

Is the atopic march related to confounding by genetics and early-life environment? A systematic review of sibship and twin data

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Abstract

A popular hypothesis known as the *atopic march* proposes a set of sequential allergy and respiratory disorders in early childhood contributes enormously to the burden of disease in developed countries. Although the concept of the atopic march has been refined and strengthened by many cross-sectional and longitudinal studies linking eczema as the initial manifestation with progression to hay fever and then asthma, there is yet no definitive proof that the atopic march is the primary causal factor in childhood allergic disease. This debate is mainly related to the controversy around potential confounding of these associations by genetic and environmental factors. Family studies are ideally suited to unravelling the role of these factors. While multiple reviews have synthesized evidence from studies investigating this question, no review to date has explored specific evidence generated by twin and sibling studies to understand the aetiology of atopic march diseases. Our aim was to conduct a systematic review of twin and sibling studies that examine the allergic phenotypes that form the atopic march, to determine whether such analyses of data from these studies attempt to control for the effect confounding by shared factors, and to report estimates of the magnitude of associations between multiple phenotypes. Our review suggests that (1) genetics play a bigger role predisposing eczema to hay fever and eczema to asthma than environmental factors, and (2) the link between eczema and asthma and hay fever is independent of shared early-life environmental factors.

KEYWORDS

asthma, atopic march, eczema, hay fever, twin study

1 | INTRODUCTION

Atopy is an inherited tendency to develop hypersensitivity towards environmental allergens. It has multiple symptoms that are typically manifested through one or more of a series of conditions as eczema (atopic dermatitis), food allergy, asthma and hay fever (allergic rhinitis). These conditions have been observed in multiple studies to comanifest or occur in sequence. The hypothesis that has been proposed to explain these longitudinal associations has been coined the *atopic march*.¹ This concept asserts that allergic diseases start in early

life with eczema, progress through food allergy and culminates with hay fever and asthma.² The concept of the atopic march has been refined and strengthened by many cross-sectional and longitudinal studies.³⁻¹⁴ To understand the dynamics of these diseases clearly, many studies have attempted to characterize co-occurrence by calculating correlations through mainly cross-sectional and a few longitudinal studies.^{6,15-21} These studies have shown that there is a temporal relationship between these conditions included in the allergic march, but whether these relationships are confounded by genetic and environmental factors shared by these phenotypes is still controversial.

Family studies are the ideal epidemiological design to examine whether phenotypic associations are confounded by genetic factors and early-life shared environment. Data from cross-sectional studies can be used to determine whether the strength of phenotypic associations varies with the degree of relatedness. Analysis of longitudinal data can help address questions of how associations change over time.

One type of family study, the sib-pair analysis and in particular twin studies employ the degree of sharing of genetic and environmental factors among siblings. In twin studies, there are two types of twin pair: monozygotic (MZ) twins, who share a common set of genetic material, and dizygotic (DZ) twins, who share on average only 50% of their segregating genes²² in addition to similar aspects of their early environment. Twins can be considered as individually matched for which within-pair or within-sibship comparisons can be used to estimate the magnitude of exposure-outcome association free from confounding by shared factors that may occur with comparisons between unrelated individuals or across twin pairs. If there is an overlap of genes for two traits it is expected that the cross-twin cross-trait correlation in MZ twins will be higher than in DZ twins for these traits but that the within-twin phenotypic correlation due to common environment will be the same for MZ and DZ twins. This is the *Classical Twin Model*. Such analyses allow us to disentangle the genetic and environmental contributions to the aetiology of the disease or trait under study and to partition the population-level variation of traits and diseases into shared genetic, shared environmental and individual components.

Much of the published research based on the classical twin model use univariate analyses based on twin concordance and within-pair correlations to estimate the degree to which genetic and environmental factors influence disease occurrence²³⁻³¹ and to partition the phenotypic variation into genetic and environmental components.^{22,24,27,28,32-35} There are examples of multivariate analyses that study more than one phenotype to explore the comorbidity of two or more traits such as eczema, asthma and hay fever.^{22,27,28} Cotwin case-control studies are also used to study, for example, gene expression in discordant twins.^{26,36} Extending twin studies to include other relatives such as parents and siblings of twins have been used to study the shared prenatal environment, genetic and environmental interactions and imprinting (an epigenetic phenomenon resulting in parent-of-origin-specific gene expression) where data from offspring of MZ twins were also available.²²

Many studies have focused on univariate analysis reporting prevalence, incidence, heritability of asthma phenotypes, concordance rate and intraclass correlations between asthma and its phenotypes. Only a few reviews have synthesized the evidence on associations between asthma phenotypes; no systematic review to date has focused on twin and sibling studies for the atopic march at the same time. The aim of our review is to (1) identify family studies and specifically twin and sibling studies that investigated the association between two or more phenotypes of the atopic march from infantile eczema to hay fever and asthma among twins and sibling data, and (2) synthesize the evidence from studies that adjust for known, measured environmental and genetic influences

when estimating the magnitude of associations between multiple phenotypes.

