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Familial aggregation of allergen-specific sensitization and asthma

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Abstract

Familial aggregation of specific response to allergens and asthma adjusted for age and sensitization to multiple allergens was assessed in two large population cohorts. Allergen skin prick tests (SPTs) were administered to 1151 families in the Tucson Children's Respiratory Study (CRS) and 435 families in the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD). Sensitization was defined by wheal size ≥ 3 mm; physician-diagnosed asthma at age ≥ 8 years was based on questionnaires. Using S.A.G.E. 6.1 software ASSOC and FCOR, familial correlations of crude and adjusted phenotypes were evaluated. Crude estimates of parent-offspring (P-O) and sibling correlations were statistically significant for most allergens, ranging from 0.03 to 0.29. After adjusting for age of assessment and "other atopy" (SPT-positive response to additional allergens), correlations were reduced by 14–71%. Sibling correlations for specific response to allergens were consistently higher than P-O correlations, but this difference was significant only for dust mite and weed mix in the TESAOD population. Familial correlation for atopic status (any positive SPTs versus none) tended to be higher than for specific allergens. Asthma, with and without adjustment, showed greater familial correlation than either specific or general SPT response and significantly higher sibling correlation in TESAOD than in CRS, probably due to the older age of the siblings and the longer period of ascertainment. In conclusion, significant familial aggregation of specific response to allergen after adjustment for other atopy appears to reflect a genetic propensity toward atopy, dependent on shared familial exposures. Results also suggest that inheritance of asthma is independent of atopic sensitization.

Keywords

familial aggregation; specific response to allergens; atopy; asthma

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INTRODUCTION

Familial predisposition toward atopy—defined as a genetic propensity to develop IgE antibodies in response to exposure to common environmental allergens—and asthma has been clinically recognized for decades (1, 2). Evidence for familial aggregation of various atopic and asthmatic phenotypes has been widely reported in twin studies (3–5), studies of asthmatic and/or atopic families (6) and in a few general population studies (2, 7).

A large number of studies have reported associations between atopic and asthmatic phenotypes and gene variants involved in immune function or regulation (8), though most of these genetic variants are thought to confer risk only in combination (9) or under specific environmental conditions (10). These studies have not resolved whether expression of subphenotypes of atopic disease are attributable to genetic variants that regulate specific immunological pathways relevant to exposure to certain antigens (6, 8), or, conversely, given the common co-occurrence of multiple atopic traits, whether phenotypic expression might instead be associated with polymorphisms that confer a general atopic susceptibility, triggered by specific environmental exposures during developmental windows (11, 12). Yet another possibility is that asthma has origins independent of adaptive immune function.

Atopic sensitization is strongly associated with asthma and it has been speculated that susceptibility to sensitization to specific allergens may be what links certain allergens to risk of asthma (13). In the Tucson Children's Respiratory Study, skin prick test sensitization to *Alternaria* is an independent risk factor for physician-diagnosed asthma at age 6 and 11 (14). However, the relation between sensitization to specific allergens and asthma varies with geography and the intensity and timing of exposures (15, 16). Hence, determining whether a propensity to allergen-specific sensitization is heritable and is linked to asthma, and whether allergen-specific or general atopic phenotypes cluster in families, may have important implications for current prevention practice.

The objective of this study was to determine whether there is familial clustering suggestive of a heritable component of specific response to allergens, and how this compares to familial aggregation of a general predisposition to atopy and asthma in two large population-based cohorts.

METHODS

Study populations

Two population-based cohorts and their family members were evaluated in this study: 1) the Tucson Children's Respiratory Study (CRS), a birth cohort of 1246 healthy newborns, enrolled between May 1980 and October 1984, and their parents and siblings (17), and 2) the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD), a random stratified cluster sample of non-Hispanic white households, recruited beginning in 1972 (18), with additional family members enrolled until 1996. All participants were between 4 and 70 years of age at allergen testing and 8 and 70 years at asthma reporting. Ethnicity was determined by self-report. Approximately 64% of CRS children had non-Hispanic white parents and 15% had Mexican-American parents. The 20% of children that were of other or mixed ethnic backgrounds were excluded from these analyses. Both studies were approved by the Human Subjects Committee at the University of Arizona, and informed consent was obtained from all participants or their parents.

