

The use of mutually exclusive categories for atopic sensitization: A contrasting effect for family size on house dust mite sensitization compared with ryegrass sensitization

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Our aim was to examine the relative importance of family size on sensitization to two different allergens: ryegrass and house dust mite (HDM), using a mutually exclusive classification for allergen-specific sensitization. An 8-year follow-up birth cohort study of children born between 1988–89 was conducted. The follow-up sample consisted of 498 children residing in Northern Tasmania in 1997 (84% of eligible). Outcome measures included skin prick test (SPT) reaction to nine aeroallergens and parental questionnaire. Family size was defined as sibling number in 1997. Children with a positive SPT to either Der p or Der f house dust mite but not ryegrass were classified as HDM-exclusive ($n = 84$). Children with a positive SPT to ryegrass but not HDM were classified as ryegrass-exclusive ($n = 43$). Family size was associated with reduced ryegrass-exclusive sensitization [AOR 0.57 (0.39, 0.84) per increase in sibling number] but not HDM-exclusive sensitization [AOR 0.97 (0.77, 1.23)]. The difference in the family size effect on these sensitization outcomes was significant ($p = 0.02$). Similarly, family size tended to be associated with reduced asthma among ryegrass-exclusive sensitized children [AOR 0.45 (0.18, 1.12)] but not HDM-exclusive sensitized children [(AOR 1.46 (0.80–2.65)]. Large family size was strongly associated with reduced sensitization for ryegrass allergens but not HDM allergens using mutually exclusive sensitization categories. If this difference is confirmed in other studies, the contrasting effect of family size may reflect differences between these allergens with regard to level or timing of early life exposure, differences in allergen-specific potentiation for sensitization or unidentified confounding. The use of mutually exclusive categories for allergen sensitization will assist future work on child atopic disease.

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A protective effect of increased numbers of siblings on the development of atopic disease has been suggested (1, 2). It is likely that such an effect operates by altering the immune response that leads to the inflammation seen in atopic disease. This effect may be due to an increased

early exposure to virus infections, which alters the balance of the immune system away from Th2 and towards a Th1 response (3, 4).

A recent review of sibling number and atopic disease found a negative association between sibling number and atopic outcomes in 48 of the

53 studies reviewed (5). The apparent protective effect of high sibling number was more consistent for hay fever than asthma or wheezing (5). The more inconsistent findings for asthma may reflect a higher level of disease misclassification for asthma and also that the mechanisms underlying the sibling effect are atopic and the weaker effect for asthma is because not all asthma cases occur through this mechanism (5). In addition, we propose that the differing pattern of allergen-specific sensitization for atopic asthma compared with atopic hay fever may also contribute. In particular, while hay fever is closely linked to ryegrass or pollen sensitization, asthma has been shown to be more strongly linked to house dust mite (HDM) sensitization (6–8).

In this context it is important to examine the effect of family size on the development of sensitization to specific allergens considered to play a significant role in allergic disease such as grass pollen and dust mite. Several previous studies have examined the effect of family size on specific allergen sensitization (5, 9–14). These studies have examined allergen-specific outcomes such as high ryegrass IgE but concomitant sensitization to other allergens within the allergen-positive group has not been taken into account. Thus, the outcome of allergen-specific sensitization remains contaminated by concomitant sensitization to other allergens. For example, a large proportion of children allergic to ryegrass may also be allergic to HDM. Here, we use new mutually exclusive categories for allergen-specific sensitization to remove the problem of concomitant sensitization when evaluating allergen-specific sensitization. This report (i) outlines the method used to develop mutually exclusive sensitization categories and (ii) examines how the sibling effect relates to ryegrass-exclusive sensitization compared with HDM-exclusive sensitization in a prospective birth cohort.

Methods

For this report, we utilized comprehensive baseline infant data collected as part of the Tasmanian Infant Health Survey in 1988–9 (15) together with childhood data on allergic sensitization and atopic disease (16) available from a follow-up study, the Childhood Allergy and Respiratory Health Survey, which occurred later in 1997 (17).

