



Miscellaneous

How much atopy is attributable to common childhood environmental exposures? A population-based birth cohort study followed to adulthood

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Abstract

Background: The rising prevalence of atopic diseases implies a strong influence of environmental determinants. Epidemiological studies have identified several early life exposures that appear to influence the risk of developing atopic sensitization, but the combined influence of these exposures is unknown. We sought to estimate the proportion of atopy that could be attributed to common childhood exposures associated with atopic sensitization in adolescence and young adulthood.

Methods: Atopic sensitization was measured by skin-prick tests for common aeroallergens in a population-based New Zealand birth cohort at ages 13 and 32 years. The independent effects of previously identified risk and protective factors for atopic sensitization were assessed using multiple logistic regression. Population attributable fractions were calculated for atopic sensitization in childhood and adulthood.

Results: Tobacco smoke exposure, dog and cat ownership, nail-biting and thumb-sucking, attending pre-school day care, and household crowding were associated with a lower risk of atopic sensitization whereas breastfeeding was associated with a higher risk. Population attributable fractions for combined effects of these environmental factors suggest that they may account for 58% of atopic sensitization at age 13 and 49% at age 32 years.

Conclusions: A substantial proportion of atopic sensitization appears to be attributable to common childhood environmental and lifestyle factors, and the influence of these exposures persists into adulthood. The absolute risks attributable to these exposures will be different in other cohorts and we cannot assume that these associations are necessarily causal. Nevertheless, the findings suggest that identifiable childhood environmental factors contribute substantially to atopic sensitization.

Key words: Atopic hypersensitivity, breastfeeding, crowding, child day care, environmental tobacco smoke, nail-biting, pets, thumb-sucking

Key Messages

- The majority of atopic sensitization in adolescence may be attributable to the combined influence of common identifiable childhood exposures.
- The influence of these childhood exposures on atopic sensitization persists into adulthood.
- Many of the exposures that appear to increase the risk for atopy have other health and social benefits, and their avoidance may be undesirable.

Introduction

Over recent decades the prevalence of atopy and its related diseases has increased substantially in Western countries.^{1,2} Whereas the development of atopy is likely to involve interactions between genetic and environmental factors, the rapid increase in the prevalence of atopy implies a strong influence of environmental determinants.^{3,4}

Numerous environmental exposures in early childhood have been associated with atopic sensitization. Previous reports from the Dunedin Multidisciplinary Health and Development study found that breastfeeding was associated with an increased risk of atopic sensitization,⁵ whereas exposure to both cats and dogs,⁶ tobacco smoke,⁷ and thumb-sucking and nail-biting in childhood appear to be protective against atopic sensitization.⁸ The study did not find a clear association between atopy and birth order,⁹ but the risk of atopy has been found to be inversely associated with household crowding at the age of 3 years.^{6,8}

Some of these observations are controversial, as the apparent protective effect of smoking and the increased risk of atopy with breastfeeding contradict widely held beliefs, although each of these observations has been supported by other studies.^{10–12} Breastfeeding in particular has been promoted as a protective factor against atopy in childhood,¹³ yet several studies have failed to confirm these protective effects.^{14–16} Similarly, the literature is divided on whether exposure to tobacco smoke influences the risk of developing atopic sensitization.^{10,17–20}

Furthermore, despite numerous studies identifying associations with other environmental exposures such as ownership of pets,^{21–23} household crowding,^{24,25} and day care attendance,^{25–27} the overall impact of these exposures remains uncertain. The issue is made more complicated by changes in the pattern of atopic sensitization with age and sex: boys are more likely to develop atopic diseases in early childhood compared with girls,²⁸ whereas adult women report more atopy than men.²⁹ Genetic risk factors

undoubtedly play a large role: a family history of atopy is considered the strongest risk factor for atopy development, although this may be explained by shared environmental exposures as well as genes.¹²

Most studies investigating the association between environmental predictors and atopy have focused on individual exposures, and it is unclear to what extent multiple environmental exposures influence the risk of atopy. Despite the known inverse association between the number of siblings and risk for atopy, Upchurch *et al.* found that only 3% of the increase in the prevalence of atopy over recent decades could be attributed to decreasing family size.³⁰ To our knowledge there are no published studies assessing the combined effect of multiple risk factors on atopic sensitization in childhood and adulthood. To address this, we explored the combined effect of common childhood environmental exposures previously found to predict the risk for atopic sensitization in the Dunedin Multidisciplinary Health and Development study and other research. Our aim was to estimate what proportion of atopic sensitization could be attributed to these exposures in a population-based birth cohort at ages 13 and 32 years.