Allergen skin prick tests

Allergen skin tests were administered at clinic visits by trained nurses using a standard prick-test method (14, 19). Antigens were supplied by Hollister-Stier Laboratories (Everett,

WA). In CRS, SPTs were administered between 1984 and 1991, at the first in-depth survey when children in the birth cohort were on average 6.12 ± 0.85 years old. Reactions to the following six allergens were analyzed: *Alternaria alternata* (1:10), Bermuda grass (1:20), olive tree, carelessnessweed, mesquite tree (all 1:20), and house dust mix (1:10). In TESAOD, a battery of seven allergen tests were consistently administered between 1978 and 1996: *Alternaria alternata* (1:10 wt/vol); *Dermataphagoides farinae* (house dust mite) (1:50); Bermuda grass (1:20); house dust mix (1:10); tree mix (1:20); weed mix (1:20); and Dematiaceae mold mix (1:100). SPT responses from the first survey in which a participant was at least 4 years old were used in this analysis. An SPT was considered positive if the sum of the major and minor axis of the wheal minus that of the negative control was ≥ 3 mm. A person was considered “atopic” if he or she had any positive skin test responses among the set of allergens tested at initial assessment. “Other atopy” was defined in relation to any SPT response to allergens other than the specific allergen being evaluated for familial correlation. Hence, “other atopy” was generated as seven separate variables in TESAOD and six in CRS for each SPT.

Questionnaire data

In CRS, asthma in enrolled children was ascertained at a mean age of 11 years from parent response to the question of whether a physician had ever told them that their child had asthma. Asthma status for parents was assessed from parental health questionnaires from year 1 and 7, and for siblings from a health survey administered between 1982 and 1986 (mean age of 10 yrs), based on similar questions. In TESAOD, asthma status was determined from the survey questionnaire concurrent with allergen testing, or, if a child was < 8 years old or missing information from that survey, asthma status was determined from a subsequent survey. Subjects were asked if a doctor had ever told him/her that he/she had asthma.

Statistical methods

Data management and descriptive statistics were performed using PASW Statistics 18.0. SPT response and asthma status were defined (as described above) as binary traits. We used the ASSOC program in the Statistical Analysis for Genetic Epidemiology (S.A.G.E.) 6.1.0 software package (20) to incorporate covariates into a logistic model for the probability of response. ASSOC allows for multiple sources of familial correlations in the data by simultaneously estimating by maximum likelihood familial variance components. Potential confounders included in the adjusted SPT models were age at SPT and “other atopy.” Covariates in the adjusted asthma models were age at asthma assessment and atopic status. Familial aggregation of both crude observed (0,1) and residual (observed – expected probability) values were estimated using the FCOR program in S.A.G.E. 6.1. FCOR estimates correlations and the asymptotic standard errors of the correlations between familial pairs in extended pedigrees, addressing the non-independence of multiple observations among multiple relative pairs within pedigrees, without assuming multivariate normality (20, 21). Familial correlation estimates were calculated between all parent-offspring (P-O), sibling (sib) and spousal pairs for allergen-specific SPT responses, atopic status and asthma. Large-sample tests for homogeneity of correlations of subtypes (i.e., mother- vs. father-offspring, brother-brother vs. sister-sister) were performed by FCOR. Analyses were run on all informative individuals in both study populations and in asthma-concordant family members only. The equal weight to pairs option was specified, i.e., each of the observations was given the same weight in the correlation calculations. For each correlation, ASSOC computes the equivalent number of independent pairs (i.e., the number of independent pairs that would give rise to the same standard error) (20). Using these numbers, Fisher’s z' transformation was used to compare correlation coefficients.

RESULTS

The family structure and characteristics of the study populations are shown in Table 1. CRS has a total of 1151 two-generation pedigrees and 2707 individuals with early SPT data. There were 1578 individuals who received allergen SPTs in TESAOD, in 435 multigenerational pedigrees. Mean age of offspring at time of SPTs in TESAOD was significantly older and more highly variable than in CRS (17.2 ± 12.2 vs. 7.9 ± 2.8 years, $P < 0.001$), and mean age of parents was also older (42.1 ± 12.5 vs. 34.9 ± 5.2 years, $P < 0.001$).

