PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	House Dust Mite (HDM) and Storage Mite (SM) molecular sensitisation profiles and association with clinical outcomes in allergic asthma and rhinitis: protocol for a systematic review
AUTHORS	Matos-Semedo, Filipa; Cruz, Cíntia; Inácio, Filipe; Gama, Jorge; Nwaru, Bright; Taborda-Barata, Luís

VERSION 1 – REVIEW

REVIEWER	Ruperto González Pérez Allergy Department at the Hospital Universitario de Canarias, Tenerife, Spain.
REVIEW RETURNED	08-Dec-2020

GENERAL COMMENTS	Interesting protocol approach concerning storage mites (SM). Apart from disease severity, subjects´ age should be taken into account. Also the variable degree of cross-reactivity among house dust mites (HDM) and SM should be addressed. In the other hand, the protocol may not necessarily be considered as an independent paper itself, as it could be very well included as "Appendix or Supplementary Material" in the final version of the proposed final manuscript.

REVIEWER	Sheron Dzoro Medical University of Vienna, Vienna, AUSTRIA
REVIEW RETURNED	19-Feb-2021

GENERAL COMMENTS	The protocol provides a working plan to consolidate information from various publications published between 1970 and August 2020, to extract useful data on the current knowledge regarding allergic sensitization to HDM and SM and associated morbidity (asthma and rhinitis). The inclusion and exclusion criteria for publications to use in the review is clearly outlined and there is a clear plan for data collection, data review, and final analysis including details on statistical methodologies to be used. The general design of the protocol is good and relevant to current needs in Allergology.

REVIEWER	Stefania Arasi Bambino Gesù Children Research Hospital, Rome, Italy
REVIEW RETURNED	17-Mar-2021

GENERAL COMMENTS	GENERAL COMMENTS This manuscript aims to provide a protocol for a qualitative systematic review assessing exposure to House Dust Mite (HDM) and Storage Mite (SM) and association between profiles of sensitization to HDM and SM molecular allergen components and

	clinical outcomes of asthma and rhinitis based on observational epidemiological studies. The comparator will be based as predefined in respective studies to be included in the systematic review and this may be those not sensitized to HDM or to SM molecular allergen components or specific levels/thresholds of HDM or SM. A Research Registry Registration Number is provided. The topic is overall of interest. The methodology is overall well-designed and clearly presented. The search strategy looks comprehensive. No English revision is needed. SPECIFIC COMMENTS TO THE AUTHORS - No major comments from my side. Only one minor comment, authors may also want to consider alternative tools to assess the quality of observational studies for instance the Effective Public Health Practice Project (EPHPP).

REVIEWER	Dr Patrick J Owen Deakin University, Australia
REVIEW RETURNED	07-Apr-2021

GENERAL COMMENTS	The authors present a protocol for a systematic review. I have been asked to provide statistical review only. Specific comments are as follows: 1. PRISMA2020, rather than PRISMA2009, should be used. 2. Both forwards and backwards citation tracking should be used. 3. Will RCTs be included for either (a) baseline data (similar to cross-sectional studies that will be included) or (b) prospective data within true control arms (similar to cohort studies that will be included)? 4. Outcomes, Primary outcome: it is not clear what 'estimates of association' means, does this suggest meta-analysis? This needs to be clear. 5. Outcomes, Secondary outcome: sub-groups should be predefined where possible. 'Estimates of association' also needs to be elaborated upon. All secondary outcomes (e.g. exacerbations, medication use, hospitalisation) require working definitions RE: what will be included vs excluded. 6. Quality assessment: how will the tool selected account for variations in study design? It would be suitable to consider different tools for differing study methodologies. See: https://bmjopen.bmj.com/content/8/3/e019703 7. Data synthesis: for studies that do not provide data, will authors be contacted before resorting to narrative synthesis? 8. Data synthesis, 'for studies we judge to be reasonably … homogeneous': how will this be determined? This statement is currently vague 9. Data synthesis: what will be done if few studies (i.e. 5 or less) are found for certain outcomes? The DerSimonian-Laird method is not suitable in these cases and Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis will better account for low statistical power when five or fewer trials are included. This is recommended by Cochrane. The confidence interval estimated using this method will be superior to the DerSimonian-Liard method given it accounts for uncertainty/imprecision of the estimate. 10. Data synthesis: sensitivity analyses per ROB are not recommended by Cochrane. Pre-planned subgroup analyses and/or meta-regression should be included RE: exploring suspected heterogeneity 11. What measure will be used for meta-analysis? SMD, MD? If SMD, adjusted Egger's P will need to be used RE: handling data.