Both these studies received ethical approval from the Human Ethics Committee of the University of Tasmania.

The Tasmanian Infant Health Survey (TIHS)

This birth cohort study operated from hospitals in Tasmania, Australia, where approximately 93% of births in Tasmania occurred. Infants born were scored to assess the risk of sudden infant death syndrome (SIDS) using a perinatal score model based on maternal age, birthweight, infant sex, breastfeeding, season of birth and duration of second stage of labor and the top quintile of live births by score were eligible for the cohort (18). All multiple births were included. The eligibility criteria and study methods are discussed in more detail elsewhere (15). Data were obtained on three occasions. The first interview was conducted in hospital on the fourth day of life. A home interview was conducted during the fifth postnatal week. The third interview was conducted by phone when the infant was approximately 10 weeks postnatal age. In 1988/9, 609 (88% of eligible) infants in Northern Tasmania had a TIHS home interview at 1 month of age.

The 1997 Childhood Allergy and Respiratory Health Study (CARHS)

In 1997, follow up was conducted through school records (17). Eligible children and their parents were invited to attend the Launceston General Hospital for a parental interview and child assessment. The parental questionnaire included International Study of Asthma and Allergies in Childhood (ISAAC) (19) questions on asthma, wheeze, hay fever and eczema and also questions on the home environment and other factors. Baseline lung function measures were obtained as follows: the children were asked to perform forced expiratory manoeuvres standing without a nose clip following a standard protocol (20) using an electronic spirometer (Vitalograph Alpha 2, model AL0642; Vitalograph, Buckingham, UK) which was calibrated at the beginning of every session. Skin prick testing (SPT) was used to assess the cutaneous reaction to exposure to the house dust mites *Dermatophagoides pteronyssinus* (Der p) and *D. farinae* (Der f), cat, dog, alternaria, ryegrass, cow's milk, egg, and peanut (Hollister-Stier purified allergen extracts supplied by Bayer, Sydney, Australia) and positive (histamine 10 mg/ml and 1 mg/ml) and negative (glycerine) controls. Wheal allergen reactions of 2 mm or greater at 15 min were classified as positive. Children with a positive SPT were classified as atopic. Children with a positive SPT to either Der p or Der f were classified as

sensitized to HDM. For this report, as previously used in the Phase 1 ISAAC study, the report of wheezing or whistling in the chest over the past year is termed 'asthma' (19). In this study, a positive report of asthma did relate to a biologic measure of airway obstruction. Asthma ever was associated with a significant ($p = 0.008$) reduction in the FEV₁/FVC ratio, of 1.7% (17). In Northern Tasmania in 1997, 499 (84%) of the 596 children identified as participants in the 1988–89 TIHS at birth agreed to participate in the CARHS study. Skin prick test data were not obtained on one autistic child. For 456 of these children, TIHS home visit data as well as the initial TIHS hospital interview data were also available. The mean age at the time of skin prick testing was 8.24 (8.17, 8.30) years.

Statistical methods

Multiple logistic regression models were used to provide adjusted odds ratios and 95% confidence intervals. Because the outcomes studied were not rare, the odds ratios reported do not approximate relative risks well, although the p -values are valid (21). The use of odds ratios does, however, provide better comparability to previous studies on sibling size and childhood atopic disease. The main exposure of interest was sibling number. As we have previously reported that sibling number in childhood, rather than at birth was associated with asthma and hay fever (22), we examined sibling number in 1997 as the main exposure. The terms 1997 sibling number and family size are used interchangeably in the rest of this paper. Further preliminary analysis confirmed that family size at age seven rather than at birth was the more important determinant of atopic sensitization because atopic sensitization was not significantly associated with birth order and in a two-term model, room density at age seven was strongly and significantly associated with atopy but room density at birth was not (data not shown). We compared the goodness-of-fit of the model to the data when using sibling number as a categorical rather than continuous term to predictor atopy or wheeze and found no significant reduction in deviance. Thus, sibling number was retained as a continuous variable. The disease outcomes of interest were (i) specific sensitization, (ii) mutually exclusive categories of sensitization, and (iii) asthma within each allergen-specific sensitization category. To construct the mutually exclusive categories of atopy, we defined 'no sensitization' as the baseline reference group (coded as 0) for all three variables. Children with atopy were (a) coded '1' if the

