

The effect of age on the relationship between birth order and immunoglobulin E sensitization

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Summary

Background An association between birth order and IgE sensitization or allergic diseases has been reported in many studies.

Objective To assess the effect of age on the relationship between reduced IgE sensitization and increased birth order and to test the hypothesis that this would decline with increasing age.

Methods As part of a birth cohort study, IgE sensitization to common allergens was determined by skin prick testing at ages 6 and 12 months, 6 and 11 years.

Results The original cohort numbered 253 individuals of whom 96 (38%) were first born. Compared with individuals with older siblings, first-born individuals had increased IgE sensitization at 6 (odds ratio (OR) 2.4 [95% confidence interval (CI) 1.0, 6.3], $P = 0.05$, $n = 197$) and 12 months of age (OR 6.7 [1.7, 25.0] $P = 0.002$, $n = 172$) and at 6 years of age (OR 2.3 [1.0, 5.6] $P = 0.05$, $n = 113$) but not at 11 years of age (OR 1.2, $P > 0.4$, $n = 182$). When age at onset of IgE sensitization was considered ($n = 61$), 16 had infant onset IgE sensitization (nine were first born), 24 had early childhood onset IgE sensitization (nine first born) and 21 had late childhood onset IgE sensitization (two first born), $P = 0.0016$. Further analysis revealed a similar pattern for children with older brothers ($P = 0.0097$) but not older sisters ($P = 0.5$).

Conclusions These findings indicated that having an older brother delays the onset of IgE sensitization but may not prevent IgE sensitization *per se*. The apparent protective effect of older siblings on allergic diseases reported elsewhere might involve delaying the onset of IgE sensitization.

Keywords longitudinal study, siblings, skin prick positivity

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Introduction

The apparently protective effect of higher birth order on the presence of IgE sensitization, the 'sibling effect', has been confirmed in all but a few studies [1]. This association may be important, particularly as better understanding of the causal factors might allow strategies to be developed which could prevent as much as 30% of all cases of asthma, eczema and hayfever [1].

The precise mechanism behind the association between birth order and IgE sensitization is not understood and appears to be complex. One hypothesis (the 'hygiene' hypothesis) proposes that the relationship between birth order and IgE sensitization is explained by increased exposure to infections in early life for individuals with older siblings [2]. Although the hygiene hypothesis is biologically plausible, other studies have identified an association between birth order and IgE sensitization that is independent of the influence of early infection [3, 4]. The relationship between birth order and IgE sensitization is likely to be determined *in utero*, at least in part, as analysis of cord blood specimens has

indicated that the association may be evident at birth [5, 6]. Other observations that may be relevant to understanding the sibling effect are that the apparent protective influence of older siblings increases linearly with birth order [7] and may be limited to older brothers [3, 8, 9].

The effects of aging on the association between IgE sensitization and birth order remains unclear but can be investigated using a longitudinal cohort. Assuming that the relationship between IgE sensitization and birth order has *in utero* influences, one could anticipate that important environmental variables for IgE sensitization, which are influential after birth would subsume the sibling effect. IgE sensitization has been assessed at ages 1, 6 and 12 months and 6 and 11 years in a birth cohort recruited by staff in our department. In the present study we sought to test the hypothesis that being first-born was associated with increased risk of IgE sensitization but that the relationship would become less important with age.

Methods

Study subjects

The cohort was enrolled before birth and was selected from a Caucasian population attending an antenatal clinic between

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June 1987 and November 1990 as described previously [10]. There was no selection for parental asthma or allergic disease. Exclusion criteria were premature delivery (i.e. before 36 weeks gestation) and respiratory symptoms in the first month of life. The presence of older siblings and their gender was recorded at enrolment. Half-siblings who shared the enrolled child's mother and who lived with their mother were considered siblings for the purpose of this study. The following potential confounding factors for IgE sensitization were also recorded at enrolment: a history of physician diagnosed asthma in either parent ('parental asthma'); the presence of a dog; mothers' age at birth of the child; mother or father completing education at 15 years of age. The duration of breastfeeding beyond 4 months was verified from monthly postal questionnaires prospectively completed during infancy. The study was approved by the Medical Ethics Committee of Princess Margaret Hospital for Children. Written parental consent was obtained for each assessment and verbal consent from children aged 6 and 11 years.