2 | MATERIALS AND METHODS

2.1 | Sources of data and search strategy

An extensive series of searches for publications was conducted using three databases: Medline, PubMed (both from 1950 to March 2016) and Scopus. Two groups of keyword with either Medical Subject heading (*MeSH) terms or All Fields were created using "OR" within the group and using "AND" to combine the two groups in Medline and PubMed: (1) Terms identifying Atopic March: "asthma" or "wheeze" or "hay fever" or "allerg* march" or "atopic march" or "atopic eczema" or "atopic dermatitis" or "eczema" or "allergic rhinitis" or "rhinitis" or "food allergy" or "respiratory diseases" or "skin prick test" or "IgE", and (2) Terms identifying target Population: "sibpair" or "sibpair*" or "sibling" or "sibling relations" or "siblings" or "sib*" or "twin*" or "twin pair" or "twins" or "sister*" or "brother*." The similar types of keywords were used to search relevant articles in Scopus: (1) Terms identifying Atopic March: "asthma" or "wheeze" or "hay fever" or "allerg* march" or "atopic march" or "atopic eczema" or "atopic dermatitis" or "eczema" or "allergic rhinitis" or "rhinitis" or "food allergy" or "respiratory diseases" or "skin prick test" or "IgE", and (2) Terms identifying target Population: "sibpair" or "sibling" or "sibling relations" or "siblings" or "twin pair" or "twins" "sister*" or "brother*."

2.2 | Definitions

2.2.1 | Asthma

As asthma is defined as a respiratory disease which causes inflammation of airways making breathing difficult and trigger coughing, wheezing and shortness of breath. Studies presented parent-report or doctor-diagnosed or at least four episodes of asthma symptoms during the last 12 months were considered to have asthma.

2.2.2 | Eczema

Typically eczema or atopic dermatitis is defined as a chronic or recurrent inflammatory skin disease in which patches of skin become rough and inflamed with blisters which cause itching and bleeding. "Atopic Dermatitis" and "eczema" are considered interchangeable and to thus represent the same disease. Studies reported results on either terminology were included.

2.2.3 | Hay fever

Hay fever or allergic rhinitis is defined as an inflammation of the nasal mucous membranes characterized by one or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea. Allergic rhinitis and "hay fever" are considered interchangeable and to thus

represent the same disease. A diagnosis of hay fever was indicated if the person was diagnosed by a physician or parent-report for children or self-reported in a questionnaire.

2.3 | Inclusion criteria

Original peer-reviewed articles were included which examined associations between allergic outcomes using familial data focusing on siblings and twins. As the atopic march is a progression of atopic diseases measuring characteristics such as serum IgE and skin prick test, studies reporting any of the phenotypes either as outcome or as exposure were considered for inclusion in our review. Articles were retained if they have reported any of the atopic march diseases as either an exposure or an outcome, and the study sample consisted of twin pairs or siblings or both.

2.4 | Exclusion criteria

Studies were excluded if (1) they did not report any association between the selected diseases, (2) did not report either exposures or outcomes for human participants, and (3) were not published in English and no English translation was available.

2.5 | Selection of articles

A flow chart of the articles selection process is shown in Figure 1. The authors extensively reviewed all titles and abstracts for inclusion

based on the inclusion criteria. Full-text articles were then further assessed for final selection.

2.6 | Search results

A total of 1647 articles were identified using relevant keywords from different electronic databases. Of these 1520 studies were identified as unique after removing duplicates. After reading titles and abstracts, 1354 studies were eliminated as not being relevant to the research question, most frequently because they considered only (1) singletons, (2) univariate statistical analyses, or (3) birth order of siblings as the exposure. A further 152 articles of the remaining 166 were excluded after applying inclusion criteria leaving 14 articles for full-text reading. Only 10 studies (8 cohort, 1 cross-sectional and 1 case-control) reported associations among asthma phenotypes among twin and sibship data. The remaining four studies were review papers³⁷⁻⁴⁰ and were thus excluded from further consideration. These articles were assessed using PRISMA reporting guidelines. Details of the study selection process are illustrated in Figure 1 and are presented in Tables 1-4.

2.7 | Data extraction

Study characteristics were extracted from all eligible articles including study design, settings, source of participants and their eligibility criteria and outcome definitions, methods of statistical analysis, including adjustment for confounding were assessed.