child had a positive SPT to either Der p or Der f but a negative SPT to ryegrass, regardless of the other aeroallergen SPT results. This is termed the 'HDM-exclusive' sensitization. (b) Or coded '1' if the child had a negative SPT to Der p and Der f but a positive SPT to ryegrass, regardless of the other aeroallergen SPT results. This is termed 'ryegrass-exclusive' variable. (c) Or coded '1' if the child had a positive SPT to Der p and Der f and a positive SPT to ryegrass, regardless of the other aeroallergen SPT results. This is termed 'mixed sensitization'. Children with other forms of atopy ($n = 6$) were excluded. To compare the effect of sibling number on ryegrass-exclusive sensitization compared with HDM-exclusive sensitization, we used a logistic model with a binary outcome of one for rye-exclusive sensitization and zero for HDM-exclusive sensitization. This model also allowed for the difference in effect to be assessed after taking into account perinatal score or other confounders. To examine the relationship between sibship size and asthma by allergen-specific sensitization subgroups, a truncated continuous sibling variable was used with the highest value assigned to three or more children. Multiple logistic regression models were used to assess the effect of sibling number on each binary outcome with and without adjustment for confounders. The confounders examined included the numerical perinatal score used for cohort entry. For models which incorporated infant factors measured at home visit as confounders, the number of children with full data available was less ($n = 456$). Similar results were obtained when a cut off of 3 mm or greater rather than 2 mm or greater was used to define SPT positivity. We approached the analyses using an atopic asthma model where (i) factors determine initial sensitization and (ii) factors induce asthma among sensitized individuals. This conceptual model has previously been discussed in relation to HDM allergen-induced airway disease (23). The analyses were conducted using STATA 7 (24).

Results

Allergen-specific sensitization and atopic disease

The prevalence of various types of atopic sensitization and atopic diseases for this sample are shown in Table 1. Figure 1 shows the pattern of overlapping sensitization to different aeroallergens. Overall, 41% (206/498) of children were sensitized to at least one of the aeroallergens tested. For mutually exclusive allergen-specific sensitization, the HDM-exclusive pattern ($n = 84$;

Table 3. The association between increasing sibling number and allergen-specific sensitization

	Total n	Percentage sensitized by sibling number				Odds ratio	95%CI	p-value	Adjusted odds ratio	95%CI	p-value
		0	1	2	3 or more						
Any ryegrass sensitization	498	30.0	29.9	22.6	14.4	0.71	0.57–0.87	0.001	0.66	0.53–0.84	0.001
Any HDM sensitization	498	33.3	33.8	31.2	28.8	0.92	0.78–1.08	0.31	0.90	0.75–1.09	0.29
Ryegrass-exclusive sensitization	498	13.3	11.5	8.1	4.8	0.62	0.44–0.88	0.007	0.57	0.39–0.84	0.004
HDM-exclusive sensitization	498	16.7	15.3	16.7	19.2	0.97	0.79–1.19	0.76	0.97	0.79–1.23	0.83

Odds ratios have been adjusted for maternal smoking in pregnancy, family history of asthma at birth, infant sheepskin use, breastfeeding, infant plastic mattress liner, child feather quilt use and child fish consumption.

contamination of any observed effect of family size on HDM-sensitized children due to concomitant sensitization to ryegrass or vice versa. On univariate or multivariate analysis, family size was not associated with HDM-exclusive sensitization but large family size was clearly associated with a significant reduction in ryegrass-exclusive sensitization. Larger family size was also associated with a reduced likelihood of mixed sensitization [AOR 0.57 (0.39, 0.84), per sibling]. Figure 2 shows that the effect of increasing sibling number was strongly associated with reduced ryegrass-exclusive sensitization ($p = 0.001$) but not HDM-exclusive sensitization ($p = 0.80$). The difference in the sibling effect for HDM-exclusive and ryegrass-exclusive sensitization was significant ($p = 0.02$) (Fig. 2).