Overall prevalence of skin prick test sensitization was similar in CRS and TESAOD (Table 2), higher for pollen than non-pollen allergens. Some generational differences were apparent. In general, parents had a higher rate of sensitization than offspring, though *Alternaria* and mold mix sensitization were significantly lower in TESAOD parents than offspring (both $P < 0.006$). Over 50% of all CRS and TESAOD subjects were atopic—i.e., SPT-positive to one or more of the allergens tested—but only a small proportion of atopic subjects were mono-sensitized to any allergen. For example, 11.1% of CRS and 7.1% of TESAOD participants were mono-sensitized to Bermuda grass, 4.3% and 2.1%, respectively, to *Alternaria*, and fewer than 2.5% in either cohort to dust mix or dust mite (not shown). Overall, CRS has a lower proportion of subjects who reported asthma than TESAOD (17.3 vs. 20.5%, respectively, $P = 0.010$). In both study populations, approximately one-quarter of SPT positive subjects also reported asthma, and three-fourths of the subjects with asthma were SPT positive to ≥ 1 allergen.

Estimates of familial aggregation of specific SPT responses, atopy and asthma were similar in CRS (Table 3) and TESAOD (Table 4). There was a negligible effect of adjusting any of the outcomes for age at ascertainment. Adjusting specific response to allergens for other SPT-positive responses (“other atopy”), to account for a general predisposition to mount an atopic response, reduced correlation estimates by 14–71%. Adjusting asthma for atopic status had a negligible effect on the estimates.

Spousal correlations for adjusted response to specific allergens ranged from -0.08 to 0.08 and were not significant in either population. Statistically significant but low parent-offspring (P-O) correlations were observed for most of the allergens tested, with adjusted correlations all ≤ 0.11 . There was no consistent trend in terms of higher maternal versus paternal contribution to P-O correlation in either study population (not shown). Sibling pairs in CRS showed low ($\rho = 0.07$ – 0.09) but statistically significant adjusted correlations for all SPTs except *Alternaria*. TESAOD siblings showed no significant correlations for adjusted response to *Alternaria*, Bermuda grass or dust mix, though correlation for dust mite allergens ($\rho = 0.12 \pm 0.05$, $P < 0.05$), tree mix ($\rho = 0.16 \pm 0.05$, $P < 0.01$), mold ($\rho = 0.18 \pm 0.05$, $P < 0.001$) and weed mix ($\rho = 0.25 \pm 0.06$, $P < 0.0001$) were statistically significant.

In CRS, age-adjusted P-O and sibling correlations for atopic status tended to be slightly higher than the estimates for specific allergens, but there was no significant difference between P-O and sibling correlations. Sibling correlations for atopic status in TESAOD were significantly higher than P-O correlation ($\rho_{P-O} = 0.10 \pm 0.03$ and $\rho_{SIB} = 0.29 \pm 0.06$; Fisher’s z-test, $P < 0.001$).

In both cohorts, familial correlations for asthma, adjusted and crude, tended to be higher than correlations for specific response to allergens. Adjusted P-O correlations for asthma were 0.12 ± 0.02 in CRS and 0.18 ± 0.03 in TESAOD (both $P < 0.0001$). Sibling correlation for asthma in CRS was slightly higher ($\rho = 0.15 \pm 0.04$), but not significantly different, from P-O correlation. In TESAOD, correlation for asthma among siblings was significantly higher ($\rho = 0.32 \pm 0.06$) than in parent-offspring pairs ($P = 0.012$).

There were no significant differences in familial correlation estimates for specific sensitization or atopic status in asthma-concordant versus non-asthma concordant P-O pairs in either study population, though correlations among asthmatics in CRS tended to be higher than among non-asthmatics (not shown). No trend was observed in TESAOD. In each study the number of asthma-concordant familial pairs was small and there were large standard errors associated with the correlation estimates.

