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How does parental history of atopic disease predict the risk of atopic dermatitis in a child? - a systematic review and meta-analysis

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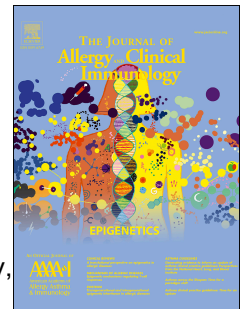
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Title page

Title

How does parental history of atopic disease predict the risk of atopic dermatitis in a child? - a systematic review and meta-analysis

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for Sanofi-Genzyme, Union Therapeutics and Eli Lilly & Co, and received speaker honorarium from LEO Pharma and Sanofi-Genzyme, and been an investigator for Sanofi-Genzyme, Eli Lilly & Co, LEO Pharma and Abbvie. Dr. Silverberg has received honoraria as an advisory board member or consultant from Abbvie, Anaptysbio, Asana, Eli Lilly, Galderma, GlaxoSmithKline, Kiniksa, Leo, Menlo, Pfizer, Regeneron-Sanofi, Realm, Roivant, and as a speaker for Regeneron-Sanofi.

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Abbreviations used

AD: atopic dermatitis

CI: Confidence interval

NOS: Newcastle-Ottawa scale

OR: Odds ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SOFTER: Softened Water for Eczema Prevention trial

Abstract

Background: Parental history of atopic disease is a well-established risk factor for development of atopic dermatitis (AD), but several aspects of this association remain unclear.

Objective: To determine the association of parental history of atopic disease with AD in offspring.

Methods: We searched PubMed and EMBASE through June 2018 for relevant records and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. . Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using random-effects models.

Results: 163 records covering 149 unique studies were included. Of these, 119 studies were included in the meta-analysis. Individuals with parental history of atopic disease had increased odds of AD (OR 1.81, 95% CI 1.65-1.99). Parental asthma (OR 1.56, 95% CI 1.18-2.05) and allergic rhinitis (OR 1.68, 95% CI 1.34-2.11) had a smaller effect than AD (OR 3.30, 95% CI 2.46-4.42). The effect of maternal and paternal history was comparable for all atopic diseases. An increase in odds was observed when comparing the effect of having one (OR 1.30, 95% CI 1.15-1.47) or two atopic parents (OR 2.08, 95% CI 1.83-2.36), as well as having a parent with one (OR 1.49, 95% CI 1.28-1.74) or more atopic diseases (OR 2.32, 95% CI 1.92-2.81).

Conclusions: This study provides evidence-based risk estimates that may guide physicians, who counsel parents with a history of atopic disease about their children's risk of AD. This information is of particular importance for future efforts towards establishing prophylactic interventions for AD on a general population level.

Key Messages

- Parental history of atopic disease increased the risk of atopic dermatitis (AD) independently of the affected parent's sex.
- The association strengthened when both parents were affected and when they had atopic multimorbidity.
- Parental history of AD displayed a stronger association than asthma or allergic rhinitis.

Capsule Summary

This study enables physicians to advise parents on their child's risk of developing atopic dermatitis using evidence-based risk estimates and aids in identification of high-risk individuals who could possibly benefit from future prophylactic interventions.

Introduction

Atopic dermatitis (AD) is a chronic and relapsing, inflammatory itchy skin disease that debuts in early childhood,¹ and has a life-time prevalence of 10-20%.^{2,3} Atopic diseases, such as AD, asthma and allergic rhinitis, are characterized by increased type 2 immunity;^{4,5} share environmental, epigenetic and genetic risk factors;⁶⁻⁸ and constitute some of the most common conditions seen in a general practice setting, especially in the pediatric population.^{9,10} While the so-called atopic march, i.e. the tendency to first develop AD, then asthma and allergic rhinitis, has recently been challenged¹¹ and updated,¹² evidence supports that skin barrier impairment in AD may facilitate allergen exposure and result in epicutaneous allergic sensitization.⁶ Upon subsequent exposure to these allergens in the airways allergic asthma and/or rhinitis will be expressed.

Pilot studies have suggested that prophylactic use of emollients in infants with an atopic predisposition may reduce the risk of AD.¹³⁻¹⁵ Large clinical trials are therefore being conducted to examine risk reductions of AD, and associated atopic diseases, following daily emollient application after birth.^{16,17} Similarly, the Softened Water for Eczema Prevention (SOFTER) trial is examining the effect of water softening on the prevention of AD. Since water softening devices and emollients can be expensive, and emollients may contain contact allergens^{18,19} as well as endocrine disrupting chemicals,²⁰ there is a need for improved insight in predictive factors for AD in order to more precisely identify high-risk children to enable targeting of prophylactic interventions.