Sibling number and asthma by allergen-specific sensitization

We then examined how family size was associated with asthma taking into consideration allergen-specific sensitization. Overall, family size was not significantly associated with asthma [AOR 0.85 (0.72, 1.02)]. Among non-sensitized children, no association between family size and asthma was observed [AOR 0.86 (0.68, 1.10)]. Among HDM-exclusive sensitized children, no protective effect for larger family size was evident [AOR 1.46 (0.80, 2.65)]. However, among

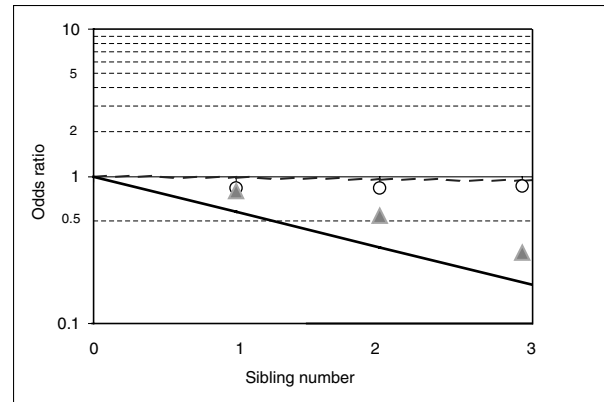


Fig. 2. The contrasting effect for sibling number and HDM-exclusive sensitization compared with ryegrass-exclusive sensitization. ○: unadjusted OR for sensitization; - - -: adjusted OR for HDM-exclusive sensitization ($p = 0.83$); ▲: unadjusted OR for ryegrass-exclusive sensitization; —: adjusted OR for ryegrass-exclusive sensitization ($p = 0.004$). Note: the difference in the sibling effect between ryegrass-exclusive sensitization and HDM-exclusive sensitization is significant ($p = 0.02$).

children sensitized to ryegrass, larger family size was significantly associated with a reduced likelihood of asthma [AOR 0.62 (0.38, 0.99)] (Table 4). Thus, the association between family size was evident among the subgroup of children with ryegrass sensitization but not among children with HDM-exclusive sensitization.

Table 4. The association between increasing sibling number and asthma by sensitization subgroup

Sensitization subgroup	n	Percentage sensitized by sibling number				Odds ratio	95%CI	p-value	Adjusted odds ratio	95%CI	p-value
		0	1	2	3 or more						
Any ryegrass sensitization	116	66.7	61.7	33.3	44.4	0.60	0.38–0.96	0.03	0.62	0.38–0.99	0.05
Any HDM sensitization	157	55.6	55.6	31.0	52.8	0.86	0.60–1.23	0.41	0.80	0.55–1.16	0.24
Ryegrass-exclusive sensitization*	43	50.0	38.9	13.3	16.7	0.46	0.19–1.12	0.09	0.45	0.18–1.12	0.09
HDM-exclusive sensitization	84	40.0	29.2	19.4	50.0	1.34	0.79–2.28	0.27	1.46	0.80–2.65	0.21

Odds ratios have been adjusted for child feather quilt use, child exposure to active smoking and home gas appliance use in childhood.

*Adjusted for child feather quilt use only, due to small sample size.

