Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey

C Svanes, D Jarvis, S Chinn, E Omenaas, A Gulsvik, P Burney, for the European Community Respiratory Health Survey

Background: The literature indicates that early exposure to children in the family and to day care permanently influences the development of allergic disease. A study was undertaken to examine the associations of family size and day care with adult asthma and hay fever and to determine whether these associations are mediated through specific IgE production and whether they vary with allergic predisposition.

Methods: 18 530 subjects aged 20–44 years from 36 areas predominantly in the market economies participated in the European Community Respiratory Health Survey and provided information through interviewer-led questionnaires. 13 932 subjects gave blood samples for measurement of specific IgE.

Results: Hay fever was less common in subjects with many siblings (OR=0.92; 95% CI 0.90 to 0.95 per sib). There was a U-shaped relationship between asthma and number of siblings (quadratic effect of siblings, p=0.014, pFEV,=0.016). In subjects without siblings but exposed to children in day care, hay fever was less common (OR=0.76; 95% CI 0.60 to 0.98) and asthma symptoms were more common (OR wheeze=1.48; 95% CI 1.12 to 1.95). Adjustment for specific IgEs did not alter these associations. The inverse association of hay fever with siblings was found in sensitised subjects (OR=0.89; 95% CI 0.84 to 0.94) and in those with parental allergy (OR=0.91; 95% CI 0.85 to 0.97), but not in subjects without such a predisposition (OR=1.02; 95% CI 0.97 to 1.09).

Conclusion: Subjects exposed to many children at home or in day care experienced less hay fever and more asthma in adulthood. Microbial challenge through children may contribute to a non-allergic immunological development giving less hay fever but more airways infections predisposing to asthma. These effects were not mediated through production of specific IgE. The protective effect of siblings on hay fever was particularly strong in those with an allergic predisposition.
METHODS
Data collection
The methodology for the ECRHS has been fully described elsewhere. Briefly, participating centres selected an area defined by pre-existing administrative boundaries with a population of at least 150,000. Where possible an up to date sampling frame was used to select randomly at least 1500 men and 1500 women aged 20–44 years. In stage 1 subjects were sent the ECRHS screening questionnaire, a self-completed questionnaire asking about symptoms suggestive of asthma, the use of medication for asthma, and the presence of hay fever or nasal allergies. In stage II a random sample of subjects who had completed the screening questionnaire was invited to attend for a more detailed interviewer-led questionnaire, lung function testing, and blood tests. Data for 18 530 subjects from 36 centres in 16 countries were included. Informed consent was obtained from all participants and the study was approved by all the ethics committees involved.

The questions from the interviewer-led questionnaire used in this analysis are given as footnotes to tables 1 and 2. Questions about asthma symptoms that did not include the word “asthma” were used as outcome variables, as diagnosing asthma in subjects with respiratory symptoms is dependent on the presence or absence of atopy according to traditions that vary between countries.

Specific IgE to house dust mite, cat, timothy grass and Cladosporium was measured in serum samples obtained by centrifugation of 10 ml whole blood at 4000 g for 10 minutes. All samples were stored at −20°C and analysed in a central laboratory by the CAP system, (Pharmacia Diagnostics, Sweden) except for samples from Melbourne which were analysed locally using the same analytical technique. The test for specific IgE was considered to be positive if values of $>0.35$ kU/l (the lowest detection limit of the assay) were obtained. The distribution of serum IgE for all but one of the centres included in the study has been described previously.

Of the 18 530 subjects included in the study, 13 932 (75%) provided a blood sample. “Atopy” was defined as specific IgE to cat, grass, house dust mite, and/or mould. The association of childhood environmental factors and atopy in this population has been described in a previous paper.

Forced expiratory volume in 1 second (FEV$_1$) and forced vital capacity (FVC) were recorded by a standard spirometric method and the ratio between FEV$_1$ and FVC was calculated. Percentage predicted FEV$_1$, was calculated by the formula from the European Community for Steel and Coal. Methacholine challenge was performed using a dosimeter (Mefar, Brescia, Italy) and the degree of bronchial responsiveness (BHR) was expressed as the ECRHS slope. Height was measured before measurement of lung function.