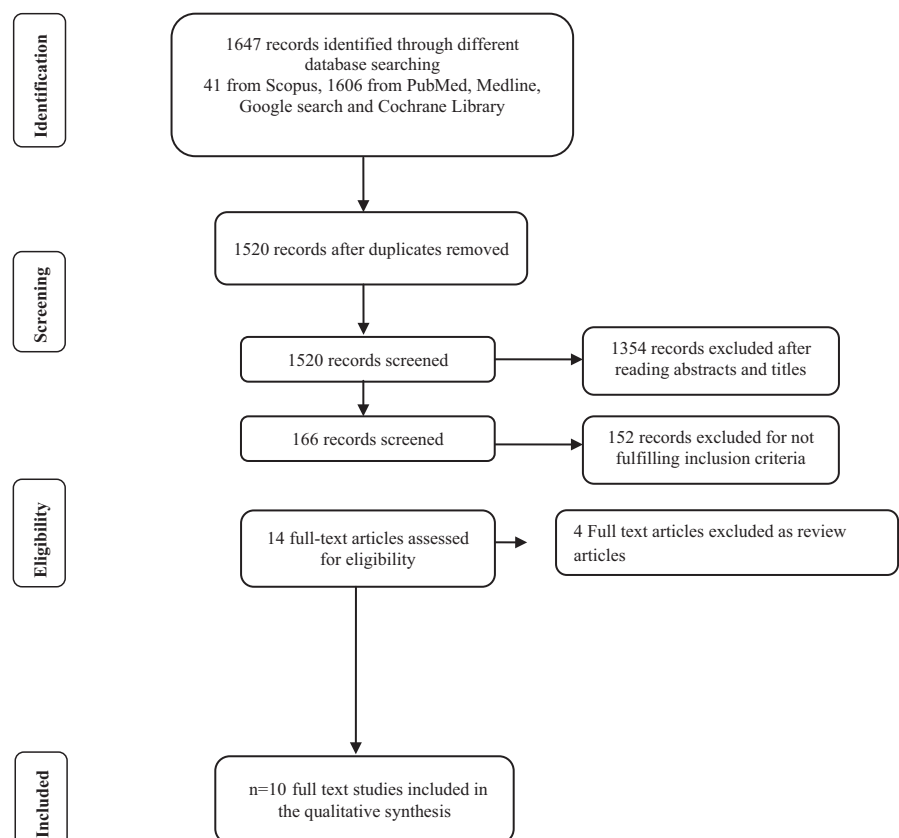


FIGURE 1 Summary of literature search and manuscript inclusion/exclusion

TABLE 1 Studies focusing eczema (atopic dermatitis), hay fever (allergic rhinitis) and asthma among twins and siblings

Twin studies						
Study	Design	Country	Sample	Age	Exposure	Outcome
1 Hopper et al. (1990) ²⁶	Cohort study (1980, 1988 and 1990)	Australia	3808 twin pair 1232 MZF 567 MZM 751 DZF 352 DZM 906 DZ opposite-sex	>18 y	Age Sex Zygosity General health Personality Physical symptoms	Asthma or wheezing or Hay fever
2 Duffy et al. (1990) ²⁶	Cohort study (1980, 1988 and 1990)	Australia	3808 twin pair 1232 MZF 567 MZM 751 DZF 352 DZM 906 DZ opposite-sex	>18 y	Age Smoking order of birth Additive and nonadditive genetic effects (G), Shared or common environment effects (C) and Nonshared environmental (E) effects	Hay fever Asthma Wheeze
3 Lichtenstein et al. (1997) ²⁸	Cohort study	Sweden	1480 twin pairs	7-9 y	Genetic effects (G), Shared or common environment effects (C) and Nonshared environmental (E) effects	Asthma Hay fever Eczema Urticarial Food allergies
4 Huovinen et al. (1999) ²⁴	Cohort study (longitudinal, 1975, 1981 and 1990)	Finland	11540	18-45 y	Hay fever Chronic bronchitis	Asthma
5 Clark et al. (2000) ⁴³	Cohort study	Australia	183 MZ 198 DZ	8-18 y		Asthma Atopy BHR

(Continues)

TABLE 1 (Continued)