Methods

The Dunedin Multidisciplinary Health and Development study is a population-based birth cohort study of 1037 participants born in Queen Mary Maternity Hospital, Dunedin, New Zealand, in 1972–73. Children still living in the greater Dunedin area were invited to the first follow-up at age 3 years. The 1037 children (91% of those eligible; 52% male) who attended this assessment formed the cohort for further follow-up assessments, which have been done at ages 5, 7, 9, 11, 13, 15, 18, 21, 26, 32 and 38 years. The cohort represents the full range of socioeconomic status in the South Island of New Zealand, and the study participants are mostly of New Zealand European

ethnicity, reflecting the ethnic mix of the South Island at that time. For each assessment, study members are invited back to the research unit. The study has a high rate of retention: 95% of the surviving cohort participated in the latest assessment at age 38. A full description of the study is reported elsewhere.³¹ The Otago Ethics Committee approved the study, and written informed consent was obtained at each assessment.

Atopic sensitization

Atopic sensitization was first measured at age 13 years when 724 of 1031 (70%) study members consented to skin prick tests for 11 common inhaled allergens: house dust mite (*Dermatophagoides pteronyssinus*; Bencard, Brentford, UK), grass, cat, dog, horse, kapok, wool, *Aspergillus fumigatus*, *Alternaria*, *Penicillium* and *Cladosporium* (Hollister-Stier, Washington, USA). Skin prick testing was performed in 946 of 1015 (93%) of the surviving study members at age 32 years. We used the same allergens at age 32 as at age 13, with the addition of cockroach, but due to necessity allergens were obtained from a different manufacturer (ALK, supplied by Allergy Canada, Thornhill, ON, Canada). In keeping with previous reports from this cohort, a positive response to skin prick testing was defined by a wheal diameter at least 2 mm greater than the negative saline control. Atopic sensitization was defined as having at least one positive response to any allergen.⁶

Environmental exposures

Environmental risk and protective factors were assessed at interviews throughout the follow-up period. At age 3 years, the child's mother was asked about the initiation and duration of breastfeeding and in the majority of cases this was verified from prospective visiting nurse records.⁵ Participants were considered to have been breastfed if they had been breastfed until at least 4 weeks of age. An index of exposure to other children/household crowding was derived from the number of children living in the house at participant age 3 years, divided by the reported number of rooms (excluding kitchens and bathrooms). Households were regarded as uncrowded if there were more than two rooms per child.⁶ Day care attendance at age 3 years was reported by the parent attending with the child. Retrospective information regarding cat and dog ownership during childhood was obtained at age 9 years. Only ownership of both a dog and a cat has been found to be associated with a lower risk of atopy in this cohort, so only children with both pets were regarded as exposed.⁶ Parental smoking history was obtained from a parent at

the assessments at ages 7, 9 and 11 years. At age 13 years, the study members themselves were asked whether their parents smoked. Participants were regarded as being exposed to parental smoking if either parent smoked at any of these ages.⁷ Children were considered to be thumb-suckers or nail-biters if their parents reported that they frequently bit their nails or sucked their thumbs at any of the assessments at ages 5, 7, 9 or 11 years.⁸ A history of asthma and hay fever in the child's natural mother and father was obtained from the parents at the age 7 years assessment and from the study members themselves at age 18 years. A parental history of atopy was considered positive if either parent had a history of hay fever or asthma.⁷ Childhood socioeconomic status was recorded at each assessment between birth and age 13 using a 6-point scale (1 = high, 6 = low) based on the occupational status of either parent as previously described.³² A mean score between 1 and 3 across these assessments was considered a high socioeconomic status.

Statistical analysis

Associations between each childhood exposures and atopic sensitization were first confirmed in unadjusted logistic regression models using a positive skin prick test to any allergen at age 13 or 32 years as the primary outcome. Protective environment factors were reverse-coded so that they appeared as risk factors. Subsequently, all exposures were included in adjusted logistic regression analyses.

Population attributable fractions associated with the exposures were calculated from these multivariable models. Sex and parental history of atopy were included in these adjusted models, but were not included in the estimates of population attributable fractions because they were not deemed to be modifiable environmental exposures.