Despite numerous efforts to uncover predictors for AD, a parental history of atopic disease remains the strongest and most well-established predictor.²¹⁻³⁶ However, the exact magnitude of the association between parental history of atopic disease and development of AD is unknown, and it is currently unclear whether having two affected parents or parents with atopic multimorbidity increase the risk,^{32,36-44} whether maternal and paternal atopic diseases affect the risk equally,^{21-35,37-40,45-59} and whether the risk of AD is increased to the same degree by parental history of AD, asthma, and allergic rhinitis.^{21-32,36-41,52-56,58-60} A maternal preponderance in inheritance of atopy has been widely hypothesized,^{61,62} and a meta-analysis found that maternal asthma increased the risk of asthma more than paternal asthma,⁶³ but AD constitutes a distinct disease entity, and results may not be transferable between atopic diseases.

The aim of this systematic review and meta-analysis was to examine i) the magnitude of the association between a parental history of atopic disease and development of AD in the offspring, ii) whether the association differs by parental sex or type of atopic disease, and iii) whether the association differs by the number of atopic diseases in the parents or the number of parents that are affected.

Methods

Search strategy

We conducted this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁶⁴ and a protocol created ahead of study commencement, which is published at the official

website of the Copenhagen Research Group for Inflammatory Skin and available as supplementary materials. . The medical databases PubMed and EMBASE were searched from their inception through June 10th 2018 for studies conducted in humans and communicated in English language. Search terms are available as supplementary materials. Literature was additionally sought from reference lists of retrieved articles and relevant review articles.

Selection criteria

Eligible studies provided information on the association between a parental history of atopic disease and development of AD in their offspring. Studies were excluded if they lacked reference individuals without AD. We included studies reporting any parental history of any atopic disease or related condition: AD, asthma, allergic rhinitis, allergic conjunctivitis, food allergy, urticaria, pollinosis and atopic sensitization. Alternative designations such as eczema for AD and hay fever for allergic rhinitis were allowed. To correctly determine the effect of atopic disease in parents, studies only reporting family history (not explicitly parental) were excluded. When studies were described in multiple publications, more than one could be included if the data fit into different analyses, but if the data overlapped only the one with most comprehensive data was included. Two reviewers (NHR and AH) independently extracted relevant literature based on title and/or abstract and assessed full-text reports for eligibility. Any disagreement was resolved through discussion with a third reviewer (JPT).

Data extraction and quality assessment

If available, the following data were extracted: author information, year of publication, study design, country, age, sex, definition of and method of identifying atopic diseases in parents and AD in their offspring, sample size, number of cases and reference individuals in total and according to each category of parental history. Categories included parental history of atopic disease overall (at least one parent with at least one atopic disease) and divided by parental sex, number of affected parents as well as type and number of atopic diseases. We recorded any information on how the association differed by the sex of the child and related to age-of-onset, persistence and severity of AD. When raw data were unavailable any other data describing the association were extracted, such as relative risk and odds ratio.

The Newcastle-Ottawa scale (NOS) was used to assess the quality of studies in the quantitative analyses. Studies were given points in three main areas: selection of participants, comparability of study groups and detection of exposure, for case-control studies, or outcome, for cohort and cross-sectional studies. Cohort and case-control studies were scored using the standard NOS: They could obtain a maximum score of nine, with scores of six or higher denoting high quality. Cross-sectional studies were scored using an adapted NOS: They could earn up to ten points, with scores of seven or higher denoting high quality.

Statistical analysis

We used StatsDirect software (version 3, StatsDirect Ltd, Cheshire, UK) to calculate pooled odds ratios (OR) with 95% confidence intervals (CI) comparing AD patients with reference individuals (i.e. people without AD) for each of the following categories: 1) parental history of, respectively, atopic disease, AD, asthma and allergic rhinitis, 2) one or

both parents history of, respectively, atopic disease and AD, 3) maternal and paternal history of, respectively, atopic disease, AD, asthma, allergic rhinitis, allergic respiratory disease and atopic sensitization, and 4) parental history of one or more than one atopic disease. For the analysis designated parental history of atopic disease, we used data covering any atopic disease in either parent, if it was available and not overlapping. If only one parental value was described, this was used. We performed sub-analyses for this category by including only high-quality studies (according to NOS score) and stratifying according to geographic area (America, Asia, Australia, Europe), study design (cohort, case-control and cross-sectional) and study size (above or below 3000 participants). If the study provided outcome data at multiple time points, the oldest age of study participants was selected for 'ever AD', while the time point with the highest proportion of AD cases was selected for 'current AD'.

The quantitative analyses were performed using raw data if available, alternatively adjusted data were converted to raw data if OR, 95% CI and total number of AD patients and reference individuals were stated.⁶⁵ In these instances, we chose the fully adjusted estimates. Data from articles in which none of the aforementioned options were available are described in the qualitative analysis. All statistical tests were two-sided with a significance level of $p < 0.05$ and were visualized by forest plots. We assessed publication bias by means of funnel plots and Egger tests and heterogeneity by means of Cochrane Q and I^2 statistics. Due to significant between-study heterogeneity, with Cochrane Q statistics P-values < 0.05 and $I^2 > 75\%$, random effects models with DerSimonian-Laird methods were used (Table I and II).

