



ORIGINAL CONTRIBUTIONS

Sibship Characteristics and Risk of Allergic Rhinitis and Asthma

Tine Westergaard¹, Klaus Rostgaard¹, Jan Wohlfahrt¹, Per Kragh Andersen^{1,2}, Peter Aaby¹, and Mads Melbye¹

¹ Division of Epidemiology Research, Danish Epidemiology Science Centre, Statens Serum Institut, Copenhagen, Denmark.

² Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark.

Received for publication December 6, 2002; accepted for publication January 5, 2005.

Studying associations between sibship characteristics and allergic diseases in detail may contribute clues to their etiology. The authors studied associations between sibship characteristics and risk of self-reported allergic rhinitis and asthma among 31,145 pregnant women participating in a nationwide study in Denmark during 1997–2000. Increasing sibship size was associated with a decreased risk of allergic rhinitis and asthma with allergic rhinitis but not with asthma without allergic rhinitis. The protective effect of having older siblings was stronger than the protective effect of having younger siblings for both allergic rhinitis and asthma with allergic rhinitis. There was no association between interval to closest older or younger sibling and risk of allergic rhinitis or asthma with allergic rhinitis, while the risk of asthma without allergic rhinitis increased with intervals of 2 or more years compared with less than 2 years to the nearest older sibling. The protective effect of having siblings on the risk of asthma with allergic rhinitis could be explained by a protective effect of siblings on the risk of allergic rhinitis alone. In conclusion, our findings suggest that different etiologic mechanisms are involved for allergic rhinitis and asthma with respect to the effect of sibship characteristics. Furthermore, the findings that allergic rhinitis was associated with the number of younger siblings but not with the age interval to younger siblings support the hypothesis of an influence of postnatal mechanisms and suggest that these mechanisms may not necessarily be operating only in early life.

asthma; birth order; hypersensitivity; rhinitis, allergic, perennial; rhinitis, allergic, seasonal; risk factors; siblings

Abbreviation: CI, confidence interval.

Editor's note: An invited commentary on this article appears on page 133, and the authors' response appears on page 139.

Studies have consistently reported on inverse associations between the number of siblings and the risk of allergic rhinitis (1–4) and allergic sensitization (4–7). So far, no factor has with certainty been found to explain this association. However, the more siblings a child has early in life, the more likely the child is to be exposed to infections at an early age, and the association has in particular been proposed to be

explained by a protective effect of common infections in early childhood on allergy risk (1, 2, 5–8). Exposure to microbial agents at an early age may exert a stimulatory effect on the developing immune system, driving it in a non-allergic direction (9).

Results from studies on the association between asthma and sibship size have, on the other hand, lacked consistency (4, 10). However, few have taken into account whether they studied asthma with or without an allergic component, such as allergic sensitization or other allergic diseases. Regarding sibship characteristics other than sibship size, the literature is furthermore sparse on studies addressing whether, for example, age interval to siblings (2, 3) and gender of siblings

Correspondence to Dr. Tine Westergaard, Division of Epidemiology Research, Danish Epidemiology Science Centre, Statens Serum Institut, 5 Artillerivej, DK-2300 Copenhagen S, Denmark (e-mail: twe@ssi.dk).

(7, 11) might affect the risk of allergy or asthma. Studying sibship characteristics and associations with allergy and asthma in more detail could contribute to our understanding of the underlying mechanism behind allergy and asthma and bring new clues to their etiology.

In this study, we investigated among pregnant women whether the risk of allergic rhinitis and the risk of asthma with and without allergic rhinitis were associated with sibship characteristics, including the total number of siblings, the number of older and younger siblings, and the number of brothers and sisters. Furthermore, the possible association of allergic rhinitis and of asthma with and without allergic rhinitis with the interval to closest older and younger sibling was studied.

MATERIALS AND METHODS

Study population

The present study is a cross-sectional study and is based on data from the Danish National Birth Cohort and the Danish Civil Registration System. Before initiation, the study was approved by the Danish Data Protection Agency and the scientific-ethical committees for Copenhagen and Frederiksberg.

The Danish National Birth Cohort Study is an ongoing study conducted in Denmark, with the main focus on studying the importance of exposures in utero and during the first years of life for later development of disease (12). Pregnant women were invited to participate in this study when they visited their general practitioner for the first time during their pregnancy. Women were eligible for inclusion if they wanted to carry their pregnancy to term and spoke Danish well enough to take part in telephone interviews. The first of four telephone interviews was conducted around weeks 12–16 of pregnancy. In this interview, the women were asked a wide variety of questions, including questions on allergic rhinitis and asthma.

