

# Socioeconomic Status, Number of Siblings, and Respiratory Infections in Early Life as Determinants of Atopy in Children

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Asthma and allergic disorders have been on the increase in recent decades, especially among children living in affluent countries; some aspects of the "Western" way of life may explain this trend. We evaluated the relation of aeroallergen skin test reactivity with socioeconomic status, number of siblings, and respiratory infections in early life. We examined a total of 2,226 schoolchildren, ages 7–11 years, in three areas of Lazio, Italy. Skin prick tests were performed to assess atopic status, and self-administered questionnaires were completed by the parents. The prevalence of prick test positivity was greater among children whose fathers were in the highest educational level than among those in the lowest [prevalence ratio (PR) = 1.58; 95% confidence interval (CI) = 1.21–2.06]. There was also a lower prevalence of atopy among larger sibships (PR =

0.38 for subjects with four or more siblings vs those without siblings; 95% CI = 0.14–0.99). A history of bronchitis or bronchiolitis before age 2 years was weakly associated with an increased risk of atopy, whereas a history of pertussis or pneumonia was not. Both the effect of father's education and the influence of larger sibship size remained when we adjusted for several potential confounding factors, including respiratory infections in early life. We infer that higher socioeconomic status and lower sibling number are determinants of atopy in this Italian population. Protection arising from early severe respiratory infections does not explain this association, although we cannot exclude a role for other viral infections. (Epidemiology 1997;8:566–570)

**Keywords:** allergy, asthma, children, respiratory tract infections, social class, viruses.

A rising prevalence of allergies and asthma has recently been reported from several developed countries<sup>1–3</sup>; hospital admissions for asthma, for example, increased by 21.5 per 10,000 between 1977 and 1990 in the United Kingdom.<sup>4</sup> Various hypotheses have been postulated to explain this secular trend, including increased circulation of allergens, indoor and outdoor pollution, better diagnostic classification and treatment of asthma, and changes in dietary habits.<sup>5,6</sup> Results from studies conducted in Germany indicate that allergic disorders and asthma may be diseases related to affluence: higher rates of skin prick test reactivity and wheezing symptoms were found in Munich, in western Germany, in comparison with Leipzig, in the East.<sup>7,8</sup> Facilitation of early circulation of viral infections among children attending day care centers in eastern Germany was suggested as a possible explanation for the difference.<sup>8</sup> The recent find-

ing of a lower prevalence of skin test positivity among children with multiple siblings supports this hypothesis.<sup>9</sup>

Although previous investigations have shown little association<sup>10,11</sup> or an inverse association<sup>12,13</sup> between socioeconomic status and asthma prevalence, several recent epidemiologic studies of eczema and hay fever have linked such allergic disorders with wealthier social classes.<sup>14,15</sup> Strachan<sup>16</sup> has postulated that higher living standards and improved personal hygiene lead to an increased risk of allergic sensitization. As a biological basis for this hypothesis, he suggested that a lower frequency of viral infections in childhood, due to a reduced opportunity for contacts, may influence the mechanisms of dysregulation of the immune response.<sup>15,16</sup> Repeated viral infections in early life can, in fact, inhibit the proliferation of Th2-like clones, with reduced production of specific immunoglobulin E (IgE).<sup>17</sup> Such a mechanism has previously been postulated to explain the association of childhood leukemia with socioeconomic status and with sibling number.<sup>18</sup>

Aside from the above-cited German studies, no investigator has examined the complex relation between family factors and the distribution of atopic status in children. We therefore used data collected in a cross-sectional study of children to examine the association of socioeconomic status and sibling number with skin test

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positivity. We also examined the frequency of respiratory infections early in life as a possible predictor of atopy, and thus as a potential intermediate factor to explain the links among social class, sibship size, and positive skin tests.

## Methods

### SUBJECTS AND DATA COLLECTION

Our survey of respiratory health among schoolchildren in three areas of the Lazio region of Italy was conducted in the periods of January-June 1987 and September-November 1987.<sup>19,20</sup> The areas included the center of Rome; Civitavecchia, a recently urbanized and industrialized town 80 km north of Rome; and three rural communities (Canino, Montalto di Castro, and Tuscania) 130 km north of Rome in the province of Viterbo. The schools within each area were randomly sampled to select at least 900 children from the second to the fifth grades (7- to 11-year-olds). A total of 17 schools were chosen (3 in Viterbo province, 10 in Rome, and 4 in Civitavecchia), and all 2,789 attending children were enrolled in the study. The children's parents were asked to complete a self-administered questionnaire, adapted from the American Thoracic Society children's instrument,<sup>21</sup> and to give written consent for prick testing; 2,226 children (79.8% of target) underwent prick testing. Descriptive data on atopic status in this population, as well as a more detailed account of the sampling procedure, have been reported.<sup>22</sup>

