory items: (i) existence of adverse food reaction; (ii) need or not for treatment; (iii) existence of previous episodes; (iv) personal history of atopy; (v) previous diagnosis of allergy; (vi) previous specialty appointment; (vii) willingness to be followed up at specialty clinic; (viii) time elapsed since the previous episode. The general temporal stability of the test had a Spearman correlation coefficient value of 0.90. Cohen's Kappa values for temporal stability (agreement level) for the relevant questions (0.41–0.60: moderate agreement; 0.61–0.80: substantial agreement; 0.81–1.00: almost perfect agreement) was as follows: (i) existence of adverse food reaction: 0.971; (ii) need or not for treatment: 0.875; (iii) existence of previous episodes: 0.806; (iv) personal history of atopy: 0.657; (v) previous diagnosis of allergy: 0.942; (vi) previous specialty appointment: 0.945; (vii) willingness to be followed at specialty clinic: 0.943; (viii) time elapsed since the latest episode: 0.581.
Conclusions: With the exception of "time elapsed since the previous episode", "existence previous episodes of food allergy" and "personal history of atopy", all items showed almost perfect agreement. In view of the excellent internal consistency and temporal reproducibility, this questionnaire is an useful tool for the study of prevalence in Portuguese patients from the centre of the country and may also apply to other similar populations.

1028
Shrimp allergy in Italy. High prevalence of sensitivity to novel high m.w. allergens. A multicenter study

Asero, R[1]; Mistrello, G[2]; Amato, S[2]; Ariano, R[3]; Colombo, G[4]; Conte, M[5]; Crivellaro, M[6]; De Carli, M[7]; Della Torre, F[8]; Emiliani, F[9]; Lodi Rizzini, F[10]; Longo, R[11]; Macchia, D[12]; Minale, P[13]; Murzilli, F[14]; Nebiolo, F[15]; Quercia, O[5]; Senna, G[5]; Villalta, D[16]
[1]Clinica San Carlo, Ambulatorio di Allergologia, Paderno Dugnano, Italy; [2]Lofarma SpA, R & D, Milano, Italy; [3]ASL N.1 Imperiese, U.O. di Medicina Interna, Bordighera, Italy; [4]IRCCS, Fondazione San Raffaele del Monte Tabor, Dipartimento di Allergologia e Immunologia Clinica, Milano, Italy; [5]Azienda Ospedaliera, U.O. Allergologia, Verona, Italy; [6]Università di Padova, 6. Servizio di Allergologia Dipartimento di Medicina Ambientale e Salute Pubblica, Padova, Italy; [7]Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Dipartimento di Medicina Interna, Udine, Italy; [8]8. I.N.R.C.A.-I.R.C.C.S. U.O.C. Pneumologia generale, U.O. Allergologia, Casatenovo, Italy; [9]Azienda Ospedaliera, Dipartimento di Allergologia, Faenza, Italy; [10]Spedali Civili, S.S.V.D. Allergologia, Brescia, Italy; [11]Azienda Sanitaria Provinciale, Ambulatorio di Allergologia, Vibo Valentia, Italy; [12]Azienda Sanitaria, U.O. Allergologia Immunologia Clinica, Firenze, Italy; [13]Ospedale San Martino, Dipartimento di Allergologia, Genova, Italy; [14]Ospedale S.S. Filippo e Nicola, U.O. Allergologia, Avezzano, Italy; [15]AO Ordine Mauriziano, Ambulatorio di Allergologia e Immunologia, Torino, Italy; [16]Dipartimento di Medicina di Laboratorio, A.O. "S. Maria degli Angeli", Allergologia e Immunologia Clinica, Pordenone, Italy

Background: Shrimp is a frequent cause of food allergy worldwide. Besides tropomyosin, several allergens have been described recently. We investigated which allergens are involved in Italian shrimp-allergic adults.
Methods: Sera from 116 shrimp-allergic patients selected in 14 Italian allergy centres were studied. SPT with house dust mite (HDM), as well as measurements of IgE to Pen a 1 (shrimp tropomyosin) and whole shrimp extract were performed. All sera underwent shrimp immunoblot analysis, and inhibition experiments using HDM extract as inhibitor were carried out on some Pen a 1-negative sera.
Results: Immunoblots showed much variability. IgE reactivity at about 30 kDa (tropomyosin) was found in < 50% of cases, and reactivity at about 67 kDa and > 90 kDa was frequent. Further reactivities at 14–18 kDa, 25 kDa, 43–50 kDa, about 60 kDa, and at about 80 kDa were detected. Most subjects had a history of shrimp-induced systemic symptoms irrespective of the relevant allergen protein. IgE to Pen a 1 were detected in sera from 46 (41%) patients. Skin reactivity to HDM was found in 43/61 (70%) Pen 1-negative subjects and inhibition studies showed that pre-adsorption of sera with HDM extract induced a marked weakening of the signal at > 67 kDa.
Conclusions: Several allergens other than tropomyosin are involved in shrimp allergy in Italian adult patients. Some hitherto not described high m.w. allergens seem particularly relevant in this population and their cross-reactivity with HDM allergens candidates them as novel potential pan-allergens of invertebrates.

1029
Knowledge and management of anaphylaxis in primary care settings in Spain and Latin America

Neffen, H[1]; Sánchez-Borges, M[2]; González-Broin, M[1]; Cardona, V[3]
[1]Centro de Alergia e Inmunologia, Santa Fe, Argentina; [2]Centro Medico-Docente La Trinidad, Allergy and Clinical Immunology Department, Caracas, Venezuela; [3]Hospitali Universitari Vall d'Hebron, Allergy Section, Department of Internal Medicine, Barcelona, Spain

Background: Despite the existence of international guidelines, knowledge among physicians about anaphylaxis is still not satisfactory. These knowledge gaps hamper the recognition and adequate treatment of this medical emergency. The aim of this research was to assess the knowledge among primary care physicians from Argentina, Spain and Venezuela about anaphylaxis.
Method: A short survey with six multiple choice questions dealing on the symptoms, diagnosis, and management of anaphylaxis was delivered to general practitioners, pediatricians and other primary care physicians (Argentina 100, Spain 100, and Venezuela 244). Chi square was used to compare results.
Result: In this survey, knowledge was quite good (correct responses > 75% for all three countries) on questions regarding symptoms, drug of choice (adrenaline) and regarding when to refer the patient to the Allergist. Knowledge was limited regarding the use of tryptase for diagnosis, the most frequent cause of anaphylaxis and the recommended route of administration of adrenaline (intramuscular). When comparing performance per country, Spanish participants performed better than those from Argentina (three questions; $P = 0.02$, $P < 0.01$ & $P < 0.01$) and Venezuela (four questions; $P < 0.01$ in all four). Participants from Argentina and Venezuela performed similarly, each country achieving better results than the other one for two questions (Argentina better than Venezuela; $P = 0.01$ and $P < 0.01$; Venezuela better that Argentina; $P = 0.044$ and $P < 0.01$). The most striking results were that the majority of participants responded that blood eosinophils were a good diagnostic test and that the route of choice for adrenaline administration was subcutaneous.
Conclusion: Knowledge on anaphylaxis remains unsatisfactory in most countries,

1027. VALIDATION OF A QUESTIONNAIRE FOR THE STUDY OF FOOD ALLERGIES IN PORTUGUESE ADULTS

Lozoya-Ibáñez, Carlos[1,2]; Macedo, Ana Filipa[2]; Rodrigues, Alexandra[3]; Silva, Laura[4]; Rodrigues, Eugénio[5]; Pimenta, Maria José[6]; Mendes, Teresa[7]; Taborda-Barata, Luís[8,2]

[1]Allergy Service, Unidade Local de Saúde de Castelo Branco, EPE [2]University of Beira Interior, CICS, Centro de Investigação em Ciências da Saúde, Covilhã, Portugal; [3]ULSCB, EPE, Emergency Service; [4]Instituto Politécnico de Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias, Castelo Branco, Portugal; [5]ULSCB, EPE, Idanha A Nova Community Health Center; [6]ULSCB, EPE, Vila Velha de Ródão CHC; [7]ULSCB, EPE, Sertã CHC; [8]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, Covilhã, Portugal

Background

One of the most important tools for the study of food allergies is a standardized and validated questionnaire. As far as we know, no such questionnaire has been applied in adults in Portugal. Therefore, the aim of the present study was to validate a questionnaire for food allergies in a sample of adult Portuguese patients.