Skin prick testing

For the three assessments in infancy, skin reactivity to cows' milk, egg white, rye grass and *Dermatophagoides farinae* was determined using the skin prick test as described by Peypys [11]. For the two assessments in childhood, skin reactivity to the following additional six allergens was also assessed: mixed grass (no.7); *Dermatophagoides pteronyssinus*; cat dander; dog dander; *Alternaria alternans* and *Aspergillus fumigatus*. All allergens were supplied by Hollister-Stier (Elkhart, IN, USA). Histamine sulphate (10 mg/mL) was used as the positive control and 0.9% saline as the negative control. The positive control was read after 10 min, all other tests were read after 15 min. A positive skin test was defined as a weal to any allergen at least 3 mm in its longest dimension. For individuals with dermatographism, a positive skin test was defined as a weal whose maximal diameter exceeded the response to the negative control. IgE sensitization was defined as at least one positive skin test. IgE sensitization in infants was defined as a positive skin test on any of the three assessments during infancy, 161 (63%) infants had skin prick testing on three occasions, 41 (16%) on two occasions and 51 (20%) on only one occasion.

Statistics

Individuals were classed as either first-born or not first-born. Individuals with IgE sensitization at 11 years of age were categorized into: infant onset IgE sensitization (i.e. sensitized in infancy and at 11 years of age including eight children not assessed aged 6 years but IgE sensitization was presumed); early childhood onset IgE sensitization (i.e. not sensitized in infancy but sensitized at 6 and 11 years of age); and late childhood onset IgE sensitization (i.e. sensitized aged 11 years but not sensitized in infancy or aged 6 years). χ^2 , Mann-Whitney *U*-test and Student's *t*-test (two-tailed and equivariance assumed) were used to compare groups. Kaplan-Meier log rank analysis was used to compare the age at onset of IgE sensitization at 11 years of age between first-born and not first-born individuals. The relationship between infant IgE sensitization and loss to follow-up at ages 6 and 11 years was

explored by introducing this variable to the logistic regression models also containing variables previously demonstrated to be associated with loss to follow-up for this population [12]. Significance was assumed at 5%. Analyses were performed using a standard statistical software package (SPSS release 10.0.7; SPSS, Chicago, IL, USA).

Results

Subjects

The original cohort numbered 253 individuals, 96 were first-born. IgE sensitization was determined in 247 children aged 1 month, 197 aged 6 months, 172 aged 12 months, 113 aged 6 years and 182 aged 11 years. Table 1 shows that the 79 children who had IgE sensitization assessed on each of the five occasions were representative of the original cohort. First-born individuals were also representative of the original cohort (Table 2). Infant IgE sensitization was not associated with loss to follow-up at ages 6 and 11 years. At 11 years of age, prior IgE sensitization had resolved in 12 children, 10 with infantile IgE sensitization.

The relationship between immunoglobulin E sensitization and birth order – cross-sectional analyses

At 1 month of age, 1/94 first-born infants were IgE sensitized compared with 1/153 with older siblings. At 6 months of age,

Table 1. Prevalences of IgE sensitization for all cohort members and for the 79 children where skin prick testing was undertaken on every assessment during the period of follow-up

	Skin prick tested on each occasion (n = 79)	All cohort members
IgE sensitized aged 6 months	9% (7/79)	8% (16/197)
IgE sensitized aged 12 months	5% (4/79)	8% (13/172)
IgE sensitized aged 6 years	32% (25/79)	35% (40/113)
IgE sensitized aged 11 years	54% (43/79)	52% (94/182)

There were no differences between groups.

Table 2. Potential confounding factors for childhood IgE sensitization for the whole cohort and first-born

	First-born individuals	Whole cohort
Male gender	58% (56/96)	56% (142/253)
Maternal age at delivery, years (SD)	28 (5)	28 (4)
Maternal education ended aged 15 years	23%* (21/88)	32% (73/230)
Paternal education ended aged 15 years	39% (32/82)	39% (85/217)
Dog present during infancy	45% (25/55)	50% (79/159)
Maternal smoking during pregnancy [†]	23% (22/96)	23% (57/252)
Paternal smoking during pregnancy [‡]	39% (34/88)	38% (90/240)
At least one parent with asthma	31% (29/93)	31% (74/242)
Breast fed for more than four months	38% (29/76)	45% (76/168)

**P* = 0.04 for comparison with whole cohort. [†]Data missing for one mother.

[‡]Data missing for 13 fathers.

