Association between sibship size and allergic diseases in the Glasgow Alumni Study

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Background: Recent epidemiological studies consistently report an inverse association between sibship size and allergic disease, but evidence from individuals born before the 1980s is inconsistent. As information on relative permanence of this finding may offer clues to its biological explanation, the association between sibship size and allergic disease in individuals born between 1918 and 1952 was investigated.

Methods: Cross sectional surveys conducted by the Student Health Service at the University of Glasgow (1948–68) provided data on 14 140 men and women aged 16–30 years at the time of examination. The main outcome measures studied were self-reported asthma, eczema-urticaria, and hay fever.

Results: A total of 1677 individuals (11.9%) provided a positive history of at least one of the three allergic diseases: 457 (3.2%) asthma, 594 (4.2%) eczema-urticaria, and 885 (6.3%) hay fever. Compared with those without siblings (reference odds ratio = 1), the odds ratios (95% confidence intervals) for having any allergic disease among those with one, two or three siblings were 0.86 (0.75 to 0.99), 0.80 (0.69 to 0.93), and 0.70 (0.60 to 0.83), respectively (p_trend<0.001). Increasing birth order and low socioeconomic position in childhood were associated with a lower risk of allergy. Adjustment for birth order, year of birth, age, sex, socioeconomic position in childhood, and family history of allergy did not materially alter the results.

Conclusions: There is a robust inverse association between sibship size and allergic disease even among people born in the first half of the 20th century. These results favour relatively time-independent explanations for this phenomenon (such as the hygiene hypothesis or parity related changes in the intrauterine environment) over new environmental exposures.

Recent epidemiological studies consistently show an inverse association between sibship size and allergic disease, but there is no biological explanation for this empirical observation.1–5 It has been estimated that up to a third of cases with allergy could be accounted for by this so-called sibling effect.1

Strachan formulated the ‘‘hygiene hypothesis’’ in 1989, suggesting that the risk of allergic diseases is reduced by infections in infancy transmitted by older siblings.3 Despite immunological plausibility, the causal role of infections in allergic diseases remains unproven as data from studies that have used more direct markers of infections have been inconclusive.7–12 Furthermore, epidemiological data supportive of a sibling effect in individuals born before the 1980s are limited and inconsistent.13–15 If infections are the underlying protective factor, one would predict the sibling effect to be stronger—not weaker—at a time when the hygiene differentials are potentially steeper. Consequently, alternative explanations for the sibling effect have been proposed that mainly relate to inherent differences in immune function (the ‘‘intrauterine programming hypothesis’’).1

Birth order may affect the fetal atopic response directly or indirectly through induction of immune tolerance in the mother.14–20 Other mechanisms suggested to explain intrauterine programming include a potential role for hormones as well as endocrine disrupters such as organochlorines.21–23

We have investigated the association between sibship size and the prevalence of allergic diseases in a historical cohort who were born in the first half of the 20th century. We hypothesised that a robust documentation of the sibling effect in this early cohort would lend support to relatively time-independent explanations offered by the hygiene hypothesis or inherent birth order related differences in immunity over new exposures such as organochlorines.

METHODS
The Glasgow Alumni Study has been described in detail elsewhere.24 Briefly, students who were registered at the University of Glasgow sometime between 1948 and 1968 were invited to an annual medical examination at the Student Health Service. Approximately 50% of the students attended. Substantial sociodemographic and medical data were collected through a physician administered questionnaire. Students provided information on their birth order, number of siblings, father’s occupation, and whether they had ever suffered any of the four allergic diseases: asthma, eczema, urticaria, or hay fever. Students were also asked to report if any of their first degree relatives (parents or siblings) suffered from one of the aforementioned allergic diseases.

Ethics committee approval was received for the study.

Statistical analysis
Logistic regression modelling was performed to examine the association between sibship size, birth order or childhood socioeconomic position and risk of having allergic disease. Eczema and urticaria were combined into one outcome to limit diagnostic misclassification between them. Associations were investigated with each of the three allergic disease outcomes—asthma, eczema-urticaria and hay fever—and also for the combined outcome—allergy—defined as having any of these diseases.

