BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

BMJ Open

PREVALENCE AND RISK FACTORS FOR FOOD ALLERGY IN ELDERLY INDIVIDUALS: PROTOCOL FOR A SYSTEMATIC REVIEW

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029633
Article Type:	Protocol
Date Submitted by the Author:	02-Feb-2019
Complete List of Authors:	Laia-Dias, Inês; Universidade da Beira Interior, Faculty of Health Sciences Lozoya-Ibáñez, Carlos; Hospital Amato Lusitano, Department of Allergy & Clinical Immunology Skypala, Isabel; Royal Brompton & Harefield NHS Trust, Royal Brompton Hospital Gama, Jorge ; Universidade da Beira Interior Centro de Matematica e Aplicacoes, Mathematics Nurmatov, Ulugbek; Division of Population Medicine, School of Medicine, Cardiff University Lourenço, Olga; Universidade da Beira Interior, Faculty of Health Sciences Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA – Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre
Keywords:	EPIDEMIOLOGY, GERIATRIC MEDICINE, Allergy < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

PREVALENCE AND RISK FACTORS FOR FOOD ALLERGY IN ELDERLY INDIVIDUALS: PROTOCOL FOR A SYSTEMATIC REVIEW

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

[1] Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal
[2]Department of Allergy & Clinical Immunology, Amato Lusitano Hospital, Castelo Branco Local Health Unit, Castelo Branco, Portugal
[3]CICS - Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal
[4]Royal Brompton & Harefield NHS Trust, London, England, United Kingdom
[5]Centre of Mathematics and Applications, Faculty of Sciences, University of Beira Interior, Covilhã, Portugal
[6]Division of Population Medicine, School of Medicine, The National Centre for Population Health & Wellbeing Research, Cardiff University, Wales, United Kingdom
[7]Department of Allergy & Clinical Immunology, Cova da Beira Hospital Centre, Covilhã, Portugal

Word Count: 2405 words

Corresponding author:
Professor Luís Taborda-Barata MD, PhD,
CICS - Health Sciences Research Centre, University of Beira Interior,
Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal
Tel.: +351 275 329 002
Fax: +351 275 329 099
E-mail: tabordabarata@fcsaude.ubi.pt

For peer review only

ABSTRACT

Introduction: Studies suggest that the prevalence of food allergy may be increasing worldwide. Results regarding the prevalence and features of adverse food reactions in the elderly 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 elderly individuals, its risk factors, clinical features, most frequently and commonly involved foods.

Methods and Analysis: This systematic review protocol has been registered with PROSPERO register (https://www.crd.york.ac.uk/prospero/) number CRD42018102140. We will conduct a systematic review and meta-analysis on the incidence, prevalence and risk factors for food allergy in elderly individuals. We will search international electronic databases including MEDLINE, EMBASE, Cochrane Library, CINAHL, AMED and ISI Web of Science for published, un-published and on-going studies from 1980 to 2019. There will be no restriction on the language or geography of publication. We will use the Critical Appraisal Skills Programme (CASP) 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 PRISMA checklist will guide reporting of the systematic review.

Ethics and Dissemination: Since this systematic review will be solely based upon 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 elderly 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.

Keywords: Elderly, Epidemiology; Food allergy; Protocol; Systematic review

For peer review only

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Food allergy is a growing problem worldwide namely in elderly individuals
- This is the first systematic review which will specifically address issues related to food allergy in elderly individuals, 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

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 (DBPCFC) [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 elderly individuals are scarce [1-3,5]. In fact, most epidemiological results of food allergy involving elderly individuals 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 elderly individuals than in young adults or in children. In this context, a previous meta-analysis has shown that it may be higher in elderly 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 elderly adults. Thus, further studies are necessary to clarify this issue. Nevertheless, the prevalence of food allergy may also be increasing in elderly individuals. For example, the analysis of the U.S. Food and Drug Administration Food Safety Surveys (FSS) 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 elderly individuals, although this was only significant in the 60-69 year old group, but not in the > 70 year old group [6].

