

Sibship size and prevalence of allergic disorders in Japan: The Ryukyus Child Health Study

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A number of epidemiological studies have reported an inverse association between increasing sibship size and allergic disorders. The present cross-sectional study assessed the association between the number of siblings and the prevalence of allergic disorders during the past 12 months in Japanese schoolchildren. Study subjects were 22,750 children aged 6–15 yr in Okinawa. The outcomes were based on diagnostic criteria from the International Study of Asthma and Allergies in Childhood. Adjustment was made for age, gender, maternal age at childbirth, duration of breastfeeding, region of residence, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level. Significant exposure–response associations were observed between increasing total sibship size and all outcomes under investigation. Having two or more older siblings was significantly inversely related to the prevalence of atopic eczema and allergic rhinoconjunctivitis, but not wheeze or asthma. Having two or more younger siblings was independently associated with a decreased prevalence of atopic eczema, but not wheeze, asthma, or allergic rhinoconjunctivitis. The inverse relationships between sibship size and the prevalence of allergic disorders under study were weakened with advancing age, although the interactions between age groups were not statistically significant. No significant interactions were found in the association of having three or more siblings with allergic disorders between children with a positive or negative parental allergic history. These results are likely to support the *in utero* programming hypothesis because it is probable that the *in utero* environment would change with parity, although our observations could not refute the hygiene hypothesis.

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In 1989, Strachan showed that increasing sibship size was related to a lower prevalence of hay fever at ages 11 and 23 and proposed a novel explanation for his findings, which was called the hygiene hypothesis (1). Since then, a number of epidemiological studies have reported an inverse association between the number of siblings and allergic disorders (2). According to the hygiene hypothesis, the decline in cross-infection within small families could increase predisposition to allergic conditions during childhood (3). One

mechanism in relation to the hygiene hypothesis is the skewing of the Th1/Th2 balance away from allergy-promoting Th2 cells toward Th1 cells (4). However, current evidence regarding associations of infections in early childhood with allergic disorders neither refutes nor supports the hygiene hypothesis (5–8).

As another explanation for the sibling effect, the *in utero* programming hypothesis has been suggested (2). Maternal immune tolerance against allergens may increase with increasing

order of birth of live offspring and the maternal immune status may be communicated to the child (9–11). In addition, the *in utero* programming hypothesis may be to some extent attributable to the role of hormones as well as to endocrine disruptors such as organochlorines (2, 12, 13).

Epidemiological evidence regarding the sibling effect on allergic disorders has been mainly accumulated in Western countries (2). To our knowledge, only one cross-sectional study reported the sibling effect in Japan, showing a significant inverse association of the number of older siblings with the prevalence of allergic rhinoconjunctivitis, but not wheeze or atopic eczema, in adolescents (14). In the current cross-sectional study, we assessed the association between the number of siblings and the prevalence of allergic disorders in Japanese schoolchildren using data from the Ryukyus Child Health Study (RYUCHS).

Methods

Study population

Okinawa Prefecture is an island located in the southernmost area in Japan, with a subtropical climate, a total population of almost 1,375,000, and an area of 2,274.59 km². Naha City, the largest city in Okinawa Prefecture and located in the south of the island, and Nago City, located in the center of the island, are two of the 41 municipalities in Okinawa Prefecture. Naha City and Nago City have a total population of almost 316,000 and 60,000, respectively, and an area of 39.04 and 210.24 km², respectively. All 35 public elementary schools and 17 junior high schools in Naha City and all 17 public elementary schools and eight junior high schools in Nago City participated in the RYUCHS between September 2004 and January 2005. The purpose of the RYUCHS, which was a cross-sectional survey, was to investigate the associations between various selected factors and child health problems. A set of two self-administered questionnaires was distributed by teachers to all 38,212 schoolchildren aged 6–15 yr. The questionnaires were completed at home by parents of the elementary schoolchildren and the junior high school students themselves and/or their parents. When missing answers or illogical data were detected by research technicians, the teachers sent the questionnaires back to the parents. Finally, 28,885 sets of the questionnaires (75.6%) were returned. Incomplete data on the variables under study caused the exclusion of 6135 children. There were

22,750 subjects left for analysis (59.5%). The RYUCHS was approved by the ethics committee of the Faculty of Medicine, Fukuoka University.