Skin prick tests were used to evaluate atopic status, using eight allergen extracts (*Dermatophagoides pteronyssinus*, grass, mugwort, *Parietaria*, cat, *olea*, mixed trees, and *Alternaria*) (Bayropharm, Milan, Italy), with histamine dihydrochloride (10 mg per ml) and diluent as positive and negative controls, respectively. After 15 minutes, the wheals were outlined, and the markings were transferred to mm<sup>2</sup> paper by means of a tape. Wheal size was calculated by multiplying the long axis by its perpendicular, with size >4 mm<sup>2</sup> considered a positive result. We considered a subject with at least one positive result as atopic. We calculated an arbitrary atopy index by subtracting the size of the negative control (NC) from the size of the largest wheal of each subject (WZ), and then dividing by the size of the histamine control (HI). The resulting ratio [(WZ - NC)/HI] was categorized into grades of increasing atopic status as follows: grade 0 (nonmeasurable wheal size, non-atopic); grade 1 [(WZ - NC)/HI < 0.5]; grade 2 [(WZ - NC)/HI = 0.5-1.0]; grade 3 [(WZ - NC)/HI > 1.0]. Results obtained with this method were validated in a pilot study of 48 children randomly chosen and tested twice at an interval of 1 month: a high level of agreement between test and re-test was found (crude agreement = 0.98; Cohen's kappa<sup>23</sup> = 0.95; standard error = 0.04).

### VARIABLES AND DATA ANALYSIS

Information regarding number of siblings, family history of respiratory disease, day care attendance during the first 5 years of life, and respiratory infections (pneumo-

TABLE 1. Characteristics of Children Undergoing Prick Testing, Lazio Region, Italy, 1987

|                                                    | N     | %             |
|----------------------------------------------------|-------|---------------|
| Subjects with prick tests                          | 2,226 | 100.0         |
| At least one positive prick test                   | 469   | 21.1          |
| Sex, male                                          | 1,126 | 50.6          |
| Age (years) (mean $\pm$ SD)                        | 9.35  | ( $\pm$ 1.24) |
| Area of residence                                  |       |               |
| Rural (Viterbo province)                           | 749   | 33.6          |
| Industrial (Civitavecchia)                         | 785   | 35.3          |
| Urban (Rome)                                       | 692   | 31.1          |
| Parental smoking                                   |       |               |
| No                                                 | 624   | 28.0          |
| Yes                                                | 1,512 | 67.9          |
| Unknown                                            | 90    | 4.0           |
| Familial respiratory diseases                      |       |               |
| No                                                 | 1,982 | 89.0          |
| Yes                                                | 244   | 10.9          |
| Father's education (years)                         |       |               |
| <6                                                 | 787   | 35.3          |
| 6-8                                                | 732   | 33.0          |
| 9-13                                               | 532   | 23.8          |
| >13                                                | 171   | 7.7           |
| Unknown                                            | 10    | 0.4           |
| Number of siblings                                 |       |               |
| 0                                                  | 388   | 17.4          |
| 1                                                  | 1,120 | 50.3          |
| 2                                                  | 500   | 22.4          |
| 3                                                  | 171   | 7.7           |
| $\geq$ 4                                           | 47    | 2.1           |
| Household crowding (inhabitants/room) <sup>1</sup> |       |               |
| Low (<1)                                           | 311   | 14.0          |
| Medium (1-2)                                       | 1,255 | 56.4          |
| High (>2)                                          | 533   | 23.9          |
| Unknown                                            | 77    | 3.5           |
| Day care attendance                                |       |               |
| No                                                 | 156   | 7.0           |
| Yes                                                | 2,070 | 93.0          |
| Unknown                                            | 40    | 1.8           |
| Respiratory infections in first 2 years of life    |       |               |
| Pneumonia                                          |       |               |
| No                                                 | 1,842 | 82.7          |
| Yes                                                | 28    | 1.3           |
| Unknown                                            | 356   | 16.0          |
| Bronchitis                                         |       |               |
| No                                                 | 1,371 | 61.6          |
| 1 episode                                          | 436   | 19.6          |
| 2 episodes                                         | 149   | 6.7           |
| $\geq$ 3 episodes                                  | 161   | 7.2           |
| Unknown                                            | 109   | 4.9           |
| Bronchiolitis                                      |       |               |
| No                                                 | 1,796 | 80.7          |
| 1 episode                                          | 41    | 1.8           |
| $\geq$ 2 episodes                                  | 26    | 1.2           |
| Unknown                                            | 363   | 16.3          |
| Pertussis                                          |       |               |
| No                                                 | 1,743 | 78.3          |
| Yes                                                | 435   | 19.5          |
| Unknown                                            | 58    | 2.6           |