It should also be taken into account that the numbers and relative percentage of elderly people are increasing worldwide. According to the United Nations [7], in 2017, 13% of the world population was aged 60 or over and 2% was aged 80 or over. In comparison

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

with 2017, by 2050, the population aged 60 and over is expected to increase twofold (962 million to 2.1 billion), and the population aged 80 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 the elderly, a situation which may be further compounded by concurrent medications and co-morbidities, as well as lack of awareness of the problem [5,8,9]. These factors may lead to underdiagnosis and undertreatment of food allergies in elderly individuals [5,8]. Furthermore, these changes might be reflected not only in the 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 the elderly. All of these points may demand a different approach regarding its diagnosis and management in comparison with non-elderly adults [5]. However, to the best of our knowledge, no previous systematic review has been published on epidemiological aspects of food allergies specifically in elderly individuals.

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

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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], 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 will search 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 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 on-going 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 the inception to present. Search terms are detailed in 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 “elderly” since our systematic review will include studies from all over the world, and the World Health

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Organisation (W.H.O.) proposed 60 years as a working definition of an "older person" in African countries [11]. In addition, although 65 years is recommended by W.H.O. as a cut off level in western countries [12,13], 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 [6]. 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.

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 PRISMA 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 elderly patients were analysed together with those from non-elderly patients, authors will be contacted in order to clarify or make available data pertaining to the former group, for subgroup analyses.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Data Items

The following information will be 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 [14]: 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.

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 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 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 (CASP) 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 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]. Sub-group analysis may eventually be carried out using the following age groups: 60-65 years, 66-80 years, > 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 Software Package for Social Sciences (SPSS) version 25.0®. Finally, the PRISMA-P 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For Peer Review Only

ETHICS AND DISSEMINATION

This systematic review, based on studies published between 1980 and December 2018, 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 elderly individuals: a) Worldwide prevalence of food allergy in this subgroup of adults; b) Geographical differences in prevalence of food allergy and related food allergens; c) Time trends in prevalence of food allergy and related food allergens; d) Predominant foods associated with food allergy; e) Most frequent symptoms/ symptom clusters, as well as their severity, associated with food allergy; f) Most frequent symptoms associated with specific foods; g) Timeframe of symptom development upon ingestion of foods; h) Need for treatment of episodes of food allergy; i) Risk factors associated with food allergy; j) 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 the elderly. This information may be crucial to analysing similarities and differences regarding food allergies between elderly and non-elderly individuals and eventually defining preventive or diagnostic approaches specifically tailored to this age range.

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 elderly 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 the elderly, we also plan to organise meetings with general practitioners and other healthcare providers, to analyse and discuss our findings and their potential implications.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 & Innovation Department of this institution, for invaluable input in terms of discussion of this manuscript

CONTRIBUTORS

ILD and CLI are equal contributors to the design and conceptualisation of this review, and drafted the protocol with primary support from UN (review guarantor) and LTB. UN, IS, 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.

ILD, CLI and LTB were involved in establishing eligibility criteria and data extraction forms. All authors provided feedback on the manuscript, at all stages.

FUNDING

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

COMPETING INTERESTS

None declared.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in BMJ Open and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

For peer review only

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. Doi: 10.1111/all.12305.

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. Doi: 10.1016/jaci.2007.05.026.

3. Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. JAMA 2010; 303: 1848-56. Doi: 10.1001/jama.2010.582.

4. Tang MLK, Mullins RJ. Food allergy: is prevalence increasing? Intern Med J. 2017; 47: 256-261. Doi: 10.1111/imj.13362.

5. Jensem-Jarolim E, Jensen SAF. Food allergies in the elderly. Collecting the evidence. Ann Allergy Asthma Immunol. 2016; 117: 472-475. Doi: 10.1016/j.anai.2016.08.036.

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: 458-467. Doi: 10.2500/aap.2015.36.3895.

7. United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP/248

8. Diesner SC, Untersmayr E, Pietschmann P, et al. Food allergy: only a pediatric disease? Gerontology. 2011; 57: 28-32. Doi: 10.1159/000279756.

9. Montanaro A. Allergic disease management in the elderly: a wakeup call for the allergy community. Ann Allergy Asthma Immunol. 2000; 85: 85-86. Doi: 10.1016/S1081-1206(10)62442-8.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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. 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. https://www.who.int/healthinfo/survey/ageingdefnolder/en/ Last accessed on 7th January 2019

12. WHO, Geneva: Switzerland. World Health Organisation. Definition of an older or elderly person. http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html . Last accessed on 28th December 2018.