Method

- Multicentre, cross-sectional study
- Simple random sample of 50 adults aged between 18 and 80 years from various parts of the centre of Portugal.
- Additionally, the questionnaire was also applied to 25 patients diagnosed with food allergy.
- A 17 question questionnaire was applied by phone to both groups, with subsequent reassessment (re-test) with a time interval ranging between 2 weeks and 10 months (median of 1.5 months).
- Eight closed questions were analyzed for internal consistency and temporal stability using SPSS 17.0.

Results

Internal Consistency

A Cronbach´s alpa value of 0.961 was determined for internal consistency.

Internal Consistency (Reliability)	Cronbach´s Alpha
Excellent	>0.9
Good	0.8-0.9
Reasonable	0.7-0.8
Weak	0.6-0.7
Unacceptable	<0.6

Temporal Stability (test-retest reliability)

- A Spearman correlation coefficient value of 0.90 (very good) was determined for general temporal stability of the test
- Cohen's Kappa values for temporal stability (agreement level) was determined for 8 relevant closed questions

Level of Agreement	Cohen´s Kappa (Range values from 0 to 1)
Almost perfect	0.81-1.00
Substantial	0.61-0.80
Moderate	0.41-0.60
Fair	0.21-0.40
Slight	0.01-0.20
Poor	<0.01

Adverse Food Reactions Questionnaire

	Item	Statistic relevant question for temporal stability	Cohen´s Kappa Value	Cronbach's Alpha if Item deleted
1	Voluntary Identity Code	No		
2	Sex	No		
3	Age in years	No		
4	Do you want to answer the questionnaire?	No		
6	Which food causes your reaction?	No		
7	What kind of reaction did you have?	No		
8	How long after food ingestion did the reactions appear?	No		
10	If answer was "yes" for item 10, Where did you received medical treatment?	No		
16	Does anybody in your family have an allergic disease?	No		
5	Do you have any adverse food reaction?	Obligatory item	0.971	0.973
9	Did you need medical treatment?	Obligatory item	0.875	0.947
11	Have you had any previous episodes with the same food?	Obligatory item	0.806	0.947
12	How long ago the last reaction take place?	Obligatory item	0.581	0.950
13	Have you been previously diagnosed with food allergy?	Obligatory item	0.942	0.947
14	Have you ever been to a specialty appointment by an Allergist doctor?	Obligatory item	0.945	0.946
15	Do you any other allergic disease? (personal history of atopy)	Obligatory item	0.657	0.976
17	Would you want to be followed up at a specialty clinic?	Obligatory item	0.943	0.947

Conclusions

With the exception of "time elapsed since the previous episode", "existence previous episodes of food allergy" and "personal history of atopy", all items showed almost perfect agreement. In view of the excellent internal consistency and temporal reproducibility, this questionnaire is an useful tool for the study of prevalence in Portuguese patients from the centre of the country and may also apply to other similar populations.

This is to certify that the abstract

1057 – Adverse reactions to food in a Portuguese population. Preliminary results in a self-reported prevalence study

was presented as poster by

Carlos Lozoya-Ibáñez

at the 30th Congress of the European Academy of Allergy and Clinical Immunology in Istanbul, Turkey
11-15 June 2011

Ömer Kalaycı
Congress President

Jan Lötvall
President of EAACI

of total IgE, cow and goat milk proteins IgE allergenspecific antibodys in coprofiltrates were measured by immunoenzymometric method using the spectrophotometer "Sunrise" (Belgium), with test-systems "Allergopharma" and "Dr. Fooke" (Germany).

Result: The cow milk protein sensibilisation was diagnosed in 42 (49.4%) infants with gastrointestinal symptoms of food allergy. Increased level of total IgE in coprofiltrates was more common in infants with constipation (57%) compared to infants with diarrhea (38%). Thirty-two infants with constipation (71%) had not sensibilisation to goat milk protein; in diarrhea sensibilisation to goat milk protein was more frequent and was found in 18 (45%) infants.

Conclusion: Revelation of total and allergenspecific IgE to cow and goat milk protein in coprofiltrates will make possible optimization of nutrition in infants with gastrointestinal symptoms of food allergy.

1056
Localised and systemic delayed hypersensitivity skin reactions to low molecular weight heparins. Allergologic study and therapeutic alternatives

Medina Alfaro, I[1]; López San Martín, M[2]; Marenco Arellano, V[2]; Reaño Martos, M[2]; Dionisio Elera, J[2]; Moriana Angulo, E[2]
[1]Hospital Universitario Puerte de Hierro de Majadahonda, Allergy, Madrid, Spain; [2]Spain

Background: Low molecular weight heparins (LMWH), may induce several types of skin lesions. Delayed-type hypersensitivity reactions are the most common. While other possible mechanisms, namely type I allergic reactions, type II hypersensitivity thrombocytopenia, necrosis and pustulosis, are less prevalent. Although rare, some skin reactions are life-threatening. Moreover, extensive cross-reactivity between different heparins often occurs. Therefore, accurate diagnosis of potentially life-threatening reactions and identification of therapeutic alternatives is required. Detailed allergologic studies can help to identify safe alternatives.

Patients and Methods: We report two cases of delayed skin reactions to LMWH. Case 1: 51 year old obese woman, treated with enoxaparin 60 UI/24 h after a fibula fracture. Since the first administration she perceived local pruritus, no skin lesions. After 10 doses, elevated erythematous plaques were noticed at the injection sites. Treatment was discontinued. Case 2: 47 year old woman, treated with bemiparin 7 500/24 h for deep venous thrombosis. Two weeks after the start of treatment, she presented itching erythema at injection sites. Treatment was continued for 2 weeks more, until noticing generalized hives and pruritus.

Results: Prick test (1/1) and intradermal test(ID) (1/10) were performed with Sodium heparin, enoxaparin, bemiparin and fondaparinux with immediate and delayed reading. Inmediate Reading: Prick test and ID test were negative in both cases. Delayed Reading: Case 1: a positive response was observed in ID test at 48 h for enoxaparin and sodium heparin. Fondaparinux persisted negative at all readings. Controlled challenges to IV sodium heparin and to subcutaneous fondaparinux were well tolerated. Case 2: positive response in ID test for bemiparin and enoxaparin 24 h after application. At 96 h: positive response to bemiparin, enoxaparin and sodium heparin. One week later a descamative erythematous plaque was observed for bemiparin, enoxaparin and sodium heparin. Fondaparinux: persisted negative at all lectures. Controlled SC challenge to fondaparinux was well tolerated.

Conclusion: Due to cross reaction, allergologic studies must include different heparins. Fondaparinux is well tolerated, becoming an alternative treatment in delayed hypersensitivity reaction to LMWH. Although sodium heparin may present skin lesions when applied SC it may be well tolerated in IV administration.

1057
Adverse reactions to food in a Portuguese population. Preliminary results in a self-reported prevalence study

Lozoya-Ibáñez, C[1]; Macedo, A[2]; Rodrigues, A[3]; Silva, L[4]; Fernandes, L[5]; Fernandes, M[6]; Amaral, F[7]; Taborda-Barata, L[8]
[1]Allergy department, Unidade Local de Saúde de Castelo Branco, EPE, CICS, Health Sciences Research centre, University of Beira Interior, Castelo Branco, Portugal; [2]University of Beira Interior, CICS, Health Sciences Research centre, Covilhã, Portugal; [3]Unidade Local de Saúde de Castelo Branco, EPE, Emergency Department, Castelo Branco, Portugal; [4]Instituto Politécnico de Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias center, Castelo Branco, Portugal; [5]Unidade Local de Saúde de Castelo Branco, EPE, Oleiros Community Health Care Center, Castelo Branco, Portugal; [6]Unidade Local de Saúde de Castelo Branco, EPE, Proença a Nova Community Health Care Center, Castelo Branco, Portugal; [7]Unidade Local de Saúde de Castelo Branco, EPE, Castelo Branco Community Health Care Center, Castelo Branco, Portugal; [8]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, CICS, Health Sciences Research centre, University of Beira Interior, Covilhã, Portugal

Background: Population-based prevalence studies of adverse reactions to food (ARF) in adults are lacking in Portugal. Therefore, the aim of the present study was to determine the prevalence of ARF in a sample of adult Portuguese patients.

Method: This study was based on simple random sampling, for which 369 randomly selected adults would be necessary in order to obtain a 95% confidence interval and an acceptable margin of error of 2%, around a prevalence estimate of 4%. In order to allow for a 40% response rate, a total of 923 adults will be randomly recruited. We have already carried out part of the survey during 2010, in various parts of the centre of Portugal, and have randomly selected 677 adult inhabitants aged between 18 and 80 years (mean age: 52.88 years, median age: 50 years) who have been booked an interview for application of a previously validated food reaction-focused questionnaire. The questionnaire has already been filled out by 410 of these individuals (mean age: 54.62 years; median age: 54 years, 49.63% female).