Analysis was restricted to students who underwent examination when they were 30 years or younger as the few older students (N = 546) were spread over a wide age range. Age at examination was calculated as the difference
between date of examination and date of birth, and divided into three groups (in completed years) for analysis (16–19, 20–24, and 25–29). The sibship size was categorised into four groups (0, 1, 2, and 3+). Childhood socioeconomic position was determined from the occupation of the father using the Registrar General’s classification (I–IV); social classes IV and V were combined because of low numbers in these two categories. Year of birth was divided into three time periods (1918–30, 1931–39, and 1940–52) to study birth cohort effects. Family history of allergy was examined as a combined variable for any first degree relatives suffering from any of the three allergic diseases, as there were low numbers in each of the groups individually.

The main exposures considered in the analyses were sibship size and birth order, along with childhood socioeconomic position which was important because of its relevance to the hygiene hypothesis. Crude models were first adjusted for age, year of birth, and the year of student examination to investigate possible confounding by age of the participant, or change over time of disease prevalence or definitions. In subsequent models we controlled for sex and family history of allergy. The final model contained terms for sibship size, birth order, childhood socioeconomic position, age, sex, year of birth, year of student examination, and family history of allergy. We also specifically looked for evidence of any important interactions between sibship size and birth order, and between either of these two with childhood socioeconomic position, period of birth, age, sex, and family history of allergy. To study the change over time, we fitted the above models independently for each of the three birth cohort periods and also calculated the age-sex standardised prevalence for each of the diseases. Direct standardisation was done using the age-sex distribution of the entire cohort as the reference.

### Table 1

Prevalence of asthma, eczema-urticaria, hay fever, and combined allergic diseases among 14,140 students of Glasgow University born 1918–52

<table>
<thead>
<tr>
<th>Participants</th>
<th>Asthma</th>
<th>Eczema-urticaria</th>
<th>Hay fever</th>
<th>Allergy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at university examination</td>
<td>% (N)</td>
<td>% (N)</td>
<td>% (N)</td>
<td>% (N)</td>
</tr>
<tr>
<td>16–19</td>
<td>59.3 (8386)</td>
<td>3.3 (277)</td>
<td>0.158</td>
<td>4.0 (332)</td>
</tr>
<tr>
<td>20–24</td>
<td>33.4 (4717)</td>
<td>3.3 (157)</td>
<td>4.4 (206)</td>
<td>6.3 (299)</td>
</tr>
<tr>
<td>25–29</td>
<td>7.3 (1037)</td>
<td>2.2 (23)</td>
<td>5.4 (56)</td>
<td>3.6 (37)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75.9 (10732)</td>
<td>3.6 (382)</td>
<td>&lt;0.001</td>
<td>3.6 (382)</td>
</tr>
<tr>
<td>Female</td>
<td>24.1 (3408)</td>
<td>2.2 (75)</td>
<td>6.2 (212)</td>
<td>6.8 (230)</td>
</tr>
<tr>
<td>Sibship size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18.6 (2634)</td>
<td>2.5 (91)</td>
<td>0.333</td>
<td>4.7 (123)</td>
</tr>
<tr>
<td>1</td>
<td>36.8 (5197)</td>
<td>3.3 (169)</td>
<td>4.6 (238)</td>
<td>6.4 (330)</td>
</tr>
<tr>
<td>2</td>
<td>23.6 (3339)</td>
<td>3.3 (109)</td>
<td>3.6 (119)</td>
<td>6.1 (203)</td>
</tr>
<tr>
<td>3+</td>
<td>21.0 (2970)</td>
<td>3.0 (88)</td>
<td>3.8 (114)</td>
<td>4.9 (145)</td>
</tr>
<tr>
<td>Birth order</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>55.8 (7885)</td>
<td>3.6 (281)</td>
<td>0.007</td>
<td>4.3 (338)</td>
</tr>
<tr>
<td>2</td>
<td>26.7 (3769)</td>
<td>3.0 (113)</td>
<td>4.4 (166)</td>
<td>5.9 (222)</td>
</tr>
<tr>
<td>3+</td>
<td>17.6 (2486)</td>
<td>2.5 (63)</td>
<td>3.6 (90)</td>
<td>4.6 (113)</td>
</tr>
<tr>
<td>Childhood socioeconomic position</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>20.9 (2952)</td>
<td>3.5 (104)</td>
<td>0.571</td>
<td>5.0 (148)</td>
</tr>
<tr>
<td>II</td>
<td>36.8 (5200)</td>
<td>3.0 (158)</td>
<td>4.2 (220)</td>
<td>6.9 (356)</td>
</tr>
<tr>
<td>III</td>
<td>35.7 (5053)</td>
<td>3.3 (168)</td>
<td>3.8 (194)</td>
<td>5.1 (257)</td>
</tr>
<tr>
<td>IV–V</td>
<td>6.6 (935)</td>
<td>2.9 (27)</td>
<td>3.4 (32)</td>
<td>4.5 (42)</td>
</tr>
<tr>
<td>Period of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1918–30</td>
<td>24.9 (3518)</td>
<td>2.7 (96)</td>
<td>0.896</td>
<td>4.8 (169)</td>
</tr>
<tr>
<td>1931–39</td>
<td>37.8 (5345)</td>
<td>3.6 (194)</td>
<td>4.2 (222)</td>
<td>6.4 (344)</td>
</tr>
<tr>
<td>1940–52</td>
<td>37.3 (5277)</td>
<td>3.2 (167)</td>
<td>3.9 (203)</td>
<td>6.8 (398)</td>
</tr>
<tr>
<td>Family history of allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>90.1 (12736)</td>
<td>2.7 (349)</td>
<td>&lt;0.001</td>
<td>3.7 (467)</td>
</tr>
<tr>
<td>Yes</td>
<td>9.9 (1404)</td>
<td>7.7 (108)</td>
<td>9.1 (127)</td>
<td>15.3 (215)</td>
</tr>
</tbody>
</table>