Overall, 39,154 women participating in the Danish National Birth Cohort for the first time had completed their first telephone interview between September 29, 1997, and March 14, 2000. These women were linked with the Civil Registration System, which is a mandatory national register containing updated demographic information on all residents in Denmark (13). From the Civil Registration System, complete information on date of birth, place of birth, and vital status of their mothers and all their siblings could be obtained as long as their mothers and siblings were born in Denmark on April 1, 1935, or later (14) and were alive or born later than April 1, 1968, when the Civil Registration System was established. The study was restricted to the 31,749 women whose mothers fulfilled these criteria. In addition, women were excluded if they were born abroad or had missing information on the place of birth or the place of residence ($n = 520$) or if they did not know whether they had allergy ($n = 84$), leaving 31,145 women in the study.

Definitions

The study is based on the lifetime prevalence of allergic rhinitis and asthma as defined below. During the first tele-

phone interview, all women were asked, “Have you ever had asthma?” and, if so, “Have you had the disease diagnosed by a doctor?” Women who answered affirmatively to these two questions were considered as cases with asthma. All women were furthermore asked, “Have you ever had allergy?” and, if so, “Have you had the disease diagnosed by a doctor?” Women who answered affirmatively to these two questions were further asked what kind of allergy they had. Women who reported allergic rhinitis and/or hay fever were considered as cases with allergic rhinitis.

Statistical analyses

The odds of allergic rhinitis and of asthma with and without allergic rhinitis were estimated using logistic regression models. Maximum likelihood estimation was performed using the GENMOD procedure in the SAS 6.12 statistical software package (15). Two-sided p values were based on likelihood ratio tests, and 95 percent confidence intervals were based on Wald’s tests. Trends were estimated as the slope when the categorical variables of interest were treated as quantitative variables.

First, possible associations were investigated between the studied outcomes and the total number of siblings at the age of 10 years, the numbers of older and younger siblings, the numbers of brothers and sisters, and the numbers of older and younger brothers and sisters, respectively. Tests for trend were performed to study the potential effect of the number of siblings, and the slope estimates were used to test for a potential difference between having older and younger siblings and having brothers and sisters.

Second, possible associations between the interval to the closest older and younger sibling and the studied outcomes were investigated. The possible association between allergic rhinitis and the interval to siblings was furthermore studied in more detail in a subanalysis on a data set restricted to women with zero, one, or two siblings and with intervals of less than 10 years to their siblings ($n = 24,540$).

In all models, we included the age at interview (<20, 20–24, 25–29, 30–34, ≥ 35 years), the age of the mother at the woman’s birth (<20, 20–24, 25–29, 30–34, ≥ 35 years), the degree of urbanization of the place of birth (five categories) and the place of residence (five categories), and occupation (six categories) (16).

Finally, we used polytomous logistic regression to investigate whether an effect of having siblings on the risk of asthma with allergic rhinitis could be due to a protective effect of siblings on the risk of allergic rhinitis alone. These analyses were done using Stata software, release 8 (17). Cases were categorized in three groups (asthma with allergic rhinitis, asthma without allergic rhinitis, allergic rhinitis without asthma) and compared with women who had neither asthma nor allergic rhinitis. The effect of confounders was allowed to be different for the three outcomes. The hypothesis was investigated by testing whether the parameters corresponding to the outcomes allergic rhinitis without asthma and asthma with allergic rhinitis could be considered identical.

RESULTS

The 31,145 women in the study were between 15 and 43 years of age. A total of 284 (1 percent) were below the age of 20 years, 3,968 (13 percent) were aged 20–24 years, 13,822 (44 percent) were aged 25–29 years, 10,824 (35 percent) were aged 30–34 years, and 2,247 (7 percent) were aged 35 years or above. The average age was 29 years (standard deviation: 3.9 years). A total of 4,202 (13.5 percent) women were identified as cases with allergic rhinitis. Among these, 74.4 percent reported being allergic against pollen, 26.1 percent against animal dander, 19.9 percent against house dust mites, and 89.5 percent against at least one of these three groups of allergens. A total of 2,629 (8.4 percent) reported having had asthma, 1,197 (3.8 percent) reported both asthma and allergic rhinitis (asthma with allergic rhinitis), and 1,432 (4.6 percent) reported having had asthma but not allergic rhinitis (asthma without allergic rhinitis).