Twin studies						
Study	Design	Country	Sample	Age	Exposure	Outcome
6 Nystad et al. (2005) ²³	Prospective cohort study (longitudinal, 1992 and 1998)	Norway	3334 pairs	Baseline: 18-25 y Endline: 24-31 y	Additive genetic effects (A), Dominant genetic factors (D), Shared or common environment effects (C) and Nonshared environmental (E) factors	Asthma or wheeze Eczema or itch Hay fever or sneezing
7 Thomsen et al. (2006) ³⁴	Prospective case-control study (cotwin control)	Denmark	126 MZ and 273 DZ discordant pairs	Baseline: 12-41 y Endline: 18-49 y	Binary variable: Hay fever Sex Eczema Smoking Leisure time physical activity Educational level Continuous: Body mass index (BMI)	Asthma (Do you have, or have you ever had asthma? Individuals who were initially unaffected in 1994 and who responded affirmatively to that question in 2002 were classified as incident)
8 Beijsterveldt et al. (2006) ³¹	Cohort study (prospective)	Netherlands	1349 MZM 1461 DZM 1592 MZF 1387 DZF and 2844 opposite-sex	5 y	Additive genetic effects (A) Dominant genetic factors (D) Shared or common environment effects (C) and Nonshared environmental (E) factors	Asthma Eczema Hay fever or rhinitis
9 Fagnani et al. (2007) ²⁷	Cohort study	Italy	392 pair 141 MZ (74 MZM, 67 MZF) 251 DZ (53 DZM, 79 DZF) 119 opposite-sex pairs	8-17 y	Lorry traffic in the living area Parental smoking, etc. Respiratory infections during the first 2 years of life Perinatal factors (premature birth, type of feeding in infancy, etc.) Family history of atopic syndromes in first-degree relatives Socioeconomic status	Ever suffered asthma (doctor-diagnosed) Ever suffered hay fever
10 Hopper et al. (2012) ³³	Cross-sectional study	Tasmania, Australia	3778 pairs	7±2 y	Infantile (baby) eczema <age 12 months Confounder: Parental hay fever and/or asthma	Hay fever and asthma <age 7 y Asthma only <age 7 y Hay fever only <age 7 y

TABLE 2 Studies examining the association between eczema and asthma among twins and siblings

Study/Design	Sample	Age (y)	Definition	Analytic method	Genetic/Environmental correlation between diseases			Measures of association	Proportion of correlation due to Genetic factor
					Genetic, r_g	Nonshared environmental, r_e			
1 Lichtenstein et al. (1997)/Cohort study	1480 twin pairs	7-9	Parent-report	Structural equation modelling (SEM)	0.35 (0.23-0.48)	0.25 (0.00-0.68)		Phenotypic correlation 0.30	85%
2 Thomsen et al. (2006)/Longitudinal prospective case-control study (cotwin control)	399 twin pairs 126 MZ discordant pairs 273 DZ discordant pairs	Baseline: 12-41	Self-report	Conditional logistic	—	—		Phenotypic correlation 0.40 OR: 0.95 (0.26-3.49) MZ OR: 1.96 (1.02-3.78) DZ	81%
3 Beijsterveldt et al. (2006)/Cohort study (prospective)	8633 twin pairs 1349 MZM 1461 DZM 1592 MZF 1387 DZF 2844 opposite-sex	5	Parent-report Doctor-diagnosed	Structural equation modelling (SEM)	0.55	0.18		Phenotypic correlation 0.55	82%
4 Hopper et al. (2012)/Cross-sectional study	3778 sib pairs	7±2	Parent-report	Logistic Regression approach	—	—		OR: 2.39 (1.96-2.92)	—

TABLE 3 Studies examining the association between eczema and hay fever among twins and sibling

Study/Design	Sample	Age (y)	Definition	Analytic method	Genetic/Environmental correlation between diseases			Measures of association	Proportion of correlation due to Genetic factor
					Genetic, r_g	Nonshared environmental, r_e			
1 Lichtenstein et al. (1997)/Cohort study	1480 twin pairs	7-9	Parent-report	Structural equation modelling (SEM)	0.73 (0.46-1.00)	0.25 (0.00-0.68)		Phenotypic correlation 0.49	96%
2 Beijsterveldt et al. (2006)/Cohort study (prospective)	8633 twin pairs 1349 MZM 1461 DZM 1592 MZF 1387 DZF 2844 opposite-sex	5	Parent-report Doctor-diagnosed	Structural equation modelling (SEM)	0.62	0.38		Phenotypic correlation 0.62	88%
3 Hopper et al. (2012)/Cross-sectional study	3778 sib pairs	7±2	Parent-report	Logistic regression approach	—	—		OR: 1.77 (1.31-2.40)	—

TABLE 4 Studies examining the association between hay fever and asthma among twins and siblings