Population attributable fractions (also known as population attributable risks) estimate the proportion of disease in the population attributable to the exposure, based on the relative risk of developing the disease among the exposed compared with the unexposed and the proportion of the population exposed to the risk factor. They provide an estimate of the fraction of disease that would be prevented if the risk factor could be eliminated from the population. Population attributable fractions can be derived from logistic regression using maximum likelihood estimation.³³ However, a known problem with population attributable fractions from multivariable models is that the individual risks can be overestimated and the sum of these can exceed the overall attributable risk (and even exceed 100%), because most individuals are exposed to more than one risk and the estimated attributable fraction is dependent on the sequence of removing each risk factor from the

Table 1. Prevalence of environmental exposures and outcomes

	<i>n</i>	Female (%)	Male (%)	<i>P</i>
Atopic sensitization at 13 years	724	132/349 (38)	196/375 (52)	<0.001
Atopic sensitization at 32 years	946	271/467 (58)	294/479 (61)	0.294
Parental history of atopy	954	201/460 (44)	219/494 (44)	0.843
Breastfed	1035	248/501 (50)	254/534 (48)	0.534
Parental smoking	972	299/468 (64)	318/504 (63)	0.797
Cat and dog ownership	815	158/387 (41)	174/428 (41)	0.960
Household crowding	1037	202/502 (40)	229/535 (43)	0.402
Thumb-sucking or nailbiting at 5–11 years	1013	164/492 (33)	153/521 (29)	0.174
Day care attendance	1027	88/497 (18)	85/530 (16)	0.475

P values <0.05 are highlighted in bold.

Table 2. Unadjusted associations between childhood exposures and atopic sensitization at ages 13 and 32 years

	Age 13				Age 32			
	<i>n</i>	OR	95% CI	<i>P</i>	<i>n</i>	OR	95% CI	<i>P</i>
Male sex	724	1.80	1.33, 2.42	<0.001	946	1.15	0.89, 1.49	0.294
Parental history of atopy	712	1.69	1.25, 2.28	0.001	893	1.79	1.36, 2.35	<0.001
Breastfed for 4 weeks of longer	722	1.87	1.39, 2.52	<0.001	944	1.44	1.11, 1.87	0.006
Parents were non-smokers at ages 7 to 13	724	1.60	1.18, 2.17	0.002	903	1.42	1.01, 1.87	0.013
No household crowding at age 3	724	1.56	1.16, 2.10	0.004	946	1.49	1.14, 1.94	0.003
Didn't have a cat and a dog before age 9	688	1.84	1.35, 2.51	<0.001	767	1.56	1.16, 2.10	0.003
Didn't attend day care at age 3	718	1.45	0.96, 2.18	0.079	937	1.13	0.79, 1.61	0.508
Did not suck thumb or bite nails between ages 5 to 11 years	724	1.52	1.11, 2.10	0.010	935	1.64	1.24, 2.17	0.001

model.^{34,35} This problem can be overcome by sequentially removing each of the risk factors from the logistic regression model in every possible order and averaging the attributable fraction obtained for each factor.^{35,36} We used the averaging procedure described by Ruckinger *et al.* to do this.³⁶ This procedure does not calculate confidence intervals directly, so these were generated by bootstrapping 1000 samples and reporting the resulting bias-corrected estimates.³⁷ Analyses were performed using Stata versions 13 or 14 (StataCorp, College Station, TX, USA)

Results

At age 13 years, more boys had positive skin prick tests than girls. At age 32 years, there was no longer evidence of a sex difference in atopic sensitization. There were no sex differences observed for exposure to any of the environmental risk factors (Table 1). Only 70% of participants consented to skin prick testing at age 13 years, whereas 93% of the living cohort received skin prick testing at age 32 years. Those who did not undergo the test at age 13 years had a similar prevalence of atopic sensitization at age 32 years compared with those who did (56% vs 60%, *P* = 0.22); 33% (126/377) of those with negative tests at

age 13 had positive tests at age 32. Only 6% (18/310) of those with positive tests at age 13 had negative tests at age 32.

As expected, all previously identified environmental exposures analysed were predictors of atopic sensitization in our cohort at both age 13 and age 32 years. Not attending day care showed a tendency to an increased risk of atopic sensitization at age 13, but was not a predictor at age 32 years (Table 2).

When modelled simultaneously, most of the environmental exposures remained associated with atopic sensitization. Day care attendance was not associated with atopic sensitization at either age in adjusted models (Table 3).