Results: Of 410 interviewed adults, 33 (8%) reported ARF. Foodstuffs most frequently implicated were seafood (37%), fresh fruits (22%), fish (19%), egg (7%) and dry fruits (4%). Cutaneous reactions (urticaria) were the most frequent AFR reported upon ingestion of seafood, fish, egg and dry fruits, whereas oral allergic syndrome (OAS) was most frequently reported in the case of fresh fruits, fish and dry fruits. Most ARF developed within 30 minutes of ingestion (48% of cases), followed by 30% of cases in which symptoms arose 2 to 24 h after food ingestion. Around 56% of cases required medical treatment (47% at a Health Care Centre within the first 24 hours, and 33% at a Hospital Emergency Department). Only 14% of the cases had previously been diagnosed by a specialist doctor, although around 59% of the patients had a GP-based food "allergy" diagnosis. Only 30% of the patients had any personal or family history of atopy.

Conclusions: In this first, preliminary, study of the prevalence of food-induced self-reported symptoms in adults in Portugal, a relatively high percentage of positive cases was detected (8%), with urticaria and OAS being the most frequently observed symptoms and seafood, fresh fruits and fish the most frequently implicated foodstuffs.

1058
Cow and goat milk allergy in infants

Denisova, S; Sentsova, T; Revyakina, V; Monosova, O; Vorozhko, I; Belitskaya, M; Pavlovskaya, E
Research Institute of Nutrition RAMS, Moscow, Russian Federation

Background: Cow milk protein sensibilisation is common in bottle-fed infants. It is known about immunological cross-reaction for cow and goat milk protein.

Method: We examined 85 infants (39 girls, 46 boys), 1.5–18 months old, who were fed by artificial milk formulas. Gastrointestinal symptoms of food allergy were diagnosed

1057. ADVERSE REACTIONS TO FOOD IN A PORTUGUESE POPULATION. PRELIMINARY RESULTS IN A SELF-REPORTED PREVALENCE STUDY

Lozoya-Ibáñez, Carlos[1,2]; Macedo, Ana Filipa[2]; Rodrigues, Alexandra[3]; Silva, Laura[4]; Fernandes,Luís[5]; Fernandes, Mário[6]; Amaral, Fernanda[7]; Taborda-Barata, Luís[8,2]

[1]Allergy Service, Unidade Local de Saúde de Castelo Branco, EPE [2]University of Beira Interior, CICS, Centro de Investigação em Ciências da Saúde, Covilhã, Portugal;[3] ULSCB, EPE, Emergency Service; [4]Instituto Politécnico de Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias, Castelo Branco, Portugal; [5]ULSCB, EPE, Oleiros Community Health Center; [6]ULSCB, EPE, Proença a Nova CHC; [7]ULSCB, EPE, Castelo Branco CHC; [8]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, Covilhã, Portugal

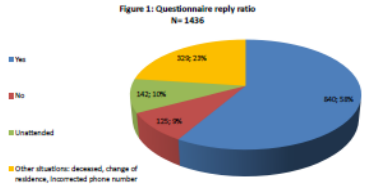
Background

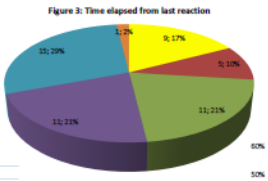
Population-based prevalence studies of adverse reactions to food (ARF) in adults are lacking in Portugal. Therefore, the aim of the present study was to determine the prevalence of ARF in a sample of adult Portuguese patients

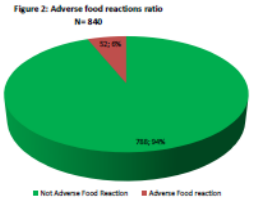
Method

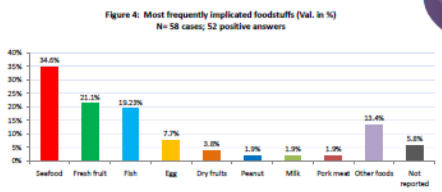
- Multicentre, cross-sectional study based on simple random sampling, already carried out part of the survey during 2010 and 2011, in various parts of the centre of Portugal.
- A calculated 369 randomly selected adults would be necessary in order to obtain a 95% confidence interval and an acceptable margin of error of 2%, around a prevalence estimate of 4%. In order to allow for a 40% response rate, a total of 923 adults will be randomly recruited.
- 1436 adult inhabitants randomly selected distribuited proporcionally for populational ratio areas, aged between 18 and 91 years (mean age: 48 years, median age: 45 years) who have been booked a phone interview for application of a previously validated questionnaire.
- The questionnaire has already been filled out by 965 of these individuals (mean age: 48.9 years; median age: 46 years, 51.3 % female).

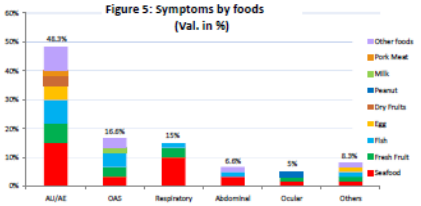
Results

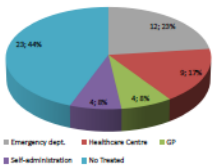


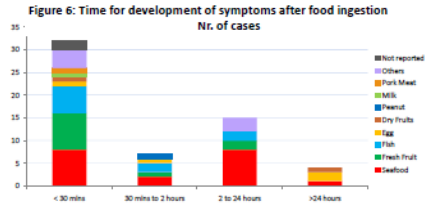


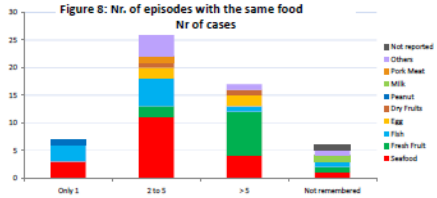


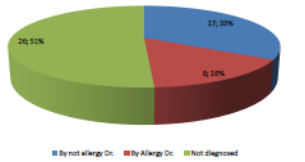


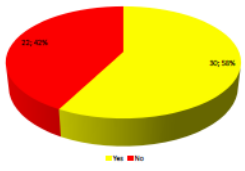


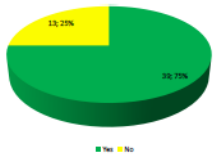












Conclusions

In this first, preliminary, study of the prevalence of food-induced self-reported symptoms in adults from the general population in Portugal, a relatively high percentage of positive cases was detected (6.20%), with urticaria and OAS being the most frequently observed symptoms and seafood, fresh fruits and fish the most frequently implicated foodstuffs.

V.3.1.2. Geneva 2012

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI 2012 GENEVA

This is to certify that the abstract

267 – Frequency of food allergy in an allergy department in Portugal using the Portuguese Allergy Society case-report form over 29 months

was presented as a Poster Discussion by

Carlos Lozoya-Ibáñez

at the EAACI 2012 Congress of the European Academy of Allergy and Clinical Immunology in Geneva, Switzerland

16-20 June 2012

Philippe Eigenmann
Congress EAACI 2012 Chair

Lars K. Poulsen
Scientific Programme Committee
Co-ordinator

EAACI Congress 2012 Secretariat
c/o Congrex Sweden AB, Attn: EAACI 2012 P.O. Box 5619, SE-114 86 Stockholm, Sweden Telephone: +46 8 459 66 00 Fax: +46 8 661 91 25 E-mail: eaaci2012@congrex.com Website: www.eaaci2012.com

EAACI Headquarters
Genferstrasse 21, CH-8002 Zurich, Switzerland Telephone: + 41 44 205 55 33 Fax: +41 44 205 55 39 E-mail: info@eaaci.net Website: www.eaaci.net

267. Frequency of food allergy in an Allergy Department in Portugal using the Portuguese Allergy Society case-report form over 29 months

Lozoya-Ibáñez, Carlos[1,2]; Rodrigues, Alexandra[3]; Lobo, Cláudia[4,2]; Taborda-Barata, Luís[5,2]

[1]Allergy Department, Unidade Local de Saúde de Castelo Branco (ULSCB), EPE; [2]University of Beira Interior, CICS, Centro de Investigação em Ciências da Saúde, Covilhã, Portugal; [3]ULSCB, EPE, Emergency Service; [4]ULSCB, EPE, Clinical Pathology Department; [5]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, Covilhã, Portugal

European Academy of Allergy and Clinical Immunology Congress 2012
16 – 20 June, Geneva, Switzerland

Background

Since the implementation in 2009, of a new Case-Report Form (CRF) by the Portuguese Allergy Society (SPAIC) Food Allergy Interest Group, no studies of food allergy (FA) prevalence have been carried out in Portuguese hospitals. Therefore, the aim of the present study was to determine the prevalence of FA in patients attending an Allergy Outpatient Department, using this new tool

Method

- 1597 patients clinical histories (aged 1-74 years), seen at the Allergy department of the Local Health Unit in Castelo Branco (Portugal) between June 2009 and November 2011.
- Patients were subdivided according to age: children (<18 years old) and adults (≥18 years-old).
- Descriptive statistical analysis was carried out.