13. Orimo H, Ito H, Suzuki T, et al. Reviewing the definition of "elderly" Geriatr Gerontol Int. 2006; 6: 149–158. Doi:10.1111/j.1447-0594.2006.00341.x.

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. Doi: 10.1186/2045-7022-3-13.

15. CASP checklist for systematic reviews. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf. Last accessed on 22nd December 2018.

16. CASP checklist for cohort studies. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Cohort-Checklist-2018_fillable_form.pdf. Last accessed on 22nd December 2018.

17. CASP checklist for case–control studies. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Case-Control-Checklist-2018_fillable_form.pdf. Last accessed on 22nd December 2018.

For peer review only

18. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011: 64: 401-406. Doi: 10.1016/j.clinepi.2010.07.015.

19. Guyatt G, Oxman AS, Akl EA, et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011: 64: 383-394. Doi: 10.1016/j.clinepi.2010.04.026.

20. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Statis 1998; 52: 119-126. Doi: 10.2307/2685469.

21. Borenstein M, Hedges LV, Higgins JPT, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Sunth Methods 2010: 1: 97-111. Doi: 10.1002/jrsm.12.

22. Rice K, Higgins JPT, Lumley T. A re-evaluation of fixed effect(s) meta-analysis. J Royal Stat Soc: Series A. 2017; 181: 205-227. Doi: 10.1111/rssa.12275.

23. Sterne JAC, Harbord RM. Funnel plots in meta-analysis. Stata J. 2004; 4: 127-141. Available at: http://ageconsearch.umn.edu/bitstream/116233/2/sjart_st0061.pdf.

24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088–1101. Doi: 10.2307/2533446.

25. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634. Doi: 10.1136/bmj.315.7109.629.

26. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560. Doi: 10.1136/bmj.327.7414.557.

27. Liberati A, Altman DG, Tetzlaff J, 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; 6: e1000100. Doi: 10.1371/journal.pmed.1000100.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647. Doi: 10.1136/bmj.g.7647.

For peer review only

Appendix 1: Search Strategy

Search Strategy 1

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.

For peer review only

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

33. incidence.mp. or exp Incidence/

34. prevalence.mp. or exp Prevalence/

35. risk factors.mp. or exp Risk Factors/

36. (incidence or prevalence or epidemiol$).ti.

37. Or/33-36

38. exp Epidemiologic Methods/

39. *cohort studies/ or cohort.ti,ab.

40. (longitudinal or prospective).ti,ab.

41. *case-control studies/

42. Control groups/ or control group*.ti,ab.

43. Matched-pair analysis/

44. (case* adj5 control*).ti,ab.

45. (case* adj3 comparison*).ti,ab.

46. (case* adj3 referen*).mp.

47. (case* adj1 base).mp.

48. (case* adj1 cohort).mp.

49. exp cross-sectional studies/ or cross-sectional.ti,ab.

50. Or/38-49

51. Adult

52. 32 AND 37 AND 50 AND 51

53. advertisements/ or animation/ or architectural drawings/ or bibliography/ or biography/ or book illustrations/ or bookplates/ or charts/ or comment/ or letter/ or editorial/ or news/ or patient education handout/ or published erratum/ or "retraction of publication"/

54. 52 Not 53

55. limit 54 to year=”1980-current”

For peer review only

Search strategy 2

(Cochrane Library, CINAHL, ISI Web of Science)

(Food hypersensitivity or food allergy or milk allergy or egg allergy or nut allergy or peanut allergy or arachis hypogaea allergy or tree nut allergy or hazelnut allergy or legumes allergy or wheat allergy or soy allergy or fish allergy or seafood allergy or shellfish allergy or kiwi allergy or apple allergy or peach allergy or additives hypersensitivity or additives allergy)

AND

(Epidemiological studies or observational studies or cohort studies or cohort analysis or follow up studies or longitudinal studies or case control studies or case-control studies or cross sectional studies or cross-sectional studies or retrospective studies)

AND

("risk of developing" or prevalence or incidence or risk factors or protective factors or time trends)

AND

Adult

For peer review only

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1,2,5
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Sources	#5a	Indicate sources of financial or other support for the review	N/A
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Rationale	#6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such	6,7

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

For peer review only

		as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supl
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7,8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8,9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8,9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

