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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

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3 **House Dust Mite (HDM) and Storage Mite (SM) molecular sensitisation profiles**
4 **and association with clinical outcomes in allergic asthma and rhinitis: protocol for**
5 **a systematic review**
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ABSTRACT

Introduction: Identification and characterisation of single allergens at molecular level is important. Component-resolved-diagnostics offers the possibility of higher diagnostic precision, thereby allowing better patient management. House dust mites (HDM) have a worldwide distribution. Studies from different countries have shown that IgE-mediated allergy to Storage mites (SM) is important in rural and urban populations. With the availability of HDM and SM molecular allergen components, studies have investigated whether different molecular sensitisation profiles are associated with clinical disease outcomes. However, no previous systematic review has synthesised the underlying evidence.

Methods and Analysis: We will search 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) from inception to March 2020. Unpublished and ongoing work, as well as research in progress will be searched in www.ClinicalTrials.gov; www.controlledtrials.com; www.anzctr.org.au. We will contact an international panel of experts in this field. No language restrictions will apply; translations will be undertaken where necessary. The Critical Appraisal Skills Programme (CASP) quality assessment tool will be used to appraise the methodological quality of included studies. A descriptive summary with data tables will be constructed, and if adequate, meta-analysis using random-effects will be performed. The PRISMA checklist will be followed for reporting.

Ethics and Dissemination: Since this systematic review will be only based on published and retrievable literature, no ethics approval is required. We will publish the systematic review in an international peer-reviewed journal.

Research Registry Registration Number: reviewregistry959

Keywords: Allergic rhinitis; Asthma; Clinical outcomes; Component-Resolved Diagnosis; House dust mites; Molecular allergens; Sensitisation profiles; Storage mites; Systematic review

ARTICLE SUMMARY SECTION

Strengths and limitations of this study

- This review will produce the first synthesis addressing the relationship between profiles of sensitisation to HDM and SM molecular allergen components and clinical outcomes in asthma and rhinitis.
- A thorough search strategy using leading databases in medicine and biological sciences will maximise the probability that the relevant articles will be identified.
- This search without geographical or language restrictions, will allow achieving a comprehensive view on the possible clinical impact of sensitisation to different mite allergens.
- This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- Differences among study designs, sample characteristics and poor methodological quality may restrict comparison of the selected studies and negatively affect the quality of the evidence obtained.

INTRODUCTION

The prevalence of allergic diseases is steadily rising, with a large number of affected individuals, worldwide [1-6]. House dust mites (HDM) such as *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* are one of the main triggers of allergic disease in sensitised individuals [7-9]. In fact, HDM-induced allergic diseases affect approximately 2% of the world's population, thereby being a cause of major healthcare and economic burden [10].

Blomia tropicalis and *Lepidoglyphus destructor*, which are storage mites (SM), were earlier found predominantly in agricultural environments but are now being recognised as an important contributors to the allergen content in house dust in indoor urban dwellings [11]. Several investigations have demonstrated that allergens from these SM may play an important role in sensitisation and allergic symptoms [12,13].

Progress in molecular biology over the past few years has allowed us to identify and characterise single allergens in detail, at a molecular level. Component-resolved-diagnostics (CRD) offers the possibility of higher diagnostic precision and allows better management of each patient [14,15]. With the availability of a comprehensive set of molecular HDM and SM allergens, it is now possible to study molecular reactivity profiles that might be associated with certain manifestations of HDM- and SM-induced allergic respiratory symptoms [16]. Yet, very few data are available regarding the possibility of different molecular sensitisation patterns being associated with diverse clinical phenotypes [17,18]. Furthermore, sensitisation to allergens is not a static phenomenon and has been shown to have the potential to change over time [19]. Recently, CRD studies have shown that Immunoglobulin E (IgE) responses to allergens, namely dust mites, during childhood may increase in molecular complexity over time [20]. In this context, sensitisation to a single allergen molecule might thus expand to polymolecular recognition and this phenomenon seems to correlate with clinical symptoms [19,21].

If a patient has perennial symptoms due to being only allergic to one mite, skin prick tests or specific IgE against whole HDM- or SM- extract are sufficient for diagnosis of mite respiratory allergy [22]. However, if there is multiple mite sensitisation, CRD with species-specific components is mandatory [23]. *Lepidoglyphus destructor*, being considered a SM historically found mainly where plant or animal foods are processed and

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3 stored, has been detected in significant amounts in house dust from various regions of the
4 world [24-26]. Although the pyroglyphid HDM *Dermatophagoides pteronyssinus* and
5 *Dermatophagoides farinae* seem to predominate, glycyphagid SM mites, such as
6 *Lepidoglyphus destructor* and *Blomia tropicalis* may also be important in some regions
7 [27]. Taking these aspects into account, it is vital to study the clinical relevance of
8 *Lepidoglyphus destructor* [28]. *Blomia tropicalis* was also initially described as an
9 occupational mite. It is now regarded as a house dust mite of tropical and sub-tropical
10 areas, whose role as a trigger for allergic rhinitis and asthma is well described [29].