Results

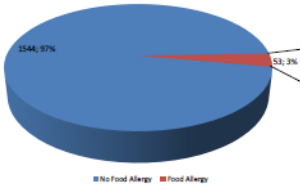


Figure 1: Food Allergy ratio
N= 1597

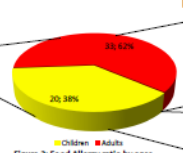


Figure 2: Food Allergy ratio by ages

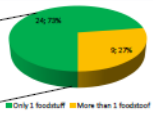


Figure 3: Polisensitization ratio: Adults

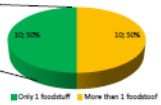


Figure 4: Polisensitization ratio: Children

Table 1: Patient Characterization

	Mean age (years)	Median age (years)	Female sex (%)
Total	26.8	26.5	62.2
Children	9.1	7.5	50
Adults	37.4	36	69.7

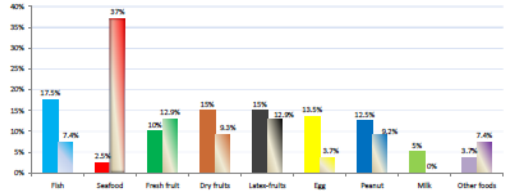


Figure 5: Most frequently implicated foodstuffs (Val. in %)
Left bar: Children; Right bar: Adults

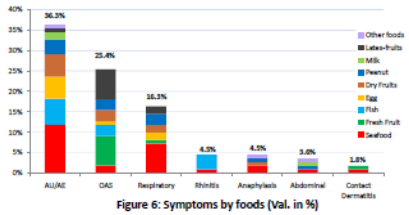


Figure 6: Symptoms by foods (Val. in %)

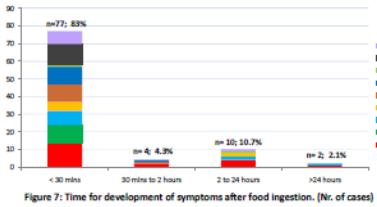


Figure 7: Time for development of symptoms after food ingestion. (Nr. of cases)

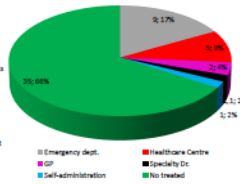


Figure 8: Need for treatment

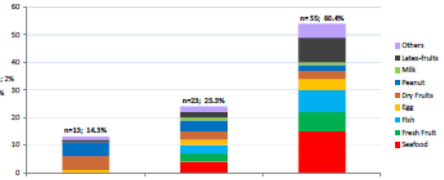


Figure 9: Nr. of episodes with the same food. (Nr of cases)

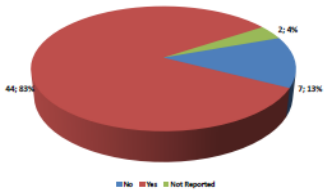


Figure 10: Personal History of Atopy

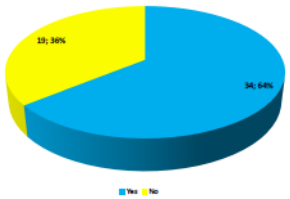


Figure 11: Family History of Atopy

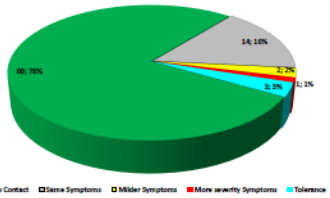


Figure 12: Severity of Reactions in Accidental Contact after FA diagnosis

Conclusions

In this first study of the prevalence of FA using the new SPAIC tool in Portugal, the prevalence of FA in adults, but not in children, is similar to that observed in other allergy departments reported in the literature. Urticaria and OAS were the most frequent symptoms. Seafood, fresh fruits and latex-related fruits in adults and fish, dry fruits and latex-related fruits in children were the most frequently implicated foodstuffs. *In relation to this presentation, I declare that there are no conflicts of interest*

V.3.1.3. Milan 2013

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI-WAO
World Allergy & Asthma Congress
22 – 26 June 2013
Milan, Italy

WAO
WORLD ALLERGY ORGANIZATION
A World Federation of Allergy, Asthma & Clinical Immunology Societies

This is to certify that the abstract

302– Adverse reactions to food in Portuguese schoolchildren. Preliminary results in a self-reported prevalence study

was presented as a Poster Discussion presentation by

Carlos Lozoya-Ibánez

at the EAACI-WAO Congress 2013 of the European Academy of Allergy and Clinical Immunology in Milan, Italy

22-26 June 2013

Authors of this abstract are:
Lozoya-Ibáñez C., Rodrigues A., Fernandes P., Taborda-Barata L.

Cezmi Akdis
EAACI President
Congress President

Ruby Pawankar
WAO President
Congress President

G. Walter Canonica
Local Organising Committee Chair

Marek Jutel
Scientific Programme Committee
Co-ordinator

Lanny Rosenwasser
Scientific Programme Committee
Co-ordinator

EAACI–WAO World Allergy & Asthma Congress 2013 Secretariat
c/o Congrex Sweden AB, Attn: EAACI-WAO 2013 P.O. Box 5619, SE-114 86 Stockholm, Sweden Telephone: +46 8 459 66 00 Fax: +46 8 661 91 25
E-mail: eaaci-wao2013@congrex.com Website: www.eaaci-wao2013.com

EAACI Headquarters
Genferstrasse 21, CH-8002 Zurich, Switzerland
Telephone: + 41 44 205 55 33 Fax: +41 44 205 55 39
E-mail: info@eaaci.org Website: www.eaaci.net

World Allergy Organization
555 E. Wells Street, Suite 1100, Milwaukee, WI 53202, USA
Telephone: +1 414 276 1791 Fax: +1 414276 3349
E-mail: info@worldallergy.org Website: www.worldallergy.org

302. Adverse reactions to food in Portuguese schoolchildren. Preliminary results from a self-reported prevalence study

Lozoya-Ibáñez, Carlos[1,2]; Rodrigues, Alexandra[3]; Fernandes, Patrícia[4]; Taborda-Barata, Luís[2,5]

[1]Allergy Department, Unidade Local de Saúde de Castelo Branco (ULSCB), EPE; [2]CICS - Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal; [3]ULSCB, EPE, Emergency Service; [4]ULSCB, EPE, Clinical Pathology Department; [5]Department of Allergy & Clinical Immunology, Cova da Beira University Hospital, Covilhã, Portugal

European Academy of Allergy and Clinical Immunology & World Allergy Organization
World Allergy & Asthma Congress 2013, 22 – 26 June, Milan, Italy

Background

Population-based prevalence studies of adverse reactions to food (ARF) in schoolchildren are lacking in Portugal.
Therefore, the aim of the present study was to determine the prevalence of ARF in a sample of Portuguese schoolchildren.

Method

•Cross-sectional study based on simple random sampling, in secondary and third cycle schools of Castelo Branco city (center of Portugal) in 2012.
•752 randomly selected children would be necessary in order to obtain a 95% confidence interval and an acceptable margin of error of 2%, around a prevalence estimate of 4%. In order to allow for a 40% response rate, a total of 779 schoolchildren would have to be randomly recruited.
•However, we decided to analyze all schoolchildren between 10 and 23 years of age (2105 students)
The questionnaire was answered by 779 children (37% reply ratio) and filled out by 729 of these individuals (mean age: 14.7 years, median age: 14 years, 61.6% female).