Study/Design	Sample	Age (y)	Definition	Analytic method	Genetic/Environmental correlation between diseases			Proportion of correlation due to Genetic factor
					Genetic, r_g	Nonshared environmental, r_e	Measures of association	
1 Duffy et al. (1990)/Cohort Study	3808 twin pair 1232 MZF 567 MZM 751 DZF 352 DZM 906 DZ opposite-sex	>18	Self-report	Path analysis	0.65 (Female) 0.52 (Male)	0.33 (Female) 0.53 (Male)	Phenotypic correlation 0.59 (Male) 0.425 (Female)	74%
2 Lichtenstein et al. (1997)/Cohort study	1480 twin pairs	7-9	Parent-report	Structural equation modelling (SEM)	0.90(0.67-1.00)	0.00(0.00-0.42)	Phenotypic correlation 0.54	100%
3 Thomsen et al. (2006)/Longitudinal prospective case-control study (cotwin control)	399 twin pairs 126 MZ discordant pairs 273 DZ discordant pairs	Baseline: 12-41	Self-report	Conditional logistic	—	—	OR: 3.16 (1.29-7.73) MZ OR: 2.44 (1.44-4.13) DZ	
4 Beijsterveldt et al. (2006)/Cohort study (prospective)	8633 twin pairs 1349 MZM 1461 DZM 1592 MZF 1387 DZF 2844 opposite-sex	5	Parent-report Doctor-diagnosed	Structural equation modelling (SEM)	0.47	0.73	Phenotypic correlation 0.47	96%
5 Fagnani et al.(2007)/Cohort study	392 pair 141 MZ (74 MZM, 67 MZF) 251 DZ (53 DZM, 79 DZF) 119 opposite-sex pairs	8-17	Parent-report	Structural equation modelling (SEM)	0.58 (0.40-0.75)	—	Within-individual OR: 5.32 (3.13-9.06) Cotwin OR: 5.55 (1.47-20.94) MZ 3.55 (1.37-9.20) DZ	100%

3 | RESULTS

3.1 | Study characteristics

Tables 1-4 list the features of the included studies. All studies were conducted in developed countries. Of the included studies, four reported measures of association between eczema and asthma. The sample sizes range from 399 to 8633 twin pairs. The age of study participants ranged from 5 years to 49 years. Three of these studies reported measures of association between eczema and hay fever. The age distribution of participants in those studies was between 5 to 9 years and sample sizes ranged from 1480 to 8633 twin pairs. Five studies focused on finding association between hay fever and asthma. Four cohort studies were conducted on children aged 5-9 years, one cross-sectional study included 7-year-old children and one longitudinal study comprised of adults of 12-41 years and 18-49 years of age with samples of 399-8633 twin pairs and 3778 sib pairs. No twin/sib study was found reporting association between eczema and food allergy.

3.2 | Relationship between atopic diseases

3.2.1 | Contribution of twin and sib studies to the association of asthma with specific comorbidities

The primary goal of most genetic research published in papers included in our systematic review was to find associations of asthma with phenotypes such as Total IgE, with less focus given to the presence or absence of concomitant allergic diseases such as hay fever and eczema.⁴¹ Because asthma, hay fever, and eczema share common systemic characteristics, it is reasonable to propose that a number of susceptibility genes could contribute to the allergic process regardless of the specific clinical phenotype. Early research from twin studies often used models of average within-family correlations based on gene-sharing arguments to dissect the genetic architecture of complex traits like atopic diseases as well as the contribution of environmental effects on the pathogenesis of asthma. All such studies reporting multiple phenotypes of asthma that concentrated on finding association whether genetic or phenotypic are listed in Table 1.

Two Australian studies^{26,42} with 3808 pairs of twins targeted for the occurrence of either self-reported asthma and/or hay fever were analysed using structural equation models and path analysis for evidence of genetic transmission. The prevalence of comorbidity of asthma and hay fever was high (32%) indicating a possible genetic contribution. Disease occurrence was found to be significantly correlated among twins. Monozygotic (MZ) twins were more susceptible to disease occurrence compared to dizygotic (DZ) twins and male MZ twins were more vulnerable than the female MZ twins. Environmental causes of both diseases also were correlated ($r=.53$ for men and $r=.33$ for women).

Another Australian study⁴³ aimed to measure the associations of physician-diagnosed asthma, bronchial hyper-responsiveness (BHR) and atopy within MZ and DZ twin pairs, aged 8-18 years. Comparing

MZ pairs with DZ pairs, the associations between twins, measured by an odds ratio, were found to be greater in MZ pairs for asthma: 25.6 (95% CI 11.3-57.8) versus 1.9 (1.0-3.5); for atopy: 14.6 (7.1-30.1) versus 2.5 (1.4-4.5); and for BHR: 14.1 (6.4-31.0) versus 4.2 (2.1-8.6) (all $P<.002$). They analysed the physician-diagnosed asthma, BHR and atopy to assess the evidence for genetic factors influencing the aetiology of each of these conditions. This study suggested the strong cross-sectional associations between these two traits are due to common genetic factors.