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There is no systematic evaluation of the role of sensitisation profiles of HDM and SM
molecular allergens in asthma or rhinitis. A comprehensive understanding of the
underlying evidence based on existing literature will help to clarify the clinical utility of
IgE molecular response to mites in allergic and respiratory diseases, thus helping to
inform future research in this area.

OBJECTIVES

Given this important gap, this systematic review aims to identify, critically appraise, and
synthesise the evidence from observational epidemiological studies investigating
sensitisation to HDM and SM molecular allergen components in asthma and/or allergic
rhinitis, and to study the relationship between sensitisation profiles of respective
molecular allergen components and clinical outcomes of asthma and rhinitis.

METHODS AND ANALYSIS

This study has been registered with the International prospective register of systematic
reviews (Research Registry), registration number: reviewregistry959.

This systematic review will be conducted in accordance with the Preferred Reporting
Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30].

The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
(PRISMA-P) checklist [31] has been followed and is attached as online supplementary
file 1.

Any modifications in the protocol during the systematic review will be reported.

Search strategy

We have developed a comprehensive search strategy for retrieving published and unpublished studies on the topic (as [online supplementary file 2.](#)). 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). Search dates will be from the inception to present.

The bibliographies of all eligible studies will be scrutinised to identify possible additional studies. We will identify unpublished and in progress studies by searching key Internet-based relevant databases – www.ClinicalTrials.gov; www.controlledtrials.com; www.anzctr.org.au In addition, we will contact authors who have published in this field to ask for potentially additional papers. No language restrictions will be imposed; translations will be undertaken where necessary.

Inclusion criteria for study designs

We will include all analytical observational epidemiological studies, including cohort, case-control and cross-sectional studies. We will select 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. This will be a systematic review assessing exposure to HDM and 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 molecular allergen components as defined in respective studies. We will exclude narrative literature reviews, discussion papers, non-research letters and editorials, case studies and case series and animal studies.

Study selection

Papers retrieved from the databases will be exported to a reference management program where screening will be undertaken. Removal of duplicate publications will be

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3 performed, thereafter, the titles and abstracts of retrieved papers will be independently
4 checked by two investigators. The full text of all potentially eligible studies will be
5 retrieved and independently assessed against the inclusion criteria (see above) by two
6 reviewers. The reviewers will decide which of the studies fit the inclusion criteria. Any
7 disagreements will be resolved by discussion, with a third reviewer arbitrating in the
8 circumstance of unresolved discrepancies. The process of selection will be summarised
9 using a PRISMA flow diagram.
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17 **Data extraction and management**

18 Data from selected articles will be transferred from their original presentation in each
19 paper unto a data extraction form made in Microsoft Excel© software, with each study
20 receiving a reference code. If necessary, we will collect indirect data from figures and
21 charts, adapting their interpretation from two different authors by consensus, and authors
22 of original articles will also be contacted for further information and data not reported in
23 the papers. For all included studies, we will collect the following information: study
24 design, number of participants and their characteristics, country of study, year of
25 publication, types and profiles of sensitization to HDM and SM molecular allergens,
26 including frequency of sensitization, determinants of sensitization, subgroups at risk of
27 sensitization, geographical differences; estimates (hazard ratio, risk ratio, odds ratio, 95%
28 confidence intervals, mean and SD) of the association between profiles of sensitization to
29 HDM and SM molecular allergen components and clinical outcomes of asthma and
30 rhinitis. Data extraction will be completed independently by two reviewers and
31 discrepancies will be decided by a third reviewer.
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45 **Outcomes**

46 *Primary outcome*

47 Frequency and patterns of sensitisation to HDM and SM molecular allergen components
48 (using descriptive statistics measures) and estimates of association between HDM and
49 SM molecular allergen components and severity of asthma and rhinitis.
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54 *Secondary outcome*

55 Determinants of sensitisation to HDM and SM molecular allergen components and
56 population sub-groups at risk and estimates of association between HDM and SM
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3 molecular allergen components and prevalence, exacerbations, medication use,
4 hospitalization, and quality of life of asthma and rhinitis.
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8 **Quality assessment**

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10 Assessment of risk of bias will be independently verified by two different reviewers,
11 using the Critical Appraisal Skills Programme (CASP) [32] quality assessment tool. All
12 studies and their individual elements will be graded in terms of adequacy of the study
13 regarding the research question, risk of selection bias, measurement of exposure, and
14 assessment of outcomes. Disagreements will be resolved by a third reviewer.
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20 **Data synthesis**