Results

Figure 1: Adverse Food Reactions Ratio

Figure 2: Time since last reaction

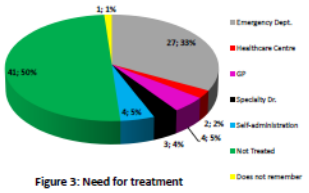


Figure 3: Need for treatment

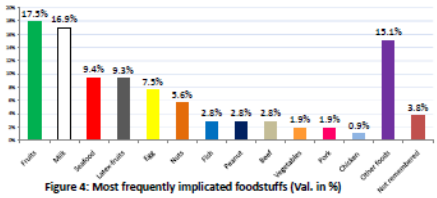


Figure 4: Most frequently implicated foodstuffs (Val. in %)

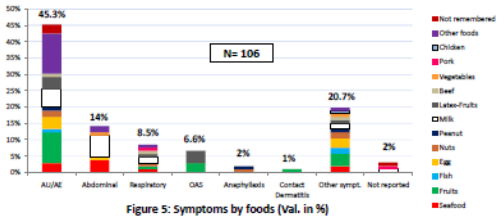


Figure 5: Symptoms by foods (Val. in %)

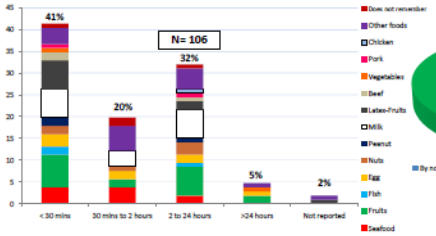


Figure 6: Time for development of symptoms upon food ingestion. (Val. in %)

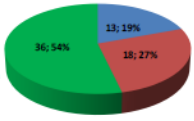


Figure 7: Previous diagnosis of food allergy

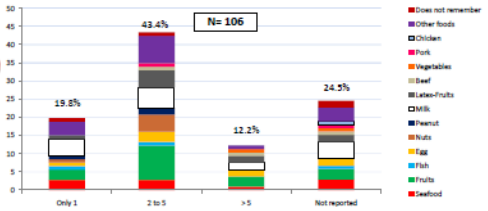


Figure 8: Nr. of episodes with the same food (Val. in %)

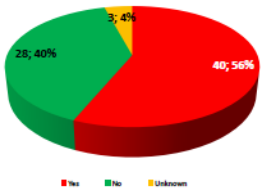


Figure 9: Personal History of Atopy

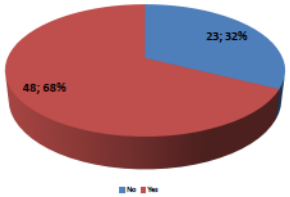


Figure 10: Family History of Atopy

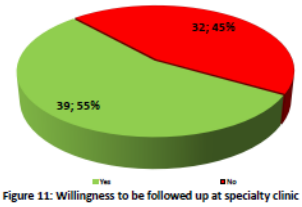
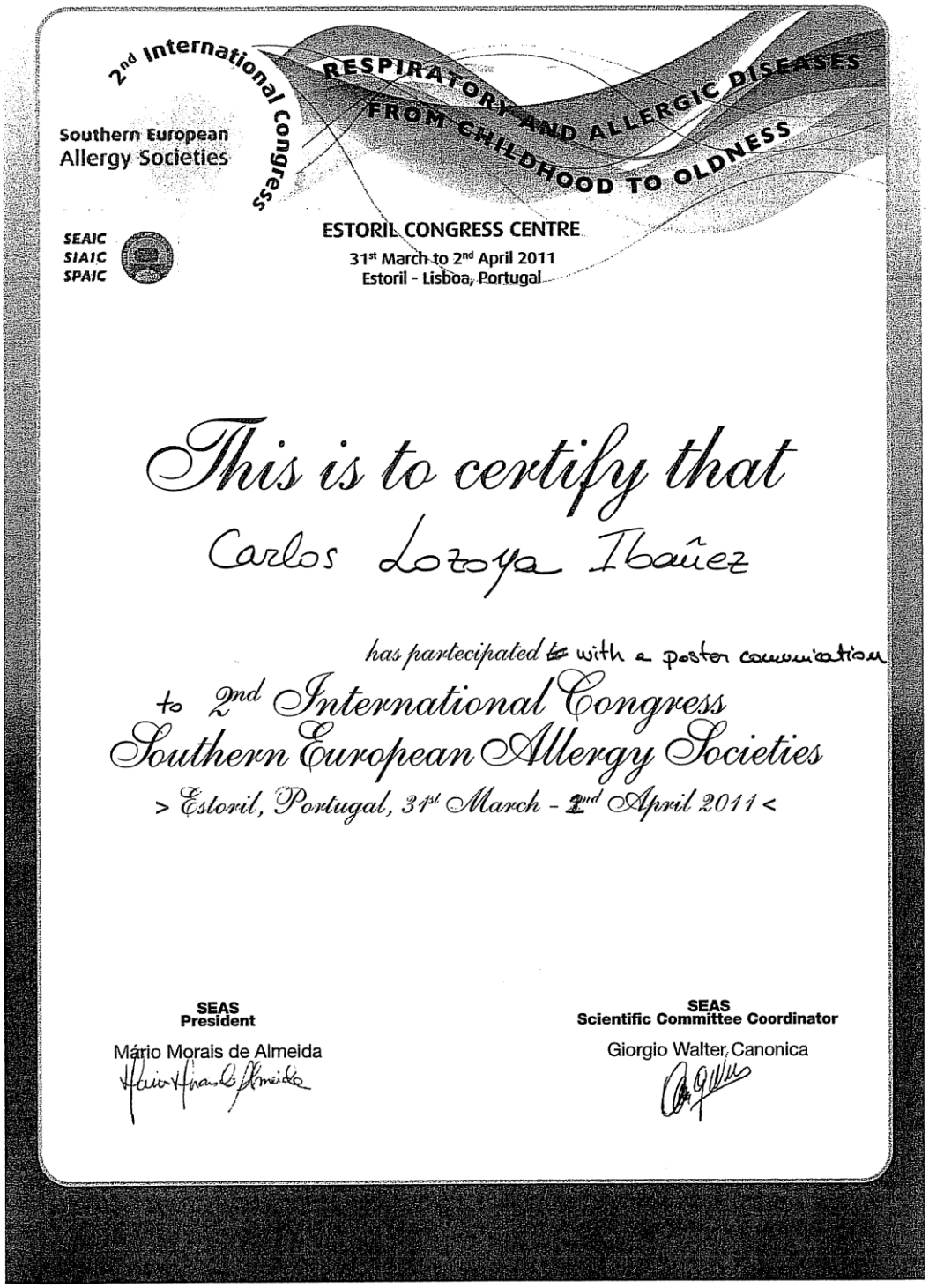


Figure 11: Willingness to be followed up at specialty clinic

Conclusions

In this first, preliminary, study of the prevalence of food-induced self-reported symptoms in schoolchildren in Portugal, a relatively high percentage of positive cases were detected (9.73%) in comparison with other European countries. Urticaria and OAS were the most frequently observed symptoms and fresh and latex-related fruits milk and seafood the most frequently implicated foodstuffs. *In relation to this presentation, I declare that there are no conflicts of interest.*

V.3.2. 2nd International SEAS Congress, Cascais 2011



2nd International Congress

Southern European Allergy Societies

SEAIC
SIAIC
SPAIC

RESPIRATORY AND ALLERGIC DISEASES
FROM CHILDHOOD TO OLDNESS

ESTORIL CONGRESS CENTRE
31st March to 2nd April 2011
Estoril - Lisboa, Portugal

This is to certify that

Carlos Lozoya Ibañez

has partecipated ~~to~~ with a poster communication

to 2nd International Congress
Southern European Allergy Societies
> Estoril, Portugal, 31st March - 2nd April 2011 <

SEAS
President
Mário Morais de Almeida

SEAS
Scientific Committee Coordinator
Giorgio Walter Canonica

17. A NEW VALIDATED QUESTIONNAIRE FOR THE STUDY OF ADVERSE REACTIONS TO FOOD IN PORTUGUESE ADULTS

Lozoya-Ibáñez, Carlos[1,2]; Macedo, Ana Filipa[2]; Rodrigues, Alexandra[3]; Silva, Laura[4]; Rodrigues, Eugénio[5]; Pimenta, Maria José[6]; Mendes, Teresa[7]; Taborda-Barata, Luís[8,2]

[1]Allergy Service, Unidade Local de Saúde de Castelo Branco, EPE [2]University of Beira Interior, CICS, Centro de Investigação em Ciências da Saúde, Covilhã, Portugal;[3]ULSCB, EPE, Emergency Service; [4]Instituto Politécnico de Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias, Castelo Branco, Portugal; [5]ULSCB, EPE, Idanha A Nova Community Health Center; [6]ULSCB, EPE, Vila Velha de Ródão CHC; [7]ULSCB, EPE, Sertã CHC; [8]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, Covilhã, Portugal

Background

One of the most important tools for the study of food allergies is a standardized and validated questionnaire. As far as we know, no such questionnaire has been applied in adults in Portugal. Therefore, the aim of the present study was to validate a questionnaire for food allergies in a sample of adult Portuguese patients.