BMJ Open

PREVALENCE AND RISK FACTORS FOR FOOD ALLERGY IN ELDERLY INDIVIDUALS: PROTOCOL FOR A SYSTEMATIC REVIEW

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029633.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Jul-2019
Complete List of Authors:	Laia-Dias, Inês; Universidade da Beira Interior, Faculty of Health Sciences Lozoya-Ibáñez, Carlos; Hospital Amato Lusitano, Department of Allergy & Clinical Immunology Skypala, Isabel; Royal Brompton & Harefield NHS Trust, Royal Brompton Hospital Gama, Jorge ; Universidade da Beira Interior Centro de Matematica e Aplicacoes, Mathematics Nurmatov, Ulugbek; Division of Population Medicine, School of Medicine, Cardiff University Lourenço, Olga; Universidade da Beira Interior, Faculty of Health Sciences Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA – Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Geriatric medicine
Keywords:	EPIDEMIOLOGY, GERIATRIC MEDICINE, Allergy < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

PREVALENCE AND RISK FACTORS FOR FOOD ALLERGY IN ELDERLY INDIVIDUALS: PROTOCOL FOR A SYSTEMATIC REVIEW

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

[1] Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal
[2]Department of Allergy & Clinical Immunology, Amato Lusitano Hospital, Castelo Branco Local Health Unit, Castelo Branco, Portugal
[3]CICS - Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal
[4]Royal Brompton & Harefield NHS Trust, London, England, United Kingdom
[5]Centre of Mathematics and Applications, Faculty of Sciences, University of Beira Interior, Covilhã, Portugal
[6]Division of Population Medicine, School of Medicine, The National Centre for Population Health & Wellbeing Research, Cardiff University, Wales, United Kingdom
[7]Department of Allergy & Clinical Immunology, Cova da Beira Hospital Centre, Covilhã, Portugal

Word Count: 2405 words

Corresponding author:
Professor Luís Taborda-Barata MD, PhD,
CICS - Health Sciences Research Centre, University of Beira Interior,
Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal
Tel.: +351 275 329 002
Fax: +351 275 329 099
E-mail: tabordabarata@fcsaude.ubi.pt

For peer review only

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: This systematic review protocol has been registered with PROSPERO register (https://www.crd.york.ac.uk/prospero/) number CRD42018102140. 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 to 2019. There will be no restriction on the language or geography of publication. We will use the Critical Appraisal Skills Programme (CASP) 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 PRISMA checklist will guide reporting of the systematic review.

Ethics and Dissemination: Since this systematic review will be solely based upon 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.

Keywords: Elderly, Epidemiology; Food allergy; Older people; Protocol; Systematic review

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 individuals, 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

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 (DBPCFC) [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 elderly individuals 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 elderly 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 elderly individuals. For example, the analysis of the U.S. Food and Drug Administration Food Safety Surveys (FSS) 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 60-69 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

the world population was aged 60 or over and 2% was aged 80 or over. In comparison with 2017, by 2050, the population aged 60 and over is expected to increase twofold (962 million to 2.1 billion), and the population aged 80 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 the elderly, a situation which may be further compounded by concurrent medications and co-morbidities, 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 the elderly. All of these points may demand a different approach regarding its diagnosis and management in comparison with non-elderly 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 individuals, 2) to describe clinical manifestations and predominant foods associated with food allergy in the elderly; 3) to analyse risk and prognostic factors associated with food allergy in the elderly.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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], 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 will search 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 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 until December 2018. Search terms are detailed in 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 “elderly” or “older adult” since our systematic review will include studies from all over the world, and the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

World Health Organisation (W.H.O.) proposed 60 years as a working definition of an "older person" in African countries [11]. In addition, although 65 years is recommended by W.H.O. 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 elderly 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 PRISMA 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 elderly patients were analysed together with those from non-elderly patients, authors will be contacted in order to clarify or make available data pertaining to the former group, for subgroup analyses.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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]: 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.