nia, bronchitis, bronchiolitis, and pertussis) in the first 2 years of life was derived from the parents' questionnaires. We assessed socioeconomic status on the basis of the

**TABLE 2. Prevalence of Positive Skin Tests, Prevalence Ratios (PR), and 95% Confidence Intervals (95% CI) for Various Family Factors and Early Respiratory Infections**

| Variable                                        | %    | PR   | 95% CI    |
|-------------------------------------------------|------|------|-----------|
| Father's education (years)                      |      |      |           |
| <6*                                             | 17.8 | 1.00 |           |
| 6-8                                             | 21.1 | 1.18 | 0.96-1.47 |
| 9-13                                            | 22.5 | 1.26 | 1.00-1.58 |
| >13                                             | 28.1 | 1.58 | 1.21-2.06 |
| Number of siblings                              |      |      |           |
| 0*                                              | 19.6 | 1.00 |           |
| 1                                               | 22.5 | 1.15 | 0.92-1.44 |
| 2                                               | 21.1 | 1.08 | 0.82-1.42 |
| 3                                               | 15.8 | 0.81 | 0.49-1.32 |
| ≥4                                              | 7.4  | 0.38 | 0.14-0.99 |
| Day care attendance                             |      |      |           |
| No*                                             | 17.3 | 1.00 |           |
| Yes                                             | 21.3 | 1.23 | 0.86-1.75 |
| Household crowding (inhabitants/room)           |      |      |           |
| Low (<1)*                                       | 22.9 | 1.00 |           |
| Medium (1-2)                                    | 21.8 | 0.95 | 0.62-1.52 |
| High (>2)                                       | 22.7 | 0.99 | 0.61-1.60 |
| Respiratory infections in first 2 years of life |      |      |           |
| Pneumonia                                       |      |      |           |
| No*                                             | 21.2 | 1.00 |           |
| Yes                                             | 17.2 | 0.82 | 0.34-2.01 |
| Bronchitis                                      |      |      |           |
| No*                                             | 21.0 | 1.00 |           |
| 1 episode                                       | 18.3 | 0.87 | 0.70-1.09 |
| 2 episodes                                      | 25.5 | 1.21 | 0.91-1.63 |
| ≥3 episodes                                     | 26.7 | 1.27 | 0.97-1.68 |
| Bronchiolitis                                   |      |      |           |
| No*                                             | 20.9 | 1.00 |           |
| 1 episode                                       | 19.5 | 0.93 | 0.50-1.75 |
| ≥2 episodes                                     | 34.6 | 1.66 | 0.97-2.83 |
| Pertussis                                       |      |      |           |
| No*                                             | 21.6 | 1.00 |           |
| Yes                                             | 19.5 | 0.90 | 0.73-1.12 |

\* Referent category.

father's education (<6, 6-8, 9-13, and >13 years of education, corresponding to the Italian educational levels of primary school, secondary school, high school, and university, respectively). We had data on the number of inhabitants in the dwelling and the dwelling size (number of rooms); we calculated household crowding by dividing the number of inhabitants by the number of rooms (low = <1, medium = 1-2, high = >2). Other factors potentially linked with atopy were also collected: parental smoking, birthweight (<2,500 gm, ≥2,500 gm), maternal age, breast feeding (no, yes), presence of pets (no, yes), and season of testing (spring, other seasons).

We compared the crude prevalence of positive skin tests across the categories of the explanatory variables of *a priori* interest (father's education, number of siblings, household crowding, day care attendance, and respiratory infections in the first 2 years of life), calculating the prevalence ratio (PR) and 95% confidence interval (CI).<sup>24</sup> We also calculated an odds ratio (OR) from logistic regression to adjust for potential confounders.