The risk of developing atopic sensitization increased with the number of risk factors that children were exposed to. Only two participants were exposed to none of the risk factors. Children with one risk factor or fewer had a 25% risk of sensitization, whereas those with all six (breastfeeding, and absence of exposures to dogs and cats, parental smoking, household crowding, nail-biting or thumb-sucking, and day care attendance) had a 70% risk of sensitization (Figure 1). Similarly, the prevalence of atopic sensitization at age 32 increased with the number of childhood risk factors (Figure 2).

Table 3. Adjusted analyses of the association between independent environmental exposures and atopic sensitization at 13 and 32 years

	Age 13 (<i>n</i> = 671)			Age 32 (<i>n</i> = 743)		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Male sex	1.94	1.41, 2.68	<0.001	1.29	0.95, 1.76	0.098
Parental history of atopy	1.63	1.17, 2.26	0.003	1.53	1.12, 2.10	0.008
Breastfed for 4 weeks of longer	1.70	1.23, 2.35	0.001	1.53	1.12, 2.10	0.007
Parents were non-smokers at ages 7 to 13	1.38	0.99, 1.93	0.058	1.32	0.95, 1.83	0.095
No household crowding at age 3	1.43	1.03, 1.99	0.034	1.43	1.04, 1.96	0.025
Didn't have a cat and a dog before age 9	1.63	1.16, 2.28	0.004	1.38	1.01, 1.89	0.044
Didn't attend day care at age 3	1.50	0.96, 2.34	0.078	1.36	0.90, 2.05	0.141
Did not suck thumb or bite nails between ages 5 to 11 years	1.56	1.10, 2.20	0.012	1.65	1.19, 2.27	0.003

P values <0.05 are highlighted in bold.

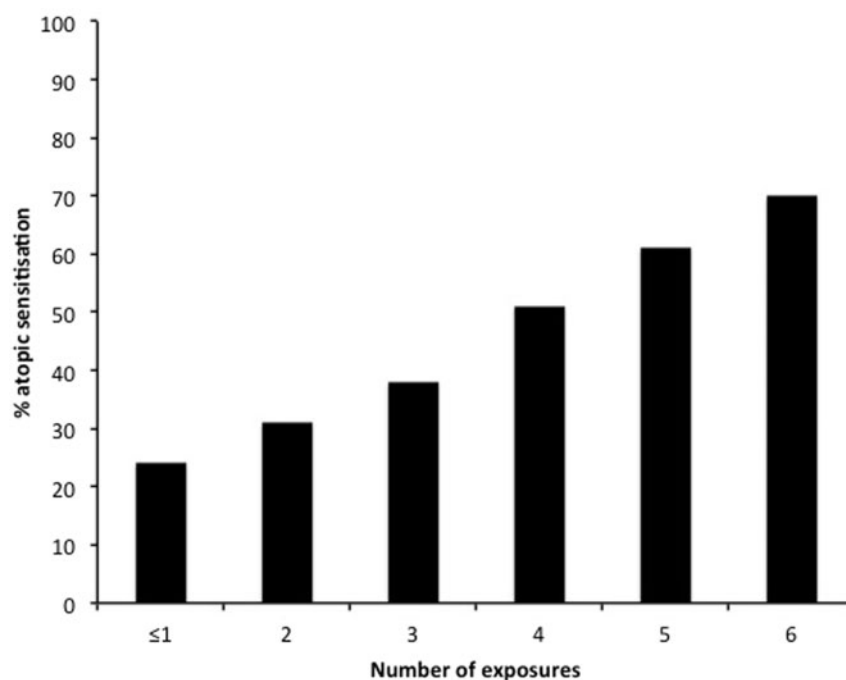


Figure 1. Association between atopic sensitization at age 13 years and the number of exposed environmental factors. Exposures assessed were: breastfeeding, no childhood exposure to tobacco smoke, no cat and dog ownership, no thumb-sucking or nail-biting, no day care attendance, and no household crowding. Non-parametric test of statistical significance across ordered groups $P < 0.001$.

Population attributable risk (PAF) analyses estimated that 58% of atopic sensitization in our cohort at age 13 years and 49% at age 32 years could be 'attributed' to the modifiable environmental risk factors in the multivariable models (Table 4). Whereas the focus here is on potentially modifiable factors, adding sex and parent report of atopy to the calculation of the PAFs increased these to 80% and 61%, respectively.