Results

The literature search generated 7,317 non-duplicate records. Of these, 476 records underwent full-text review, and 163 publications^{21-60, 66-188} covering 149 unique studies with 656,711 non-overlapping participants were included. Figure 1 outlines the screening process and lists reasons for exclusion. Studies originated from Northern Europe ($n = 31$), Western Europe ($n=21$), Southern Europe ($n=6$), Eastern Europe ($n=6$), Western Asia ($n=12$), Eastern Asia ($n=44$), South-Eastern Asia ($n=2$), South Asia ($n=1$), North America ($n = 12$), Central America ($n=3$), South America ($n=1$), Eastern Africa ($n=3$), South Africa ($n=1$) and Australia ($n=4$). Additionally, two studies were multinational with one being European and the other European and North American. Detailed information on all included articles is available in supplementary materials. The quantitative meta-analysis included 128 publications^{21-42, 44-47, 49-58, 60, 66-155} covering 119 unique studies. Of these, 109 publications reached a NOS-score indicating high quality, while the rest obtained a NOS score of at least five.^{24, 31, 34, 35, 39, 40, 44, 66-73, 144, 152}

Quantitative analysis

A meta-analysis of 66 studies (38,505 AD patients and 203,146 reference individuals) showed that those with a parental history of atopic disease had significantly increased odds of AD (OR 1.81, 95% CI 1.65-1.99) (Table I). No significant changes were observed when only high-quality studies were included, or when studies were stratified by geographic area or study size (Table II). Cross-sectional studies (OR 2.12, 95% CI 1.83-2.46) yielded a higher OR than cohort studies (OR 1.57, 95% CI 1.40-1.76).

Parental history of asthma (6,604 AD patients and 49,179 reference individuals), allergic rhinitis (7,365 AD patients and 47,100 reference individuals), and AD (9,095 AD patients and 61,736 reference individuals) was associated with increased odds of AD (OR 1.56, 95% CI 1.18-2.05; OR 1.68, 95% CI 1.34-2.11 and OR 3.30; 95% CI 2.46-4.42, respectively), but parental history of AD did so to a greater extent than asthma and allergic rhinitis (Table I and Fig 2). The stronger association with parental history of AD, compared to asthma and allergic rhinitis, was independent of which parent that was affected.

More studies reported maternal compared to paternal information. Most studies had information about history of atopic disease (n=60), followed by AD (n=43), asthma (n=30), allergic rhinitis (n=22), and allergic respiratory disease (n=7). Additionally, eight studies provided information about maternal and/or paternal atopic sensitization, however, using this as a marker for parental atopic predisposition did not result in greater risk estimates (OR 1.65, 95% CI 1.40-1.96 and OR 1.26, 95% CI 0.81-1.98, respectively) than using history of atopic disease (OR 1.89, 95% CI 1.73-2.08 and OR 1.99, 95% CI 1.73-2.29, respectively). The effect of maternal and paternal inheritance was comparable in all analyses (Table I and Fig 2). The only parental category that did not yield a significant association with AD was paternal atopic sensitization (OR 1.26, 95% CI 0.81-1.98), but only few data were available (646 AD patients and 2,361 reference individuals).

An increase in odds was observed when comparing the odds of AD in offspring with, respectively, one (OR 1.30, 95% CI 1.15-1.47) or two parents (OR 2.08, 95% CI 1.82-2.36) with a history of atopic disease (Table I and Fig 2). A similar trend was observed for a history of AD in one or both parents, but without the difference reaching statistical significance (Table I). The highest OR of AD in offspring was found when both parents had a history of AD (OR 3.66, 95% CI 2.08-6.44). An increase in odds was furthermore observed when comparing the odds of AD in offspring whose parents had, respectively, one (OR 1.49, 95% CI 1.27-1.74) or more than one atopic disease (OR 2.32, 95% CI 1.92-2.81) (Table I and Fig 2).

Egger tests detected significant presence of publication bias in 3 of the 31 analyses: maternal history of atopic disease (p=0.042), one parent history of atopic disease (p=0.025) and parental history of atopic disease in studies with > 3000 participants (p=0.049).