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 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 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

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 (CASP) 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 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]. Sub-group analysis may eventually be carried out using the following age groups: 60-65 years, 66-80 years, > 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 Software Package for Social Sciences (SPSS) version 25.0®. Finally, the PRISMA-P 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ETHICS AND DISSEMINATION

This systematic review, based on studies published between 1980 and December 2018, 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: a) Worldwide prevalence of food allergy in this subgroup of adults; b) Geographical differences in prevalence of food allergy and related food allergens; c) Time trends in prevalence of food allergy and related food allergens; d) Predominant foods associated with food allergy; e) Most frequent symptoms/ symptom clusters, as well as their severity, associated with food allergy; f) Most frequent symptoms associated with specific foods; g) Timeframe of symptom development upon ingestion of foods; h) Need for treatment of episodes of food allergy; i) Risk factors associated with food allergy; j) 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 the elderly. This information may be crucial to analysing similarities and differences regarding food allergies between elderly and non-elderly individuals and eventually defining preventive or diagnostic approaches specifically tailored to this age range.

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 the elderly, we also plan to organise meetings with general practitioners and other healthcare providers, to analyse and discuss our findings and their potential implications.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 & 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

ILD and CLI are equal contributors to the design and conceptualisation of this review, and should therefore be regarded as joint first authors, and drafted the protocol with primary support from UN (review guarantor) and LTB. UN, IS, 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. ILD, CLI and LTB were involved in establishing eligibility criteria and data extraction forms. All authors provided feedback on the manuscript, at all stages.

FUNDING

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

COMPETING INTERESTS

None declared.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in BMJ Open and any other BMJ products and to exploit all rights, as set out in our licence.

For peer review only

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

For peer review only

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. Doi: 10.1111/all.12305.

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. Doi: 10.1016/jaci.2007.05.026.

3. Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. JAMA 2010; 303: 1848-56. Doi: 10.1001/jama.2010.582.

4. Tang MLK, Mullins RJ. Food allergy: is prevalence increasing? Intern Med J. 2017; 47: 256-261. Doi: 10.1111/imj.13362.

5. Jensem-Jarolim E, Jensen SAF. Food allergies in the elderly. Collecting the evidence. Ann Allergy Asthma Immunol. 2016; 117: 472-475. Doi: 10.1016/j.anai.2016.08.036.

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: 458-467. Doi: 10.2500/aap.2015.36.3895.

7. United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP/248

8. Diesner SC, Untersmayr E, Pietschmann P, et al. Food allergy: only a pediatric disease? Gerontology. 2011; 57: 28-32. Doi: 10.1159/000279756.

9. Montanaro A. Allergic disease management in the elderly: a wakeup call for the allergy community. Ann Allergy Asthma Immunol. 2000; 85: 85-86. Doi: 10.1016/S1081-1206(10)62442-8.

For peer review only

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. 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. https://www.who.int/healthinfo/survey/ageingdefnolder/en/ Last accessed on 7th January 2019

12. WHO, Geneva: Switzerland. World Health Organisation. Definition of an older or elderly person. http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html . Last accessed on 28th December 2018.

13. Orimo H, Ito H, Suzuki T, et al. Reviewing the definition of "elderly" Geriatr Gerontol Int. 2006; 6: 149–158. Doi:10.1111/j.1447-0594.2006.00341.x.

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. Doi: 10.1186/2045-7022-3-13.

15. CASP checklist for systematic reviews. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf. Last accessed on 22nd December 2018.

16. CASP checklist for cohort studies. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Cohort-Checklist-2018_fillable_form.pdf. Last accessed on 22nd December 2018.

17. CASP checklist for case–control studies. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Case-Control-Checklist-2018_fillable_form.pdf. Last accessed on 22nd December 2018.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

18. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011: 64: 401-406. Doi: 10.1016/j.clinepi.2010.07.015.

19. Guyatt G, Oxman AS, Akl EA, et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011: 64: 383-394. Doi: 10.1016/j.clinepi.2010.04.026.

20. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Statis 1998; 52: 119-126. Doi: 10.2307/2685469.

21. Borenstein M, Hedges LV, Higgins JPT, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Sunth Methods 2010: 1: 97-111. Doi: 10.1002/jrsm.12.

22. Rice K, Higgins JPT, Lumley T. A re-evaluation of fixed effect(s) meta-analysis. J Royal Stat Soc: Series A. 2017; 181: 205-227. Doi: 10.1111/rssa.12275.

23. Sterne JAC, Harbord RM. Funnel plots in meta-analysis. Stata J. 2004; 4: 127-141. Available at: http://ageconsearch.umn.edu/bitstream/116233/2/sjart_st0061.pdf.

24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088–1101. Doi: 10.2307/2533446.

25. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634. Doi: 10.1136/bmj.315.7109.629.

26. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560. Doi: 10.1136/bmj.327.7414.557.

27. Liberati A, Altman DG, Tetzlaff J, 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; 6: e1000100. Doi: 10.1371/journal.pmed.1000100.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647. Doi: 10.1136/bmj.g.7647.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Appendix 1: Search Strategy

Search Strategy 1

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.

For peer review only

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

33. incidence.mp. or exp Incidence/

34. prevalence.mp. or exp Prevalence/

35. risk factors.mp. or exp Risk Factors/

36. (incidence or prevalence or epidemiol$).ti.

37. Or/33-36

38. exp Epidemiologic Methods/

39. *cohort studies/ or cohort.ti,ab.

40. (longitudinal or prospective).ti,ab.

41. *case-control studies/

42. Control groups/ or control group*.ti,ab.

43. Matched-pair analysis/

44. (case* adj5 control*).ti,ab.

45. (case* adj3 comparison*).ti,ab.

46. (case* adj3 referen*).mp.

47. (case* adj1 base).mp.

48. (case* adj1 cohort).mp.

49. exp cross-sectional studies/ or cross-sectional.ti,ab.

50. Or/38-49

51. Adult

52. 32 AND 37 AND 50 AND 51

53. advertisements/ or animation/ or architectural drawings/ or bibliography/ or biography/ or book illustrations/ or bookplates/ or charts/ or comment/ or letter/ or editorial/ or news/ or patient education handout/ or published erratum/ or "retraction of publication"/

54. 52 Not 53

55. limit 54 to year=”1980-current”

For peer review only

Search strategy 2

(Cochrane Library, CINAHL, ISI Web of Science)

(Food hypersensitivity or food allergy or milk allergy or egg allergy or nut allergy or peanut allergy or arachis hypogaea allergy or tree nut allergy or hazelnut allergy or legumes allergy or wheat allergy or soy allergy or fish allergy or seafood allergy or shellfish allergy or kiwi allergy or apple allergy or peach allergy or additives hypersensitivity or additives allergy)

AND

(Epidemiological studies or observational studies or cohort studies or cohort analysis or follow up studies or longitudinal studies or case control studies or case-control studies or cross sectional studies or cross-sectional studies or retrospective studies)

AND

("risk of developing" or prevalence or incidence or risk factors or protective factors or time trends)

AND

Adult

For peer review only

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1,2,5
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	6

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

For peer review only

		changes; otherwise, state plan for documenting important protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	N/A
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Rationale	#6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6,7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supl
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7,8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8,9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8,9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

BMJ Open

PREVALENCE AND RISK FACTORS FOR FOOD ALLERGY IN OLDER PEOPLE: PROTOCOL FOR A SYSTEMATIC REVIEW

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029633.R2
Article Type:	Protocol
Date Submitted by the Author:	09-Jul-2019
Complete List of Authors:	Laia-Dias, Inês; Universidade da Beira Interior, Faculty of Health Sciences Lozoya-Ibáñez, Carlos; Hospital Amato Lusitano, Department of Allergy & Clinical Immunology Skypala, Isabel; Royal Brompton & Harefield NHS Trust, Royal Brompton Hospital Gama, Jorge ; Universidade da Beira Interior Centro de Matematica e Aplicacoes, Mathematics Nurmatov, Ulugbek; Division of Population Medicine, School of Medicine, Cardiff University Lourenço, Olga; Universidade da Beira Interior, Faculty of Health Sciences Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA – Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Geriatric medicine
Keywords:	EPIDEMIOLOGY, GERIATRIC MEDICINE, Allergy < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

PREVALENCE AND RISK FACTORS FOR FOOD ALLERGY IN OLDER PEOPLE: PROTOCOL FOR A SYSTEMATIC REVIEW

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

[1] Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal
[2]Department of Allergy & Clinical Immunology, Amato Lusitano Hospital, Castelo Branco Local Health Unit, Castelo Branco, Portugal
[3]CICS - Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal
[4]Royal Brompton & Harefield NHS Trust, London, England, United Kingdom
[5]Centre of Mathematics and Applications, Faculty of Sciences, University of Beira Interior, Covilhã, Portugal
[6]Division of Population Medicine, School of Medicine, The National Centre for Population Health & Wellbeing Research, Cardiff University, Wales, United Kingdom
[7]Department of Allergy & Clinical Immunology, Cova da Beira Hospital Centre, Covilhã, Portugal