Discussion

This study suggests that a substantial proportion of atopic sensitization may be attributable to common identifiable

childhood exposures, with 58% of the risk for atopic sensitization at age 13 years and 49% of atopic sensitization at age 32 years apparently explained by the combined influence of breastfeeding, and the absence of exposure to dogs and cats, parental smoking, household crowding, nail-biting or thumb-sucking, and day care attendance.

To our knowledge this is the first prospective study to report the combined effect of multiple environmental factors on objective measures of atopic sensitization in childhood and adulthood. It must be acknowledged that the calculation of population attributable risks is based on the assumption that the risk factors are causal, rather than simply associated with the outcome through other

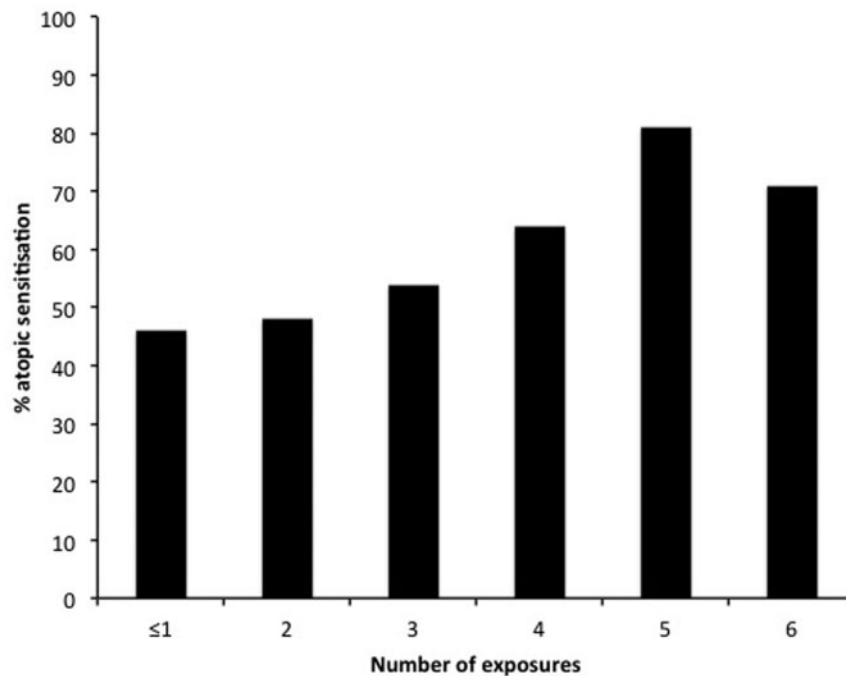


Figure 2. Association between atopic sensitization at age 32 years and the number of exposed environmental factors. Exposures assessed were: breastfeeding, no childhood exposure to tobacco smoke, no cat and dog ownership, no thumb-sucking or nail-biting, no day care attendance, and no household crowding. Non-parametric test of statistical significance across ordered groups $P < 0.001$.

Table 4. Population attributable fractions (PAFs) for early childhood exposures on atopic sensitization

	Age 13 ($n = 671$)		Age 32 ($n = 743$)	
	PAF	95% CI	PAF	95% CI
Breastfed	0.10	0.04, 0.17	0.08	0.02, 0.14
No parental smoking	0.05	0.00, 0.10	0.04	0.00, 0.09
No household crowding	0.08	0.01, 0.15	0.08	0.00, 0.15
No cats and dogs	0.11	0.04, 0.20	0.07	0.00, 0.14
No day care	0.12	0.00, 0.25	0.10	0.00, 0.22
No thumb-sucking/nail-biting	0.11	0.03, 0.20	0.13	0.04, 0.20
Total	0.58	0.43, 0.70	0.49	0.32, 0.64

95% confidence intervals from 1000 bootstrapped samples (see text).