Qualitative analysis

Overall, the data available for qualitative synthesis supported the results of the quantitative analyses in regards to the association between AD and parental history of, respectively, atopic disease,^{48, 73, 160-166, 179-183} AD,^{59, 157-160, 173-178, 187} asthma,^{157, 169-171, 175, 188} and allergic rhinitis^{59, 164, 171, 172} as well as the comparability of maternal and paternal inheritance^{48, 56, 59, 159-162, 177-179} and the increased odds when both parents compared to one parent were affected.^{43, 184} Limited data examined how other atopic-related diseases such as urticaria, conjunctivitis, and food allergy in parents influenced the risk of AD in offspring.^{41, 55, 70, 99}

Three birth cohorts investigated the association between maternal symptoms of atopic disease during pregnancy and AD in offspring. A German study found a positive association with symptoms of any atopic disease (aOR 1.74, 95% CI 1.00-3.02, $p=0.045$),¹⁵⁰ a Canadian study with symptoms of asthma,¹⁷¹ while an American study only found this for symptoms of AD (RR 1.70, 95% CI 1.10-2.60, $p=0.033$) and asthma (RR 1.80, 95% CI 1.20-2.70, $p=0.015$), but not allergic rhinitis (RR 1.27, 95% CI 0.91-1.80, $p=0.155$).¹⁷⁰ Notably, only the German study considered, and adjusted for, the influence of an underlying history of atopic disease. Two studies examined if symptom severity during pregnancy affected the association: While a Japanese cross-sectional study found an association between AD and the number of maternal symptoms of different atopic diseases during pregnancy ($p<0.01$),¹⁶⁷ a Canadian birth cohort study showed no influence of asthma severity.¹⁷¹

Three studies found that the effect of atopic predisposition was independent of the child's sex,^{37, 43, 177} whereas two studies found that maternal AD only was only associated with AD in girls^{49, 156} and one study that paternal AD was associated with AD in boys at all ages up to ten years of age, but only in girls at two years of age.⁴⁹ One study found that the between-sex differences in association were dependent on the type of atopic disease, with parental AD showing no difference and parental asthma and allergic rhinitis only being significantly associated with AD in girls.⁵⁹

Four studies compared early- and late-onset AD and found that the age of AD onset was independent of a parental history of atopic disease.^{37, 93, 120, 153} Parental history of atopic disease increased the severity of AD in two studies,^{76, 77} but not in a third.⁷⁴ Several methodological differences between these studies should be considered. Of the two studies that found a positive association, one was a Japanese cross-sectional study of current AD in adolescents which evaluated severity by nights kept awake by itch,⁷⁷ and the other was a Swedish birth cohort followed to 18 months of age which evaluated severity by frequency of symptoms,⁷⁶ while the study that found no association was a Finnish birth cohort followed to 5 years of age which defined severe AD as having a generalized distribution and signs of acute inflammation.⁷⁴ Another study discovered an association between severity of AD in parents and severity of AD in their offspring.³⁹ A Swedish birth cohort study³⁷ found that a parental history of allergic respiratory disease without AD exhibited a stronger association with the offspring developing IgE-associated AD compared to non-IgE-associated AD, while parental history of AD increased the risk of AD in offspring irrespective of IgE status.

Discussion

Principal findings

This systematic review and meta-analysis showed that a parental history of atopic disease was significantly associated with AD in the offspring, and that the relative effect size was similar for both parents. Parental history of AD conferred a stronger association compared to asthma and allergic rhinitis, and the association strengthens with the number of parental atopic diseases and the number of affected parents.

Comparison with other studies

Parental history of atopic disease may increase the risk of AD through multiple pathways. Twin studies indicate that genetics play a considerable role, with the heritability of AD being 75%, and genetic pleiotropy accounting for 85% of the association between AD and asthma.¹⁸⁹ Shared genetic risk variants, predominantly affecting the immune system, may therefore in part explain the positive association between AD and parental history of asthma or allergic rhinitis. However, some genetic risk variants are specific to AD, providing an explanation for the comparatively greater risk conferred by parental history of AD than asthma or allergic rhinitis.^{7, 190-193} Filaggrin gene mutations are observed in 1/3 of AD patients and cause significant skin barrier impairment.^{194, 195} While these mutations also increase the risk of food allergy, asthma and allergic rhinitis, this is only, or predominately, in the context of AD, demonstrating a potential genetic mechanism underlying the atopic march.^{190, 196-201} Maternal filaggrin gene mutations increase the risk of AD even if the offspring does not inherit the mutations,²⁰² indicating that heredity goes beyond genetics. Other pathways mediating some of the parental effect could include inheritance of epigenetic modifications and clustering of environmental hazards.²⁰³⁻²⁰⁶

A meta-analysis, covering 33 studies, found a tendency towards maternal history of asthma increasing the risk of asthma more than paternal history of asthma (OR 3.04, 95% CI 2.59-3.56 and OR 2.44, 95% CI 2.14-2.79, respectively).⁶³ Hypotheses concerning a greater maternal effect in inheritance of atopy^{61, 62} include paternal genomic imprinting^{207, 208} as well as in-utero and neonatal influences. While one study found maternal linkage on a locus associated with AD,²⁰⁹ no studies have found evidence of paternal imprinting in AD,²¹⁰⁻²¹² and no clear mediating pathways have been established related to IgE,^{51, 58, 114, 136, 173, 213-215} inflammatory cytokines^{28, 173, 213, 216-220} and cellular immunity^{104, 221-223} measured in cord blood or breastmilk composition.²²⁴⁻²²⁷ Consequently, the hypothesis of preferential maternal inheritance in AD remains unsupported by robust biological models, and we observed a comparable effect of maternal and paternal inheritance.