Allergic rhinitis

As seen in table 1, the odds ratio of allergic rhinitis decreased with the increasing number of siblings ($p_{\text{trend}} < 0.0001$). There was an inverse association between allergic rhinitis and the number of older siblings ($p_{\text{trend}} < 0.0001$), as well as the number of younger siblings ($p_{\text{trend}} = 0.0008$) (table 1). For each additional older sibling, the odds of allergic rhinitis decreased by a factor of 0.80 (95 percent confidence interval (CI): 0.76, 0.84), while for each additional younger sibling the risk decreased by a factor of 0.92 (95 percent CI: 0.87, 0.97). The effect of having older siblings was significantly stronger than the effect of having younger siblings ($p = 0.0001$). The odds ratio of allergic rhinitis for combinations of the numbers of older and younger siblings can be seen in table 2. The table shows that the protective effect of younger siblings primarily was in subjects with additional older siblings, whereas the protective effect of older siblings was observed regardless of the number of younger siblings. The association between the number of siblings and the risk of allergic rhinitis was not modified by birth cohort.

There was a significant inverse association between allergic rhinitis and having brothers ($p_{\text{trend}} < 0.0001$) and sisters ($p_{\text{trend}} < 0.0001$). The odds of allergic rhinitis decreased by a factor of 0.85 (95 percent CI: 0.81, 0.89) for each additional brother and by 0.87 (95 percent CI: 0.83, 0.91) for each additional sister (table 1), and the trends did not differ from each other ($p = 0.34$). Likewise, the inverse associations were similar for older brothers and sisters and for younger brothers and sisters, respectively (table 1).

There was no association between allergic rhinitis and the interval to closest older sibling or the interval to closest younger sibling (table 3), and the gender of the sibling did not affect the risks (data not shown). The subanalysis on the data restricted to the 24,540 women with zero, one, or two siblings and with intervals of less than 10 years to their siblings showed a tendency of lower odds ratios for intervals to older siblings than to younger siblings but did not show any consistent pattern of association between specific age intervals to younger or older siblings, respectively, and the risk of allergic rhinitis (table 4).

Asthma

Using polytomous logistic regression, we found that the effects of siblings on asthma with and without allergic rhinitis differed significantly from each other (this analysis is further described below). Therefore, the effect of sibship characteristics will not be presented for asthma overall but will be presented for asthma with and without allergic rhinitis separately.

Asthma with allergic rhinitis. As seen in table 5, the risk of asthma with allergic rhinitis decreased with the increasing number of siblings ($p_{\text{trend}} = 0.0006$). There were a significant inverse association with the number of older siblings ($p_{\text{trend}} = 0.0004$) and a borderline significant association with the number of younger siblings ($p_{\text{trend}} = 0.06$) (table 5). The trends of 0.86 (95 percent CI: 0.79, 0.94) for number of older siblings and of 0.92 (95 percent CI: 0.84, 1.00) for number of younger siblings did not differ significantly from each other ($p = 0.20$).

There was a significant inverse association between having had asthma with allergic rhinitis and number of brothers ($p_{\text{trend}} = 0.002$) and number of sisters ($p_{\text{trend}} = 0.01$) (table 5). The trends of 0.87 (95 percent CI: 0.80, 0.95) for brothers and of 0.90 (95 percent CI: 0.82, 0.98) for sisters were not significantly different ($p = 0.54$). Likewise, there was a similar inverse association with having older brothers and sisters, while there was no significant association with having younger brothers and sisters (table 5).

There was no association between the interval to the closest older or younger sibling and the risk of asthma with allergic rhinitis (table 3). Furthermore, there was no interaction between the intervals and the gender of the sibling (data not shown).

Asthma without allergic rhinitis. There was no significant association between having had asthma without allergic rhinitis and the number of siblings or the number of brothers or sisters (table 5). However, the odds of asthma without allergic rhinitis increased significantly with the number of older siblings ($p_{\text{trend}} = 0.02$), while there was no association with the number of younger siblings ($p_{\text{trend}} = 0.92$) (table 5), but the trends for the numbers of older and younger siblings were not significantly different. The odds of asthma without allergic rhinitis increased significantly with the number of older brothers but not with the number of older sisters (table 5). The trends, however, did not differ significantly from each other. There was no association with having younger brothers or sisters (table 5).