Word Count: 2405 words

Corresponding author:
Professor Luís Taborda-Barata MD, PhD,
CICS - Health Sciences Research Centre, University of Beira Interior,
Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal
Tel.: +351 275 329 002
Fax: +351 275 329 099
E-mail: tabordabarata@fcsaude.ubi.pt

For peer review only

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: This systematic review protocol has been registered with PROSPERO register (https://www.crd.york.ac.uk/prospero/) number CRD42018102140. 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 to January 2019. There will be no restriction on the language or geography of publication. We will use the Critical Appraisal Skills Programme (CASP) 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 PRISMA checklist will guide reporting of the systematic review.

Ethics and Dissemination: Since this systematic review will be solely based upon 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.

Keywords: Epidemiology; Food allergy; Older people; Protocol; Systematic review

For peer review only

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

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 (DBPCFC) [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 U.S. Food and Drug Administration Food Safety Surveys (FSS) 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 60-69 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 or over and 2% was aged 80 or over. In comparison

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

with 2017, by 2050, the population aged 60 and over is expected to increase twofold (962 million to 2.1 billion), and the population aged 80 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 co-morbidities, 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.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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], 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 will search 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 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 until January 2019. Search terms are detailed in 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 World Health

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Organisation (W.H.O.) proposed 60 years as a working definition of an "older person" in African countries [11]. In addition, although 65 years is recommended by W.H.O. 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 PRISMA 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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]: 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.

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 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 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

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 (CASP) 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 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]. Sub-group analysis may eventually be carried out using the following age groups: 60-65 years, 66-80 years, > 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 Software Package for Social Sciences (SPSS) version 25.0®. Finally, the PRISMA-P 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For Peer Review Only

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

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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: a) Worldwide prevalence of food allergy in this subgroup of adults; b) Geographical differences in prevalence of food allergy and related food allergens; c) Time trends in prevalence of food allergy and related food allergens; d) Predominant foods associated with food allergy; e) Most frequent symptoms/ symptom clusters, as well as their severity, associated with food allergy; f) Most frequent symptoms associated with specific foods; g) Timeframe of symptom development upon ingestion of foods; h) Need for treatment of episodes of food allergy; i) Risk factors associated with food allergy; j) 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 & 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

ILD and CLI are equal contributors to the design and conceptualisation of this review, and should therefore be regarded as joint first authors, and drafted the protocol with primary support from UN (review guarantor) and LTB. UN, IS, 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. ILD, CLI and LTB were involved in establishing eligibility criteria and data extraction forms. All authors provided feedback on the manuscript, at all stages.

FUNDING

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

COMPETING INTERESTS

None declared.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in BMJ Open and any other BMJ products and to exploit all rights, as set out in our licence.

For peer review only

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

For peer review only

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. Doi: 10.1111/all.12305.

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. Doi: 10.1016/jaci.2007.05.026.

3. Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. JAMA 2010; 303: 1848-56. Doi: 10.1001/jama.2010.582.

4. Tang MLK, Mullins RJ. Food allergy: is prevalence increasing? Intern Med J. 2017; 47: 256-261. Doi: 10.1111/imj.13362.

5. Jensem-Jarolim E, Jensen SAF. Food allergies in the elderly. Collecting the evidence. Ann Allergy Asthma Immunol. 2016; 117: 472-475. Doi: 10.1016/j.anai.2016.08.036.

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: 458-467. Doi: 10.2500/aap.2015.36.3895.

7. United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP/248

8. Diesner SC, Untersmayr E, Pietschmann P, et al. Food allergy: only a pediatric disease? Gerontology. 2011; 57: 28-32. Doi: 10.1159/000279756.

9. Montanaro A. Allergic disease management in the elderly: a wakeup call for the allergy community. Ann Allergy Asthma Immunol. 2000; 85: 85-86. Doi: 10.1016/S1081-1206(10)62442-8.

For peer review only

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. 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. https://www.who.int/healthinfo/survey/ageingdefnolder/en/ Last accessed on 7th January 2019

12. WHO, Geneva: Switzerland. World Health Organisation. Definition of an older or elderly person. http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html . Last accessed on 28th December 2018.