Measurements

One of the self-administered questionnaires included questions on symptoms of wheeze, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months based on the validated International Study of Asthma and Allergies in Childhood (ISAAC) phase-I questionnaire, which had been reported in detail elsewhere (15–18). We translated these questions into Japanese by using standard forward–backward translation. The definition of wheeze used in this study was determined by a positive response to the question, ‘Have you (Has your child) had wheezing or whistling in the chest in the last 12 months?’. A positive response to both the aforementioned question and another question ‘Have you (Has your child) ever had asthma?’ were considered to indicate asthma. A positive response to questioning about the presence of an itchy relapsing skin rash that had affected a child’s skin creases in the past 12 months was considered to indicate atopic eczema. For the definition of allergic rhinoconjunctivitis, affirmative answers to the following two questions were required: ‘In the last 12 months, have you (has your child) had a problem with sneezing or running or blocked nose when you (he/she) did not have a cold or flu?’ and ‘In the last 12 months, has this nose problem been accompanied by itchy-watery eyes?’. The questionnaire also inquired about age, gender, number of older and younger siblings, maternal age at childbirth, duration of breastfeeding, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level. A paternal or maternal history of asthma, atopic eczema, and allergic rhinitis was defined as positive if the respective parent had contracted any of these allergic disorders since the parent’s birth.

Statistical analysis

Age, gender, maternal age at childbirth, duration of breastfeeding, region of residence, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level were selected *a priori* as potential confounding factors. Age was classified into three categories (6–8, 9–11, and 12–15 yr), maternal age at childbirth into three (<28, 28–31, and 32+ yr), duration of

breastfeeding into four (<4, 4–6, 7–12, 13+ months), region of residence into two (Naha City and Nago City), smoking in the household into three (never, former, and current), paternal and maternal educational level into four (junior high school, high school, junior college or vocational technical school, and university), number of siblings into four (0, 1, 2, and 3+), number of older siblings into three (0, 1, and 2+), and number of younger siblings into three (0, 1, and 2+). Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) for associations between the number of siblings and the prevalence of allergic disorders were estimated with multiple logistic regression analysis. Trend of association was assessed by a logistic regression model assigning consecutive integers to the levels of the independent variable. Two-sided p-values <0.05 were regarded as statistically significant. All computations were performed using the SAS software package, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

In this study, the prevalence values for symptoms of wheeze, asthma, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months were 11.0%, 7.8%, 7.1%, and 7.9%, respectively, among 22,750 schoolchildren. About half of the subjects had one or more smokers in the household at the time of the RYUCHS (Table 1). Many more children had parents with a history of allergic rhinitis than parents with a history of asthma or atopic eczema. About 20% had three or more siblings and two or more younger siblings. A quarter of the subjects had two or more older siblings.

Table 2 provides adjusted ORs and their 95% CIs for allergic disorders according to the number of siblings. Significant exposure–response associations were observed between increasing total sibship size and all outcomes under investigation, although the adjusted OR of wheeze for extreme categories was just short of the significance level: the adjusted ORs of wheeze, asthma, atopic eczema, and allergic rhinoconjunctivitis for three or more vs. no siblings were 0.84 (95% CI, 0.71–1.001; p for trend = 0.048), 0.77 (95% CI, 0.63–0.95; p for trend = 0.009), 0.60 (95% CI, 0.49–0.74; p for trend < 0.0001), and 0.77 (95% CI, 0.63–0.95; p for trend = 0.0001), respectively. Having two or more older siblings was significantly inversely related to the prevalence of atopic eczema and allergic rhinoconjunctivitis, showing clear inverse exposure–response relationships. There was no statistically

Table 1. Distribution of selected characteristics in 22,750 schoolchildren, RYUCHS, Japan