Further examination of the effect of confounding factors

We further assessed the potential confounding effect of the cohort entry criteria and other factors. The following factors did not predict the outcomes in Table 3 and the addition of each of these individual variables to the final confounder set did not alter the adjusted odds ratios reported in Table 3 by more than 10%: components of the cohort entry scoring system (maternal age, birthweight, infant sex, intention to bottle feed, season of birth, duration of second stage of labor, multiple birth), the composite perinatal score, domestic gas used for cooking or heating in infancy, infant or child exposure to active cigarette smoking in the same room, history of a cold by 1 month of age, history of a chest infection by 12 weeks of age or mould observed in the baby's bedroom at 1 month by the research interviewer.

In particular, the difference in the effect of sibling number on ryegrass-exclusive compared with HDM-exclusive sensitization persisted after controlling for the confounders listed in Table 3 and also after controlling for perinatal score ($p = 0.02$).

Further comparison of rye-exclusive and HDM-exclusive sensitization

The results above indicated that both the association between family size and initial sensitization and also family size and asthma were more evident for children with rye-exclusive than HDM-exclusive sensitization. We then examined whether this difference was also evident for other possible determinants of atopy. Male sex was not related to atopy overall [OR 1.03 (0.69, 1.53)]. However, the difference in association between male sex and rye-exclusive sensitization [OR 0.56 (0.42, 1.08)] and HDM-exclusive sensitization [OR 1.29 (0.74, 2.27)] was significant ($p = 0.04$). Similarly, any fish consumption in childhood was negatively associated with rye-exclusive sensitization [OR 0.36 (0.17, 0.78)] but not HDM-exclusive sensitization [OR 1.00 (0.46, 2.20)]; difference in effect, $p = 0.04$. Thus, there is some evidence that the contrasting effect of family size on rye-exclusive sensitization compared with HDM-exclusive sensitization also occurs for other possible determinants of atopy.

Discussion

This report examines how a previously identified factor for atopic sensitization, large family size, related to allergen-specific sensitization. The observation that larger family size had a clear protective effect for ryegrass but not HDM

sensitization, if confirmed in other work, suggests that the apparent protective effect of a high number of siblings does not occur to the same extent for all allergens.

The main strength of this study was the delineation of mutually exclusive sensitization outcomes, allowing a clearer assessment of the effect of family size on HDM-exclusive sensitization without any possible contamination due to concomitant sensitization to ryegrass allergen. This is the first study to examine the association between family size and atopic sensitization using this approach. The birth cohort was not representative of all births in Tasmania but adjustment for the perinatal scoring components did not alter the study findings and these children should not differ in a material way to other children with regard to the development of allergic sensitization. The prospective cohort design allowed us to control for pertinent infant factors. A significant difference in effect for ryegrass-exclusive sensitization compared with HDM-exclusive sensitization was also observed for other factors associated with atopy. However, the sample size here is smaller than that used to examine family size and atopy in many cross-sectional studies. Thus, it would be important to confirm these findings by examining whether a significant difference in effect for family size and ryegrass-exclusive compared with HDM-exclusive sensitization was also evident in these larger studies. However, the observed lack of effect of larger family size on HDM sensitization is unlikely to have occurred by chance because the proportion of children with HDM-exclusive sensitization was large in our location, the magnitude of the effect was low and relatively unaltered by adjustment for confounding factors. Furthermore, a similar contrasting pattern was also found for atopic asthma, with no effect of family size on asthma among children sensitized exclusively to HDM but a strong protective effect of larger family size among ryegrass-sensitized children.

The interpretation of these results in the context of past work on family size and atopy

Karmaus and Botezan recently reviewed the association between sibling number and allergy (5). They identified 16 studies that examined sibling number and sensitization as defined by a positive SPT reaction or a positive specific IgE serum antibody to any of the allergens tested (5). Although the definitions of positivity varied, sensitization to specific allergens was negatively associated with three or more siblings in 14 of 16

studies with a summary odds ratio (weighted for sample size) of 0.62 (5). Only two studies reported a positive association (5). For one of these, data on allergen-specific sensitization patterns could not be found (25). The second report indicated an AOR of 1.11 for more than three siblings and atopy (14). The sample for this study was younger children at 3–5 years and among the atopic children, sensitization to HDM (69%) was more common than ryegrass sensitization (42%) (14). From our results, the high proportion of HDM-atopic children in this sample may have contributed to the lack of any apparent protective effect for sibling number.