13. Orimo H, Ito H, Suzuki T, et al. Reviewing the definition of "elderly" Geriatr Gerontol Int. 2006; 6: 149–158. Doi:10.1111/j.1447-0594.2006.00341.x.

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. Doi: 10.1186/2045-7022-3-13.

15. CASP checklist for systematic reviews. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf. Last accessed on 22nd December 2018.

16. CASP checklist for cohort studies. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Cohort-Checklist-2018_fillable_form.pdf. Last accessed on 22nd December 2018.

17. CASP checklist for case–control studies. https://www.casp-uk.net/wp-content/uploads/2018/03/CASP-Case-Control-Checklist-2018_fillable_form.pdf. Last accessed on 22nd December 2018.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

18. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011: 64: 401-406. Doi: 10.1016/j.clinepi.2010.07.015.

19. Guyatt G, Oxman AS, Akl EA, et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011: 64: 383-394. Doi: 10.1016/j.clinepi.2010.04.026.

20. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Statis 1998; 52: 119-126. Doi: 10.2307/2685469.

21. Borenstein M, Hedges LV, Higgins JPT, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Sunth Methods 2010: 1: 97-111. Doi: 10.1002/jrsm.12.

22. Rice K, Higgins JPT, Lumley T. A re-evaluation of fixed effect(s) meta-analysis. J Royal Stat Soc: Series A. 2017; 181: 205-227. Doi: 10.1111/rssa.12275.

23. Sterne JAC, Harbord RM. Funnel plots in meta-analysis. Stata J. 2004; 4: 127-141. Available at: http://ageconsearch.umn.edu/bitstream/116233/2/sjart_st0061.pdf.

24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088–1101. Doi: 10.2307/2533446.

25. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634. Doi: 10.1136/bmj.315.7109.629.

26. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560. Doi: 10.1136/bmj.327.7414.557.

27. Liberati A, Altman DG, Tetzlaff J, 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; 6: e1000100. Doi: 10.1371/journal.pmed.1000100.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647. Doi: 10.1136/bmj.g.7647.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Appendix 1: Search Strategy

Search Strategy 1

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.

For peer review only

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

33. incidence.mp. or exp Incidence/

34. prevalence.mp. or exp Prevalence/

35. risk factors.mp. or exp Risk Factors/

36. (incidence or prevalence or epidemiol$).ti.

37. Or/33-36

38. exp Epidemiologic Methods/

39. *cohort studies/ or cohort.ti,ab.

40. (longitudinal or prospective).ti,ab.

41. *case-control studies/

42. Control groups/ or control group*.ti,ab.

43. Matched-pair analysis/

44. (case* adj5 control*).ti,ab.

45. (case* adj3 comparison*).ti,ab.

46. (case* adj3 referen*).mp.

47. (case* adj1 base).mp.

48. (case* adj1 cohort).mp.

49. exp cross-sectional studies/ or cross-sectional.ti,ab.

50. Or/38-49

51. Adult

52. 32 AND 37 AND 50 AND 51

53. advertisements/ or animation/ or architectural drawings/ or bibliography/ or biography/ or book illustrations/ or bookplates/ or charts/ or comment/ or letter/ or editorial/ or news/ or patient education handout/ or published erratum/ or "retraction of publication"/

54. 52 Not 53

55. limit 54 to year=”1980-January 2019”

For peer review only

Search strategy 2

(Cochrane Library, CINAHL, ISI Web of Science)

(Food hypersensitivity or food allergy or milk allergy or egg allergy or nut allergy or peanut allergy or arachis hypogaea allergy or tree nut allergy or hazelnut allergy or legumes allergy or wheat allergy or soy allergy or fish allergy or seafood allergy or shellfish allergy or kiwi allergy or apple allergy or peach allergy or additives hypersensitivity or additives allergy)

AND

(Epidemiological studies or observational studies or cohort studies or cohort analysis or follow up studies or longitudinal studies or case control studies or case-control studies or cross sectional studies or cross-sectional studies or retrospective studies)

AND

("risk of developing" or prevalence or incidence or risk factors or protective factors or time trends)

AND

Adult

For peer review only

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1,2,5
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	6

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

For peer review only

		changes; otherwise, state plan for documenting important protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	N/A
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Rationale	#6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6,7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supl
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7,8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8,9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8,9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-029633 on 24 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.