## Results

We found positive skin test results in 469 individuals (21.1%) of the 2,226 persons under study (Table 1); 7.7% of the cohort had atopy grade 1, 6.5% had grade 2, and 6.9% had grade 3. It may be noted that a relatively high proportion of responses was missing for the questions regarding early respiratory infections (from 4.9% for bronchitis to 16.3% for bronchiolitis) (Table 1).

Prevalence of positive skin tests and prevalence ratios for various family characteristics are reported in Table 2. The prevalence of atopy increased in families with a higher paternal educational level, from 17.8% in the lowest group (<6 years) to 28.1% in the highest group (>13 years) (PR = 1.58; 95% CI = 1.21-2.06; *P*-value for trend = 0.001). Severity of atopic sensitization also increased with increasing educational levels: only 5.0% of children belonging to the lowest social class showed an atopy index grade 3 compared with 13.4% of children whose fathers had the highest level of education (PR = 2.70; 95% CI = 1.69-4.30). Prick test positivity decreased with increasing number of siblings (from 19.6% for no siblings to 7.4% for four or more siblings; PR = 0.38; 95% CI = 0.14-0.99). A similar pattern was present for atopy severity: the prevalence of grade 3 wheal size was 1.9% among those having four or more siblings and 6.7% among children without siblings (PR = 0.26; 95% CI = 0.04-1.85). The association between atopy and day care attendance, household crowding, and a history of pertussis or pneumonia early in life were all close to unity. A history of 3 or more episodes of bronchitis or 2 or more episodes of bronchiolitis before age 2 years was weakly associated with a higher probability of atopy (PR = 1.27, 95% CI = 0.97-1.68 for bronchitis; PR = 1.66, 95% CI = 0.97-2.83 for bronchiolitis).

Table 3 shows the crude and adjusted odds ratios (OR<sub>1</sub> and OR<sub>2</sub>) for father's education and number of siblings. In a logistic regression model containing sex, age, area of residence, familial respiratory diseases, father's education, number of siblings, household crowding, and day care attendance, atopy remained associated with father's educational level (>13 vs <6 years: OR<sub>2</sub> = 1.80; 95% CI = 1.25-2.60) and with number of siblings (four or more vs no siblings: OR<sub>2</sub> = 0.36; 95% CI = 0.13-1.06). We found no substantial change when we included early respiratory infections (pneumonia, bronchitis, and bronchiolitis) in the logistic model (OR<sub>3</sub>). In a further sensitivity analysis, we considered additional potential predictors of atopy (parental smoking, birthweight, maternal age, breast feeding, pets, and season of testing), but again we found no substantial change in the regression coefficients for the variables of interest (data not shown).

## Discussion

This study indicates that atopic sensitization to common aeroallergens is positively associated with the level of socioeconomic status and negatively and independently associated with the number of siblings. The results con-

**TABLE 3. Association of Prick Test Positivity with Father's Education and Number of Siblings: Multivariate Analysis\***

| Variable                   | OR <sub>1</sub> | 95% CI    | OR <sub>2</sub> | 95% CI    | OR <sub>3</sub> | 95% CI    |
|----------------------------|-----------------|-----------|-----------------|-----------|-----------------|-----------|
| Father's education (years) |                 |           |                 |           |                 |           |
| <6†                        | 1.00            |           | 1.00            |           | 1.00            |           |
| 6–8                        | 1.23            | 0.94–1.60 | 1.16            | 0.89–1.53 | 1.17            | 0.89–1.54 |
| 9–13                       | 1.33            | 1.00–1.77 | 1.26            | 0.94–1.69 | 1.25            | 0.93–1.69 |
| >13                        | 1.79            | 1.26–2.57 | 1.80            | 1.25–2.60 | 1.84            | 1.26–2.69 |
| Number of siblings         |                 |           |                 |           |                 |           |
| 0†                         | 1.00            |           | 1.00            |           | 1.00            |           |
| 1                          | 1.19            | 0.89–1.58 | 1.23            | 0.92–1.65 | 1.24            | 0.91–1.68 |
| 2                          | 1.09            | 0.77–1.56 | 1.13            | 0.79–1.61 | 1.12            | 0.77–1.63 |
| 3                          | 0.77            | 0.43–1.39 | 0.79            | 0.43–1.46 | 0.79            | 0.43–1.46 |
| ≥4                         | 0.33            | 0.12–0.95 | 0.36            | 0.13–1.06 | 0.36            | 0.12–1.06 |

\* OR<sub>1</sub> = crude odds ratio and 95% confidence interval (CI); OR<sub>2</sub> = odds ratio adjusted in the logistic model for sex, age, area of residence, familial respiratory disease, household crowding, and day care attendance; OR<sub>3</sub> = odds ratio adjusted in the logistic model for sex, age, area of residence, familial respiratory diseases, household crowding, day care attendance, and respiratory infections in the first 2 years of life (pneumonia, bronchitis, bronchiolitis).