Variable	n (%)
Male gender	11,194 (49.2)
Age (yr)	
6–8	6977 (30.7)
9–11	8358 (36.7)
12–15	7415 (32.6)
Maternal age at childbirth (yr)	
<28	8037 (35.3)
28–31	6896 (30.3)
32+	7817 (34.4)
Duration of breastfeeding (months)	
<4	8568 (37.7)
4–6	5291 (23.3)
7–12	5531 (24.3)
13+	3360 (14.8)
Region of residence	
Naha City	18,679 (82.1)
Nago City	4071 (17.9)
Smoking in household	
Never	9852 (43.3)
Former	2270 (10.0)
Current	10,628 (46.7)
Paternal history of asthma	1568 (6.9)
Paternal history of atopic eczema	606 (2.7)
Paternal history of allergic rhinitis	3968 (17.4)
Maternal history of asthma	1921 (8.4)
Maternal history of atopic eczema	991 (4.4)
Maternal history of allergic rhinitis	4948 (21.8)
Paternal educational level	
Junior high school	1748 (7.7)
High school	10,067 (44.3)
Junior college or vocational technical school	3402 (15.0)
University	7533 (33.1)
Maternal educational level	
Junior high school	1120 (4.9)
High school	9989 (43.9)
Junior college or vocational technical school	9600 (42.2)
University	2041 (9.0)
Total siblings	
0	1870 (8.2)
1	7671 (33.7)
2	8733 (38.4)
3+	4476 (19.7)
Older siblings	
0	9405 (41.3)
1	7532 (33.1)
2+	5813 (25.6)
Younger siblings	
0	9860 (43.3)
1	8152 (35.8)
2+	4738 (20.8)

significant relationship between the number of older siblings and the prevalence of wheeze or asthma. Having two or more younger siblings was independently associated with a decreased prevalence of atopic eczema, and the trend of this association was significant. No evident exposure–response relationship was observed between the number of younger siblings and the prevalence of wheeze, asthma, or allergic rhinoconjunctivitis,

Table 2. Adjusted odds ratios and 95% confidence intervals for allergic disorders according to the number of siblings in 22,750 schoolchildren, RYUCHS, Japan

	Wheeze		Asthma		Atopic eczema		Allergic rhinoconjunctivitis	
	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)
Total siblings								
0	12.3	1.00	8.9	1.00	9.4	1.00	8.3	1.00
1	11.5	0.91 (0.78–1.07)	8.3	0.89 (0.74–1.07)	7.7	0.78 (0.66–0.94)	8.8	1.02 (0.85–1.23)
2	10.7	0.88 (0.75–1.03)	7.6	0.84 (0.70–1.01)	6.7	0.70 (0.58–0.84)	7.6	0.88 (0.73–1.06)
3+	10.4	0.84 (0.71–1.00)	7.2	0.77 (0.63–0.95)	5.7	0.60 (0.49–0.74)	6.7	0.77 (0.63–0.95)
p for trend		0.05		0.009		<0.0001		0.0001
Older siblings								
0	11.3	1.00	8.2	1.00	7.6	1.00	8.7	1.00
1	11.6	1.06 (0.95–1.17)	8.1	1.02 (0.91–1.15)	7.3	0.97 (0.86–1.10)	8.1	0.92 (0.82–1.03)
2+	9.9	0.92 (0.82–1.04)	6.8	0.89 (0.77–1.02)	6.0	0.82 (0.71–0.96)	6.3	0.71 (0.62–0.82)
p for trend		0.34		0.16		0.02		< 0.0001
Younger siblings								
0	11.0	1.00	7.8	1.00	7.3	1.00	7.2	1.00
1	10.9	0.95 (0.86–1.06)	7.8	0.94 (0.83–1.05)	7.2	0.92 (0.81–1.04)	8.8	1.20 (1.07–1.35)
2+	11.3	0.97 (0.86–1.10)	8.1	0.95 (0.82–1.09)	6.3	0.80 (0.68–0.93)	7.8	1.03 (0.89–1.19)
p for trend		0.58		0.39		0.004		0.35

Adjustment for age, gender, maternal age at childbirth, duration of breastfeeding, region of residence, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.

although there was a significant positive relationship between having one younger sibling and allergic rhinoconjunctivitis.

After further adjustment for the number of older siblings, inverse associations of having three or more total siblings with the prevalence of asthma and atopic eczema remained significant, whereas an inverse relationship between having three or more siblings and the prevalence of allergic rhinoconjunctivitis did not reach statistical significance; however, the adjusted OR for having two or more older siblings in relation to allergic rhinoconjunctivitis was statistically significant. Additional adjustment for the number of younger siblings did not change significant inverse relationships between having three or more total siblings and asthma, atopic eczema, and allergic rhinoconjunctivitis, whereas the inverse association of the number of younger siblings with atopic eczema was no longer present.