*Allergy refers to the participant reporting any of the three diseases (asthma, eczema-urticaria, or hay fever).

### RESULTS

The Glasgow Alumni cohort consists of 15,322 former students of whom 11,755 (77%) are men. After excluding students over the age of 30 years (n = 546), those with unknown year of birth (n = 2) and those with missing data on sibling number or birth order (n = 169) and father’s occupation (n = 465), complete data were available on 14,140 individuals (92%), 10,732 (76%) of whom were men. The students were born between 1918 and 1952 and their median age at the time of university medical examinations was 19.4 years (range 16–30).

A total of 1677 individuals (11.9%) provided a positive history of at least one of the three allergic diseases: 457 (3.2%) asthma, 594 (4.2%) eczema-urticaria, and 885 (6.3%) hay fever. A further 1404 (9.9%) reported having at least one first grade relative who suffered from any one of these diseases (table 1). After standardising for age-sex distribution, the prevalence of each of these diseases across the birth cohort categories was very similar (data not presented). For any allergy, the standardised prevalence (95% confidence interval (CI)) was 12.2% (10.5 to 13.9), 12.0% (11 to 12.9), and 11.7% (10.6 to 12.9) for birth periods 1918–29, 1930–39, and 1940–52, respectively.

The odds ratios for having at least one allergic disease decreased with increasing number of siblings, with individuals who had three or more siblings having a 30% lower risk of being affected than those without siblings (table 2). A similar effect size and trend was noted with increasing birth order. Individuals from the least affluent backgrounds had the lowest risk of allergic disease. Adjustment for year of birth, year of examination, age, sex, and family history of allergic disease and further adjustment, as appropriate, for sibship size, birth order and childhood socioeconomic position did not materially alter these findings. Among the allergic diseases, hay fever showed the strongest association and asthma the weakest association with sibship size.
The association between sibship size or birth order and the risk of allergic disease was at least as strong, if not stronger, in the earlier birth cohort period as in the later ones (table 3). Similar patterns were noted for each of the individual diseases (data not presented). Most of the interactions outlined in the Methods section were non-contributory. However, an important interaction was noted between birth order and childhood socioeconomic position, such that the inverse association between sibship size or birth order and risk of allergic disease was at least as strong, if not stronger, in the earlier birth cohort period as in the later ones (table 3). Lower socioeconomic position in childhood was associated with lower odds of allergic disease among the offspring. Unlike most previous studies related to fertility; if true, maternal history of allergy may evidence to suggest that allergic predisposition may be availability of family history data. There is some widespread use), another important strength of this study timing (before antibiotics and immunisation came into prevalence of these diseases over the duration of the study, changes in diagnosis of allergic diseases over the study period (1948–68). No significant changes were noted in the strength of the true association. Diagnostic criteria can also change over time; however, we are not aware of any major changes in diagnosis of allergic diseases during the study period (1948–68). Significant changes were noted in the prevalence of these diseases during the study period, nor were there any important interactions between year of examination, year of birth, year of examination, and family history of allergy.