Implications for future research and clinical practice

Atopic diseases constitute a considerable global disease burden due to their common occurrence, chronic nature and substantial morbidity,²²⁸ making primary prevention highly desirable. Efforts to uncover prevention strategies for other atopic diseases than AD have been largely unsuccessful,²²⁹⁻²³⁵ but prevention of AD may present a possibility to also reduce the occurrence of these diseases by blocking the entry point to the atopic march. Numerous trials have been conducted investigating primary prevention strategies for AD,²³⁶⁻²³⁸ and interventions such as daily emollient application,¹³⁻¹⁷ domestic water softening,^{239, 240} and pre- and probiotic supplementation,^{233, 234, 241, 242} are currently being trialed. Thus, the implementation of AD prophylaxis in clinical practice may be on the horizon. Our results enable researchers and physicians to identify high-risk children more accurately based on parental history of atopic disease, thus facilitating improved counseling of parents with atopic diseases and targeting of interventions both in clinical trials and clinical practice. To further improve counseling and targeting, future studies are needed to establish whether the phenotype of atopic disease in parents affects the association,^{39, 243} and to take into consideration whether the child has siblings with a history of atopic disease.^{37, 44, 59, 72}

Strengths and limitations of the study

Despite the strict methodology of this systematic review and meta-analysis using PRISMA guidelines, as well as the large number of included studies, certain limitations should be considered. The different definitions and methods of identification used to ascertain AD and parental history of atopic disease could introduce heterogeneity,²⁴⁴ but this was to some extent accounted for by using random effects analyses. Since parental history of atopic disease was rarely the primary exposure of interest in the included articles, publication bias was less likely occur and was only detected in three analyses. While we only included studies written in English, which may reduce generalizability,²⁴⁵ our risk estimates were similar across different geographic areas. However, the global yield was dominated by Northern and Western Europe, Western and Eastern Asia as well as North America, making it difficult to make claims about other regions with sparse data available.

Studies mainly surveyed parental history of atopic disease through self-reports, but it is unclear how well parents can remember their personal history of atopic disease. Studies have indicated that 30-40% of adults cannot recall having had AD in their childhood,²⁴⁶⁻²⁴⁹ whereas better recall rates have been observed for asthma and allergic rhinitis.²⁴⁷ This discrepancy is possibly explained by some AD patients only experiencing a short duration of mild AD early in life, while asthma and allergic rhinitis have a later onset and are more prevalent in adult life. As parental atopic history is generally ascertained at baseline in birth cohorts, this will cause non-differential misclassification and reduce the risk estimate. However, recall bias is a concern in other study designs, e.g. one study detected a switch from reporting negative to positive paternal history of atopic disease when children developed atopic diseases.²⁵⁰ This may explain why the risk estimate was significantly higher in cross-sectional studies compared with cohort studies in our analyses. Through these mechanisms, the study design may contribute to the observed between-study heterogeneity.

It is important to consider whether the association with parental history of asthma and allergic rhinitis is due to confounding by a concurrent parental history of AD. However, two birth cohorts, from New Zealand³⁶ and Sweden,³⁷ found that parents having allergic respiratory disease but no AD still increased odds of AD in their offspring, suggesting that parental history of asthma and allergic rhinitis constitute independent risk factors for AD.

Some aspects concerning identification of AD in offspring could overestimate the risk estimates. Parents with a history of atopic disease might be more alert regarding the occurrence of AD in their children than parents without such history and a family history of AD or allergic respiratory disease is one of the diagnostic major criteria for AD according to the UK Working Party, in children under 4 years of age,²⁵¹ and the Hanifin and Rajka criteria.²⁵² Consequently, misclassification of children with other dermatoses as having AD may be more common in those with a family history of atopic disease, and some children presenting clinically with AD may not fulfill the diagnostic criteria due to a lack of family history. It is reassuring that one study omitted this criterion in their analyses⁵⁸ and found similar risk estimates to us. Several different AD endotypes and phenotypes are recognized.^{253, 254} While increased type 2 inflammation is expressed across atopic diseases,^{5, 6} only about 1/3 of AD patients have elevated IgE levels.²⁵⁵ An association with parental history related to IgE status was only examined in one study in relation to AD in the offspring³⁷ and none addressed the AD subtype in the parents. Asthma and rhinitis can be divided into allergic and nonallergic subtypes,²⁵⁶

²⁵⁷ but while rhinitis was generally specified as being allergic, only three studies specified asthma as being allergic.^{21, 52,}

¹¹⁰ More detailed characterization and reporting of subtypes, both regarding atopic diseases in parents and AD in the offspring, could enhance the accuracy with which we are able to predict AD in the offspring.