mechanisms. The size of the attributable risks would also differ in other populations: not only because there are likely to be differences in the strength of association between these risk factors and the development of atopy, but also because the prevalences of the exposures will be different. Nevertheless, the overall findings of this study suggest that a large proportion of atopic sensitization can be explained by specific childhood exposures. As might be expected, the attributable risks due to early life exposures were higher in childhood than adulthood. A third of those with negative skin prick tests at age 13 years had positive tests at age 32. None of the early childhood exposures that we studied predicted the development of sensitization

between ages 13 and 32 years (data not shown), but we have previously shown that adolescent and early adult exposures to dogs and cats and smoking influence the risk of atopy developing after age 13,^{6,7} and we would expect other adolescent or adult exposures to influence this as well. Despite this, half of adult atopic sensitization could still be attributed to these childhood exposures. If we included the additional influences of non-modifiable factors, namely a parental history of atopy and male sex, the attributable risks were 80% and 61% at ages 13 and 32 years, respectively. Perhaps surprisingly, the strength of association between a family history of atopy and atopic sensitization was of a similar magnitude to several of the individual environmental exposures (Tables 2 and 3). Although this may partly be due to the fact that the family history was based on self-reports of atopic disease rather than objective testing, this finding also indicates that genetic and other familial factors may be less important than the combined influence of the environment.

Although we focused on potentially modifiable childhood exposures, altering these exposures would not necessarily be easy or desirable. There are many reasons to encourage breastfeeding and to avoid exposure to environmental tobacco smoke and household overcrowding, even if these were proven to increase the risk of atopic sensitization. Nail-biting and thumb-sucking may have other adverse effects and are widely regarded as undesirable habits,^{38,39} and cat and dog ownership is highly dependent on

family and living circumstances. The public health implications of these findings are therefore unclear. Despite this, the extent of the relationship between environmental exposures and atopy remains poorly understood, and knowledge of the early life exposures that lead to these diseases is needed to enable early prevention.

Many of the risk factors that we have studied are controversial: some of the environmental exposures that we found to be associated with atopy have also been reported to be protective factors (and vice versa). Hence, it may be that the direction as well as the strength of the associations between these exposures and atopic sensitization may be different in other populations. Several explanations have been proposed for the heterogeneity of results from different studies, including differences in measurement outcomes (different ages tested, dissimilar environmental exposures)¹³ and differences in the quality of the collected data (retrospective vs prospective collection, lack of standard definitions).¹⁹ There are also reported effects of genetic polymorphisms affecting the response to exposures such as breastfeeding, which we have not assessed in this analysis.⁴⁰

Although higher socioeconomic status is also associated with atopic sensitization in this cohort in univariable analyses,³² we did not include it in our main analyses because we think that it is likely to be an indirect measure of other exposures rather than a direct exposure. When added to the multivariable analyses, a high childhood socioeconomic status did not predict sensitization at either age 13 [odds ratio (OR)=1.13; 95% confidence interval (CI): 0.79, 1.62; $P=0.507$] or 32 years (OR=1.01; 95% CI: 0.72, 1.42; $P=0.958$). Adding socioeconomic status also did not materially change any of the associations reported in Table 3.

Strengths of this study include the prospective design, the objective measurement of atopic sensitization, and measures of exposure data over multiple assessments. The study has a very high cohort retention rate, although a lower proportion (70%) of the participants consented to skin prick testing at age 13 years. However, those who did not undergo skin prick test at age 13 years had a similar prevalence of atopic sensitization at age 32 years compared with those who did not.

A limitation of this study is that the environmental exposures were self-reported rather than objectively measured, and not all were recorded at every age from birth to 13 years. There may also be other important environmental exposures that we have not recorded. For example, other household members may have smoked tobacco, resulting in childhood exposure, but we only assessed the parental status. However, these errors in exposure measurements would be most likely to bias to the null and may have led to underestimation of the attributable fractions.

Although a strength of this study is that we used an objective measure of atopic sensitization, many of those with positive skin prick tests may not have symptoms of allergic disease. We also cannot eliminate the possibility that parents avoided certain exposures if their child was atopic or at risk for atopy. However, we have previously found that the prevalence of breastfeeding⁵ and pet ownership⁶ did not differ for children with a family history of atopy, making reverse causation an unlikely explanation for our findings. Smoking was less prevalent among parents with a history of atopy,⁷ however, and it is possible that this inflated the risk of sensitization associated with not being exposed to tobacco smoke.

In conclusion, this study found that breastfeeding was associated with increased risk of atopic sensitization, whereas childhood exposure to tobacco smoke, cat and dog ownership, thumb-sucking and nail-biting, and household crowding, all appeared to protect against atopic sensitization. Within our cohort the combined effect of these environmental exposures (or lack thereof) may explain 58% of atopic sensitization at age 13 years. This effect persists into adult life and may explain 49% of atopic sensitization at age 32 years.

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