One Swedish study from 1997²⁸ aimed to identify and confirm the importance of genetic and environmental factors in asthma, hay fever, eczema and urticaria targeting 7- to 9-year-old children. Their results for each pair of phenotypes are presented below.

In 1999, a Finnish study²⁴ with twin pairs 18-45 years old reported the prevalence of asthma to be increased slightly from 2.0% to 2.9% in men and from 2.2% to 3.1% in women over the 15 years of the study. The prevalence of hay fever showed much larger increases in both men and women (from 6.8% and 9.8% to 11.8% and 15.3%, respectively). Hay fever and chronic bronchitis were usually diagnosed before asthma. Both diseases increased the risk of asthma significantly on the basis of analyses of all individuals in the study and also among outcome-discordant twin pairs.²⁴

A Norwegian study²³ focused on how common sets of genes and environmental factors contribute to the relationship between diseases and symptoms. The phenotypic correlation between disease and symptom was found to be $r=.54$ for eczema and itch. Decomposition of these correlations into genetic (G) and environmental (E) pathways revealed that $r_G=.34$ and $r_E=.20$ for eczema and itch. For each of the diseases, the specific sources of genetic variance accounted for more variation than the specific environmental variance.

The Danish cotwin study by Thomsen et al.⁴⁴ found that the odds ratio for the association between asthma and hay fever in MZ twins was 3.16 (95% CI: 1.29-7.73, $P=.008$) whereas in DZ twins it was 2.44 (95% CI: 1.44-4.13, $P=.001$). This cotwin analysis also generated an odds ratio of 1.96 (95% CI: 1.02-3.78) for eczema, which was a significant predictor of asthma.

An Italian study²⁷ of twin pairs aged 8-17 aimed to find association between asthma and hay fever. Analysis suggested that genetic factors account for 92% and 78% of the variance in the underlying liability of asthma and hay fever, respectively, with the remaining contributions due to environmental influences. The genetic correlation between the two conditions was $r=.58$. This study reported a within-individual/cross-trait odds ratio of 5.32 (95% CI: 3.13-9.06), clearly indicating a substantial co-occurrence of the two conditions.

In 2012, Hopper et al.³³ aimed to assess the evidence for a causal effect of infantile eczema on childhood hay fever, asthma, or both. Their results for each pair of phenotypes are presented below.

3.2.2 | Association between eczema and asthma

Only 4 studies (Table 2) have examined the association between asthma and eczema, most of the results of which were included in a

recent review paper by Elmoose and Thomsen³⁷ The first study was conducted in Sweden by Lichtenstein and Svartengen which reported a phenotypic correlation between eczema and asthma of 0.30. They also reported correlation between genetic and environmental factors and proportion of correlation due to genetic and environmental factors for two atopic diseases. The contribution of genetic and nonshared environmental factors to the proportion of correlation was reported to be 85% and 15%, respectively, with no evidence of shared environmental effects for asthma was detected.

Another twin study by Thomsen et al. found a phenotypic correlation between eczema and asthma as $r=.40$, with 81% of the proportion of phenotypic overlap between eczema and asthma was due to genetic pleiotropy (same phenotype influenced by multiple variants in different genes), the remaining 19% being due to environmental factors. Also, atopic diseases were significantly associated within the same individual with an odds ratio of developing asthma if one had eczema of almost five, and also the risk of developing any atopic disease was dramatically increased in a subject if the subject's twin brother or sister was affected, either by the same disease or by another. The effect was more pronounced in MZ twins compared with DZ twins, consistent with the assertion that asthma and eczema are genetically related.

Van Beijsterveldt and Boomsma conducted a twin study in Norway reported a correlation between eczema and asthma of $r=.55$ with the contribution of genetic and environmental factors to the proportion of correlation was reported to be 82% and 18%, respectively.

Focusing only on the association between infantile eczema and asthma in childhood, Hopper et al. found a modest association between eczema in infancy and asthma. Their findings included no significant associations with sibling with infantile eczema and only a very small proportion of cases were explained by parental asthma. The familial component of the above associations could be genetic, shared environmental, or both in origin, but unlike previous reports they did not explore the contribution of genetic and environmental factors to the proportion of correlation.

3.2.3 | Association between eczema and hay fever

Only two twin studies and one sib study presented in Table 3 found associations between eczema and hay fever. Lichtenstein and Svartengen reported a phenotypic correlation between eczema and hay fever as 0.49. Also the contribution to the proportion of correlation was solely due to genetic and nonshared environmental factors of 96% and 4%, respectively.