Statistical analysis
Logistic regression models were used to assess the independent effects of the childhood exposure variables (number of siblings, bedroom sharing, day care attendance, and serious respiratory infection; questions given in footnote to table 1) on symptoms of asthma, hay fever, and eczema (questions given in footnote to table 2). Multiple linear regression models were used to assess the independent effects of the childhood exposure variables on lung function and bronchial responsiveness. The number of siblings was categorised as 0, 1, 2, 3, and 4 or more or entered as a continuous variable. A U-shaped distribution of asthma symptoms and lung function measures with number of siblings was revealed by analyses of categorised data and fitted into models using a continuous plus a quadratic effect of siblings. In all analyses adjustments were made for sex, age, parental smoking (paternal smoking, maternal smoking, maternal smoking in pregnancy), adult smoking habits (never, ex-smoker, current smoker), current occupation (European Economic Community status groups 14) and study centre. Potential heterogeneity between centres in the effect of each exposure variable on asthma and on hay fever was studied by meta-analyses according to DerSimonian and Laird. Analyses of day care were stratified by presence of siblings, and analyses of siblings and hay fever were stratified by allergic predisposition (atopy, parental allergy). Stratification by sex did not reveal differences in the associations of symptoms of allergic disease with exposure to children (data not given). All analyses were carried out using the statistical software program Stata 5.0.

RESULTS
Sibships were relatively large in Ireland and small in Estonia, otherwise there were relatively small differences between countries with regard to family size (table 1). Attendance at day care before the age of 5 varied greatly from 20% in Sweden to 87% in Belgium.

Mutually adjusted estimates for associations of family size, bedroom sharing, day care attendance, and serious respiratory infections with symptoms are presented in table 2. Hay fever and eczema consistently decreased with increasing number of siblings. Bedroom sharing and day care attendance before the age of 5 years were not significantly related to symptoms after adjustment for other factors in the total sample. Asthma symptoms were more common in subjects who reported severe respiratory infections before the age of 5. The increased risk for hay fever and eczema related to severe respiratory infections was slightly attenuated but still statistically significant after adjustment for siblings.

Asthma symptoms were related to family size in a non-linear pattern, with an initial decrease and a subsequent

**Table 1** Prevalence of childhood environmental factors (%) by country in subjects born between 1945 and 1970

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<th>France</th>
<th>Spain</th>
<th>Italy</th>
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<td>1579</td>
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<td>53</td>
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<td>Serious respiratory infection‡</td>
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<td>11</td>
<td>15</td>
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*“Did you regularly share your bedroom with any older children before the age of five years?”
†“Did you go to a school, play school, or nursery with any older children before the age of five years?”
‡“Did you have a serious respiratory infection before the age of five years?”
increase in risk with increasing number of siblings (table 2). This U-shaped relation as a quadratic effect of siblings was statistically significant (p<0.014). When analysed using two siblings as the baseline category, having more than two siblings was significantly related to increased risk for asthma symptoms (ORwheeze =1.12 (95% CI 1.01 to 1.23); ORwheeze with SOB =1.25 (95% CI 1.10 to 1.42); ORwheeze without cold =1.17 (95% CI 1.04 to 1.32); ORwaking with SOB=1.23 (95% CI 1.04 to 1.46)). Having less than two siblings was related to a slight non-significant increase in risk for asthma symptoms (odds ratios ranging from 1.03 to 1.10).

When atopic asthma (symptoms plus atopy) and non-atopic asthma (symptoms but no atopy) were analysed as separate outcome variables, a U-shaped association with the number of siblings was pronounced and highly significant for non-atopic asthma while atopic asthma showed no significant association with the number of siblings, although a U-shaped effect was indicated.

In subjects with no siblings day care attendance was associated with a reduced risk for hay fever but an increased risk for asthma symptoms (table 3). Day care was not associated with symptoms in subjects with siblings. The associations of day care with hay fever and wheeze were significantly different for those with and without siblings. No such interaction was indicated for eczema, for which there was no association with day care in those with or without siblings.

The association of hay fever with number of siblings was not accounted for by atopy (defined as specific IgE to grass, cat, house dust mite, and/or mould). Adjustment for atopy or specific IgE to grass did not attenuate the effect of having siblings on hay fever (adjustment for atopy: ORwheeze=0.93
A suggested explanation for this association is the “hygiene hypothesis”, the theory that the microbial stimulation in childhood provided by contact with other children may contribute to a non-allergic immunological maturation. In agreement with Krämer et al., we found a “protective” effect of day care on hay fever only in subjects without siblings. This suggests that the effect of exposure to children is not dose dependent; in children who are already exposed to children in the family, exposure to more children in day care provides no further “protection”. The effect of siblings on hay fever appears to be dose related. However, this increased “protection” with increasing number of siblings could reflect a higher probability of receiving the hypothesised immunological stimulation during the sensitive age window.