Apart from the large sample size and its unique historical timing (before antibiotics and immunisation came into widespread use), another important strength of this study is the availability of family history data. There is some evidence to suggest that allergic predisposition may be related to fertility; if true, maternal history of allergy may confound the association between sibship size and allergic disease among the offspring. Unlike most previous studies which did not have these data, we were able to control for family history of disease.

Comparison of results with other studies There are few large scale epidemiological studies with data available from a similar time period with which to compare the prevalence of these diseases. As expected, the prevalence found in this study was lower than that reported in recent studies such as the ISAAC. The Midspan 1972–76 study of parents and their offspring from two towns in the west of Scotland reported age standardised prevalence of 5.4–5.8% for hay fever and 1.4–2.8% for asthma among parents aged

**DISCUSSION**

This study has shown that the inverse association between sibship size or birth order and risk of allergic diseases was evident even in the first half of the 20th century. The association was at least as strong, if not stronger, in the earlier birth cohort period (1918–30) as in the later ones. Lower socioeconomic position in childhood was associated with lower odds of allergic disease. These associations were robust to adjustments for each other and other potential confounders including year of birth or examination, age, sex, and family history of allergic disease. The protective effect of higher birth order to allergy was strongest in the poorest households.

**Strengths and limitations of the study**

Participants were asked to provide a history of allergic diseases. Although physicians collected the data, we are not aware if any clear diagnostic criteria were established beforehand, and this may have introduced measurement error in the outcome. Such error, if present, is likely to be non-differential and so would have acted only to reduce the strength of the true association. Diagnostic criteria can also change over time; however, we are not aware of any major changes in diagnosis of allergic diseases during the study period (1948–68). Significant changes were noted in the prevalence of these diseases during the study period, nor were there any important interactions between year of examination, year of birth, and sibship size or birth order.

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45–54 years at the time.28 Both these figures, which were self-reported, are comparable to the data in our study (6.3% for hay fever and 3.2% for asthma), as are the setting and the timing, since the participants were born between 1918 and 1931. The offspring survey in the same study indicated that there had been a doubling of the prevalence over a 20 year period.28

Recent epidemiological studies have reported similar associations between sibship size, birth order or socio-economic position, and allergic diseases.1–5 Most of these studies, however, were conducted over the last two decades while those from before that time have generally been small and inconsistent in their findings.11–15 Smaller and often case-based studies have reported similar associations.11 12 On the other hand, large scale epidemiological studies based on unselected samples from the general population born before the 1980s have often failed to reproduce these results.13–15 One plausible explanation for the inconsistency in results could be related to the choice of asthma as the outcome, since the sibling effect has generally been observed to be weaker for asthma than for other allergic diseases and the same was true in our study.5 It is unclear whether the relatively weaker associations reported with asthma represent diagnostic difficulties or differences in disease aetiology, as not all asthma is allergic in origin.29

Competing hypotheses that seek to explain the sibling effect

If the sibling effect has existed unchanged for some time, then the most parsimonious explanations would have to be time-independent. For this, two categories of hypotheses exist.5 The first, and by far the most popular, is the hygiene hypothesis.6 The hygiene hypothesis predicts that the sibling effect would be as strong, if not stronger, in the earlier cohorts (due to greater differentials in hygiene) and among the less affluent (due to greater potential for infections). Both these predictions held true in our study. In addition, we found an interaction between birth order and socioeconomic position.