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22 We will produce a descriptive summary table of all included studies, to summarize the
23 literature. For studies without required data (e.g. relative risk estimates of effect of
24 sensitisation to HDM and SM and clinical outcomes), we will undertake a narrative
25 synthesis of data in which we use texts to describe overall findings, highlight their
26 strengths and weaknesses, and make textual comparisons between studies in light of the
27 study question. For studies we judge to be reasonably clinically and methodologically
28 homogeneous (i.e. have used similar methods for subject selection and inclusion,
29 definition of sensitisation to molecular components of HDM and SM allergens, outcome
30 definition and assessment, and statistical analyses), we will perform meta-analyses using
31 random-effects models to estimate the combined effect of sensitisation to HDM and SM
32 molecular allergens on each of the study outcomes. Meta-analysis for the association
33 between sensitisation and each outcome will be undertaken separately. We will quantify
34 heterogeneity between studies using the I^2 statistic, which is a measure (range 0-100%)
35 used to quantify the proportion of variance in the pooled estimates attributable to
36 differences in estimates between studies included in the meta-analysis, with values up to
37 25%, 50% and 75% indicating low, medium and high levels of heterogeneity or
38 inconsistency, respectively [33-36], although this statistic is not an absolute measure of
39 such heterogeneity [35]. Between-study variance will be estimated using the τ^2 (T2)
40 statistic, derived from the DerSimonian-Laird approach [37]. We will perform sensitivity
41 analyses on the basis of the risk of bias results in the studies to assess robustness of our
42 findings to different assumptions. We will estimate the combined effect estimates from
43 all studies regardless of their quality grading (low, moderate, high). Then we will exclude
44 all low-quality studies; we will then compare the results to the results when all studies
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3 were combined regardless of their quality. We will repeat the process by excluding the
4 moderate quality studies, and then we will compare the results to those from the previous
5 results. We will assess evidence of publication bias using funnel plots and statistically
6 using Begg and Egger tests [38,39]. Meta-analyses will be performed using Stata
7 Statistical Software (Release 13; StataCorp LP., College Station, TX, USA). The
8 PRISMA checklist will be followed for reporting of the systematic review.
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14 15 **Ethics and data management**

16 No ethical approval required because the data that will be collected and analysed will be
17 only based on published literature and cannot be associated with specific individuals.
18 Retrieved data will be stored in a specific database that will have protected access and
19 will only be used by the authors. However, anonymised data will be placed in an open
20 repository.
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26 27 **Patient and public involvement**

28 Since this will be a systematic review, there will be no direct patient or public
29 involvement.
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33 34 **ETHICS AND DISSEMINATION**

35 This systematic review will synthesise the underlying evidence concerning different
36 molecular sensitisation sets and association with alternative clinical phenotypes. This will
37 allow us, for the first time, to have a clearer picture of the relationship between HDM and
38 SM molecular allergen components and current expression and risk of asthma and rhinitis
39 in sensitised patients.
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45 Methodologically, this review will be based on publications published between 1970 and
46 august 2020, and will allow us to thoroughly analyse methodological aspects of selected
47 studies namely in terms of study design, questions asked, methods used and risk of
48 selection bias.
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53 Our results will be quite novel and will allow us to fill in relevant gaps in the field of
54 molecular allergology. In more specific terms, our study will yield relevant and up-to-
55 date information on current knowledge regarding HDM and SM molecular patterns and
56 allergic diseases. This will be accomplished by accessing information without language
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3 or geographical restrictions, regarding not only analysis of molecular patterns of the most
4 relevant HDM and SM, but also the relationship between such patterns and details of
5 clinical expression of relevant allergic diseases such as asthma and allergic rhinitis, both
6 of which have significant morbidity burdens. Finally, we will also evaluate whether HDM
7 and SM molecular patterns can be used to predict future outcomes in these diseases, as
8 well as therapeutic responses, namely in terms of allergen-specific immunotherapy.
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15 We believe our results will allow us to draw meaningful conclusions about the relevance
16 of HDM and SM molecular sensitisation profiles in clinical diseases such as asthma and
17 allergic rhinitis, which may have significant clinical impact.
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21 Our dissemination strategy will involve presentations at national and international
22 scientific meetings, as well as preferential publication of article(s) in international, peer-
23 reviewed, open-access journals, whenever possible.
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AUTHOR CONTRIBUTIONS

All authors contributed to the design and conceptualisation of this review. FS drafted the protocol with primary support from LTB. FS and CC carried out the database searches and conflicts were solved by LTB. LTB, JRG and BN were involved in checking various steps of the search strategy, including keywords, as well as the final version of the protocol. BN was the guarantor of the review. JRG was involved in the statistical strategy for data analysis.

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

PATIENT INVOLVEMENT

There was no involvement of patients or the public in the design or dissemination plans of this protocol for a systematic review.