Sensitivity analyses

To assess potential effect modification by ethnic background in CRS, separate analyses were repeated in 93 Hispanic families and 445 non-Hispanic white families. SPT sensitization did not differ by ethnicity, though prevalence of asthma was 18.4% among non-Hispanic whites and only 10.5% among Hispanic whites ($P < 0.001$). A comparison of P-O and sib-sib correlation in *Alternaria* and Bermuda grass SPT response in Hispanic and non-Hispanic families showed no significant differences (not shown).

Because prevalence of sensitization has been shown to increase from age 6 to 16 (19, 22), we also attempted to assess the effect of age at SPT on familial correlation in the CRS cohort. SPTs were performed only once on parents and siblings, but enrolled children were tested at year 6, 11 and 16. In a sensitivity analysis, we assessed familial aggregation of sensitization at any of the childhood surveys to the same set of allergens. Crude P-O and sib-sib correlations for sensitization at any of these surveys tended to be higher (ρ_{P-O} between 0.09–0.13 and ρ_{SIB} between 0.09–0.18) than for year 6 only, but not significantly different (data not shown).

DISCUSSION

In this study we first address the question of whether specific response to allergens, as assessed by allergen skin prick tests, is aggregated in families. Using data from two, large, general population studies with pedigree (family) data, familial correlations of response to specific allergen skin prick tests were estimated, with and without adjustment for “other atopy” (SPT sensitization to other allergens tested) and age at assessment. Other atopy (SPT sensitization to allergens other than the phenotype being assessed) was a significant confounder in the models used to compute residual SPT values, and adjusted correlations for individual SPTs were 14–71% lower than the crude estimates. Although the adjusted estimates of parent-offspring and sibling correlation in allergen-specific response remained statistically significant for most allergens in both cohorts, there was higher sibling than parent-offspring correlation, suggesting a greater role of common, shared environmental allergen exposures among siblings.

Atopy is generally defined as a genetic predisposition toward development of an immune response to common environmental antigens, involving the production of allergen-specific IgE (11). Clearly, specific sensitization involves environmental exposures in addition to a genetic propensity to mount an immunologic response. We cannot assume that we have adequately adjusted for “other atopy” given that there is no way to test for all possible allergens, and we cannot rule out the possibility that specific sensitization is aggregated due to similarities in allergen exposures in families predisposed to atopy. Our results suggest a trend toward increased correlations among siblings, who tend to share more environmental factors than parents and offspring. From the lack of significant spousal correlation in our populations, we can infer that similarities in exposure in adulthood are not by themselves sufficient causes of correlation in sensitization.

The second question we address is whether familial correlation of asthma is independent of atopy. Expression of atopy is heterogeneous, but atopic phenotypes, such as skin prick test

sensitization and high serum IgE, and associated conditions, such as asthma, hay fever, and eczema, tend to run in families and also to co-occur in individuals (23, 11). Adjusting asthma for any SPT reactivity did not reduce the moderate-high aggregation of asthma in families. Despite co-occurrence with asthma, the implication is that atopy does not directly influence familial correlation of asthma. Furthermore, this association between atopic phenotypes and asthma does not necessarily imply that atopy contributes to the development of asthma or that atopy and asthma have a common genetic origin.

Familial correlation analysis of specific response to allergens has been addressed primarily in twin studies and in studies of families with asthmatic probands. The evidence for correlation of specific allergen responses (both SPTs and specific IgE) is very strong in twin studies, with estimates ranging from 0.40–0.71 in monozygotic twins, and up to 0.50 in dizygotic twins, raised apart or together (3–5). Most studies of correlation of these traits in families report significant P-O and sibling correlation of allergen-specific SPTs, IgE, and IgG1 response, with estimates in the range of 0.13–0.20 (6, 24, 25). In contrast, Jackola and colleagues report no evidence of familial response patterns to specific allergens and conclude that allergen-specific responses, after adjustment for the non-allergen-specific fraction of total IgE, are random and unrelated to the phenotypes expressed by relatives (26, 27). Our results suggest that familial aggregation of specific response to allergens is not entirely random. However, the extent of concordance that might be due to polygenic effects as opposed to unmeasured, shared environmental factors could not be evaluated.