The risk of asthma without allergic rhinitis was higher for intervals of 2 or more years to the closest older sibling (odds ratio = 1.25, 95 percent CI: 1.02, 1.53) compared with intervals of less than 2 years (table 3). There was no association with the interval to the closest younger sibling. There was no interaction between the interval to the closest older or younger sibling and gender (data not shown).

Comparisons of the effects of having siblings

The observed protective effect of having siblings on the risk of asthma with allergic rhinitis could potentially be due to the protective effect of siblings on the risk of allergic

TABLE 1. Distribution and odds ratio* of allergic rhinitis according to the total number of siblings, the numbers of older and younger siblings, the numbers of brothers and sisters, and the numbers of older and younger brothers and sisters, among 31,145 Danish women, 1997–2000

	Total no. of women	Allergic rhinitis					
		%	Odds ratio	95% confidence interval	Trend†	95% confidence interval	<i>P</i> _{trend}
Total siblings							
0	2,295	14.7	1	Referent	0.85	0.82, 0.89	<0.0001
1	15,595	14.8	1.01	0.90, 1.15			
2	9,893	12.3	0.82	0.72, 0.94			
3	2,606	10.6	0.70	0.59, 0.83			
≥4	756	8.5	0.56	0.42, 0.74			
Older siblings							
0	15,399	14.8	1	Referent	0.80	0.76, 0.84	<0.0001
1	10,758	12.8	0.77	0.71, 0.84			
2	3,893	11.8	0.68	0.60, 0.77			
≥3	1,095	7.9	0.43	0.34, 0.55			
Younger siblings							
0	12,736	13.3	1	Referent	0.92	0.87, 0.97	0.0008
1	13,681	13.9	0.92	0.84, 0.99			
2	4,096	12.7	0.81	0.72, 0.91			
≥3	632	12.8	0.84	0.65, 1.07			
Brothers							
0	12,515	14.4	1	Referent	0.85	0.81, 0.89	<0.0001
1	14,194	13.5	0.85	0.79, 0.92			
2	3,765	11.4	0.70	0.62, 0.79			
≥3	671	9.1	0.56	0.43, 0.74			
Sisters							
0	13,519	14.2	1	Referent	0.87	0.83, 0.91	<0.0001
1	13,318	13.3	0.84	0.78, 0.91			
2	3,679	11.9	0.73	0.65, 0.82			
≥3	629	12.1	0.78	0.61, 1.00			
Older brothers							
0	21,715	14.3	1	Referent	0.78	0.73, 0.83	<0.0001
1	7,633	12.1	0.75	0.69, 0.82			
≥2	1,797	10.1	0.60	0.50, 0.71			
Older sisters							
0	22,284	14.1	1	Referent	0.83	0.77, 0.88	<0.0001
1	7,280	12.0	0.77	0.70, 0.84			
≥2	1,581	12.0	0.75	0.63, 0.88			
Younger brothers							
0	20,393	13.5	1	Referent	0.92	0.87, 0.98	0.01
1	9,412	13.5	0.89	0.82, 0.97			
≥2	1,340	13.1	0.86	0.72, 1.01			
Younger sisters							
0	20,970	13.5	1	Referent	0.92	0.86, 0.97	0.005
1	8,802	13.5	0.89	0.83, 0.97			
≥2	1,373	12.9	0.82	0.70, 0.98			

* Adjusted for age, age of the mother at the woman's birth, degree of urbanization of the place of birth, degree of urbanization of the place of residence, occupation, and the other variables in the same section, the sections being 1) total siblings, 2) older and younger siblings, 3) brothers and sisters, and 4) older and younger brothers and sisters.

† Trend: the relative increase in odds per increase in the number of siblings (total siblings, older or younger siblings, brothers or sisters, and younger or older brothers or sisters, respectively).

TABLE 2. The odds ratio* and 95% confidence interval of allergic rhinitis according to combinations of the number of older and younger siblings among 31,145 Danish women, 1997–2000

No. of older siblings	No. of younger siblings							
	0		1		2		≥3	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
0	1	Referent	1.08	0.95, 1.22	0.92	0.79, 1.08	1.05	0.80, 1.38
1	0.92	0.81, 1.06	0.73	0.63, 0.86	0.72	0.54, 0.96	0.29	0.11, 0.81
2	0.80	0.68, 0.94	0.63	0.49, 0.82	0.49	0.26, 0.95	0.83	0.25, 2.82
≥3	0.44	0.33, 0.59	0.70	0.43, 1.13	0.53	0.19, 1.49	—†	—

* Adjusted for age, maternal age at birth, degree of urbanization of the place of birth, degree of urbanization of the place of residence, and occupation.