When we stratified our results into two by age, the inverse relationships between the number of total siblings and the prevalence of allergic disorders under study were weakened with advancing age (Table 3). There were significant inverse associations between increasing sibship size and all outcomes under investigation among children aged 6–10 yr. Among subjects aged 11–15 yr, a significant relationship was observed between the number of siblings and the prevalence of atopic eczema, but not wheeze, asthma, or allergic rhinoconjunctivitis. The interactions between age groups associated with having three or more siblings and allergic disorders were not statistically significant ($p = 0.13, 0.92, 0.39$, and

0.08 for homogeneity of OR for wheeze, asthma, atopic eczema, and allergic rhinoconjunctivitis, respectively).

Table 3. Adjusted odds ratios and 95% confidence intervals for allergic disorders according to the number of total siblings in 22,750 schoolchildren 6–10 yr of age or 11–15 yr of age, RYUCHS, Japan

Total siblings	OR (95% CI)	
	Children aged 6–10 yr (n = 12,635)	Children aged 11–15 yr (n = 10,115)
Wheeze		
0	1.00	1.00
1	0.92 (0.75–1.13)	0.90 (0.69–1.17)
2	0.91 (0.74–1.11)	0.83 (0.65–1.08)
3+	0.73 (0.58–0.92)	0.98 (0.75–1.30)
p for trend	0.006	0.94
Asthma		
0	1.00	1.00
1	0.98 (0.77–1.24)	0.77 (0.58–1.04)
2	0.95 (0.75–1.20)	0.70 (0.53–0.93)
3+	0.74 (0.57–0.97)	0.79 (0.59–1.08)
p for trend	0.01	0.23
Atopic eczema		
0	1.00	1.00
1	0.82 (0.65–1.04)	0.73 (0.55–0.98)
2	0.70 (0.55–0.88)	0.70 (0.53–0.93)
3+	0.54 (0.41–0.71)	0.67 (0.50–0.92)
p for trend	<0.0001	0.04
Allergic rhinoconjunctivitis		
0	1.00	1.00
1	0.95 (0.74–1.23)	1.10 (0.84–1.45)
2	0.82 (0.64–1.06)	0.96 (0.74–1.27)
3+	0.64 (0.47–0.86)	0.92 (0.69–1.24)
p for trend	0.0002	0.12

Adjustment for gender, maternal age at childbirth, duration of breastfeeding, region of residence, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.

When subjects were divided according to whether there was a positive or negative allergic history in at least one parent, inverse exposure–response associations between the number of total siblings and the prevalence of wheeze were no longer of statistical significance among children regardless of parental allergic history (Table 4). Having three or more siblings was significantly inversely related to the prevalence of asthma only among subjects without a parental allergic history. A significant inverse association between larger sibship size and atopic eczema was slightly more prominent in children with a positive parental allergic history than in those without a parental allergic history. Inverse exposure–response relationships between an increasing number of siblings and the prevalence of allergic rhinoconjunctivitis were statistically significant, although the adjusted ORs for having three or more siblings were not significant among children with both a positive and negative parental allergic history. No significant interactions were found in the association of having three or more siblings with allergic disorders

Table 4. Adjusted odds ratios and 95% confidence intervals for allergic disorders according to the number of total siblings in 22,750 schoolchildren with a positive or negative parental allergic history, RYUHS, Japan

Total siblings	OR (95% CI)	
	Positive parental allergic history (n = 9597)	Negative parental allergic history (n = 13,153)
Wheeze		
0	1.00	1.00
1	0.92 (0.76–1.13)	0.94 (0.73–1.22)
2	0.85 (0.70–1.04)	0.97 (0.76–1.25)
3+	0.94 (0.75–1.17)	0.83 (0.64–1.10)
p for trend	0.43	0.23
Asthma		
0	1.00	1.00
1	0.98 (0.79–1.23)	0.79 (0.58–1.08)
2	0.87 (0.70–1.10)	0.85 (0.64–1.16)
3+	0.92 (0.72–1.19)	0.70 (0.51–0.99)
p for trend	0.22	0.14
Atopic eczema		
0	1.00	1.00
1	0.77 (0.61–0.97)	0.86 (0.64–1.15)
2	0.73 (0.58–0.91)	0.68 (0.51–0.92)
3+	0.58 (0.45–0.76)	0.65 (0.47–0.90)
p for trend	0.0002	0.0008
Allergic rhinoconjunctivitis		
0	1.00	1.00
1	1.04 (0.83–1.32)	1.06 (0.78–1.46)
2	0.91 (0.73–1.15)	0.85 (0.63–1.18)
3+	0.80 (0.61–1.03)	0.76 (0.55–1.08)
p for trend	0.006	0.006