While some of the included studies provided information on how parental history of atopic disease may affect the AD phenotype, such as severity, persistence and age of onset, we are unable to provide a comprehensive investigation of this due to the study design; Since this study required reference individuals without AD, studies limited to AD patients, that may provide data on this topic, were excluded. To elucidate if parental history of atopic disease increases AD severity, persistence and recurrence or relates to age of onset, IgE levels and atopic multimorbidity, a similar meta-analysis should be performed comparing AD patients with these different subtypes.

Conclusion

We identified robust associations between parental history of atopic disease and AD in the offspring. While genetic risk scores for AD have been developed, these are far from complete and not yet applicable in a clinical setting. Our findings are useful for future parents and the physicians who guide them when assessing risk of having a child with AD and should serve to improve targeting of future prophylactic strategies to reduce the occurrence of AD, and possibly other atopic diseases by preventing the initiation of an atopic march.

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TABLE I. Odds of developing atopic dermatitis (AD) according to parental history of atopic disease. * p<0.05

**p<00001

Parental history	Studies included in analysis	AD patients /Reference individuals	Pooled odds ratio (95% confidence interval)	Cochrane Q	I ² (95% confidence interval)
Parental history of atopic disease	66 ^{21, 32, 36-42, 44, 47, 67, 68, 72-82, 84-91, 94, 99, 101, 103, 104, 106, 108-113, 115-119, 121-127, 129, 131, 145-151, 154}	38,505/ 203,146	1.81 (1.65-1.99)**	P < 0.0001	89.9% (88.2-91.3)
Parental history of AD	14 ^{36, 37, 39, 47, 60, 95, 97-103, 140}	9,095/ 61,736	3.30 (2.46-4.42)**	P < 0.0001	92.1% (89.0-94.0)
Parental history of asthma	7 ^{36, 60, 76, 96-99}	6,604/ 49,179	1.56 (1.18-2.05)**	P < 0.0001	79.6% (50.6-88.5)
Parental history of allergic rhinitis	6 ^{60, 96-100}	7,365/ 47,100	1.68 (1.34-2.11)**	P < 0.0001	85.0% (65.4-91.3)
Maternal history of atopic disease	60 ^{22, 24, 32-35, 38, 40, 42, 45-47, 49-52, 57, 69, 71, 75, 76, 81-84, 86, 87, 93, 102, 104, 105, 107-110, 112-114, 116, 120-123, 126-128, 130, 132, 133, 135, 141, 143, 144, 148, 150, 152-155}	32,714/ 169,280	1.89 (1.73-2.08)**	P < 0.0001	83.1% (79.0-86.0)
Paternal history of atopic disease	41 ^{22, 24, 32-35, 38, 42, 45-47, 49-52, 57, 69, 71, 73, 76, 81, 83, 102, 107, 108, 114, 120, 130-135, 141, 143, 144, 148, 150, 152, 153, 155}	17,248/ 96,296	1.99 (1.73-2.29)**	P < 0.0001	83.3% (78.3-86.7)
Maternal history of AD	43 ^{21-34, 37, 38, 40, 47, 49, 52-56, 58, 69, 70, 92, 102, 105, 112, 113, 135-143, 154, 156}	23,176/ 135,731	2.40 (2.10-2.75)**	P < 0.0001	84.7% (80.4-87.6)
Paternal history of AD	36 ^{21-34, 37, 38, 40, 47, 49, 52-56, 58, 69, 102, 135-143}	20,726/ 130,348	2.46 (2.01-3.00)**	P < 0.0001	89.1% (86.2-91.0)
Maternal history of asthma	30 ^{21-25, 27-29, 31, 32, 38, 40, 52-57, 66, 70, 86, 92, 123, 127, 137-142}	14,473/ 78,147	1.59 (1.43-1.78)**	P = 0.0083	42.4% (1.5-61.9)
Paternal history of asthma	24 ^{21-25, 27-29, 31, 32, 38, 40, 52-56, 66, 137-142}	11,802/ 69,500	1.65 (1.39-1.96)**	P < 0.0001	66.1% (44.1-76.9)
Maternal history of allergic rhinitis	22 ^{21-25, 28, 29, 31, 32, 38, 40, 52-56, 66, 70, 137, 138, 140, 141}	12,599/ 72,126	1.45 (1.34-1.60)**	P = 0.0067	48.0% (2.8-67.3)
Paternal history of allergic rhinitis	21 ^{21-25, 28, 29, 31, 32, 38, 40, 52-56, 66, 137, 138, 140, 141}	11,171/ 67,445	1.44 (1.28-1.62)**	P < 0.0001	68.4% (46.5-78.8)
Maternal history of allergic respiratory disease	7 ^{26, 30, 37, 58, 75, 109, 136}	8,284/ 61,942	1.60 (1.28-1.99)**	P < 0.0001	83.2% (62.9-90.1)
Paternal history of allergic respiratory disease	5 ^{26, 30, 37, 58, 136}	2,688/ 24,389	1.59 (1.30-1.95)**	P = 0.0805	51.9% (0-80.4)
Maternal atopic sensitization	8 ^{30, 58, 82, 92, 104, 130, 139, 150}	1,317/ 4,210	1.65 (1.40-1.96)**	P = 0.2912	17.6% (0-63.5%)
Paternal atopic sensitization	4 ^{30, 58, 130, 139}	646/ 2,361	1.26 (0.81-1.98)	P = 0.0129	72.2% (0-88.1)
One parent history of atopic disease	16 ^{32, 38, 40-42, 44, 72, 76, 78, 79, 89, 108, 115, 145, 148, 151}	8,445/ 55,984	1.30 (1.15-1.47)**	P < 0.0001	78.2% (63.3-85.3)
Both parents history of atopic disease	16 ^{21, 32, 38, 40-42, 44, 76, 78, 79, 89, 108, 115, 145, 148, 151}	10,369/ 67,949	2.08 (1.82-2.36)**	P = 0.0001	65.9% (35-78.6)