Table 3  Association of sibship size and birth order with prevalence of allergy by three periods of birth

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>Partially adjusted</th>
<th>Fully adjusted</th>
</tr>
</thead>
</table>
|                  | OR    | 95% CI             | p trend       | OR    | 95% CI          | p trend      | OR    | 95% CI          | p trend
| Sibship size     |       |                    |               |       |                 |              |       |                 |              |
|                   |       |                    |               |       |                 |              |       |                 |              |
| Born 1918–1930   |       |                    |               |       |                 |              |       |                 |              |
| Sibship size     |       |                    |               |       |                 |              |       |                 |              |
|                   |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |
| Birth order      |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |
| Born 1931–1939   |       |                    |               |       |                 |              |       |                 |              |
| Sibship size     |       |                    |               |       |                 |              |       |                 |              |
|                   |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |
| Birth order      |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |
| Born 1940–1952   |       |                    |               |       |                 |              |       |                 |              |
| Sibship size     |       |                    |               |       |                 |              |       |                 |              |
|                   |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |
| Birth order      |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |
|                  |       |                    |               |       |                 |              |       |                 |              |

OR, odds ratio; 95% CI, 95% confidence intervals.

*Adjusted for age, sex, year of birth, year of examination, and family history of allergy.
†Adjusted for sibship size, birth order, childhood socioeconomic position, age, sex, year of birth, year of examination, and family history of allergy.

Table 4  Odds ratios (95% CI) for prevalence of allergy by birth order and childhood socioeconomic position

<table>
<thead>
<tr>
<th>Childhood socioeconomic position</th>
<th>Birth order</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>IV–V</td>
<td>1</td>
</tr>
</tbody>
</table>

Test for interaction between birth order and childhood socioeconomic position, p=0.035.
have been shown to be related to later risk of allergy.\textsuperscript{16–18} It is not
surprising that siblings with higher birth order; the cord blood IgE levels of
organochlorines has been shown to decrease with birth order and to be
associated with higher cord blood IgE levels.\textsuperscript{22 23} The burdenNE of these variables used in the analyses and R = 0.63 for
full range of the variables), thereby requiring large sample
sizes to manifest independent effects. Studies that have shown
independent effects of birth order (or the number of older
siblings) and sibship size (or the number of younger siblings) generally had larger sample sizes (often in excess of 10 000 participants) than “negative” studies which had wide
overlapping confidence intervals for these variables.\textsuperscript{14} The
finding of independent effects of sibship size and birth order is
important as the two may represent different underlying
mechanisms. While a sibling effect, independent of birth
order, would be more supportive of postnatal influences such
as early childhood infections (that is, the hygiene hypothesis), a birth
effect, independent of sibling number, would suggest a predominantly prenatal mechanism (that is, in
trauterine programming). Equally, a common underlying
exposure operating across both the intrauterine and postnatal
periods may give rise to these findings.

Public health implications

Epidemiological data suggest a steady rise in the prevalence of allergic disease over the last century but more so in the last
two or three decades.\textsuperscript{21} The reasons for this are unknown. It
has been suggested that the same unknown environmental factor(s) may underlie both the rise in the prevalence of these
deconditions globally and the inverse association between the
risk of these conditions and sibship size noted at an
individual level.\textsuperscript{17} It has been suggested that up to a third of cases with allergy could be accounted for by the sibling
effect. Knowledge of factors underlying the sibling effect may
help to prevent some of these cases.\textsuperscript{22}

In conclusion, this study has shown that the inverse association between sibling size and allergic disease was
evident even in the first half of the last century. The finding of the sibling effect in this early cohort argues against an
important role for new environmental exposures in favour of
relatively time-independent explanations offered by the hygiene
hypothesis or parity related changes in the intrauterine
environment. The key findings of this study are shown in box 1.

Authors’ affiliations
SK is the guarantor.

GDS had the original idea for the study. SK analysed the data and wrote
the final manuscript. SK is the guarantor.

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Sibship size and allergic diseases

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