Method

- Multicentre, cross-sectional study
- Simple random sample of 50 adults aged between 18 and 80 years from various parts of the centre of Portugal.
- Additionally, the questionnaire was also applied to 25 patients diagnosed with food allergy.
- A 17 question questionnaire was applied by phone to both groups, with subsequent reassessment (re-test) with a time interval ranging between 2 weeks and 10 months (median of 1.5 months).
- Eight closed questions were analyzed for internal consistency and temporal stability using SPSS 17.0.

Results

Internal Consistency

A Cronbach´s alpa value of 0.961 was determined for internal consistency.

Internal Consistency (Reliability)	Cronbach´s Alpha
Excellent	>0.9
Good	0.8-0.9
Reasonable	0.7-0.8
Weak	0.6-0.7
Unacceptable	<0.6

Temporal Stability (test-retest reliability)

- A Spearman correlation coefficient value of 0.90 (very good) was determined for general temporal stability of the test
- Cohen's Kappa values for temporal stability (agreement level) was determined for 8 relevant closed questions

Level of Agreement	Cohen´s Kappa (Range values from 0 to 1)
Almost perfect	0.81-1.00
Substantial	0.61-0.80
Moderate	0.41-0.60
Fair	0.21-0.40
Slight	0.01-0.20
Poor	<0.01

Adverse Food Reactions Questionnaire

	Item	Statistic relevant question for temporal stability	Cohen´s Kappa Value	Cronbach's Alpha if item deleted
1	Voluntary Identity Code	No		
2	Sex	No		
3	Age in years	No		
4	Do you want to answer the questionnaire?	No		
6	Which food causes your reaction?	No		
7	What kind of reaction did you have?	No		
8	How long after food ingestion did the reactions appear?	No		
10	If answer was "yes" for item 10, Where did you received medical treatment?	No		
16	Does anybody in your family have an allergic disease?	No		
5	Do you have any adverse food reaction?	Obligatory item	0.971	0.973
9	Did you need medical treatment?	Obligatory item	0.875	0.947
11	Have you had any previous episodes with the same food?	Obligatory item	0.806	0.947
12	How long ago the last reaction take place?	Obligatory item	0.581	0.950
13	Have you been previously diagnosed with food allergy?	Obligatory item	0.942	0.947
14	Have you ever been to a specialty appointment by an Allergist doctor?	Obligatory item	0.945	0.946
15	Do you any other allergic disease? (personal history of atopy)	Obligatory item	0.657	0.976
17	Would you want to be followed up at a specialty clinic?	Obligatory item	0.943	0.947

Conclusions

With the exception of "time elapsed since the previous episode", "existence previous episodes of food allergy" and "personal history of atopy", all items showed almost perfect agreement. In view of the excellent internal consistency and temporal reproducibility, this questionnaire is an useful tool for the study of prevalence in Portuguese patients from the centre of the country and may also apply to other similar populations.

18. STUDY OF SELF-REPORTED PREVALENCE OF ADVERSE REACTIONS TO FOOD IN A PORTUGUESE POPULATION. PRELIMINARY RESULTS

Lozoya-Ibáñez, Carlos[1,2]; Macedo, Ana Filipa[2]; Rodrigues, Alexandra[3]; Silva, Laura[4]; Fernandes,Luís[5]; Fernandes, Mário[6]; Amaral, Fernanda[7]; Taborda-Barata, Luís[8,2]

[1]Allergy Service, Unidade Local de Saúde de Castelo Branco, EPE [2]University of Beira Interior, CICS, Centro de Investigação em Ciências da Saúde, Covilhã, Portugal;[3]ULSCB, EPE, Emergency Service; [4]Instituto Politécnico de Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias, Castelo Branco, Portugal; [5]ULSCB, EPE, Oleiros Community Health Center; [6]ULSCB, EPE, Proença a Nova CHC; [7]ULSCB, EPE, Castelo Branco CHC; [8]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, Covilhã, Portugal

Background

Population-based prevalence studies of adverse reactions to food (ARF) in adults are lacking in Portugal. Therefore, the aim of the present study was to determine the prevalence of ARF in a sample of adult Portuguese patients

Method

- Multicentre, cross-sectional study based on simple random sampling, already carried out part of the survey during 2010 and 2011, in various parts of the centre of Portugal.
- A calculated 369 randomly selected adults would be necessary in order to obtain a 95% confidence interval and an acceptable margin of error of 2%, around a prevalence estimate of 4%. In order to allow for a 40% response rate, a total of 923 adults will be randomly recruited.
- 1121 adult inhabitants randomly selected distribuited proporcionally for populational ratio areas, aged between 18 and 91 years (mean age: 49.4 years, median age: 47 years) who have been booked a phone interview for application of a previously validated questionnaire.
- The questionnaire has already been filled out by 763 of these individuals (mean age: 50.6 years; median age: 77 years, 50.9 % female).

Results

Figure 1: Questionnaire reply ratio N= 1121

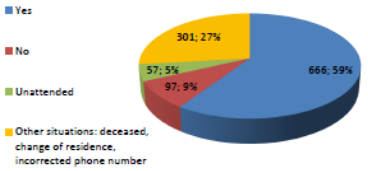


Figure 2: Time elapsed from last reaction

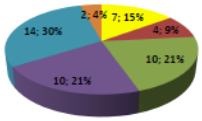


Figure 3: Adverse food reactions ratio N= 666

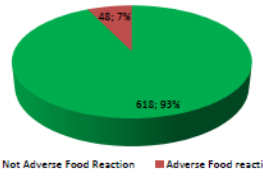


Figure 4: Most frequently implicated foodstuffs (Val. in %) N= 58 cases; 48 positive answers

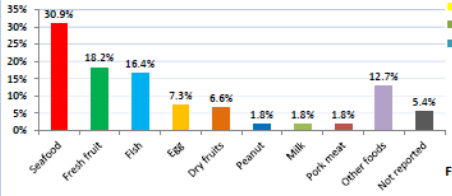


Figure 5: Symptoms by foods (Val. in %)

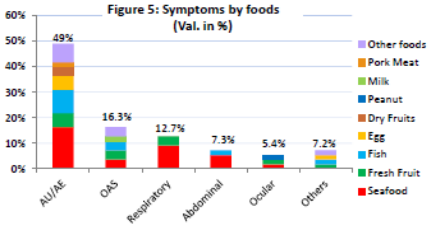


Figure 6: Time for development of symptoms after food ingestion Nr. of cases

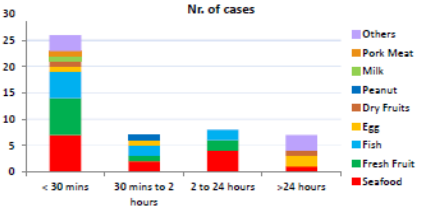


Figure 7: Need for treatment

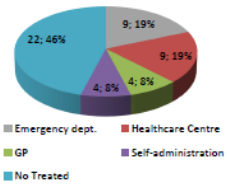


Figure 8: Nr. of episodes with the same food Nr of cases

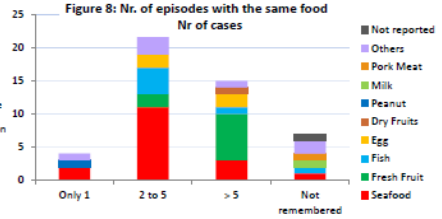


Figure 9: Previous diagnosis of food allergy

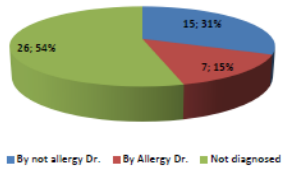


Figure 10: Personal history of atopy

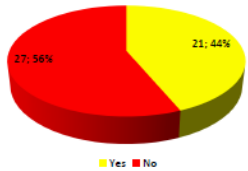
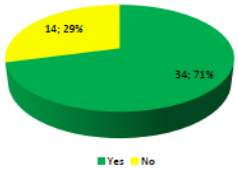