Certain allergens appear to be closely associated with asthma, and it has been hypothesized that these “asthmagenic” allergens instigate an immune reaction that facilitates their passage into the lung, eliciting bronchial constriction and inflammation (28). We did not find evidence of greater familial correlation for sensitization to *Alternaria*, which has been shown to be an important risk factor for asthma in Tucson, than for other allergens.

Our findings strongly suggest independent inheritance of general atopy and asthma. Several genetic studies support the hypothesis that atopic and asthmatic phenotypes are affiliated with different genetic variants and immune pathways. A recent genomewide association study found no overlap in genes associated with asthma and those associated with total IgE (29). Another study found that gene loci associated with specific IgE to mites were completely distinct from those linked to asthma (30).

The research presented in this paper involved analysis of familial aggregation of specific allergen skin prick test response in two study populations. Both of these studies, CRS and TESAOD, were prospective and population-based. Our objectives were to assess aggregation in non-selected families in a general population study, to validate our results with a second cohort, and to compare correlation in asthmatic and non-asthmatic familial pairs.

There are a number of limitations to this study. In both cohorts, there were insufficient numbers of asthma-concordant familial pairs to assess differences in aggregation of SPT response in asthmatic and non-asthmatic families. It should also be noted that there were important differences in CRS and TESAOD in recruitment, study design, population structure and age at assessment that could not be completely accounted for in analysis, and it is possible that there were period or cohort effects that differentially influenced allergen exposures or outcomes.

In general, the effect size was similar between studies, though in TESAOD only, siblings often showed higher correlations than parents and offspring. This may be due to the older mean age at assessment in TESAOD parents and offspring, and thus increased time to develop atopic and asthmatic phenotypes and perhaps share environmental exposures. Age

of onset of sensitization was not known, so SPT data from earliest assessment was utilized. This was at a mean age of 8 years for offspring in CRS, and age 17 years for offspring in TESAOD. While for CRS this implies childhood onset (and exposure), the earliest SPTs in TESAOD offspring were often performed in adulthood. Essentially, we were only able to adjust our outcomes for age of assessment and we assumed that allergen responses were persistent.

Overall, there was corroboration of results between populations. Our results show evidence in support of the independent inheritance of atopy and asthma, and may help clarify the current argument regarding co-occurrence and familial aggregation of these traits and the genetic evidence suggesting disparate genes. Our analysis of familial correlation of allergen-specific sensitization shows slight aggregation of sensitization to specific allergens, after adjustment for age and a general predisposition toward atopy, that appears to be a function of shared allergen exposures. In conclusion, specific allergen responses do not appear to define distinct subphenotypes of atopic disease.

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Table 1

Comparison of study design and familial structure in the Tucson Children's Respiratory Study (CRS) and Tucson Epidemiologic Study of Airway Obstructive Disease (TESAOD).

	CRS	TESAOD
Study design	Prospective cohort	Prospective cohort
Population sample	Birth cohort (1980–84) and nuclear family	Random stratified cluster sample, Tucson households
Surveys, dates of SPTs	In-depth 1, 1984–92	Surveys 6–13, 1978–96
Surveys, dates of asthma ascertainment	In-depth 2, 1990–96 In-depth 3, 1996–2003	Surveys 6–13, 1978–96
N of pedigrees with SPT data	1151	435
N individuals	2707	1578
Parent-offspring pairs	2450	1307
Sibling pairs	916	535
Spousal pairs	555	357
Mean ± S.D. age at SPT in years (min-max)		
Offspring	7.9±2.8 (4–25)	17.2±12.1 (4–70)
Parents	34.9±5.2 (21–70)	42.1±12.5 (18–70)
Mean ± S.D. age at asthma ascertainment in years (min-max)		
Offspring	10.8±1.9 (8–25)	19.8±11.2 (8–70)
Parents	37.2±5.3 (21–73)	42.1±12.5 (18–70)

Table 2

Prevalence of sensitization to allergens and asthma in CRS and TESAOD parents and offspring.