REVIEWER	Christian Wieg Klinikum Aschaffenburg
REVIEW RETURNED	07-Apr-2021

GENERAL COMMENTS	I would suggest to describe exactly the excluded and/or not eligible studies. It is of great value that the criteria for exclusion are defined. It may be of interest how many studies meeting each specific criterion where excluded and if any hypothesis generating information could be drawn from these studies.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Rupert González-Pérez, Hospital Universitario de Canarias

Comments to the Author:
Interesting protocol approach concerning storage mites (SM). Apart from disease severity, subjects´ age should be taken into account. Also the variable degree of cross-reactivity among house dust mites (HDM) and SM should be addressed. In the other hand, the protocol may not necessarily be considered as an independent paper itself, as it could be very well included as "Appendix or Supplementary Material" in the final version of the proposed final manuscript.
Reply: We would like to thank the reviewer for the important feedback and comments. As suggested, we will also take the subjects age into account (page 7, Data extraction and management; line 10) and will also incorporate the variable degree of cross-reactivity among HDM and SDM (page 7; Data extraction and management, lines 9-10; page 7; Outcomes, Primary outcome, line 3).
Regarding eventually using the protocol as an appendix of the final manuscript, we believe that we will prefer to have the protocol first published, not only to clearly indicate that we are carrying this type of secondary research but also because carrying out the systematic review itself will still take some time.

Reviewer: 2
Dr. Sheron Dzoro, Medical University of Vienna

Comments to the Author:
The protocol provides a working plan to consolidate information from various publications published between 1970 and August 2020, to extract useful data on the current knowledge regarding allergic sensitization to HDM and SM and associated morbidity (asthma and rhinitis).
The inclusion and exclusion criteria for publications to use in the review is clearly outlined and there is a clear plan for data collection, data review, and final analysis including details on statistical methodologies to be used. The general design of the protocol is good and relevant to current needs in Allergology.
Reply: We would like to thank the reviewer for the kind and important feedback on our SR protocol.

Reviewer: 3
Dr. Stefania Arasi, Bambino Gesù Hospital Rome

Comments to the Author:
GENERAL COMMENTS
This manuscript aims to provide a protocol for a qualitative systematic review assessing exposure to House Dust Mite (HDM) and Storage Mite (SM) and association between profiles of sensitization to HDM and SM molecular allergen components and clinical outcomes of asthma and rhinitis based on observational epidemiological studies. The comparator will be based as predefined in respective

studies to be included in the systematic review and this may be those not sensitized to HDM or to SM molecular allergen components or specific levels/thresholds of HDM or SM. A Research Registry Registration Number is provided. The topic is overall of interest. The methodology is overall well-designed and clearly presented. The search strategy looks comprehensive. No English revision is needed.
SPECIFIC COMMENTS TO THE AUTHORS
- No major comments from my side. Only one minor comment, authors may also want to consider alternative tools to assess the quality of observational studies for instance the Effective Public Health Practice Project (EPHPP).

Reply: We would like to thank the reviewer for the relevant feedback on our SR protocol. Regarding using an alternative tool such as EPHPP to assess the quality of observational studies, we would indeed be prepared to use such a tool. However, we have no experience with this tool and, in any case, the CASP tool we have chosen to use for quality appraisal has different versions for different study designs and we believe it will be adequate for also assessing observational studies. We have now made this clarification in the manuscript (Page 8; Quality Assessment, lines 2 -3)

Reviewer: 4
Dr. Patrick Owen, Deakin University

Comments to the Author:
The authors present a protocol for a systematic review. I have been asked to provide statistical review only. Specific comments are as follows:
Reply: We would really like to thank the reviewer for his thorough and extremely useful comments and suggestions which will definitely improve the quality of our SR protocol.

1. PRISMA2020, rather than PRISMA2009, should be used.
Reply: We agree with the reviewer to follow PRISMA2020 rather than PRISMA2009. At the time of submitting our protocol, PRISMA2020 was not published. We have now changed the related reference accordingly (Reference 30 - Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. Doi: 10.1136/bmj.n71.)
2. Both forwards and backwards citation tracking should be used.
Reply: We have now indicated this in the database search section of the paper as follows: "We will implement backward and forward article tracking within ISI Web of Science and by using Google Scholar." (Page 6; Search strategy, lines 6-7).
3. Will RCTs be included for either (a) baseline data (similar to cross-sectional studies that will be included) or (b) prospective data within true control arms (similar to cohort studies that will be included)?
Reply: We agree with the reviewer and have indicated that we will include clinical trials in the review (Page 6; Inclusion criteria for study designs, line 1).
4. Outcomes, Primary outcome: it is not clear what 'estimates of association' means, does this suggest meta-analysis? This needs to be clear.
Reply: We have now added the "estimates of association" in the text (Page 7; Outcomes, Primary outcome, lines 2-3)
5. Outcomes, Secondary outcome: sub-groups should be predefined where possible. 'Estimates of association' also needs to be elaborated upon. All secondary outcomes (e.g. exacerbations, medication use, hospitalisation) require working definitions RE: what will be included vs excluded.
Reply: We agree that we should further clarify this section and also make our study more thorough. We have now defined sub-groups that we believe may be relevant to better summarising current evidence (pages 7; Data extraction and management, lines 10-11).