Van Beijsterveldt and Boomsma reported a phenotypic correlation between eczema and hay fever of $r=.62$ and the contribution of genetic and environmental factors to the proportion of correlation were reported to be 88% and 12%, respectively. The genetic correlations differ in the above two studies and the phenotypic correlations were found to be mainly genetically mediated.

Hopper et al. suggested the existence of association between eczema in infancy and hay fever only in childhood because of the

existence of familial factors predisposing to both outcomes. A proportion of the familial association between these two childhood conditions (24%-25%) was explained by parental hay fever.

3.2.4 | Association between asthma and hay fever

Five twin studies explored the association between asthma and hay fever (Table 4). The Australian study²⁶ found genetic factors play a common role in the occurrence of asthma and hay fever, with a correlation in genetic liability between the traits of .52 for men and .65 for women and phenotypic correlation of .59 for men and .425 for women. The study could not detect the role for an effect of shared environment in explaining the correlation between diseases within a twin pair. The apparent "sameness" of twins appeared to be more genetic in origin compared to the simultaneous exposure to different environmental entities.

The Swedish study of Lichtenstein and Svartengen found a phenotypic correlation between asthma and hay fever as $r=.54$. For the association between asthma and hay fever, the genetic correlation is $r=.90$ and the association is completely (100%) due to genetic effects. The claim about existing knowledge that hay fever significantly predicts the development of asthma was supported by Thomsen et al. They found the underlying genetic and environmental shared factors by both MZ and DZ twins are associated with asthma and hay fever and that these factors could potentially influence the occurrence independently.

Van Beijsterveldt and Boomsma reported a phenotypic correlation between asthma and hay fever of 0.47. The extent to which the same environmental factors overlap in the determination of asthma and hay fever was estimated to be 0.73. The contribution of genetic and environmental factors to this phenotypic correlation between asthma and hay fever reported to be 96% and 4%, respectively.

Fagnani et al. found no shared environmental factors influencing the comorbidity of asthma and hay fever, implying the phenotypic correlation between the two diseases was entirely genetically mediated. The genetic correlation was estimated to be .58, suggesting that asthma and hay fever share many of the same genetic influences.

4 | DISCUSSION

This is the first systematic review of twin and sibship studies of the atopic march. Our review suggests that genetics play an important role predisposing those with eczema to hay fever and to asthma. In comparison, the contribution of shared environmental factors to the atopic march was found to be relatively small.

Asthma is linked to hay fever and eczema through intermediate phenotypes like clinical measures of lung function, physiological measures of airway responsiveness and the biomarker exhaled nitric oxide all of which are influenced by hereditary factors. A few reviews on twin studies with eczema, asthma genetics and intermediate phenotypes showed the presence of hereditary influences in

the pathogenesis of asthma.³⁷⁻⁴⁰ Thus eczema, asthma and hay fever are highly heritable diseases with genetic factors accounting for 75% for eczema, 70%-91% for asthma and 72%-84% for hay fever with the remaining variance in underlying liabilities due to nongenetic factors. Some of the variation in these estimates for all three diseases is due to differences in target populations and study designs.

Researchers from various parts of the world have also studied the genetics of asthma and atopic diseases in twin populations. Their findings are limited to reporting the importance of some genetic effects on the risk of asthma, hay fever, eczema, bronchial hyper-responsiveness and some environmental effects. Los et al. found that additive genetic effects and individual-specific environmental factors both make large contributions to the variation in risk of asthma among twins. The studies included in our review have shown strong genetic pleiotropy, which might partially explain the association between eczema and asthma. The clustering of atopic diseases among family members suggests the existence of a common set of genes but each disease manifestation might also have important disease-specific genes. Many genetic linkages previously reported for asthma are now thought to reflect an overall predisposition for allergic disease.⁴¹ Asthma shares more genetic determinants with hay fever than eczema and most studies discover strong associations between atopic comorbidity identifying trait-specific responsible genes.³⁹ Twin studies of the association between asthma and eczema find that 85% of the variation is explained by genes³⁷ between eczema and hay fever about 85% and between asthma and hay fever 90% of the variation is explained by genes. Smaller studies presented genetic explanations for atopic comorbidity while larger studies focused on the role of trait-specific genes. As asthma and hay fever represent a range of diseases, those individuals with less severe disease can express hay fever without asthma and those individuals with more severe disease express more than 1 phenotype.^{41,45}

Our study found that the contribution of shared environmental factors to the proportion of correlation are very low (from 4% to 18%) and does not explain the familial patterns seen for asthma and hay fever. This finding contradicts various analyses where smoking behaviour, indoor-outdoor pollution, and house dust mites were found to be significant risk factor for asthma and hay fever that are shared by siblings.^{46,47} It reflects that there may exist a collection of genes that affect asthma and the intermediate phenotypes such a way that the individual might be more or less sensitive to a particular environment.^{40,48} Whether familial clustering of asthma and related phenotypes is due to genetic inheritance, environmental influences, gene-environment interaction or shared genetic and nongenetic factors is a puzzling question to which the analysis of data from twin and sibship studies has already provided some answers.