FUNDING

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COMPETING INTERESTS

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

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

House Dust Mite (HDM) molecular sensitisation profiles and association with clinical outcomes in allergic asthma and rhinitis: protocol for a systematic review

Filipa Matos Semedo, Cíntia Cruz, Filipe Inácio, Jorge MR Gama, Bright I. Nwaru, Luís Taborda-Barata

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1,2,4,6
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	2,6
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	12
	#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	4-6

1	Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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6	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	6-8
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13	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	7
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20	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 2
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25	Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
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29	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)	7-9
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36	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	8
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43	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
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48	Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8,9
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53	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	9
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1	Data synthesis	#15a	Describe criteria under which study data will be	9,10
2			quantitatively synthesised	
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5		#15b	If data are appropriate for quantitative synthesis, describe	10
6			planned summary measures, methods of handling data and	
7			methods of combining data from studies, including any	
8			planned exploration of consistency (such as I ² , Kendall's τ)	
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11		#15c	Describe any proposed additional analyses (such as	10
12			sensitivity or subgroup analyses, meta-regression)	
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15		#15d	If quantitative synthesis is not appropriate, describe the type	10
16			of summary planned	
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19	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	10
20			publication bias across studies, selective reporting within	
21			studies)	
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24	Confidence in	#17	Describe how the strength of the body of evidence will be	10
25	cumulative		assessed (such as GRADE)	
26	evidence			
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 32 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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House Dust Mite (HDM) and Storage Mite (SM) molecular sensitisation profiles and association with clinical outcomes in allergic asthma and rhinitis: a systematic review
Matos-Semedo F, Cruz C, Inácio F, Gama JMR, Nwaru BI, Taborda-Barata L

Supplementary File 2

Search strategy for Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register), MEDLINE, EMBASE, AMED

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1. house dust mites.mp. or exp house dust mites/
 2. exp storage mites/ or storage mites.mp.
 3. mites.mp. or exp mites/
 4. exp pyroglyphidae/ or pyroglyphidae.mp.
 5. glycyphagidae.mp or exp glycyphagidae/
 6. exp echimyopodidae/ or echimyopodidae.mp.
 7. chortoglyphidae.mp or exp chortoglyphidae/
 8. exp acaridae/ or acaridae.mp
 9. Dermatophagoides pteronyssinus.mp. or exp Dermatophagoides pteronyssinus/
 10. Dermatophagoides farinae.mp. or exp Dermatophagoides farinae/
 11. Euroglyphus maynei.mp or exp Euroglyphus maynei/
 12. Glycyphagus domesticus.mp or exp Glycyphagus domesticus/
 13. Lepidoglyphus destructor.mp. or exp Lepidoglyphus destructor/
 14. Blomia tropicalis.mp. or exp Blomia tropicalis/
 15. Chortoglyphus arcuatus.mp or exp Chortoglyphus arcuatus/
 16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
 17. exp molecular allergens/ or molecular allergens.mp
 18. Der p 1.mp or exp Der p 1/
 19. Der p 2.mp or exp Der p 2/
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 33. exp asthma/ or asthma.mp.
 34. wheez*.mp. or exp wheezing/
 35. exp allergic rhinitis/ or rhinit*.mp. or exp rhinitis/
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- 3 37. exp Epidemiologic Methods/
- 4 38. *cohort studies/ or cohort.ti,ab.
- 5 39. (longitudinal or prospective).ti,ab.
- 6 40. *case-control studies/
- 7 41. Control groups/ or control group*.ti,ab.
- 8 42. Matched-pair analysis/
- 9 43. (case* adj5 control*).ti,ab.
- 10 44. (case* adj3 comparison*).ti,ab.
- 11 45. (case* adj3 referen*).mp.
- 12 46. (case* adj1 base).mp.
- 13 38. (case* adj1 cohort).mp.
- 14 47. exp cross-sectional studies/ or cross-sectional.ti,ab.
- 15 48. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
- 16 49. 16 and 32 and 48
- 17 50. limit 49 to yr="1970 -Current"
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24 **Search strategy for ISI Web of Science (Science and Social Science Index), CINAHL.**

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BMJ Open

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

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Secondary Subject Heading:	Immunology (including allergy), Ear, nose and throat/otolaryngology, Respiratory medicine
Keywords:	Allergy < THORACIC MEDICINE, Adult otolaryngology < OTOLARYNGOLOGY, Asthma < THORACIC MEDICINE, Immunology < THORACIC MEDICINE

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3 **House Dust Mite (HDM) and Storage Mite (SM) molecular sensitisation profiles**
4 **and association with clinical outcomes in allergic asthma and rhinitis: protocol for**
5 **a systematic review**
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ABSTRACT

Introduction: Identification and characterisation of single allergens at molecular level is important. Component-resolved-diagnostics offers the possibility of higher diagnostic precision, thereby allowing better patient management. House dust mites (HDM) have a worldwide distribution. Studies from different countries have shown that IgE-mediated allergy to Storage mites (SM) is important in rural and urban populations. With the availability of HDM and SM molecular allergen components, studies have investigated whether different molecular sensitisation profiles are associated with clinical disease outcomes. However, no previous systematic review has synthesised the underlying evidence.

Methods and Analysis: We will search 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) from inception to March 2020. Unpublished and ongoing work, as well as research in progress will be searched in www.ClinicalTrials.gov; www.controlledtrials.com; www.anzctr.org.au. We will contact an international panel of experts in this field. No language restrictions will apply; translations will be undertaken where necessary. The Critical Appraisal Skills Programme (CASP) quality assessment tool will be used to appraise the methodological quality of included studies. A descriptive summary with data tables will be constructed, and if adequate, meta-analysis using random-effects will be performed. The PRISMA checklist will be followed for reporting.