† —, no cases available.

rhinitis alone. To investigate this, we used polytomous logistic regression. The analysis revealed that, when categorizing cases in three outcomes (asthma with allergic rhinitis, asthma without allergic rhinitis, allergic rhinitis without asthma) and compared with women with neither asthma

nor allergic rhinitis, the differences in the effect of having siblings could be ascribed to the presence of allergic rhinitis in the case definition or not. In other words, the fitted model showed that the associations between having siblings and allergic rhinitis without asthma and allergic rhinitis with

TABLE 3. Distribution and odds ratio* of allergic rhinitis and asthma, with and without allergic rhinitis, according to interval to closest older and younger siblings among 31,145 Danish women, 1997–2000

	Total no. of women	Allergic rhinitis				Asthma							
		%	Odds ratio	95% confidence interval	<i>p</i> value†	With allergic rhinitis				Without allergic rhinitis			
						%	Odds ratio	95% confidence interval	<i>p</i> value†	%	Odds ratio	95% confidence interval	<i>p</i> value†
Interval to closest older sibling (years)													
No older sibling	15,401	14.8				4.1				4.5			
<2	3,161	10.9	1	Referent		3.1	1	Referent		3.9	1	Referent	
2–3	7,480	12.4	1.08	0.94, 1.23		3.6	1.11	0.87, 1.40		4.9	1.26	1.02, 1.56	
4–5	3,295	12.5	1.07	0.91, 1.25		3.3	0.92	0.69, 1.23		4.7	1.20	0.93, 1.54	
6–7	1,143	13.3	1.17	0.94, 1.44		4.0	1.03	0.71, 1.50		4.9	1.19	0.85, 1.67	
≥8	665	13.2	1.14	0.87, 1.50	0.66	5.3	1.17	0.76, 1.81	0.54	6.2	1.47	0.99, 2.19	0.20
<2	3,161	10.9	1	Referent		3.1	1	Referent		3.9	1	Referent	
≥2	12,583	12.5	1.08	0.95, 1.23	0.22	3.7	1.06	0.84, 1.33	0.64	4.9	1.25	1.02, 1.53	0.03
Interval to closest younger sibling (years)													
No younger sibling	12,737	13.3				4.1				4.8			
<2	3,373	12.6	1	Referent		3.5	1	Referent		4.8	1	Referent	
2–3	8,639	14.3	1.10	0.97, 1.24		3.8	1.04	0.83, 1.29		4.4	0.89	0.73, 1.08	
4–5	3,964	13.0	1.01	0.87, 1.16		3.7	1.04	0.81, 1.35		4.0	0.81	0.64, 1.03	
6–7	1,704	13.7	1.11	0.93, 1.33		3.8	1.11	0.80, 1.53		4.9	0.98	0.74, 1.30	
≥8	728	12.9	1.07	0.84, 1.37	0.39	3.4	1.04	0.66, 1.63	0.98	5.2	1.03	0.71, 1.50	0.36
<2	3,373	12.6	1	Referent		3.5	1	Referent		4.8	1	Referent	
≥2	15,035	13.8	1.08	0.96, 1.21	0.21	3.7	1.04	0.85, 1.29	0.68	4.4	0.89	0.74, 1.07	0.20

* Adjusted for age, age of the mother at the woman's birth, number of older and number of younger siblings, degree of urbanization of the place of birth, degree of urbanization of the place of residence, and occupation.

† *p* values are derived from tests for homogeneity.

TABLE 4. The odds ratio* and 95% confidence interval of allergic rhinitis according to the interval between siblings and the index woman among 24,540 Danish women with zero, one, or two siblings, 1997–2000†

Interval (years) between sibling 1‡ (if present) and index woman§	Interval (years) between sibling 2¶ (if present) and index woman§											
	No sibling 2		–9 to –3		–2 to <0		0 to 2		3 to 4		5 to 9	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
No sibling 1	1	Referent										
–9 to –3	1.05	0.91, 1.22	0.89	0.71, 1.12								
–2 to <0	1.04	0.89, 1.22	0.91	0.75, 1.09	1.08	0.62, 1.88						
0 to 2	0.96	0.81, 1.13	0.61	0.49, 0.76	0.74	0.56, 0.99	0.84	0.50, 1.42				
3 to 4	0.84	0.71, 1.01	0.87	0.67, 1.12	0.74	0.51, 1.07	0.62	0.45, 0.85	0.77	0.39, 1.51		
5 to 9	0.86	0.69, 1.08	0.79	0.50, 1.24	0.59	0.31, 1.11	0.73	0.52, 1.01	0.84	0.66, 1.07	0.81	0.62, 1.07

* Adjusted for age, maternal age at own birth, degree of urbanization of the place of birth, degree of urbanization of the place of residence, and occupation.