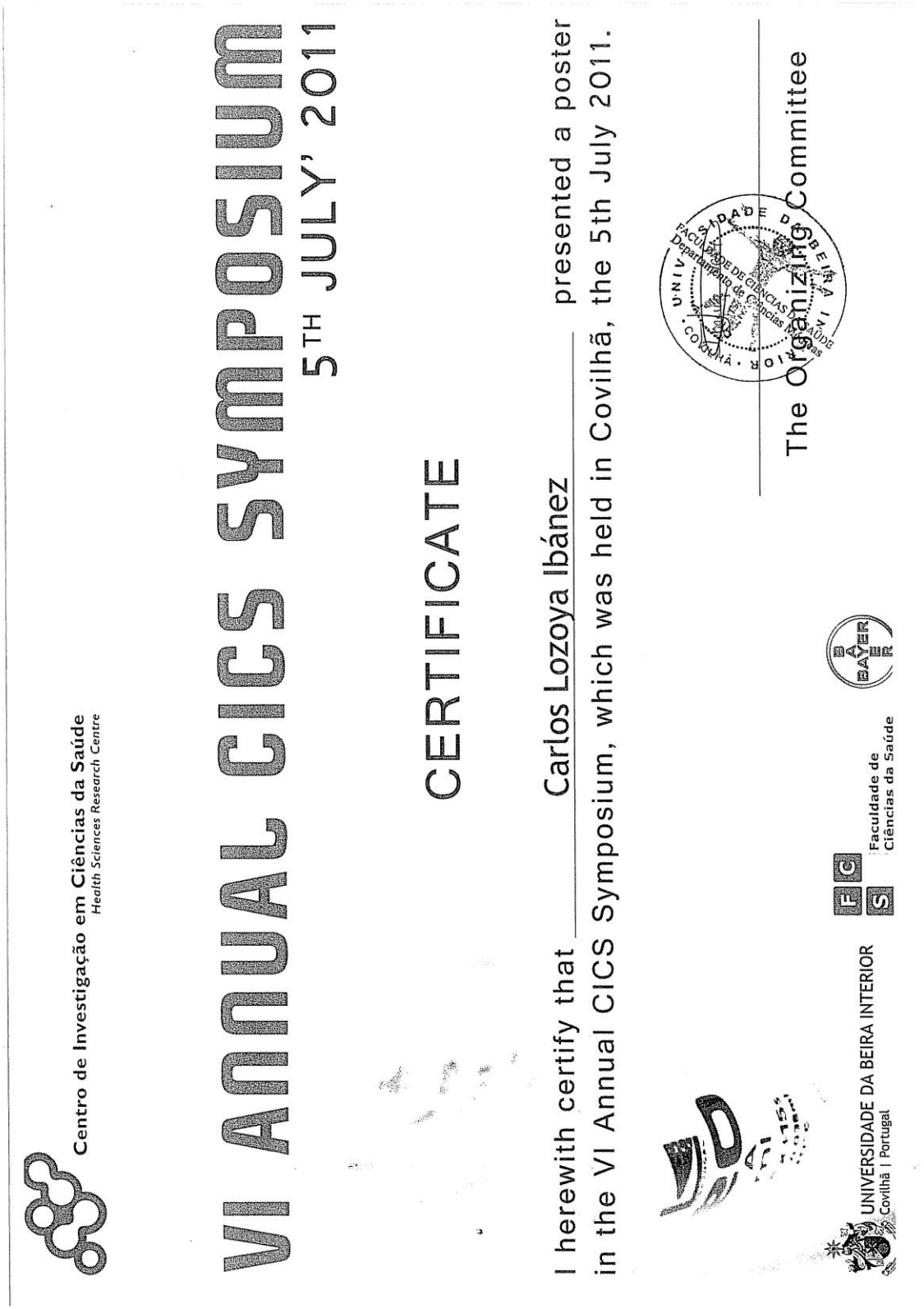
Figure 11: Willingness to be followed up at specialty clinic



Conclusions

In this first, preliminary, study of the prevalence of food-induced self-reported symptoms in adults from the general population in Portugal, a relatively high percentage of positive cases was detected (7.20%), with urticaria and OAS being the most frequently observed symptoms and seafood, fresh fruits and fish the most frequently implicated foodstuffs.

V.4 Local and national scientific congress
V.4.1. V Annual CICS Symposium, Covilhã 2011



VALIDATION OF A QUESTIONNAIRE FOR THE STUDY OF FOOD ALLERGIES IN PORTUGUESE ADULTS

Lozoya-Ibáñez, Carlos[1,2]; Macedo, Ana Filipa[2]; Rodrigues, Alexandra[3]; Silva, Laura[4]; Rodrigues, Eugénio[5]; Pimenta, Maria José[6]; Mendes, Teresa[7]; Taborda-Barata, Luís[8,2]

[1]Allergy Service, Unidade Local de Saúde de Castelo Branco, EPE [2]University of Beira Interior, CICS, Centro de Investigação em Ciências da Saúde, Covilhã, Portugal; [3]ULSCB, EPE, Emergency Service; [4]Instituto Politécnico de Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias, Castelo Branco, Portugal; [5]ULSCB, EPE, Idanha A Nova Community Health Center; [6]ULSCB, EPE, Vila Velha de Ródão CHC; [7]ULSCB, EPE, Sertã CHC; [8]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, Covilhã, Portugal

Background

One of the most important tools for the study of food allergies is a standardized and validated questionnaire. As far as we know, no such questionnaire has been applied in adults in Portugal. Therefore, the aim of the present study was to validate a questionnaire for food allergies in a sample of adult Portuguese patients.

Method

- Multicentre, cross-sectional study
- Simple random sample of 50 adults aged between 18 and 80 years from various parts of the centre of Portugal.
- Additionally, the questionnaire was also applied to 25 patients diagnosed with food allergy.
- A 17 question questionnaire was applied by phone to both groups, with subsequent reassessment (re-test) with a time interval ranging between 2 weeks and 10 months (median of 1.5 months).
- Eight closed questions were analyzed for internal consistency and temporal stability using SPSS 17.0.

Results

Internal Consistency

A Cronbach´s alpa value of 0.961 was determined for internal consistency.

Internal Consistency (Reliability)	Cronbach´s Alpha
Excellent	>0.9
Good	0.8-0.9
Reasonable	0.7-0.8
Weak	0.6-0.7
Unacceptable	<0.6

Temporal Stability (test-retest reliability)

- A Spearman correlation coefficient value of 0.90 (very good) was determined for general temporal stability of the test
- Cohen's Kappa values for temporal stability (agreement level) was determined for 8 relevant closed questions

Level of Agreement	Cohen´s Kappa (Range values from 0 to 1)
Almost perfect	0.81-1.00
Substantial	0.61-0.80
Moderate	0.41-0.60
Fair	0.21-0.40
Slight	0.01-0.20
Poor	<0.01

Adverse Food Reactions Questionnaire

	Item	Statistic relevant question for temporal stability	Cohen´s Kappa Value	Cronbach's Alpha if item deleted
1	Voluntary Identity Code	No		
2	Sex	No		
3	Age in years	No		
4	Do you want to answer the questionnaire?	No		
6	Which food causes your reaction?	No		
7	What kind of reaction did you have?	No		
8	How long after food ingestion did the reactions appear?	No		
10	If answer was "yes" for item 9, Where did you received medical treatment?	No		
16	Does anybody in your family have an allergic disease?	No		
5	Do you have any adverse food reaction?	Obligatory item	0.971	0.973
9	Did you need medical treatment?	Obligatory item	0.875	0.947
11	Have you had any previous episodes with the same food?	Obligatory item	0.806	0.947
12	How long ago the last reaction take place?	Obligatory item	0.581	0.950
13	Have you been previously diagnosed with food allergy?	Obligatory item	0.942	0.947
14	Have you ever been to a specialty appointment by an Allergist doctor?	Obligatory item	0.945	0.946
15	Do you any other allergic disease? (personal history of atopy)	Obligatory item	0.657	0.976
17	Would you want to be followed up at a specialty clinic?	Obligatory item	0.943	0.947

Conclusions

With the exception of "time elapsed since the previous episode", "existence previous episodes of food allergy" and "personal history of atopy", all items showed almost perfect agreement. In view of the excellent internal consistency and temporal reproducibility, this questionnaire is an useful tool for the study of prevalence of adverse food reactions in Portuguese patients from the centre of the country and may also apply to other similar populations.