Ethics and Dissemination: Since this systematic review will be only based on published and retrievable literature, no ethics approval is required. We will publish the systematic review in an international peer-reviewed journal.

Research Registry Registration Number: [reviewregistry959](https://www.crd.york.ac.uk/PROSPERO/record/reviewregistry959)

Keywords: Allergic rhinitis; Asthma; Clinical outcomes; Component-Resolved Diagnosis; House dust mites; Molecular allergens; Sensitisation profiles; Storage mites; Systematic review

ARTICLE SUMMARY SECTION

Strengths and limitations of this study

- This review will produce the first synthesis addressing the relationship between profiles of sensitisation to HDM and SM molecular allergen components and clinical outcomes in asthma and rhinitis.
- A thorough search strategy using leading databases in medicine and biological sciences will maximise the probability that the relevant articles will be identified.
- This search without geographical or language restrictions, will allow achieving a comprehensive view on the possible clinical impact of sensitisation to different mite allergens.
- This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- Differences among study designs, sample characteristics and poor methodological quality may restrict comparison of the selected studies and negatively affect the quality of the evidence obtained.

INTRODUCTION

The prevalence of allergic diseases is steadily rising, with a large number of affected individuals, worldwide [1-6]. House dust mites (HDM) such as *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* are one of the main triggers of allergic disease in sensitised individuals [7-9]. In fact, HDM-induced allergic diseases affect approximately 2% of the world's population, thereby being a cause of major healthcare and economic burden [10].

Blomia tropicalis and *Lepidoglyphus destructor*, which are storage mites (SM), were earlier found predominantly in agricultural environments but are now being recognised as an important contributors to the allergen content in house dust in indoor urban dwellings [11]. Several investigations have demonstrated that allergens from these SM may play an important role in sensitisation and allergic symptoms [12,13].

Progress in molecular biology over the past few years has allowed us to identify and characterise single allergens in detail, at a molecular level. Component-resolved-diagnostics (CRD) offers the possibility of higher diagnostic precision and allows better management of each patient [14,15]. With the availability of a comprehensive set of molecular HDM and SM allergens, it is now possible to study molecular reactivity profiles that might be associated with certain manifestations of HDM- and SM-induced allergic respiratory symptoms [16]. Yet, very few data are available regarding the possibility of different molecular sensitisation patterns being associated with diverse clinical phenotypes [17,18]. Furthermore, sensitisation to allergens is not a static phenomenon and has been shown to have the potential to change over time [19]. Recently, CRD studies have shown that Immunoglobulin E (IgE) responses to allergens, namely dust mites, during childhood may increase in molecular complexity over time [20]. In this context, sensitisation to a single allergen molecule might thus expand to polymolecular recognition and this phenomenon seems to correlate with clinical symptoms [19,21].

If a patient has perennial symptoms due to being only allergic to one mite, skin prick tests or specific IgE against whole HDM- or SM- extract are sufficient for diagnosis of mite respiratory allergy [22]. However, if there is multiple mite sensitisation, CRD with species-specific components is mandatory [23]. *Lepidoglyphus destructor*, being considered a SM historically found mainly where plant or animal foods are processed and

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3 stored, has been detected in significant amounts in house dust from various regions of the
4 world [24-26]. Although the pyroglyphid HDM *Dermatophagoides pteronyssinus* and
5 *Dermatophagoides farinae* seem to predominate, glycyphagid SM mites, such as
6 *Lepidoglyphus destructor* and *Blomia tropicalis* may also be important in some regions
7 [27]. Taking these aspects into account, it is vital to study the clinical relevance of
8 *Lepidoglyphus destructor* [28]. *Blomia tropicalis* was also initially described as an
9 occupational mite. It is now regarded as a house dust mite of tropical and sub-tropical
10 areas, whose role as a trigger for allergic rhinitis and asthma is well described [29].

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There is no systematic evaluation of the role of sensitisation profiles of HDM and SM
molecular allergens in asthma or rhinitis. A comprehensive understanding of the
underlying evidence based on existing literature will help to clarify the clinical utility of
IgE molecular response to mites in allergic and respiratory diseases, thus helping to
inform future research in this area.

OBJECTIVES

Given this important gap, this systematic review aims to identify, critically appraise, and
synthesise the evidence from observational epidemiological studies investigating
sensitisation to HDM and SM molecular allergen components in asthma and/or allergic
rhinitis, and to study the relationship between sensitisation profiles of respective
molecular allergen components and clinical outcomes of asthma and rhinitis.

METHODS AND ANALYSIS

This study has been registered with the International prospective register of systematic
reviews (Research Registry), registration number: reviewregistry959.

This systematic review will be conducted in accordance with the Preferred Reporting
Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30].

The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
(PRISMA-P) checklist [31] has been followed and is attached as online supplementary
file 1.