† Intervals between siblings and index women were less than 10 years.

‡ Sibling 1: the oldest sibling of the index woman, provided that she has at least one sibling.

§ Intervals to older siblings are positive, while intervals to younger siblings are negative.

¶ Sibling 2: the second oldest sibling of the index woman, provided that she has two siblings.

asthma were similar when compared with women with neither asthma nor allergic rhinitis. Thus, one can interpret the protective effect of having siblings on the risk of asthma with allergic rhinitis as due to the protective effect of siblings on the risk of allergic rhinitis alone.

DISCUSSION

Overall, we found similar risk patterns for allergic rhinitis and asthma with allergic rhinitis. The risk of both allergic rhinitis and asthma with allergic rhinitis decreased with the increasing number of siblings. In contrast, the risk of asthma without allergic rhinitis was not associated with sibship size. The protective effect of having siblings on the risk of asthma with allergic rhinitis could, however, be explained by a protective effect of having siblings on allergic rhinitis alone. Our findings suggest that different etiologic mechanisms are involved for allergic rhinitis and asthma overall with respect to the effect of sibship characteristics. Our finding of a diverse pattern between asthma with and without allergic rhinitis may be one of the explanations for conflicting findings in previous studies on asthma and sibship characteristics.

We found that having both older and younger siblings was associated with a protective effect on allergic rhinitis but that the effect of having older siblings was stronger than the effect of having younger siblings. According to the theory that in particular having infections during the first few years of life should protect against allergic sensitization, we would also expect that among younger siblings only younger siblings very close in age to the subject would have a protective effect. However, no specific age interval either to the closest younger or older sibling, respectively, was found to be associated with a particularly protective effect on allergic rhinitis. This suggests that exposures later in childhood also may be involved in the etiology.

Some studies have suggested that the association between allergy and the number of older siblings as measured by birth

order might rather be explained by an association with immune development in utero than by postnatal exposure. One study found a tendency of a decrease (18), and another more recent study reported a significant decrease in cord blood immunoglobulin E with increasing birth order and found the cord blood immunoglobulin E concentration to be a significant predictor of allergic sensitization in childhood (19). Furthermore, proliferative responses of cord blood mononuclear cells to allergens have recently been found to decrease significantly with increasing birth order (20). Such findings do not, however, explain the independent association between allergy and the number of younger siblings that has been found in the present study and in previous large studies on allergic rhinitis and allergic sensitization (1, 2, 6, 7).

Interestingly, Strachan et al. (11) found in a study of 11,042 pregnant women that the inverse association between having many siblings and the risk of inhalant allergy was restricted to the number of brothers the women had, while there was no association with having sisters. This finding was supported by a study of 13,932 subjects by Svanes et al. (7), who found a stronger protective effect of having brothers than sisters on the risk of atopy among women as well as men. Svanes et al. suggested that having brothers compared with sisters may have a particularly protective effect on developing allergy, perhaps because boys are more likely to contract serious respiratory infections and thereby provide a stronger exposure to infectious agents (7). There was a slight tendency in our data of a more protective effect of having brothers than sisters, but none of the trend estimates differed significantly from each other.

Information on allergic rhinitis and asthma in our study was based on self-reported information obtained in young adult life. It cannot be excluded that some misclassification of the outcomes could have occurred. However, bias from self-reporting was reduced by using questions on physician-diagnosed conditions, which have been found suitable

TABLE 5. Distribution and odds ratio* of asthma with allergic rhinitis and asthma without allergic rhinitis according to the total number of siblings, the numbers of older and younger siblings, the numbers of brothers and sisters, and the numbers of older and younger brothers and sisters, among 31,145 Danish women, 1997–2000

