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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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ABSTRACT

Introduction Identification and characterisation of single allergens at molecular level is important. Component-resolved diagnosis 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 Unpublished and ongoing work, as well as research in progress will be searched in www.ClinicalTrials.gov; www.controlledtrials.com and wwwanzctrorgau. 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 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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.

Trial registration number reviewregistry959.

Strengths and limitations of this study

- This review will produce the first synthesis addressing the relationship between profiles of sensitisation to house dust mites and storage mites 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 Reviews and Meta-Analyses 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 diagnosis (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-induced 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 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] *L. destructor*, being considered an SM historically found mainly where plant or animal foods are processed and stored, has been detected in significant amounts in house dust from various regions of the world.[24–26] Although the pyroglyphid HDM *D. pteronyssinus* and *D. farinae* seem to predominate, glyciphagid SM mites, such as *L. destructor and B. tropicalis* may also be important in some regions.[27] Taking these aspects into account, it is vital to study the clinical relevance of *L. destructor*.[28] *B. tropicalis* was also initially described as an occupational mite. It is now regarded as an HDM of tropical and subtropical areas, whose role as a trigger for allergic rhinitis and asthma is well described.[29]

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

The PRISMA Protocols checklist[31] has been followed and is attached as online supplemental 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 (online supplemental 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 and 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 diagnosis has been used to evaluate sensitisation to HDM and SM (at least one of *D. pteronyssinus, D. farinae, B. tropicalis, L. destructor*) in HDM-sensitised 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 sensitisation 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 sensitised 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 programme 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 'Inclusion criteria for study designs' section) 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 sensitisation to HDM and SM molecular allergens, including frequency of sensitisation, determinants of sensitisation, degree of cross-reactivity among molecular allergens, subgroups at risk of sensitisation (including age—children, adults, elderly; gender—male, female; urban and rural), geographical differences; estimates (HR, risk ratio, OR, 95% CIs, mean and SD) of the association between profiles of sensitisation 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 (HR, risk ratio, OR, 95% CIs, mean and SD) between HDM and SM molecular allergen components (and their degree of cross-reactivity) and severity of asthma and rhinitis.

Secondary outcome

Frequency and patterns of sensitisation to HDM and SM molecular allergen components and estimates of association (HR, risk ratio, OR, 95% CIs, mean and SD) between HDM and SM molecular allergen components and prevalence, exacerbations, medication use, hospitalisation and quality of life of asthma and rhinitis.

We will include the various approaches that have been employed by the authors of articles we find, regarding definitions of asthma and rhinitis, in our scoping systematic review. For asthma, we will include the number or frequency of asthma exacerbations. An exacerbation can be defined as a deterioration of asthma symptoms requiring short-term systemic corticosteroid treatment, an asthma-related hospitalisation or an emergency room visit. We will also evaluate changes in asthma symptoms using measurement tools as Asthma Control Test, Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire. We will also include lung function indicators, including prebronchodilator forced expiratory volume in 1 s (FEV1), FEV1% of predicted value and Peak Expiratory Flow (PEF), and changes in fractional exhaled nitric oxide (FeNO) level from baseline. Other indicators such as the number or frequency of inhalations of beta-agonists with or without corticosteroids for rescue use and eosinophil counts in blood or sputum will be taken into account. For rhinitis, the assessment of exacerbations will be according to severity of nasal symptoms, evaluated by any appropriate scores or other forms of measurement, such as the Total Nasal Symptom Score recorded from validated daily or weekly diaries or visual analogue scales. Use of conventional medication assessed by any instrument such as the Medication Quantification Scale (V.III) to record the administration frequency and quantity of allergic rhinitis relief medication. Laboratory indicators such as eosinophil count and/or serum IgE levels or any other validated index will be included. Quality of life will be evaluated by any general and/or disease-specific scales, such as the Rhinoconjunctivitis Quality of Life Questionnaire.

Quality assessment

Assessment of risk of bias will be independently verified by two different reviewers, using the Critical Appraisal Skills Programme (CASP)[32] quality assessment tool. The CASP tool has different versions for different study designs. 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.