Any modifications in the protocol during the systematic review will be reported.

Search strategy

We have developed a comprehensive search strategy for retrieving published and unpublished studies on the topic (as [online supplementary file 2.](#)). 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). Search dates will be from the inception to present. We will implement backward and forward article tracking within ISI Web of Science and by using Google Scholar.

The bibliographies of all eligible studies will be scrutinised to identify possible additional studies. We will identify unpublished and in progress studies by searching key Internet-based relevant databases – www.ClinicalTrials.gov; www.controlledtrials.com; www.anzctr.org.au In addition, we will contact authors who have published in this field to ask for potentially additional papers. No language restrictions will be imposed; translations will be undertaken where necessary.

Inclusion criteria for study designs

We will include clinical trials and all analytical observational epidemiological studies, including cohort, case-control and cross-sectional studies. We will select 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 will exclude analyses involving other types of isolated perennial sensitisations. This will be a systematic review assessing exposure to HDM and 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 molecular allergen components as defined in respective studies. We will exclude narrative literature reviews, discussion papers, non-research letters and editorials, case studies and case series and animal studies.

Study selection

Papers retrieved from the databases will be exported to a reference management program where screening will be undertaken. Removal of duplicate publications will be performed, thereafter, the titles and abstracts of retrieved 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, in Inclusion for study designs) 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 reviewer arbitrating in the circumstance of unresolved discrepancies. The process of selection will be summarised using a PRISMA flow diagram.

Data extraction and management

Data from selected articles will be transferred from their original presentation in each paper unto a data extraction form made in Microsoft Excel© software, with each study receiving a reference code. 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 not reported in the papers. For all included studies, we will collect the following information: study design, number of participants and their characteristics, country of study, year of publication, types and profiles of sensitization to HDM and SM molecular allergens, including frequency of sensitization, determinants of sensitization, degree of cross-reactivity among molecular allergens, subgroups at risk of sensitization (including age - children, adults, elderly; gender – male, female; urban and rural), geographical differences; estimates (hazard ratio, risk ratio, odds ratio, 95% confidence intervals, mean and SD) of the association between profiles of sensitization to HDM and SM molecular allergen components and clinical outcomes of asthma and rhinitis. Data extraction will be completed independently by two reviewers and discrepancies will be decided by a third reviewer.

Outcomes

Primary outcome

Frequency and patterns of sensitisation to HDM and SM molecular allergen components (using descriptive statistics measures) and estimates of association (hazard ratio, risk ratio, odds ratio, 95% confidence intervals, mean and SD) between HDM and SM

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3 molecular allergen components (and their degree of cross-reactivity) and severity of
4 asthma and rhinitis.
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8 *Secondary outcome*

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10 Frequency and patterns of sensitisation to HDM and SM molecular allergen components
11 and estimates of association (hazard ratio, risk ratio, odds ratio, 95% confidence intervals,
12 mean and SD) between HDM and SM molecular allergen components and prevalence,
13 exacerbations, medication use, hospitalization, and quality of life of asthma and rhinitis.
14
15 We will include the various approaches that have been employed by the authors of articles
16 we find, regarding definitions of asthma and rhinitis, in our scoping systematic review.
17
18 For asthma, we will include the number or frequency of asthma exacerbations. An
19 exacerbation can be defined as a deterioration of asthma symptoms requiring short-term
20 systemic corticosteroid treatment, an asthma-related hospitalisation or an emergency
21 room visit. We will also evaluate changes in asthma symptoms using measurement tools
22 as Asthma Control Test, Asthma Control Questionnaire and the Asthma Quality of Life
23 Questionnaire. We will also include lung function indicators, including prebronchodilator
24 FEV1, FEV1% of predicted value and PEF, and changes in fractional exhaled nitric oxide
25 (FeNO) level from baseline. Other indicators such as the number or frequency of
26 inhalations of beta-agonists with or without corticosteroids for rescue use and eosinophil
27 counts in blood or sputum will be taken into account. For rhinitis, the assessment of
28 exacerbations will be according to severity of nasal symptoms, evaluated by any
29 appropriate scores or other forms of measurement, such as the Total Nasal Symptom
30 Score (TNSS) recorded from validated daily or weekly diaries or visual analogue scales.
31
32 Use of conventional medication assessed by any instrument such as the Medication
33 Quantification Scale (Version III) to record the administration frequency and quantity of
34 allergic rhinitis relief medication. Laboratory indicators such as eosinophil count and/or
35 serum IgE levels or any other validated index will be included. Quality of life will be
36 evaluated by any general and/or disease-specific scales, such as the Rhinoconjunctivitis
37 Quality of Life Questionnaire (RQLQ).
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57 **Quality assessment**

58 Assessment of risk of bias will be independently verified by two different reviewers,
59 using the Critical Appraisal Skills Programme (CASP) [32] quality assessment tool. The
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3 CASP tool has different versions for different study designs. All studies and their
4 individual elements will be graded in terms of adequacy of the study regarding the
5 research question, risk of selection bias, measurement of exposure, and assessment of
6 outcomes. Disagreements will be resolved by a third reviewer.
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10 11 **Data synthesis**