The effect of siblings and day care attendance on hay fever was not mediated through atopic sensitisation. Adjustment for atopy, for number of positive specific IgEs, for the level of each specific IgE hardly altered the effect of siblings on hay fever. Further, within the group of atopic subjects there was a strong inverse association between number of siblings and hay fever. The general belief has been that the microbial challenge represented by number of siblings contributes to a Th1 stimulation that downregulates IgE responses and thereby leads to less allergic disease. Our findings indicate that production of specific IgE antibodies is not the link between Th1 stimulation (if this is what contact with other children represents) and the observations made in this study. The significance of the “hygiene hypothesis” in studies on atopy is yet to be determined.

**DISCUSSION**

Childhood exposure to other children in the family or in day care was associated with less hay fever and more asthma symptoms in young adults. The consistency of the associations with both family size and with day care (in subjects with no siblings) suggests that early exposure to other children is the factor of importance rather than the sociocultural effects of family size or day care. This view is supported by the consistency of the findings across centres with varying rates of day care attendance, varying family sizes, and varying socioeconomic conditions.

The particular strength of this study, apart from the large number of subjects, was the ability to compare findings between 36 socioculturally, genetically, and geographically different centres across the western world. One limitation of the study was the retrospectively collected information about childhood environmental factors. The information on childhood respiratory infection is likely to be biased and is therefore not used for major conclusions but for a minor argument in the discussion. The number of siblings was the most important exposure variable and is not likely to be affected by recall bias. Information about childhood day care attendance as given by adults may be imprecise, but an error in recall is not likely to be systematic with regard to adult asthma or hay fever. The question on day care referred to attendance before the age of 5 years which, for the purpose of this paper, is rather imprecise although easier to recall. These problems will probably tend to attenuate rather than to produce associations with adult allergic symptoms. The tendency towards better lung function in subjects who attended day care suggests that these children were healthier, but this needs to be assessed by longitudinal analyses.

The observation of less hay fever in subjects exposed to other children in the family or in day care is in agreement with previous studies. A suggested explanation for this observation is the “hygiene hypothesis”, the theory that the microbial stimulation in childhood provided by contact with other children may contribute to a non-allergic immunological maturation. In agreement with Krämer et al., we found a “protective” effect of day care on hay fever only in subjects without siblings. This suggests that the effect of exposure to children is not dose dependent; in children who are already exposed to children in the family, exposure to more children in day care provides no further “protection”. The effect of siblings on hay fever appears to be dose related. However, this increased “protection” with increasing number of siblings could reflect a higher probability of receiving the hypothesised immunological stimulation during the sensitive age window.

The effect of siblings and day care attendance on hay fever was not mediated through atopic sensitisation. Adjustment for atopy, for number of positive specific IgEs, for the individual specific IgEs separately, or for the level of each specific IgE hardly altered the effect of siblings on hay fever. Furthermore, within the group of atopic subjects there was a strong inverse association between number of siblings and hay fever. The general belief has been that the microbial challenge represented by number of siblings contributes to a Th1 stimulation that downregulates IgE responses and thereby leads to less allergic disease. Our findings indicate that production of specific IgE antibodies is not the link between Th1 stimulation (if this is what contact with other children represents) and the observations made in this study. The significance of the “hygiene hypothesis” in studies on atopy is yet to be determined.
lack of allergic symptoms. Atopy could be a marker of a group with high risk for allergic responses, but within this group other factors could determine whether the individual develops allergic symptoms or not.

The association between the number of siblings and hay fever was observed only in individuals with an allergic disposition—that is, serologically measured atopy or parental allergy. We have previously reported that the presence of specific IgE is related to the number of siblings only in subjects with no parental allergy. Both these interactions were statistically significant and consistent to different methods of analysis. The strong genetic predisposition for IgE production in subjects with parental allergy might be inherited independently of additional microbial stimulation, which such stimulation could inhibit development of IgE immunity in subjects with a less strong genetic predisposition. With regard to symptoms, however, microbial stimulation could be particularly important in subjects who already have signs of a poor Th1 cell development (indicated by atopy or parental allergy). In subjects with no parental allergy and no atopy the Th1 cell function may be satisfactory and additional microbial stimulation from siblings not necessary.