	Asthma with allergic rhinitis						Asthma without allergic rhinitis					
	%	Odds ratio	95% confidence interval	Trend†	95% confidence interval	p_{trend}	%	Odds ratio	95% confidence interval	Trend†	95% confidence interval	p_{trend}
Total siblings												
0	4.4	1	Referent	0.89	0.82, 0.95	0.0006	4.7	1	Referent	1.05	0.99, 1.12	0.11
1	4.1	9.98	0.79, 1.21				4.6	1.03	0.84, 1.28			
2	3.4	0.81	0.64, 1.02				4.6	1.08	0.87, 1.35			
3	3.4	0.79	0.58, 1.06				4.5	1.08	0.82, 1.42			
≥4	2.8	0.60	0.37, 0.98				5.3	1.27	0.87, 1.86			
Older siblings												
0	4.1	1	Referent	0.86	0.79, 0.94	0.0004	4.5	1	Referent	1.09	1.02, 1.18	0.02
1	3.5	0.75	0.64, 0.87				4.5	1.05	0.91, 1.20			
2	3.9	0.77	0.62, 0.96				5.2	1.27	1.05, 1.54			
≥3	3.2	0.57	0.39, 0.83				4.9	1.18	0.86, 1.61			
Younger siblings												
0	4.1	1	Referent	0.92	0.84, 1.00	0.06	4.8	1	Referent	1.00	0.93, 1.09	0.92
1	3.7	0.84	0.72, 0.97				4.4	0.96	0.84, 1.10			
2	3.7	0.81	0.66, 1.00				4.3	0.95	0.79, 1.16			
≥3	3.5	0.79	0.50, 1.24				5.4	1.24	0.86, 1.80			
Brothers												
0	4.0	1	Referent	0.87	0.80, 0.95	0.002	4.7	1	Referent	1.05	0.98, 1.14	0.16
1	3.9	0.92	0.80, 1.05				4.5	0.98	0.87, 1.11			
2	3.4	0.77	0.62, 0.96				4.4	1.01	0.83, 1.22			
≥3	2.1	0.45	0.26, 0.78				6.4	1.47	1.06, 2.05			
Sisters												
0	4.0	1	Referent	0.90	0.82, 0.98	0.01	4.6	1	Referent	1.05	0.97, 1.13	0.22
1	3.7	0.85	0.75, 0.98				4.7	1.05	0.93, 1.19			
2	3.8	0.85	0.70, 1.05				4.2	0.96	0.79, 1.17			
≥3	3.3	0.76	0.48, 1.20				5.7	1.33	0.93, 1.90			
Older brothers												
0	4.0	1	Referent	0.83	0.75, 0.93	0.0009	4.5	1	Referent	1.12	1.02, 1.22	0.02
1	3.6	0.82	0.70, 0.96				4.7	1.07	0.93, 1.23			
≥2	3.4	0.71	0.53, 0.94				5.3	1.27	1.00, 1.61			
Older sisters												
0	4.0	1	Referent	0.89	0.79, 0.99	0.03	4.5	1	Referent	1.07	0.97, 1.18	0.18
1	3.3	0.76	0.65, 0.89				4.8	1.13	0.99, 1.30			
≥2	4.4	0.95	0.73, 1.25				4.4	1.02	0.78, 1.33			
Younger brothers												
0	3.9	1	Referent	0.92	0.82, 1.03	0.13	4.7	1	Referent	0.99	0.90, 1.09	0.85
1	3.9	0.94	0.82, 1.08				4.3	0.96	0.84, 1.09			
≥2	3.1	0.74	0.53, 1.02				4.6	1.03	0.78, 1.35			
Younger sisters												
0	3.9	1	Referent	0.92	0.82, 1.03	0.13	4.6	1	Referent	1.02	0.92, 1.13	0.71
1	3.7	0.88	0.77, 1.02				4.5	0.99	0.87, 1.13			
≥2	3.6	0.85	0.62, 1.15				4.9	1.11	0.85, 1.45			

* Adjusted for age, age of the mother at the woman's birth, degree of urbanization of the place of birth, degree of urbanization of the place of residence, occupation, and the other variables in the same section, the sections being 1) total siblings, 2) older and younger siblings, 3) brothers and sisters, and 4) older and younger brothers and sisters.

† Trend: the relative increase in odds per increase in the number of siblings (total siblings, older or younger siblings, brothers or sisters, younger or older brothers or sisters, respectively).

for risk factor studies because of their high specificity and positive predictive value (21). In addition, in Denmark, asthma-like symptoms that occur only in the presence of colds during early childhood and are not due to allergy are usually not diagnosed as asthma but as asthmatic bronchitis. This is likely to have reduced misclassification of the asthma outcome, since asthma and asthmatic bronchitis in most cases are likely to be different diseases with different etiologies (22).