Other studies also provide some support that the sibling effect may be less evident for HDM-induced atopic disease. In the 1958 British cohort, the negative association between older sibling number and sensitization was of stronger magnitude for grass than HDM sensitization and an apparent protective effect for younger siblings was only evident for ryegrass sensitization (10). A cross-sectional study in East Anglia found a negative association between family size and atopy (a positive SPT to any one of five allergens tested) of borderline significance ($p = 0.05$) that was largely due to a strong negative association between family size and grass atopy (9). The association between family size and HDM sensitization was not significant (9). In the European Community Respiratory Health Survey, a strong association between family size and grass IgE but not HDM IgE was found (11). Among young adult Danish, a strong negative association between family size and grass atopy, but not HDM atopy was found (13). Two or more siblings (compared with none) have been shown to be inversely associated with grass or pollen-induced rhinitis [AOR 0.80 (0.64–0.99)] but not HDM or animal-induced rhinitis [AOR 1.00 (0.81–1.24)] (12). Thus, the findings from these studies also indicate that the protective effect of family size may be more evident for ryegrass than HDM sensitization. However, these studies did not use mutually exclusive sensitization categories nor conduct formal tests of significance with regard to difference in effect because, unlike this report, the studies did not aim to assess whether a contrasting effect was evident.

Possible explanations for a contrasting effect of family size

We now discuss possible explanations for the contrasting effect of family size on HDM sensitization compared with ryegrass sensitization in light of the hygiene hypothesis that the protective effect of large sibling size is most likely to be

acting through infection-induced immune deviation.

Differences in the timing of early life exposure to HDM compared with ryegrass allergens. A postulated mechanism for the sibship effect is earlier and more frequent infections associated with a large sibship. Repeated infections may deviate the developing immune system from an atopy-prone profile to either Th1 (3) or modified Th2 (26) responses. The time interval between viral infection and allergen exposure may be critical. In mice, intranasal exposure to influenza A before ovalbumin allergen challenge induces T cell tolerance but concurrent infection at the time of ovalbumin allergen challenge lead to airway hyper-reactivity and promotion of Th2 cytokines (27). It could be expected that the protective effect of repeated infections inducing immune deviation would be greater if this occurred prior to allergen exposure, as would often be the case with ryegrass. In contrast, infection concurrent or after allergen exposure such as occurs with HDM would be less likely to be protective and perhaps even adverse through mucosal inflammation leading to enhanced allergen penetration or a direct Th2 enhancement, as has been shown for respiratory syncytial virus infection (28). The concept of a critical window for infection-induced immune deviation before a major allergen challenge and subsequent sensitization is consistent with the previous finding in our location that the protective effect of large family size was evident only for late onset asthma, beginning after age four (22).

Thus, newborns could have a larger window of opportunity for immune-deviating repeated infections to occur with regard to ryegrass rather than HDM sensitization. High ryegrass allergen levels are experienced only seasonally and modern infants spend most of the first year of life indoors. In contrast, the window of opportunity for infection-induced immune deviation prior to HDM allergen exposure could be narrower – in our location, infant mattresses harbored HDM allergen even at 1 month of age (29). In addition, studies have shown that ryegrass sensitization develops at a later age than HDM sensitization. For example, in a natural history cohort, HDM sensitization was four times more common than grass sensitization at age two but only 1.5 times by age four (30).