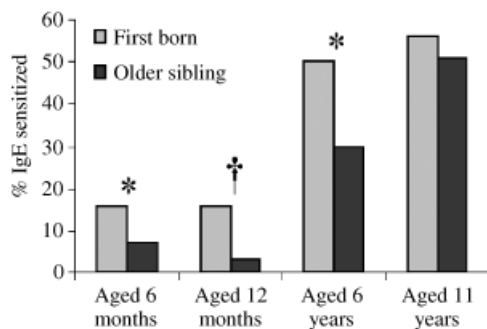


Fig. 1. A bar chart demonstrating the proportion of IgE sensitized study subjects at ages 6 and 12 months, 6 and 11 years for first-born and not first-born individuals. * $P=0.05$, † $P=0.002$.

12/74 (16%) first-born infants were IgE sensitized compared with 9/123 (7%) with older siblings (odds ratio (OR) 2.4 [95% confidence interval (CI) 1.0, 6.3], $P=0.05$) (Fig. 1). At 12 months of age, 10/64 (16%) first-born infants were IgE sensitized compared with 3/108 (3%) with older siblings (OR 6.7 [1.7, 25.0], $P=0.002$) (Fig. 1). At 6 years of age, 15/30 (50%) first-born infants were IgE sensitized compared with 25/83 (30%) with older siblings (OR 2.3 [1.0, 5.6], $P=0.05$) (Fig. 1). At 11 years of age, 33/59 (56%) first-born infants were IgE sensitized compared with 61/123 (50%) with older siblings (OR 1.2 [0.7, 2.3], $P>0.4$) (Fig. 1).

The relationship between immunoglobulin E sensitization and birth order – longitudinal analyses

There were 94 subjects in the 11-year follow-up who were IgE sensitized and categorization of age at onset of IgE sensitization was possible for 61 (66%) of these. Of these 61 children, 16 had infant onset IgE sensitization (nine first born), 24 had early childhood onset IgE sensitization (nine



Fig. 2. A 1-survival curve showing the age at onset of IgE sensitization for first-born and not first-born individuals. Log-rank analysis $P=0.0019$, 61 individuals were included in his analysis (20 first-born). The shaded area represents the excess IgE sensitization because of being first born.

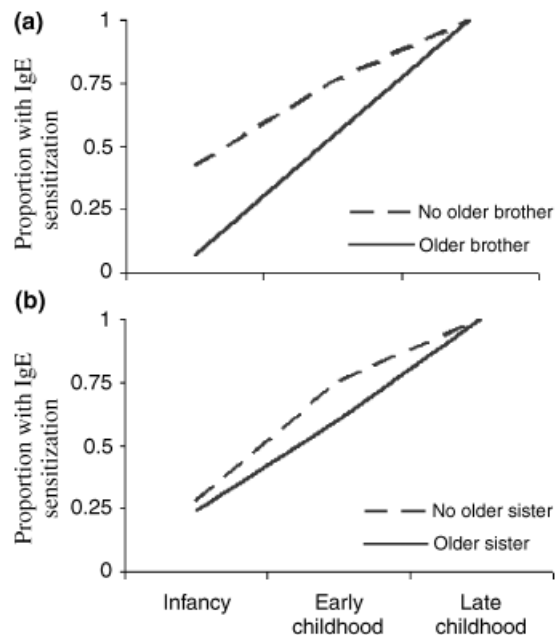


Fig. 3. Two 1-survival curves showing the age at onset of IgE sensitization for first born children and children with older brothers (a) and sisters (b). For curve a, log-rank analysis $P=0.0097$; 61 individuals were included in the analysis (33 had no older brother). For curve b, log-rank analysis $P=0.48$; 61 individuals were included in the analysis (36 had no older sister).

first born) and 21 late childhood onset IgE sensitization (two first born), Kaplan–Meier log rank statistic 9.97, df 1 $P=0.0016$ (Fig. 2). Among these 61 children, for those who had at least one older brother ($n=28$), two of the subjects had infant onset IgE sensitization, 13 had early childhood onset IgE sensitization and 13 had late childhood onset IgE sensitization; the respective numbers for children with no older brothers ($n=33$) were 14, 11 and 8, Kaplan–Meier log rank statistic 6.68, df 1 $P=0.0097$ (Fig. 3a). The age at onset of IgE sensitization did not differ between the 25 children with older sisters compared with the 36 children without older sisters (Fig. 3b).