	CRS n (%)		TESAOD n (%)	
	Parents	Offspring	Parents	Offspring
ALTERNARIA	237 (18.0)	267 (19.2)	96 (13.4)	157 (18.2)
BERMUDA	576(43.7)	455 (32.8)	300 (41.9)	315 (36.6)
DUST	227 (17.2)	92 (6.7)	126 (17.6)	110 (12.8)
CARELESSWEED	526 (40.0)	256 (18.4)	--	--
MESQUITE	343 (26.0)	226 (16.3)	--	--
OLIVE	583 (44.3)	296 (21.3)	--	--
DUST MITE	--	--	109 (15.2)	96 (11.2)
WEED	--	--	248 (34.6)	277 (32.2)
TREE	--	--	301 (42.2)	276 (32.2)
MOLD	--	--	59 (8.2)	126 (14.7)
ATOPIC ¹	838 (63.6)	630 (45.4)	427 (59.6)	472 (54.9)
ASTHMA	202 (15.4)	255 (19.2)	141 (19.9)	160 (21.1)

¹ Atopic is defined as any positive skin prick test response.

Table 3

Unadjusted and adjusted familial correlation (ρ) for sensitization to specific allergens, atopic status and asthma in CRS using FCOR (S.A.G.E. 6.1.0).

	$\rho_{P-O} \pm \text{s.e. (n=2450)}$	$\rho_{SIBS} \pm \text{s.e. (n=916)}$	Fisher's z-test $\rho_{SIBS} > \rho_{P-O}$	$\rho_{SPOUSAL} \pm \text{s.e. (n=555)}$
ALTERNARIA ⁰	0.08±0.02 [‡]	0.07±0.04 [*]		-0.02±0.04
+ age ¹	0.08±0.02 [‡]	0.07±0.03 [*]		-0.02±0.04
+ age & other atopy ²	0.05±0.02 [*]	0.06±0.04	n.s.	-0.04±0.04
BERMUDA ⁰	0.11±0.02 [*]	0.10±0.04 [‡]		0.07±0.04
+ age ¹	0.11±0.02 [*]	0.11±0.04 [‡]		0.07±0.04
+ age & other atopy ²	0.07±0.02 [‡]	0.08±0.04 [*]	n.s.	0.05±0.04
DUST	0.11±0.02 [*]	0.10±0.04 [‡]		0.08±0.04 [*]
+ age ¹	0.11±0.02 [*]	0.11±0.04 [‡]		0.07±0.04
+ age & other atopy ²	0.07±0.02 [‡]	0.08±0.04 [*]	n.s.	0.05±0.04
CARELESSWEED ⁰	0.12±0.02 [*]	0.09±0.04 [‡]		0.11±0.04 [*]
+ age ¹	0.11±0.02 [*]	0.10±0.04 [‡]		0.11±0.04 [‡]
+ age & other atopy ²	0.07±0.02 [‡]	0.07±0.04 [*]	n.s.	0.07±0.04
MESQUITE ⁰	0.06±0.02 [*]	0.12±0.04 [‡]		0.03±0.04
+ age ¹	0.05±0.02 [*]	0.13±0.04 [‡]		0.03±0.04
+ age & other atopy ²	0.03±0.02	0.08±0.04 [*]	n.s.	-0.01±0.04
OLIVE ⁰	0.11±0.02 [*]	0.12±0.04 [‡]		0.07±0.04
+ age ¹	0.11±0.02 [*]	0.12±0.04 [‡]		0.08±0.04
+ age & other atopy ²	0.07±0.02 [‡]	0.09±0.04 [*]	n.s.	0.07±0.04
ATOPIC STATUS ⁰	0.12±0.02 [*]	0.12±0.04 [‡]		0.06±0.04
+ age ¹	0.12±0.02 [*]	0.14±0.04 [‡]	n.s.	0.06±0.04
ASTHMA ⁰	0.13±0.02 [*]	0.16±0.04 [*]		-0.02±0.04
+ age ¹	0.13±0.02 [*]	0.16±0.04 [*]		-0.02±0.04
+ age & any atopy ³	0.12±0.02 [*]	0.15±0.04 [‡]	n.s.	-0.03±0.04

⁰ Unadjusted outcomes;

¹ models adjusted for age at ascertainment (centered at mean);

² "other atopy" is defined as having an SPT positive response to allergens other than the SPT outcome of interest;

³ models adjusted for age at which asthma was ascertained (centered at mean) and for any positive SPT response. *P*-values for correlation estimates: n.s. > 0.05,

* < 0.05,

[‡] < 0.01,

^{‡‡} < 0.001,

^{‡‡‡} < 0.0001;

[§]Fisher's z -test, $P < 0.05$.