The concept of the atopic march focuses primarily on the relationship between asthma and other allergic diseases during childhood. Bergen et al.⁴⁹ found evidence of increased heritability throughout the adolescent and early adult period which can affect the proportions of genetic and environmental variability in atopic march sequence, resulting in environmental effects dominating to the total phenotypic variance. There is evidence that the comorbidity

is high for all three atopic diseases up to age 12.²⁵ This suggests that different phenotypic correlations will result if estimates are generated using data at different ages including, potentially, in adults. The literature search in this systematic review featured a wide range of different age spans between studies, and many seem to include only adult study subjects. More research on twins and siblings of different ages could potentially address the questions about age-varying phenotypic correlations.

If the atopic march was proven to be caused by putative genetic and environmental factors then preventing its onset and arresting its development would have significant public health implications. There are two possible interventions that can decrease the incidence of asthma and hay fever. Firstly, introducing an intervention before a child gets eczema, secondly, introducing an intervention to a child with eczema who has not yet developed asthma and/or hay fever. The risk of eczema for those with filaggrin defects is twice as great based on results from family studies and about five times as great in case-control studies.⁵⁰ On the basis of several longitudinal studies, approximately half of eczema patients will develop asthma, particularly with severe eczema, and two-thirds will develop hay fever.¹ Preliminary prevention studies with oral antihistamines provide evidence that early intervention might slow the atopic march.¹ The resulting dehydration of the skin can be protected through soaking baths, where the addition of rice starch to bath water was shown to improve barrier function in patients with eczema.⁵¹ More recently, two randomized control trials^{52,53} showed moisturizing the skin can prevent mild-to-moderate eczema and long term studies are needed to see whether such intervention will prevent development of asthma and hay fever. These are examples of interventions that resulted from identifying genetic risk factors for which interventions in the child's environment might slow down the severity of progression of eczema at its earliest onset and, ultimately, interrupt the atopic march.

Our systematic review and the original studies included within it have multiple strengths and limitations. The selection process of all the papers included in this systematic review was justified by meeting the AMSTAR criteria. Most of the original studies large registries and therefore included large sample size of twins and sib pair and had high statistical power to test their hypothesis. However, most used questionnaires to ascertain disease phenotypes while only few studies used clinical investigations. The studies that used questionnaires may suffer from nondifferential misclassification of disease resulting in an underestimation of the findings. Another limitation is that twins may not represent the general population as several factors can cause twins to deviate from the norm.³¹ Usually twins are prematurely born and preterm birth can increase the risk of damaging lungs which can easily lead to the increasing risk of the development of respiratory diseases; the Dutch study clearly showed the prevalence of asthma was more than the general population. On the other hand, there exist contradictory results showing that the prevalence rate of asthma decreases among twins than individuals and that growing up with a sib increases the chance of exposure to infections in early life which in turn protects against the development of allergic diseases.⁴⁷ We note also that the Swedish register-

based study by Ullemar et al.⁵⁴ showed that twinship is not an independent risk factor for asthma in childhood and that the higher prevalence of asthma among twins as compared to singletons could instead be attributed to premature birth and low birthweight. Another limitation of the original studies was that only a few studies have reported measure of associations such as relative risk or odds ratio. The availability of such measures could have been used to interpret the increased or decreased nature in risk among the diseases on the atopic march pathway.

In summary, current evidence of twin and sibship studies suggests that the link between eczema and asthma and hay fever is independent of shared early-life environmental factors suggesting that further causal risk factors remain to be discovered despite there being a clear sequential association and plausible biological mechanisms to explain such an association.

AUTHOR CONTRIBUTIONS

SJK and LCG performed the search for papers included in the systematic review separately, and then, SJK collated and analysed the data from the search and wrote a draft of the manuscript. LCG and SCD cosupervised the development of the work and helped in determining the search strategy and data interpretation. MCM worked with SJK to substantially revise the first draft of the manuscript. All authors contributing to the writing of the final draft of the manuscript and reviewed it for critically important content.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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