Discussion

This study was designed to determine the association between age, being first-born and the presence of IgE sensitization within a longitudinal cohort study. In infancy, an association between being first-born and IgE sensitization was apparent by 6 months and persisted at 12 months of age. In childhood, the association between being first-born and IgE sensitization was apparent at 6 but not at 11 years of age. The longitudinal design of this study facilitated the finding that, in this population, at 11 years of age the presence of older siblings was associated with delayed onset of IgE sensitization rather than reduced IgE sensitization *per se*. Furthermore, the data suggested that older brothers and not older sisters conferred the apparent protective effect on the development of early IgE sensitization in their younger siblings.

There are some aspects of our study that should be considered when the data are interpreted. Firstly, compared with many other studies of the sibling effect, our study

involved a relatively fewer individuals; however the longitudinal design of the study affords it strength not available to other study populations. Secondly, the follow-up of our cohort was incomplete and this may have influenced the outcomes, particularly since we have reported risk factors for loss to follow-up include being first-born [12]. However, we have been able to demonstrate that infantile IgE sensitization was not a risk factor for loss to follow-up at ages 6 and 11 years and have previously shown that 'missingness' at these ages was not associated with parental allergic disease [12]. These observations suggest that the cohort assessed in childhood had not become enriched with children at increased risk for allergic disease. Since the outcomes we have noted were consistent with previous reports [2, 3, 5, 7–9, 13], incomplete follow-up of our cohort is unlikely to have substantially influenced the outcomes. We therefore consider our outcomes to be valid but we recommend that our findings are confirmed elsewhere.

The mechanism responsible for an association between birth order and IgE sensitization is uncertain and a single causation appears unlikely. Evidence for 'in utero programming' comes from studies of cord blood samples [5, 6] where neonates with older siblings had attenuated markers of IgE sensitization compared with first-born infants. Further support for an *in utero* influence comes from an observation that mothers with menarche at later age have reduced IgE sensitization among adult offspring [14]. The association between reduced IgE sensitization and the presence of older brothers is intriguing and previously reported [3, 8, 9]. A mechanism, possibly apparent *in utero*, whereby older brothers confer protection against the early development of IgE sensitization should be sought since this could have implications for prevention of allergic disease.

In the present study and elsewhere [1], increasing birth order has been associated with reduced IgE sensitization, however not all sensitized individuals have allergic disease indicating that factors other than IgE sensitization are important to the development of allergic disease. A positive relationship between higher birth order and pulmonary function has been described [15] and this is consistent with the hypothesis that birth order might be associated with asthma by a mechanism that is independent of IgE sensitization. The mechanism for a relationship between birth order and allergic diseases such as asthma may involve interactions between IgE sensitization and organ-specific factors which are also influenced by the sibling effect.

In this study, maternal age at delivery did not differ between first-born children and their peers with older siblings and this suggested that parents of first-born children in this cohort started their families at a later age. An association between younger maternal age at delivery and increased reported IgE sensitization is described elsewhere [8] although younger mothers are not at increased risk for delivering male infants. Thus there may be a common mechanism underlying the sibling effect and the relationship between maternal age and childhood IgE sensitization although the protective association of older brothers (the 'big brother effect') does not appear to be explained by older maternal age at delivery.

For first-born individuals in our population, there was a small but non-significant increase in the prevalence of IgE sensitization at 11 years of age but they did have earlier onset

IgE sensitization that may be of clinical relevance. The onset of IgE sensitization before the age of 10 years is associated with persistent wheeze [16] and severe asthma [17] in adulthood whereas later onset IgE sensitization is not associated with an adverse respiratory outcome [16].

In this study, the presence of older siblings was associated with delayed onset IgE sensitization and other studies [16, 17] suggest that later onset IgE sensitization is associated with less severe allergic disease. The apparent protective effect of older siblings on allergic diseases reported elsewhere [1] might involve delaying the onset of IgE sensitization. Thus, strategies aimed at reducing the burden of allergic disease in the population might aim to postpone the onset of IgE sensitization rather than prevent IgE sensitization *per se*.

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