Differences in the level of early life exposure to HDM compared with ryegrass allergens. In addition, regardless of timing, an infant's personal exposure allergen may be higher for HDM

than ryegrass. Bedding harbors large amounts of HDM allergen (31) and with high continuous exposure, allergen presence alone may be sufficient to induce sensitization while with lower or more intermittent exposure, additional cofactors such as host susceptibility may be important. Here, for children with mixed sensitization, HDM exposure may have occurred later or at a lower level than the HDM exposure that HDM-exclusive allergic children experienced. In a lower HDM allergen environment, the allergen-induced stimulatory signal for sensitization would be weaker and thus, the existence of a co-factor such as incomplete infection-initiated immune deviation would appear as an important co-determinant. This concept that high cumulative allergen exposure could attenuate the relative importance of host susceptibility factors, is reinforced by the findings that HDM or cat sensitization occur at lower levels of allergen exposure for children with genetic atopic susceptibility than those without (32, 33). Thus, in an analogous fashion, host susceptibility due to a lack of infection may be more important for lower dose allergen exposure. For children exposed to very high levels of HDM allergen, sensitization may occur regardless of host susceptibility due to genetic predisposition or a lack of early infection. Thus, high cumulative allergen exposure could attenuate the relative importance of host susceptibility factors related to sibship size.

Differences in allergen-specific confounders or potentiators of sensitization. If other unmeasured factors were strong determinants of only HDM exposure but not ryegrass exposure (for example, a bedding microclimate encouraging high HDM levels), then failure to control for these confounders could lead to a masking of the effect of sibship on HDM sensitization. Another possible explanation is the presence of an allergen-specific potentiator that operates for HDM sensitization but not ryegrass sensitization. In this cohort, early exposure to domestic gas appliances was associated with an increased risk of HDM but not ryegrass sensitization (17) suggesting the possibility that poor indoor air quality potentiates the adverse of HDM exposure on HDM sensitization but for ryegrass, an outdoor allergen, this co-factor does not operate on the casual pathway for ryegrass sensitization. This could also diminish the relative importance of infection-induced immune deviation for sensitization to HDM compared with ryegrass.

We have delineated two mutually exclusive forms of atopic asthma: (a) airway disease among children sensitized to HDM and other allergens

but not ryegrass and (b) airway disease among children sensitized to ryegrass. Tables 3 and 4 show that large family size appeared to operate as a protective factor for both sensitization and asthma symptoms related to ryegrass sensitization but large family size was not significantly protective for either facet of atopic asthma related to HDM sensitization. In fact, increasing sibling number tended to increase, not decrease, the likelihood of asthma among HDM-exclusive sensitized children, possibly reflecting that higher resident number is associated with higher Der p levels (29) or the influence of infections on the development of asthma symptoms in sensitized subjects.

These findings indicate that the protective effect of a large family with regard to childhood asthma could operate at the level of initial sensitization and also may influence symptoms post-sensitization. However, our study was not large enough to fully examine the issue of respiratory symptoms among mutually exclusive sensitization subgroups and larger studies are required. It is clear, however, that in childhood asthma the protective effect of large family size will be related to the specific pattern of inhalant allergen sensitization. This allergen-specific difference may explain why the sibling effect has been less consistently observed for asthma than hay fever (2, 5) in addition to any lack of effect due to the existence of non-atopic asthma. Our results indicate that the protective effect of large sibship size is important for ryegrass-induced rhinoconjunctivitis than non-atopic asthma or HDM-induced airway disease. These findings also suggest that the protective effect of large family size is not operating by a generalized immune deviation but in a more allergen-specific way.

If a contrasting effect of family size on ryegrass-exclusive compared with HDM-exclusive sensitization is also observed in other studies, further work should test whether differences in cumulative allergen exposure during early infant life may explain the contrasting findings of the effect of family size on sensitization to ryegrass compared with HDM. This report has highlighted the importance of careful delineation of allergen-specific subgroups within the broad spectrum of atopic sensitization, an approach that is likely to assist future investigations of the causal pathways underlying the development of atopic disease in childhood.

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