Adjustment for age, gender, maternal age at childbirth, duration of breast-feeding, region of residence, smoking in the household, and paternal and maternal educational level.

between children with a positive and negative parental allergic history ($p = 0.63, 0.23, 0.50$, and 0.99 for homogeneity of OR for wheeze, asthma, atopic eczema, and allergic rhinoconjunctivitis, respectively).

Discussion

In this study, the preventive effect of older siblings on the prevalence of atopic eczema and allergic rhinoconjunctivitis was demonstrated whereas only the protective effect of younger siblings on atopic eczema was observed, although there were significant exposure–response relationships between increasing sibship size and the outcomes under study. Moreover, because inverse relationships between sibship size and the prevalence of atopic eczema persisted after additional allowance for having older or younger siblings, increasing sibship size might explain the associations of the number of older and younger siblings with atopic eczema. Mutual control for total sibship size and having older siblings completely removed the inverse relationship between increasing sibship size and allergic rhinoconjunctivitis, although the adjusted OR for having two or more older siblings was significant. The inverse relationship between sibship size and allergic rhinoconjunctivitis might be attributed to the effect of older siblings. Children aged 6–7 yr with more than two siblings had a significantly lower prevalence of current rhinitis and life-time eczema in a cross-sectional study in Hong Kong (19). In a retrospective cohort study in Denmark, a significant exposure–response relationship was found between the number of older siblings and the risk of atopic eczema at the age of 7 (20). These findings are generally consistent with our results. A cross-sectional study among Australian children aged 7 yr showed significant inverse associations of increasing sibship size and the prevalence of asthma and hay fever, but not eczema (21). A case–control study in UK children aged 1–5 yr reported that the presence of older, but not younger, siblings was significantly related to a reduced risk of atopic eczema (22). Among children at the age of 6 in the Netherlands, birth order, which equals the number of older siblings plus one, was significantly related to a decreased risk of food allergy and/or eczema and allergy such as to house dust mites and hay fever, but not asthma, whereas sibship size was not associated with any of the atopic diseases (23). Significant inverse associations of the number of both older and younger siblings with the risk of hay fever were found in UK adolescents (5).

Another UK study showed that an increasing number of total and older siblings was inversely related to the prevalence of eczema and hay fever, but not asthma, whereas there was a significant inverse association between having three or more younger siblings and asthma, but not eczema or hay fever, among children aged 10–14 yr (24). These findings are in partial agreement with the present results. The presence of two or more older siblings was associated with a decreased risk of asthma among 16-yr-old Finnish adolescents (25). That observation is in disagreement with our results. The present findings indicate that the investigated outcomes have different etiological mechanisms. However, our results are partially compatible with the hygiene hypothesis that having infections in early life might be preventive against allergic disorders, although we could not examine associations between the interval to the closest older and younger siblings and the studied outcomes. Also, data on the personal history of infections in childhood were not available in this study.

The current observations, especially significant inverse relationships between having older siblings and the prevalence of atopic eczema and allergic rhinoconjunctivitis, are also likely to support the *in utero* programming hypothesis because the *in utero* environment would probably change with parity. In a study in the UK, women who had had higher numbers of intervening pregnancies were more likely to have lost their atopy and symptoms of hay fever, but not asthma (10). Another UK study found that the number of live offspring significantly reduced the maternal IgE level (11). Maternal immunomodulation might be transmitted to the developing fetus. A potential role of hormones is suggested; progesterone and testosterone seem to promote the preferential development of Th2-like cells (2). Endocrine disruptors are thought to exert adverse health effects. The organochlorine burden appears to decrease with birth order (12). Increasing concentrations of dichlorodiphenyldichloroethylene at birth were significantly related to the risk of wheezing at 4 yr of age (26). However, the Glasgow Alumni Study reported inverse associations between sibship size and the prevalence of eczema–urticaria and hay fever among people born in the first half of the 20th century when organochlorines had not come into widespread use (27).