One parent history of AD	4 ^{37, 38, 41, 72}	5,048/ 17,942	1.81 (1.17-2.81)*	P < 0.0001	96.5% (94.3-97.6)
Both parents history of AD	4 ^{21, 37, 38, 41}	6,972/ 29,907	3.66 (2.08-6.44)**	P < 0.0001	88.0% (66.6-93.6)
Parental history of one atopic disease	4 ^{36, 37, 42, 121}	6,344/ 13,708	1.49 (1.27-1.74)**	P = 0.0602	59.5% (0- 84.4)
Parental history of more than one atopic disease	4 ^{36, 37, 42, 121}	6,344/ 13,708	2.32 (1.92-2.81)**	P = 0.1177	49.% (0- 81.6)

TABLE II. Odds of developing atopic dermatitis (AD) according to parental history of atopic disease stratified by study quality, design, size and geographic area. * p<0.05 **p<0.0001

Parental history of atopic disease	Studies included in analysis	AD patients/ Reference individuals	Pooled odds ratio (95% confidence interval)	Cochrane Q	I ² (95% confidence interval)
Studies with high quality (evaluated by Newcastle-Ottawa scale)	57 ^{21, 32, 36-38, 41, 42, 47, 74-79, 81, 82, 84-91, 94, 99, 101, 103, 104, 106, 108, 109, 111-113, 115, 116, 118, 119, 121-127, 129, 131, 145-151, 154}	34,635/ 170,124	1.81 (1.64-2.01)**	P < 0.0001	90.3% (88.5-91.6)
Cohort studies	34 ^{32, 36-38, 72, 74-76, 78, 79, 82, 84-86, 88, 94, 103, 104, 106, 109, 111-113, 115, 116, 118, 121, 123, 126, 127, 145, 150, 151, 154}	22,195/ 91,632	1.57 (1.40-1.76)**	P < 0.0001	86.5% (82.4-89.2)
Case-control studies	4 ^{87, 90, 122, 131}	503/ 1,418	3.11 (1.17-8.24)*	P = 0.0012	81.2% (25.9-91.0)
Cross-sectional studies	27 ^{21, 39-42, 44, 47, 67, 68, 73, 77, 80, 81, 89, 91, 99, 101, 108, 117, 119, 124, 125, 129, 146-149}	15,787/ 109,984	2.12 (1.83-2.46)**	P < 0.0001	91.5% (89.2-93.0)
Studies with > 3000 participants	20 ^{21, 37, 38, 40, 41, 67, 68, 77, 79, 94, 99, 101, 108, 109, 119, 121, 129, 146, 147, 149}	30,120/ 168,059	1.93 (1.68-2.22)**	P < 0.0001	95.5% (94.6-96.3)
Studies with < 3000 participants	46 ^{32, 36, 39, 42, 44, 47, 72-76, 78, 80-82, 84-91, 103, 104, 106, 110-113, 115-118, 122-127, 131, 145, 148, 150, 151, 154}	8,385/ 35,087	1.76 (1.53-2.02)**	P < 0.0001	79.4% (73.0-83.7)
America	9 ^{39, 47, 73, 75, 87, 116, 119, 123, 127}	1,573/ 9,561	2.21 (1.70-2.87)**	P = 0.0395	50.6% (0- 75.2%)
Asia	30 ^{40-42, 68, 77, 81, 88-91, 99, 104, 106, 108, 110-113, 115, 117, 118, 122, 124-126, 131, 146-149}	12,596/ 76,695	1.81 (1.57-2.08)**	P < 0.0001	85.3% (80.2-88.5)
Australia	3 ^{32, 36, 85}	495/ 2,036	2.38 (1.49-3.82)*	P = 0.0922	58.1% (0-86.3)
Europe	24 ^{21, 37, 38, 44, 67, 72, 74, 76, 78-80, 82, 84, 86, 94, 101, 103, 109, 121, 129, 145, 150, 151, 154}	23,841/ 114,854	1.69 (1.46-1.95)**	P < 0.0001	94.0% (92.6-95.0)