12 We will produce a descriptive summary table of all included studies, to summarize the
13 literature. For studies without required data (e.g. relative risk estimates of effect of
14 sensitisation to HDM and SM and clinical outcomes), we will contact authors before
15 carrying out narrative synthesis. In case specific data cannot be obtained, we will
16 undertake a narrative synthesis of data in which we use texts to describe overall findings,
17 highlight their strengths and weaknesses, and make textual comparisons between studies
18 in light of the study question. For studies we judge to be reasonably clinically and
19 methodologically homogeneous (i.e. have used similar methods for subject selection and
20 inclusion, definition of sensitisation to molecular components of HDM and SM allergens,
21 outcome definition and assessment, and statistical analyses), we will perform meta-
22 analyses using random-effects models to estimate the combined effect of sensitisation to
23 HDM and SM molecular allergens on each of the study outcomes. Meta-analysis for the
24 association between sensitisation and each outcome will be undertaken separately. For
25 continuous outcomes reporting means, we use standardized mean differences (SMDs) for
26 the meta-analyses. We will quantify heterogeneity between studies using the I^2 statistic,
27 which is a measure (range 0-100%) used to quantify the proportion of variance in the
28 pooled estimates attributable to differences in estimates between studies included in the
29 meta-analysis, with values up to 25%, 50% and 75% indicating low, medium and high
30 levels of heterogeneity or inconsistency, respectively [33-36], although this statistic is not
31 an absolute measure of such heterogeneity [35]. Between-study variance will be estimated
32 using the τ^2 (T2) statistic, derived from the DerSimonian-Laird approach [37]. In cases
33 where five or fewer studies are found for certain outcomes, we will use Hartung-Knapp-
34 Sidik-Jonkman method for random effects to better account for low statistical power, as
35 recommended by Cochrane [38] We will perform pre-planned subgroup analyses and/or
36 meta-regressions for assessment of suspected heterogeneity. We will assess evidence of
37 publication bias using funnel plots and statistically using Begg and Egger tests [39,40].
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Meta-analyses will be performed using Stata Statistical Software (Release 13; StataCorp

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3 LP., College Station, TX, USA). The PRISMA checklist will be followed for reporting
4 of the systematic review.
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8 **Ethics and data management**

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10 No ethical approval required because the data that will be collected and analysed will be
11 only based on published literature and cannot be associated with specific individuals.
12 Retrieved data will be stored in a specific database that will have protected access and
13 will only be used by the authors. However, anonymised data will be placed in an open
14 repository.
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19 **ETHICS AND DISSEMINATION**

20
21 This systematic review will synthesise the underlying evidence concerning different
22 molecular sensitisation sets and association with alternative clinical phenotypes. This will
23 allow us, for the first time, to have a clearer picture of the relationship between HDM and
24 SM molecular allergen components and current expression and risk of asthma and rhinitis
25 in sensitised patients.
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31 Methodologically, this review will be based on publications published between 1970 and
32 august 2020, and will allow us to thoroughly analyse methodological aspects of selected
33 studies namely in terms of study design, questions asked, methods used and risk of
34 selection bias.
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41 Our results will be quite novel and will allow us to fill in relevant gaps in the field of
42 molecular allergology. In more specific terms, our study will yield relevant and up-to-
43 date information on current knowledge regarding HDM and SM molecular patterns and
44 allergic diseases. This will be accomplished by accessing information without language
45 or geographical restrictions, regarding not only analysis of molecular patterns of the most
46 relevant HDM and SM, but also the relationship between such patterns and details of
47 clinical expression of relevant allergic diseases such as asthma and allergic rhinitis, both
48 of which have significant morbidity burdens. Finally, we will also evaluate whether HDM
49 and SM molecular patterns can be used to predict future outcomes in these diseases, as
50 well as therapeutic responses, namely in terms of allergen-specific immunotherapy.
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3 We believe our results will allow us to draw meaningful conclusions about the relevance
4 of HDM and SM molecular sensitisation profiles in clinical diseases such as asthma and
5 allergic rhinitis, which may have significant clinical impact.
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10 Our dissemination strategy will involve presentations at national and international
11 scientific meetings, as well as preferential publication of article(s) in international, peer-
12 reviewed, open-access journals, whenever possible.
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For peer review only

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AUTHOR CONTRIBUTIONS

All authors contributed to the design and conceptualisation of this review. FS drafted the protocol with primary support from LTB. FS and CC carried out the database searches and conflicts were solved by LTB. LTB, JRG and BN were involved in checking various steps of the search strategy, including keywords, as well as the final version of the protocol. BN was the guarantor of the review. JRG was involved in the statistical strategy for data analysis.

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

PATIENT INVOLVEMENT

There was no involvement of patients or the public in the design or dissemination plans of this protocol for a systematic review.