ADVERSE REACTIONS TO FOOD IN A PORTUGUESE POPULATION. PRELIMINARY RESULTS IN A SELF-REPORTED PREVALENCE STUDY

Lozoya-Ibáñez, Carlos[1,2]; Macedo, Ana Filipa[2]; Rodrigues, Alexandra[3]; Silva, Laura[4]; Fernandes,Luís[5]; Fernandes, Mário[6]; Amaral, Fernanda[7]; Taborda-Barata, Luís[8,2]

[1]Allergy Service, Unidade Local de Saúde de Castelo Branco, EPE [2]University of Beira Interior, CICS, Centro de Investigação em Ciências da Saúde, Covilhã, Portugal; [3]ULSCB, EPE, Emergency Service; [4]Instituto Politécnico de Castelo Branco, Escola Superior de Saúde Dr. Lopes Dias, Castelo Branco, Portugal; [5]ULSCB, EPE, Oleiros Community Health Center; [6]ULSCB, EPE, Proença a Nova CHC; [7]ULSCB, EPE, Castelo Branco CHC; [8]Department of Allergy & Clinical Immunology, Centro Hospitalar Cova da Beira, Covilhã, Portugal

UNIVERSIDADE DA BEIRA INTERIOR Covilhã | Portugal

Centro de Investigação em Ciências da Saúde Health Sciences Research Centre

ULS

Background

Population-based prevalence studies of adverse reactions to food (ARF) in adults are lacking in Portugal. Therefore, the aim of the present study was to determine the prevalence of ARF in a sample of adult Portuguese patients

Method

- Multicentre, cross-sectional study based on simple random sampling, already carried out part of the survey during 2010 and 2011, in various parts of the centre of Portugal.
- A calculated 369 randomly selected adults would be necessary in order to obtain a 95% confidence interval and an acceptable margin of error of 2%, around a prevalence estimate of 4%. In order to allow for a 40% response rate, a total of 923 adults will be randomly recruited.
- 1436 adult inhabitants randomly selected distribuited proporcionally for populational ratio areas, aged between 18 and 91 years (mean age: 48 years, median age: 45 years) who have been booked a phone interview for application of a previously validated questionnaire.
- The questionnaire has already been filled out by 965 of these individuals (mean age: 48.9 years; median age: 46 years, 51.3 % female).

Results

Figure 1: Questionnaire reply ratio N= 1436

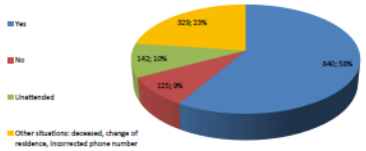


Figure 2: Adverse food reactions ratio N= 840

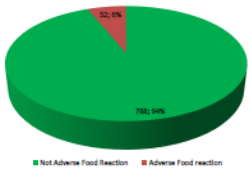


Figure 3: Time elapsed from last reaction

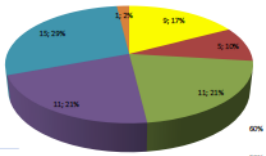


Figure 4: Most frequently implicated foodstuffs (Val. in %) N= 58 cases; 52 positive answers

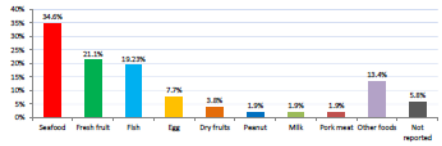


Figure 5: Symptoms by foods (Val. in %)

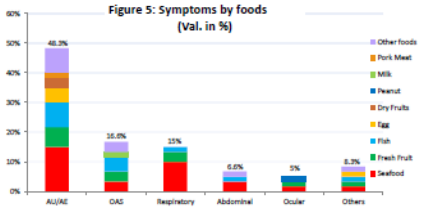


Figure 6: Time for development of symptoms after food ingestion Nr. of cases

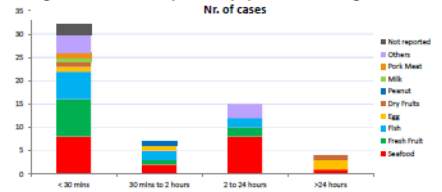


Figure 7: Need for treatment

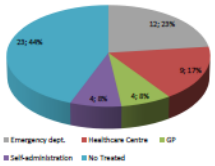


Figure 8: Nr. of episodes with the same food Nr of cases

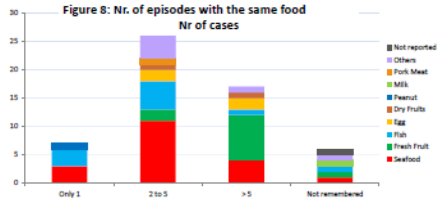


Figure 9: Previous diagnosis of food allergy

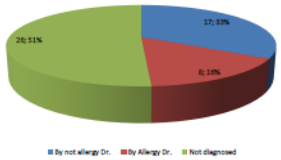


Figure 10: Personal history of atopy

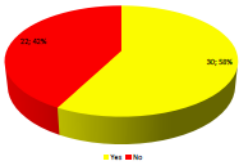
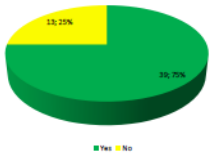


Figure 11: Willingness to be followed up at speciality clinic



Conclusions

In this first, preliminary, study of the prevalence of food-induced self-reported symptoms in adults from the general population in Portugal, a relatively high percentage of positive cases was detected (6.20%), with urticaria and OAS being the most frequently observed symptoms and seafood, fresh fruits and fish the most frequently implicated foodstuffs.

V.4.2. Reunião de Imunoalergologia do Hospital Dona Estefânia, Lisbon 2013

COMUNICAÇÕES ORAIS

I- Um caso raro de anafilaxia na criança após ingestão de castanha do maranhão

José Pedro Almeida , Fátima Duarte, Ana Célia Costa, Manuel Pereira Barbosa

Serviço de Imunoalergologia, Hospital Santa Maria, CHLN, Lisboa, Portugal

II- Indução tolerância às proteínas do leite de vaca com leite cozinhado – a propósito de um caso clínico

Leonor Paulos Viegas[1], Miguel Paiva[2], Paula Leiria Pinto[2]
[1]Serviço de Imunoalergologia, Hospital Santa Maria – CHLN, E.P.E.; Lisboa; [2]Serviço de Imunoalergologia, Hospital Dona Estefânia – CHLC, E.P.E.

III- Reacções adversas a alimentos auto-reportadas em adolescentes Portugueses. Dados preliminares de prevalência

Lozoya-Ibáñez, Carlos1,5; Rodrigues, Alexandra2; Fernandes, Patrícia3; Taborda-Barata, Luís4,5
1Imunoalergologia, Unidade Local de Saúde de Castelo Branco, EPE, Castelo Branco, Portugal; 2Serviço de Urgência, Unidade Local de Saúde de Castelo Branco, EPE, Castelo Branco, Portugal; 3Serviço de Patologia Clínica, Unidade Local de Saúde de Castelo Branco, EPE, Castelo Branco, Portugal; 4Serviço de Imunoalergologia, Centro Hospitalar Universitário Cova da Beira, Covilhã, Portugal; 5CICS – Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal

IV- Prevalência e características clínicas e serológicas de reacções IgE- e não-IgE-mediadas a alimentos em crianças em idade escolar e pré-escolar.

A. Jorge1,2, E. Soares1, L. Taborda-Barata1,3.
1 CICS – Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal
2 Serviço de Pediatria, Centro Hospitalar Universitário Cova da Beira, E.P.E., Covilhã, Portugal
3 Serviço de Imunoalergologia, Cova da Beira Hospital, Centro Hospitalar Universitário Cova da Beira, E.P.E., Covilhã, Portugal

V- Perfil de sensibilização a LTP (Pru p 3) e profilina (Pru p 4) em crianças e adultos referenciados a um Serviço de Imunoalergologia em Lisboa

P. M. Silva , L. Pestana, A. C. Costa, M. P. Barbosa
Serviço de Imunoalergologia, Hospital de Santa Maria, Lisboa, Portugal

VI- Alergia a frutos frescos: a evolução de um caso clínico

Martins, Marta; Reis, Rute; Cruz, Cíntia; Tomaz, Elza; Inácio, Filipe.
Serviço de Imunoalergologia, Hospital São Bernardo – CHS.

VII- Anafilaxia induzida por exercício dependente de alimentos – Caso clínico

Cíntia Cruz, Marta Batista, Fátima Ferreira, Ana Paula Pires, Irina Didenko, Filipe Inácio.
Serviço de Imunoalergologia, Hospital de São Bernardo, Centro Hospitalar de Setúbal

VIII- Rectocolite hemorrágica, um desafio clínico

Soares, M.1; Pereira, A. 1; Virtuoso, M.J. 1; Caetano, S. 1; Afonso, I.2
1 Hospital de Faro, E.P.E.; 2Hospital Dona Estefânia

IX- Um caso de anafilaxia à soja.

Catarina Carrusca, Vânia Sousa, Carolina Albuquerque, Cândida Mendes

Serviço de Pediatria do Hospital Vila Franca

V.4.3. I Jornadas de Investigação clínica do CACB, Covilhã 2018