

Study Protocol

Parental history of atopic disease as a risk factor for atopic dermatitis

A systematic review and meta-analysis

List of abbreviations

AD	Atopic dermatitis
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis

Aim

To determine the risk of developing AD in children with and without a parental history of atopic disease, whether a dose-response relationship exists and whether the risk differs by parental gender or type of atopic disease (AD, allergic rhinitis or asthma).

Research Methods

Study design

Systematic review and meta-analysis.

Eligibility criteria

Published studies in English language, from any year and any healthcare setting, are eligible to be included. To be eligible, studies must report on the association between atopic diseases in parents and development of AD in children and include a group of individuals without AD for comparison.

Literature search

We will search the medical databases PubMed and EMBASE from their date of inception through June 2018 using the search terms presented in Table 1. The results will be filtered to include articles with human subjects and English language.

Table 1. Search terms

Database	Search strategy
EMBASE	(exp 'atopic dermatitis' / OR 'atopic dermatitis' OR 'dermatitis atopic' OR exp 'eczema' / OR 'eczema' OR 'childhood eczema' OR 'infantile eczema' OR 'neurodermatitis' OR exp 'neurodermatitis' / OR 'Besnier's prurigo' OR ('Besnier's' AND 'prurigo')) AND ('family history' OR 'parental history' OR 'maternal' OR 'paternal' OR 'predisposition' OR 'genetic')

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MEDLINE (PubMed)	("Dermatitis, Atopic"[Mesh] OR "atopic dermatitis"[all fields] OR "dermatitis atopic"[all fields] OR "Eczema"[Mesh] OR "eczema"[all fields] OR "childhood eczema"[all fields] OR "infantile eczema"[all fields] OR "neurodermatitis"[all fields] OR "Neurodermatitis"[Mesh] OR "Besnier's prurigo"[all fields] OR ("Besnier's"[all fields] AND "prurigo"[all fields])) AND ("family history" OR "parental history" OR "maternal" OR "paternal" OR "predisposition" OR "genetic")
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Selection of studies and data extraction

Initially, all titles and abstracts resulting from the literature search will be screened, and duplicates will be removed. Two reviewers (Nina Haarup Ravn and Anne-Sofie Halling-Overgaard) will independently screen all titles and all abstracts. The full-text articles will be retrieved for studies that fulfill the inclusion criteria, as well as for studies where there is any ambiguity of the potential eligibility. In the case that data is duplicated in more than one study, the study with the most comprehensive data is included. Any disagreement between the two reviewers regarding a potential study inclusion will be resolved through discussion with a third reviewer (Jacob Pontoppidan Thyssen) if needed. If applicable, authors are contacted to obtain additional information that is missing from the studies. No reviewer-blinding will be performed regarding the journal titles or study authors. The literature selection and the reasons for study exclusion will be documented in a PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram. For included articles and relevant reviews, the reference lists are screened to identify additional studies that may have been missed in the initial search.

Each of the two reviewers will, independently and in duplicate, extract the manuscript data in order to minimize bias and errors. The following data will be sought for each publication:

- 1) Study details: author information, publication year, country, design
- 2) Population characteristics: for example, sex and mean or median age.
- 3) Exposure:
 - Definition and method of identification of parental atopic diseases.
 - Number of exposed subjects in total and in subgroups according to type of atopic disease (AD, allergic rhinitis and asthma) and parental gender.

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4) Outcomes:

- Definition and method of identification of AD.
- Number of subjects with and without AD according to parental history of atopic disease overall and in subgroups.

Quality assessment

To allow comparison by study quality, a critical appraisal will be independently performed by the reviewers. The Newcastle-Ottawa Scale (NOS) is used for quality assessment. Full results of this quality assessment will be presented in the final manuscript, and quality assessment will be discussed in the narrative data synthesis.

Data synthesis

We will group studies in the following groups and analyze data accordingly:

- 1) Parental history of atopic disease overall
 - a. Stratified by study design (cohort, case-control and cross-sectional)
 - b. Stratified by geographic area (Africa, Asia, Europe, North America, South America)
 - c. Stratified by study size (above and below 3000 participants)
 - d. Only including high quality studies (evaluated by NOS score)
- 2) According to parental gender
- 3) According to type of atopic disease in parents (AD, allergic rhinitis, asthma)
- 4) According to the number of affected parents and the number of diseases in parents

We will perform an odds ratio meta-analysis to obtain a pooled effect estimate. We will assess statistical heterogeneity using the I² statistic. The pooled odds ratio and its 95% confidence interval will be calculated using random effects models. If substantial heterogeneity is observed, we will perform sensitivity analyses to explore the reasons for such heterogeneity. Study characteristics and the odds ratio estimates for AD according to parental history of atopic disease will be presented in full (in tabular form), either in the manuscript or as supplementary materials. We will attempt to assess publication bias by standard approaches including funnel plots and Egger tests. PRISMA guidelines will be used to report the results of this study.