We have now also have endeavoured to make “estimates of association” clearer (Page 7; Outcomes, Primary outcome, lines 2-3).
As suggested we have also introduced working definitions for all secondary outcomes (e.g. exacerbations, medication use, hospitalisation) which will clarify what will be included vs excluded (page 8; Secondary Outcomes lines 6-end of page).

6. Quality assessment: how will the tool selected account for variations in study design? It would be suitable to consider different tools for differing study methodologies. See: https://bmjopen.bmj.com/content/8/3/e019703
Reply: We agree with the reviewer for the need for different tools for different study designs. Actually, the CASP tool we have chosen to use for quality appraisal has different versions for different study designs and we believe will be adequate for our purpose. We have now made this clarification in the manuscript. (Page 9; Quality Assessment, lines 2 -3).
7. Data synthesis: for studies that do not provide data, will authors be contacted before resorting to narrative synthesis?
Reply: Yes, we will contact authors for this type of situaton. We have included a sentence mentioning this aspect in the manuscript (Page 9; Data synthesis, lines 3-4) (“…we will contact authors before carrying out narrative synthesis. In case specific data cannot be obtained, we…”)

8. Data synthesis, ‘for studies we judge to be reasonably … homogeneous’: how will this be determined? This statement is currently vague
Reply: We thank the reviewer for this very pertinent comment. We clarified this statement by indicating that homogeneity of studies will be determined by having used similar methods for subject selection and inclusion, definition of sensitisation to molecular components of HDM and SM allergens, outcome definition and assessment, and statistical analyses (Page 9; Data synthesis, lines 8-10).
9. Data synthesis: what will be done if few studies (i.e. 5 or less) are found for certain outcomes? The DerSimonian-Laird method is not suitable in these cases and Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis will better account for low statistical power when five or fewer trials are included. This is recommended by Cochrane. The confidence interval estimated using this method will be superior to the DerSimonian-Liard method given it accounts for uncertainty/imprecision of the estimate.
Reply: We thank the reviewer’s suggestion, which follows Cochrane’s recommendations. We have now clarified that we will use Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis if five or fewer studies are included for a certain outcome, and the DerSimonian-Laird method for the other cases (Page 9, Data synthesis, line 21-23).
10. Data synthesis: sensitivity analyses per ROB are not recommended by Cochrane. Pre-planned subgroup analyses and/or meta-regression should be included RE: exploring suspected heterogeneity
Reply: We thank the reviewer for this important comment. We have now included mention of re-planned subgroup analyses and/or meta-regression in the protocol and removed the statement on sensitivity analyses on the basis of ROB (Page 9; Data synthesis, lines 6-11).
11. What measure will be used for meta-analysis? SMD, MD? If SMD, adjusted Egger’s P will need to be used RE: handling data.
Reply: We would like to thank the reviewer for this important question. We have clarified that we will use SMD, and adjusted Egger’s P for handling data (Page 9; Data synthesis, lines 13-15).

Reviewer: 5
Prof. Wieg Christian, Klinikum Aschaffenburg-Alzenau

Comments to the Author:
I would suggest to describe exactly the excluded and/or not eligible studies. It is of great value that the criteria for exclusion are defined. It may be of interest how many studies meeting each specific

criterion where excluded and if any hypothesis generating information could be drawn from these studies.
Reply: We really thank the reviewer for this important comment. However, we believe that in Study selection (page 7), we have mentioned that all details are included in Inclusion criteria for study designs (Page 6), and which are “studies in which component resolved-diagnostics has been used to evaluate sensitisation to HDM and SM (at least one of Dermatophagoides pteronyssinus, Dermatophagoides farinae, Blomia tropicalis, Lepidoglyphus destructor) in HDM- and SM-sensitised individuals of all ages, with bronchial asthma, and/or allergic rhinitis but also in those without clinical manifestations of these diseases.”. We have now more clearly stated the mention of such inclusion criteria (Page 7; lines 5-6). We have also included an exclusion criterium in the protocol (Page 6, lines 7-8).

VERSION 2 – REVIEW

REVIEWER	Dr Patrick J Owen Deakin University, Australia
REVIEW RETURNED	03-Jun-2021

GENERAL COMMENTS	The authors should be commended for their thorough responses to my initial queries regarding my statistical and methodological (only) review of the manuscript. I thank the authors for integrating these suggestions and believe the manuscript is now suitable for publication. I wish the authors best of luck with their project.