Data synthesis

We will produce a descriptive summary table of all included studies to summarise the literature. For studies without required data (eg, relative risk estimates of effect of sensitisation to HDM and SM and clinical outcomes), we will contact authors before carrying out narrative synthesis. In case specific data cannot be obtained, we will undertake a narrative synthesis of data in which we use texts to describe overall findings, highlight their strengths and weaknesses, and make textual comparisons between studies in light of the study question. For studies we judge to be reasonably clinically and methodologically homogeneous (ie, have 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), we will perform meta-analyses using random-effects

models to estimate the combined effect of sensitisation to HDM and SM molecular allergens on each of the study outcomes. Meta-analysis for the association between sensitisation and each outcome will be undertaken separately. For continuous outcomes reporting means, we use standardised mean differences for the meta-analyses. We will quantify heterogeneity between studies using the I^2 statistic, which is a measure (range 0%–100%) used to quantify the proportion of variance in the pooled estimates attributable to differences in estimates between studies included in the meta-analysis, with values up to 25%, 50% and 75% indicating low, medium and high levels of heterogeneity or inconsistency, respectively,[33–36] although this statistic is not an absolute measure of such heterogeneity.[35] Between-study variance will be estimated using the τ^2 (T^2) statistic, derived from the DerSimonian-Laird approach.[37] In cases where five or fewer studies are found for certain outcomes, we will use Hartung-Knapp-Sidik-Jonkman method for random effects to better account for low statistical power, as recommended by Cochrane.[38] We will perform preplanned subgroup analyses and/or meta-regressions for assessment of suspected heterogeneity. We will assess evidence of publication bias using funnel plots and statistically using the tests by Begg and Mazumdar[39] and Egger *et al*.[40] Meta-analyses will be performed using Stata Statistical Software (Release 13; StataCorp, College Station, Texas, USA). The PRISMA checklist will be followed for reporting of the systematic review.

Ethics and data management

No ethical approval required because the data that will be collected and analysed will be only based on published literature and cannot be associated with specific individuals.

Retrieved data will be stored in a specific database that will have protected access and will only be used by the authors. However, anonymised data will be placed in an open repository.

ETHICS AND DISSEMINATION

This systematic review will synthesise the underlying evidence concerning different molecular sensitisation sets and association with alternative clinical phenotypes. This will allow us, for the first time, to have a clearer picture of the relationship between HDM and SM molecular allergen components and current expression and risk of asthma and rhinitis in sensitised patients.

Methodologically, this review will be based on publications published between 1970 and august 2020, and will allow us to thoroughly analyse methodological aspects of selected studies namely in terms of study design, questions asked, methods used and risk of selection bias.

Our results will be quite novel and will allow us to fill in relevant gaps in the field of molecular allergology. In more specific terms, our study will yield relevant and up-to-date information on current knowledge regarding HDM and SM molecular patterns and allergic diseases. This will be accomplished by accessing information without language or geographical restrictions, regarding analysis of molecular patterns of the most relevant HDM and SM, and the relationship between such patterns and details of clinical expression of relevant allergic diseases such as asthma and allergic rhinitis, both of which have significant morbidity burdens. Finally, we will also evaluate whether HDM and SM molecular patterns can be used to predict future outcomes in these diseases, as well as therapeutic responses, namely in terms of allergen-specific immunotherapy.

We believe our results will allow us to draw meaningful conclusions about the relevance of HDM and SM molecular sensitisation profiles in clinical diseases such as asthma and allergic rhinitis, which may have significant clinical impact.

Our dissemination strategy will involve presentations at national and international scientific meetings, as well as preferential publication of article(s) in international, peer-reviewed, open-access journals, whenever possible.

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Contributors All authors contributed to the design and conceptualisation of this review. FM-S drafted the protocol with primary support from LT-B. FM-S and CC carried out the database searches and conflicts were solved by LT-B. LTB, JMRG 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. JMRG was involved in the statistical strategy for data analysis. FM-S, FI, JMRG and LT-B were involved in establishing eligibility criteria and data extraction forms. All authors provided feedback on the manuscript, at all stages.

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Competing interests None declared.

Patient consent for publication Not required.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

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		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

Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	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
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
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
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	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)	7-9
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
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	8,9
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

Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9,10
	#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)	10
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

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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/
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

37. exp Epidemiologic Methods/
38. *cohort studies/ or cohort.ti,ab.
39. (longitudinal or prospective).ti,ab.
40. *case-control studies/
41. Control groups/ or control group*.ti,ab.
42. Matched-pair analysis/
43. (case* adj5 control*).ti,ab.
44. (case* adj3 comparison*).ti,ab.
45. (case* adj3 referen*).mp.
46. (case* adj1 base).mp.
38. (case* adj1 cohort).mp.
47. exp cross-sectional studies/ or cross-sectional.ti,ab.
48. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. 16 and 32 and 48
50. limit 49 to yr="1970 -Current"

Search strategy for ISI Web of Science (Science and Social Science Index), CINAHL.

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