Table 4

Unadjusted and adjusted familial correlation (ρ) for sensitization to specific allergens, any of the allergens tested (“any atopy”) and asthma in TESAOD using FCOR (S.A.G.E. 6.1.0).

	$\rho_{P-O} \pm \text{s.e. (n=1307)}$	$\rho_{SIBS} \pm \text{s.e. (n=535)}$	Fisher's z-test $\rho_{SIBS} > \rho_{P-O}$	$\rho_{SPOUSAL} \pm \text{s.e. (n=357)}$
ALTERNARIA ⁰	0.07±0.03*	0.08±0.05		-0.09±0.05
+ age ¹	0.07±0.03*	0.09±0.05		-0.09±0.05
+ age & other atopy ²	0.02±0.03	0.03±0.05	n.s	-0.08±0.05
BERMUDA ⁰	0.11±0.03 [‡]	0.16±0.05 [‡]		-0.02±0.05
+ age ¹	0.11±0.03 [‡]	0.15±0.05 [‡]		-0.01±0.05
+ age & other atopy ²	0.07±0.03*	0.08±0.05	n.s	0.00±0.05
DUST	0.06±0.03*	0.11±0.05*		0.06±0.05
+ age ¹	0.06±0.03	0.11±0.05*		0.06±0.05
+ age & other atopy ²	0.02±0.03	0.04±0.05	n.s	0.07±0.05
DUST MITE	0.03±0.03	0.15±0.05 [‡]		0.10±0.05
+ age ¹	0.03±0.03	0.15±0.05 [‡]		0.10±0.05
+ age & other atopy ²	0.01±0.03	0.12±0.05*	§	0.08±0.05
MOLD ⁰	0.14±0.03	0.22±0.05 [‡]		-0.03±0.05
+ age ¹	0.14±0.03	0.22±0.05 [‡]		-0.04±0.05
+ age & other atopy ²	0.11±0.03 [‡]	0.18±0.05 [‡]	n.s	-0.02±0.05
TREE ⁰	0.16±0.03	0.23±0.06 [‡]		-0.01±0.05
+ age ¹	0.15±0.03	0.22±0.06 [‡]		-0.01±0.05
+ age & other atopy ²	0.11±0.03 [‡]	0.16±0.05 [‡]	n.s	0.04±0.05
WEED ⁰	0.11±0.03 [‡]	0.29±0.06		-0.03±0.05
+ age ¹	0.11±0.03 [‡]	0.28±0.06		-0.03±0.05
+ age & other atopy ²	0.07±0.03*	0.25±0.06	§	-0.01±0.05
ATOPIC STATUS ⁰	0.11±0.03 [‡]	0.30±0.06		-0.05±0.05
+ age ¹	0.10±0.03 [‡]	0.29±0.06	§	-0.05±0.05
ASTHMA ⁰	0.20±0.03	0.36±0.06		-0.08±0.05
+ age ¹	0.19±0.03	0.36±0.06		-0.08±0.05
+ age & any atopy ³	0.18±0.03	0.33±0.06	§	-0.08±0.05

⁰ Unadjusted outcomes;

¹ models adjusted for age at ascertainment (centered at mean);

² “other atopy” is defined as having an SPT positive response to allergens other than the SPT outcome of interest;

³ models adjusted for age at which asthma was ascertained (centered at mean) and for any positive SPT response. *P*-values for correlation estimates: n.s. > 0.05,

* < 0.05,

[†] < 0.01 ,

[‡] < 0.001 ,

[°] < 0.0001 ;

[§] Fisher's z -test, $P < 0.05$.