Figure Legends

FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow-diagram

FIG 2. Forrest plot of the pooled odds ratios (OR) and 95% confidence intervals (95% CI) for the association between parental history of atopic disease and development of atopic dermatitis (AD) in offspring.

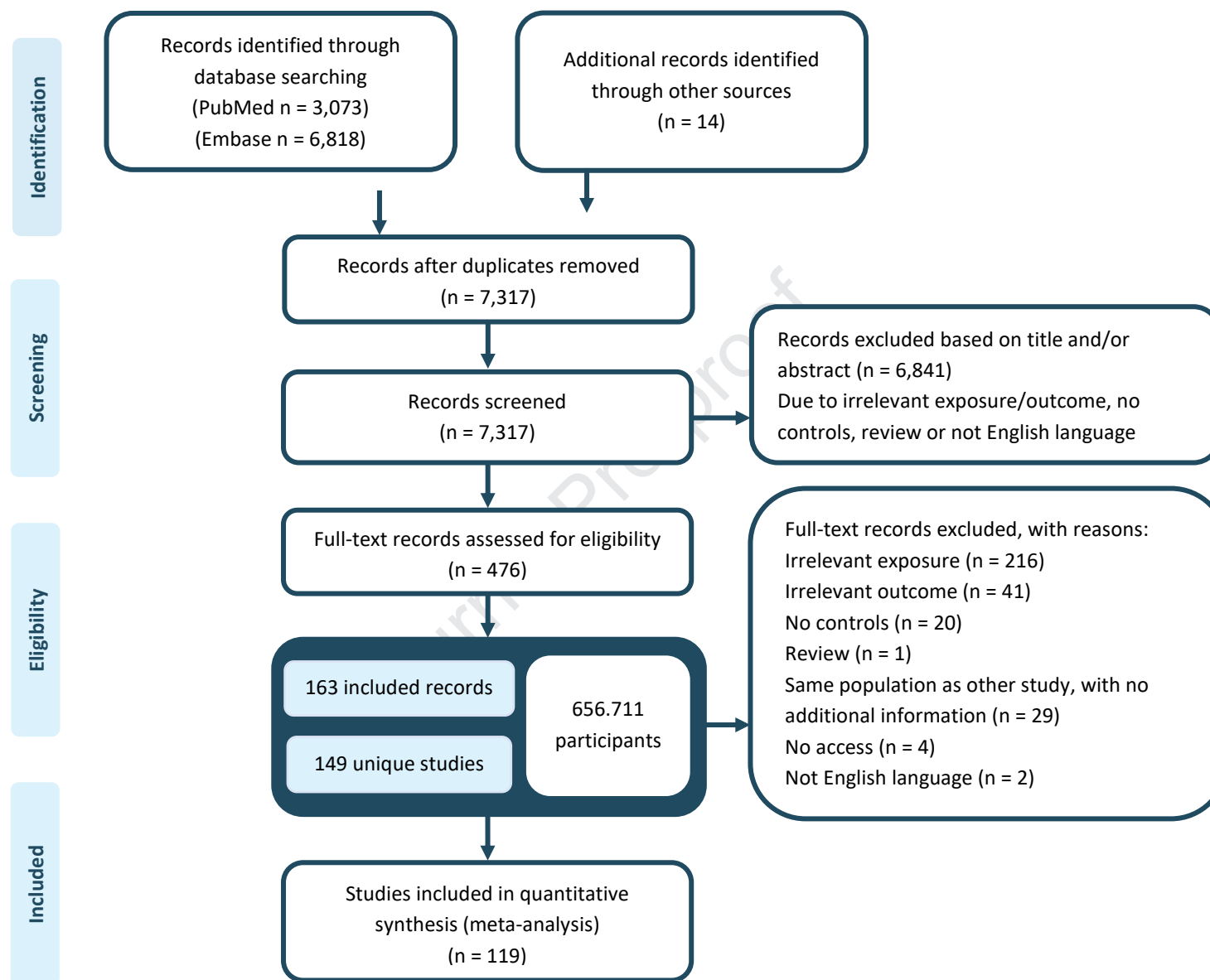


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