A U-shaped association was found between number of siblings and asthma. Although complicated, this pattern was consistent for lung function as well as symptoms and was consistent between different methods of analysis and homogeneous across centres. The increase in asthma risk in subjects with many siblings was supported by an increase in risk in subjects exposed to many children in day care. As opposed to the very consistent findings in the literature with regard to family size and atopic sensitisation or hay fever, the literature on exposure to children and asthma is inconsistent. There are reports of a protective effect of siblings on asthma, including a report from the British centres of the ECRHS, but most studies show inconsistent, non-significant or complex associations between asthma and family size. Similarly, the literature on day care attendance and asthma gives inconsistent findings.

The discrepancies in the literature regarding early exposure to children and asthma could be related to different definitions of asthma, particularly with regard to concomitant asthma, to asthma being a heterogeneous disease (a disease not only of the immune system but also of the respiratory system), and to problems in ascertaining timing of exposure. As our analysis showed a U-shaped association between asthma symptoms and number of siblings, differences in family size between countries and age groups may also contribute to discrepant observations. In countries or time periods with mostly small families, no trend or indication of a “protective” effect may be observed, while in a society with larger families an increase in risk with many siblings may be revealed.

Microbial burden could possibly explain why those from larger families experience both more asthma and less hay fever. While microbial stimulation during a sensitive stage of immunological development may enhance a non-allergic immunological maturation, this same microbial challenge could also lead to more clinically manifest airways infections, some of which could permanently damage the structure of the lungs. At ages when the immunological profile is already determined, harmful clinical infections may possibly be the only effect of microbial stimulation. An association between severe lower airways infections early in life and adult obstructive lung disease is well documented. The increase in asthma among children who attended day care in the study of Nystad et al was accounted for by more respiratory infections. Although we could not confirm this in our study population, our data on infections are crude. The decrease in asthma symptoms for subjects with one or two siblings might be explained by some protective effect of microbial stimulation, as this effect was only found in subjects with a high predisposition to allergy (as also observed for hay fever). Confounding by birth weight seems unlikely because asthma symptoms were related to total number of siblings rather than birth order.

One apparent paradox of the “hygiene hypothesis” is that no study convincingly shows a direct protective effect of clinical infections on allergic disease. In particular, no study shows a protective effect of respiratory tract infections on allergic disease, even if such infections represent a considerable microbial burden. Bacterial colonization of the respiratory and gastrointestinal mucosa may possibly provide immunological stimulation of Th1 immunity without necessarily causing clinical infections. In agreement with other studies, our study shows not only more asthma, but also more hay fever and eczema related to clinically manifest infections in childhood. Prescot et al showed poor Th1 immunity as well as boosting of the Th2 response in allergic infants, suggesting a generally poor Th1 cell function in these subjects. One might speculate whether the Th1 response to microbial stimulation in allergic subjects could be sufficient to induce some Th2 inhibition but insufficient in the defence against certain pathogenic microbes, rendering allergic subjects liable to more severe clinical infections.

In conclusion, exposure to many children at home or in day care was related to less hay fever and more asthma in adulthood. The microbial challenge that other children represent might contribute to non-allergic immunological development and, at the same time, to more clinical infections including lower airways infections adversely affecting the lungs. The increase in asthma and reduction in hay fever on exposure to other children was not mediated through changes in atopic sensitisation, questioning whether production of specific IgE is the only step on the pathway between deviation of immune responses through early microbial stimulation and the modulation of symptoms of allergic disease. Exposure to siblings led to a reduction in reported hay fever only in subjects with atopy or parental allergy. The microbial stimulation from other children could possibly be of greater importance in preventing allergic symptoms in subjects with impaired Th1 cell function.

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Authors’ affiliations

C Svanes, E Omenaas, A Gulsvik, Department of Thoracic Medicine, University of Bergen, 5021 Bergen, Norway.

D Jarvis, S Chinn, P Burney, Department of Public Health Sciences, King’s College London, London SE1 3DQ, UK.


Project Management Group: P Burney [project leader], S Chinn, C Luczynska, D Jarvis, P Vermeire (Antwerp), H Kesteloot [Leuven], J Bouquet [Montpellier], D Nowak [Hamburg], the late J Frichard (Dublin), R de Marco [Verona], B Rickejen [Groningen], J M Anto [Barcelona], J Alves [Oporto], G Boman [Luppolo], N Nielsen [Copenhagen], P Poletti [Pisa].

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