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COMPETING INTERESTS

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

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

House Dust Mite (HDM) molecular sensitisation profiles and association with clinical outcomes in allergic asthma and rhinitis: protocol for a systematic review

Filipa Matos Semedo, Cíntia Cruz, Filipe Inácio, Jorge MR Gama, Bright I. Nwaru, Luís Taborda-Barata

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1,2,4,6
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	2,6
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	12
	#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	4-6

1	Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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6	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	6-8
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13	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	7
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20	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 2
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25	Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
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29	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)	7-9
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36	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	8
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43	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
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48	Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8,9
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53	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	9
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1	Data synthesis	#15a	Describe criteria under which study data will be	9,10
2			quantitatively synthesised	
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5		#15b	If data are appropriate for quantitative synthesis, describe	10
6			planned summary measures, methods of handling data and	
7			methods of combining data from studies, including any	
8			planned exploration of consistency (such as I ² , Kendall's τ)	
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11		#15c	Describe any proposed additional analyses (such as	10
12			sensitivity or subgroup analyses, meta-regression)	
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15		#15d	If quantitative synthesis is not appropriate, describe the type	10
16			of summary planned	
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19	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	10
20			publication bias across studies, selective reporting within	
21			studies)	
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24	Confidence in	#17	Describe how the strength of the body of evidence will be	10
25	cumulative		assessed (such as GRADE)	
26	evidence			
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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](#)

House Dust Mite (HDM) and Storage Mite (SM) molecular sensitisation profiles and association with clinical outcomes in allergic asthma and rhinitis: a systematic review
Matos-Semedo F, Cruz C, Inácio F, Gama JMR, Nwaru BI, Taborda-Barata L

Supplementary File 2

Search strategy for Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register), MEDLINE, EMBASE, AMED

-
1. house dust mites.mp. or exp house dust mites/
 2. exp storage mites/ or storage mites.mp.
 3. mites.mp. or exp mites/
 4. exp pyroglyphidae/ or pyroglyphidae.mp.
 5. glycyphagidae.mp or exp glycyphagidae/
 6. exp echimyopodidae/ or echimyopodidae.mp.
 7. chortoglyphidae.mp or exp chortoglyphidae/
 8. exp acaridae/ or acaridae.mp
 9. Dermatophagoides pteronyssinus.mp. or exp Dermatophagoides pteronyssinus/
 10. Dermatophagoides farinae.mp. or exp Dermatophagoides farinae/
 11. Euroglyphus maynei.mp or exp Euroglyphus maynei/
 12. Glycyphagus domesticus.mp or exp Glycyphagus domesticus/
 13. Lepidoglyphus destructor.mp. or exp Lepidoglyphus destructor/
 14. Blomia tropicalis.mp. or exp Blomia tropicalis/
 15. Chortoglyphus arcuatus.mp or exp Chortoglyphus arcuatus/
 16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
 17. exp molecular allergens/ or molecular allergens.mp
 18. Der p 1.mp or exp Der p 1/
 19. Der p 2.mp or exp Der p 2/
 20. Der p 3.mp or exp Der p 3/
 21. Der p 10.mp or exp Der p 10/
 22. Der p 23.mp or exp Der p 23/
 23. Der f 1.mp or exp Der f 1/
 24. Der f 2.mp or exp Der f 2/
 25. Der f 3.mp or exp Der f 3/
 26. Der f 10.mp or exp Der f 10/
 27. Blo t 1.mp or exp Blo t 1/
 28. Blo t 2.mp or exp Blo t 2/
 29. Blo t 3.mp or exp Blo t 3/
 30. Blo t 10.mp or exp Blo t 10/
 31. Lep d 2.mp or exp Lep d 2/
 32. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
 33. exp asthma/ or asthma.mp.
 34. wheez*.mp. or exp wheezing/
 35. exp allergic rhinitis/ or rhinit*.mp. or exp rhinitis/
 36. 33 or 34 or 35

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- 3 37. exp Epidemiologic Methods/
- 4 38. *cohort studies/ or cohort.ti,ab.
- 5 39. (longitudinal or prospective).ti,ab.
- 6 40. *case-control studies/
- 7 41. Control groups/ or control group*.ti,ab.
- 8 42. Matched-pair analysis/
- 9 43. (case* adj5 control*).ti,ab.
- 10 44. (case* adj3 comparison*).ti,ab.
- 11 45. (case* adj3 referen*).mp.
- 12 46. (case* adj1 base).mp.
- 13 38. (case* adj1 cohort).mp.
- 14 47. exp cross-sectional studies/ or cross-sectional.ti,ab.
- 15 48. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
- 16 49. 16 and 32 and 48
- 17 50. limit 49 to yr="1970 -Current"
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24 **Search strategy for ISI Web of Science (Science and Social Science Index), CINAHL.**

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28 (house dust mites or storage mites) AND (allergens or molecular allergens) AND
29 ((asthma or bronchial asthma or wheeze or wheezing) OR (rhinitis or allergic rhinitis))
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