† Referent category.

firm previous findings from Germany.<sup>8,9</sup> Multiple episodes of bronchitis and bronchiolitis early in life may also have a role in the later development of atopy. Nevertheless, the associations of atopy with socioeconomic status and sibling number appeared to be independent of, and thus not mediated by, these early respiratory infections.

This is the first study to evaluate simultaneously the roles of socioeconomic status, number of siblings, and early respiratory infections in atopy. We obtained a high response rate and used an objective method to measure atopic sensitization. A limitation of the study is the possible inaccuracy of parental reporting of respiratory early infection, especially if inaccuracy is associated with number of siblings. Nevertheless, parental reporting of respiratory infections early in life had a good level of test-retest reliability in two separate studies that we conducted in the same population.<sup>19</sup>

Several recent studies in addition to our own have found an excess of asthma or allergic diseases in higher socioeconomic classes,<sup>8,15</sup> but others have reported no association<sup>10,11</sup> or an association in the opposite direction.<sup>12,13</sup> These contrasting results may be due to dissimilar social structures, or sets of exposures, in different populations. For instance, exposure to mouse urine, *Altaria*, and cockroaches in low-income families in the American inner city has been associated with excess risk of asthma and wheezing; an effect of unmeasured factors associated with poverty has also been hypothesized in the American inner city.<sup>13</sup> It has similarly been suggested that factors other than exposure to allergens may contribute to differences in skin test reactivity in West and East Germany.<sup>8</sup> An early study from England indicated social and life-style characteristics related to high parental educational level (a higher income, a larger home, less crowding, a smaller family) as determinants of asthma and allergic diseases.<sup>25</sup>

In our study, the social class effect was not explained by confounding due to the number of siblings, since both were independently present in the multivariate model. One may speculate that the true etiologic factors for

which father's education and number of siblings are proxies operate at early stages of life, possibly including the intrauterine period.<sup>26</sup> The fact that an effect was seen for number of siblings but not for household crowding or day care attendance similarly points to maternal and perinatal factors.<sup>27</sup>

It has recently been postulated that viral infections in early childhood might prevent allergic diseases; a low number of siblings may be associated with a reduced opportunity for cross-infections early in life.<sup>8,15</sup> Strachan<sup>16</sup> hypothesized that protection against allergic diseases could result from infections in early childhood, whether transmitted from siblings or acquired *in utero* from a mother infected by contact with her older children. Recent immunologic studies have also suggested a down-regulation of IgE production by viral and bacterial infections.<sup>17,28</sup> On the other hand, respiratory viruses have also been thought capable of promoting allergic sensitization.<sup>29</sup> Although there is little evidence available in humans,<sup>30</sup> damage to airways by respiratory syncytial virus infection (commonly, bronchiolitis) has been shown to alter the immune system, thus leading to allergic sensitization.<sup>31</sup>

Our dataset permitted evaluation of the influence of selected respiratory infections on the development of allergic sensitization. We found that multiple episodes of bronchitis and bronchiolitis in the first 2 years of life were associated with an increased risk of atopy but that adjustment for such episodes did not abolish the association with a small sibling number. These findings do not exclude a protective effect of viral infections as a factor in the decreased rate of allergic sensitization among members of large sibships. Bronchitis and bronchiolitis are, as compared with most childhood respiratory infections, relatively severe (possibly leaving structural damage that might have an allergy-promoting effect), relatively infrequent, and somewhat more likely to have a bacterial etiology, although the bulk of lower respiratory infections in developed countries is thought to be viral.<sup>32</sup> If viral infections do have a down-regulating effect on the allergic diathesis, the quantitative contribution of lower respiratory infections could be minor in comparison with that of the much more frequent upper respiratory infections, the viral gastroenteritides, and the classic childhood infections such as measles, currently on the wane in the developed world.<sup>31</sup> Interestingly, a cohort study in Guinea-Bissau suggested that young adults who had experienced measles in childhood were less likely to be atopic than those who had not had measles.<sup>33</sup> Our findings do, however, indicate a need to look be-

yond infection factors in explaining the lower rate of allergy among children from large sibships.

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