Overall, it has been estimated that approximately one half of the pregnant women in Denmark were invited to participate in the Danish National Birth Cohort, since not all general practitioners wished to be involved in the recruitment. Among women who were invited to participate, approximately two thirds did so. We have no reason to believe that selection mechanisms into the Danish National Birth Cohort should have influenced the internal validity of this study.

In conclusion, we found that having siblings was associated with a protective effect on allergic rhinitis but not on asthma. Our findings suggest that different etiologic mechanisms are involved for allergic rhinitis and asthma with respect to the effect of sibship characteristics. Although the protective effect on allergic rhinitis was stronger for older than younger siblings, the finding that allergic rhinitis was associated with the number of younger siblings, but not with the age interval to younger siblings, supports the hypothesis of an influence of postnatal mechanisms and suggests that these mechanisms may not necessarily be operating only in early life.

ACKNOWLEDGMENTS

The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation of 1991, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation. This particular study was supported by the Danish Medical Research Council and the Danish National Research Foundation.

Conflict of interest: none declared.

REFERENCES

1. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259–60.
2. Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection, and hay fever in adolescence. *Arch Dis Child* 1996;74:422–6.
3. Ponsonby AL, Couper D, Dwyer T, et al. Cross sectional study of the relation between sibling number and asthma, hay fever, and eczema. *Arch Dis Child* 1998;79:328–33.
4. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. *J Epidemiol Community Health* 2002;56:209–17.
5. von Mutius E, Martinez FD, Fritzsche C, et al. Skin test reactivity and number of siblings. *BMJ* 1994;308:692–5.
6. Matricardi PM, Franzinelli F, Franco A, et al. Sibship size, birth order, and atopy in 11,371 Italian young men. *J Allergy Clin Immunol* 1998;101:439–44.
7. Svanes C, Jarvis D, Chinn S, et al. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;103:415–20.
8. Strachan DP. Family size, infection and atopy: the first decade of the “hygiene hypothesis.” *Thorax* 2000;55(suppl 1):S2–10.
9. Martinez FD, Holt PG. Role of microbial burden in aetiology of allergy and asthma. *Lancet* 1999;354(suppl 2):S112–15.
10. Svanes C, Jarvis D, Chinn S, et al. Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey. *Thorax* 2002;57:945–50.
11. Strachan DP, Harkins LS, Golding J. Sibship size and self-reported inhalant allergy among adult women. *ALSPAC Study Team. Clin Exp Allergy* 1997;27:151–5.
12. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health* 2001;29:300–7.
13. Malig C. The Civil Registration System in Denmark. Bethesda, MD: International Institute for Vital Registration and Statistics, 1996:1–9. (IIVRS technical papers, no. 66).
14. Westergaard T, Andersen PK, Pedersen JB, et al. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. *J Natl Cancer Inst* 1997;89:939–47.
15. SAS Institute, Inc. The GENMOD procedure. In: *SAS/STAT software: changes and enhancements for release 6.12*. Cary, NC: SAS Institute, Inc, 1996:21–42.
16. Statistics Denmark. DISCO-88. Statistics Denmark's standard classification of occupations. (In Danish). Copenhagen, Denmark: Statistics Denmark, 1999.
17. StataCorp. Stata statistical software: release 8.0. College Station, TX: Stata Corporation, 2003.
18. Bergmann RL, Schulz J, Gunther S, et al. Determinants of cord-blood IgE concentrations in 6401 German neonates. *Allergy* 1995;50:65–71.
19. Karmaus W, Arshad H, Mattes J. Does the sibling effect have its origin in utero? Investigating birth order, cord blood immunoglobulin E concentration, and allergic sensitization at age 4 years. *Am J Epidemiol* 2001;154:909–15.
20. Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002;32:43–50.
21. Kilpelainen M, Terho EO, Helenius H, et al. Validation of a new questionnaire on asthma, allergic rhinitis, and conjunctivitis in young adults. *Allergy* 2001;56:377–84.
22. Dodge R, Martinez FD, Cline MG, et al. Early childhood respiratory symptoms and the subsequent diagnosis of asthma. *J Allergy Clin Immunol* 1996;98:48–54.