In this study, the sibling effect was attenuated with advancing age, although the interactions between age groups, sibship size, and the studied outcomes were not significant and a significant inverse association was observed between sibship

size and atopic eczema in the older age group. The protective effect of having siblings on the risk of wheeze, asthma, and allergic rhinoconjunctivitis may only involve children at an early age. However, once again, the Glasgow Alumni Study found an inverse association between sibship size and the prevalence of hay fever among people aged 16–30 yr (27). A cross-sectional study in Denmark showed that increasing sibship size was related to a decreased lifetime prevalence of allergic rhinitis and asthma with allergic rhinitis, but not asthma without allergic rhinitis, among pregnant women between 15 and 43 yr of age (28). These results among young adults are inconsistent with the present findings in the older age group.

With respect to differences in genetic predisposition to allergy, there were no significant interactions in the association of having three or more siblings with the study outcomes between children with a positive and negative parental allergic history in this study; although adjusted OR for having three or more siblings in relation to asthma was significant only among children without a parental allergic history, an inverse relationship between increasing sibship size and atopic eczema was slightly more evident among children with a parental allergic history. An inverse relationship between a greater number of older siblings and atopic disorders was found only in the offspring of atopic fathers in a cross-sectional study among German children (29). That finding is partially consistent with our findings regarding atopic eczema, but in disagreement with the present results in relation to wheeze, asthma, or allergic rhinoconjunctivitis. The present results indicate that a parental allergic history may affect the associations between sibship size and the prevalence of asthma and atopic eczema in different directions.

This research had several methodological advantages in that the investigated outcomes were assessed by using the validated ISAAC-based questions and study subjects were homogeneous with respect to age and geographical background. The large number of subjects and variables was likely to minimize the problems that might arise due to small sample size, inadequate data on potential confounders, and reduced statistical power. However, no adjustment was made for daycare attendance and home environment in early life, as such data were not available. Selection bias was a methodological issue that requires careful consideration, as only 59.5% of the eligible subjects were included in the current study. For 6135 participants, data were incomplete, and subsequently these subjects

were excluded. However, they did provide information that allowed us to determine some differences between those who were included and excluded. Compared with the 6135 excluded subjects, the 22,750 study subjects were less likely to have no siblings and have former smokers in the household, mothers who gave birth to the child at the age of <28 yr, mothers who had stopped breastfeeding within the first 4 months of life, and mothers with a history of asthma and atopic eczema and were more likely to be young and have a personal history of the allergic disorders under study, fathers with a history of allergic rhinitis, and both fathers and mothers with a high educational level. With regard to the other variables under study, there was no statistically significant difference between the excluded participants and study subjects. Okinawa is a subtropical island whereas the mainland of Japan is located in the temperate zone. In addition, Okinawa is less developed compared with the mainland because of Okinawa's reversion to Japanese administration in 1972. The distribution of a variety of environmental factors as well as allergy and sibship size in Okinawa is likely to be different from that in the mainland of Japan. Among Japanese adolescents in Suita City in an urban area of the mainland, the prevalence of wheeze, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months, by using the ISAAC criteria, was 6.7%, 14.5%, and 23.9%, respectively, and the proportion of adolescents with two or more older siblings was 14.5% (14). Thus, we should be cautious in generalizing the present results. Because information on whether any of the subjects came from the same family was not available in this study, we could not take clustering within families into consideration, which might have an influence on the relationship of interest.

In conclusion, this study verified an inverse relationship between sibship size and allergic disorders. Our findings suggest that unrecognized factors operating during perinatal periods explain the inverse relationships. The results on lack of associations between the number of younger siblings and the prevalence of wheeze, asthma, and allergic rhinoconjunctivitis are likely to support the *in utero* programming hypothesis, although our observations could not refute the hygiene hypothesis. Ascertaining the mechanisms underlying the sibling effect would improve strategies for the prevention of allergic disorders.

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