

Accumulation of atopic disorders within families: a sibling effect only in the offspring of atopic fathers

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Summary

Background Several studies have reported an association between a child's risk of atopic disorders and family size. However, the inverse association might not be the same in populations with a different genetic disposition for atopic disorders.

Objective This longitudinal study was designed to assess risk factors of atopy.

Methods Lifetime prevalence of asthma, hay fever and eczema of 1440 families including 3165 offspring was ascertained by means of standardized questionnaires.

Results After possible confounders had been controlled for, an inverse association between atopic disorders and the number of older siblings was found only in the offspring of atopic fathers (trend for older siblings: $\chi^2 = 13.38$, degrees of freedom [d.f.] = 1, $P = 0.0002$; odds ratio 'no older sibling' = 2.87 (95% confidence interval 2.18–3.78); '1 older sibling' = 2.11 [1.52–2.92], '2 older siblings' = 1.29 [0.74–2.23]; '3 or more older siblings' = 0.15 [0.02–0.98]). No such relationship was found for children without a history of paternal atopy (trend for older siblings: $\chi^2 = 1.51$, d.f. = 1, $P = 0.22$; odds ratio 'no older sibling' = 1 [reference]; '1 older sibling' = 0.82 [0.63–1.06]; '2 older siblings' = 0.97 [0.67–1.40]; '3 or more older siblings' = 0.64 [0.31–1.33]). The trend for older siblings in the case of paternal atopy was significantly different from the trend for older siblings without a history of paternal atopy ($\chi^2 = 8.68$, d.f. = 1, $P = 0.003$). The number of younger siblings was not related to child's risk of atopy (trend for younger siblings: $\chi^2 = 0.001$, d.f. = 1, $P = 0.97$).

Conclusions Data from this study suggest a protective effect of sibship size only in children with a history of paternal atopy and if older siblings are present. The reason for this combined effect remains unclear. Thus, further investigations are needed to interpret the biological cause of the so called 'sibling effect'.

Keywords: family size, siblings, atopy, maternal atopy, paternal atopy

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Introduction

There is a growing body of evidence that the number of siblings is a predictor of the child's individual risk of allergic manifestations, such as asthma [1], hay fever, eczema [2] and sensitization [3]. Strachan speculated that allergic sensitization could be prevented by infections

acquired during infancy and early infections would be more common in those children with older siblings [2].

However, all published data regarding the so called sibling effect has been based on the atopic history of one index child per family. Therefore, it is not known whether the inverse association of individual atopy and sibship size is reproducible when complete information of all the offspring is taken into account.

Furthermore, Strachan emphasized the importance of conducting studies on the relationship between sibship

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size and allergic manifestation in families known to be at increased risk, for example due to parental history of atopy [4]. No data that elucidates the relationship of genetic susceptibility to the inverse frequency of atopic disorders with increasing sibship size has been found.

Thus, a better epidemiological understanding is needed in order to interpret the biological cause of the indicator — or surrogate variable — 'sibship size'. For that reason this study sought to answer two questions: is there an inverse association between the prevalence of atopic disease and number of siblings if all children of a family are considered together?; and does a maternal or paternal history of atopy influence the strength of the so called sibling effect?

Methods

Population

The data was collected in a first cross-section of a longitudinal study designed to assess risk factors for allergy in schoolchildren. All parents living in three urban areas in south-western Germany (Freiburg, Kehl and Weil) with at least one elementary schoolchild who entered the first grade in fall 1989 (aged 6–9 years) were invited to participate. Questionnaires were distributed to 2604 families between February and April 1990. The study was approved by the ethics committee of the Albert-Ludwigs-University Freiburg and written consent for the children to participate was obtained.

Questionnaire

The history of atopic disease of the parents and their offspring was derived from the subject's questionnaire of the index child of the family (elementary schoolchild). The history of the index child was ascertained from questions about asthma ('Has a doctor ever diagnosed asthma in your child?'); hay fever ('Has a doctor ever diagnosed hay fever in your child?'); and eczema ('Has your child ever had itching skin rashes in the creases of the knees, elbows or wrists called eczema or atopic dermatitis?'). The history of mother, father and each sibling was ascertained by asking 'Did or does [person] suffer from one of the following diseases: asthma; hay fever; eczema or atopic dermatitis; none of these diseases?'. Additionally, the birth date of the siblings was recorded on the questionnaire. 'Atopic disorders' required a positive answer to at least one of the three items.

Statistical analyses

The individual risk of child's atopic disease (asthma, hay fever or eczema) for the total number of offspring was

estimated for the predictors (number of younger siblings and number of older siblings) in a logistic regression model using the generalized estimation equations (GEE) method [5]. This approach was applied as several children of the same family were included in the analysis and therefore an 'auto-correlated within offspring effect' had to be taken into account. Since all the offspring were analysed, the oldest child of the family and a child without siblings was the reference for the predictors 'number of older siblings'. The youngest child of the family and a child without siblings was the reference for the predictors 'number of younger siblings'. Employing logistic regression analysis, odds ratios and 95% confidence intervals were calculated to estimate the relative risk of factors. The following potential confounders were included in all models: age and gender of the child, maternal age at birth of child, maternal and paternal atopy, and educational level of the parents.

After possible confounders had been controlled for, the combined effect of the number of (younger/older) siblings and either maternal or paternal atopy was modelled on a multiplicative scale with interaction terms that were integrated into a logistic regression model. An interaction between either maternal or paternal atopy and the number of (younger/older) siblings was tested employing the Wald χ^2 test, and the interaction terms (maternal atopy/number of younger siblings; maternal atopy/number of older siblings; paternal atopy/number of younger siblings; paternal atopy/number of older siblings) were eliminated from the model if no combined effect was found ($P \geq 0.1$). Afterwards the confounding variables were eliminated with the exception of gender, following the backwards procedure of Greenberg *et al.* [6], if no change in the odds ratios of the hypothesis variables occurred ($\leq 10\%$ in change). Analyses were performed with Statistical Analysis System (SAS Institute Inc, Cary, NC, USA) [7].

Results

Of the 2604 families sent a questionnaire 1812 completed and returned it (participation: 70%). Of those 1812 families who participated, 372 were excluded from the analysis because of foreign ethnology in order to rule out genetic heterogeneity or because of missing values for the questions of interest. In the remaining 1440 families atopic disorders of the offspring were reported in 20.2% ($n = 639$) of the 3165 children.

An inverse relationship between atopic disease and the number of older but not younger siblings could be observed in the whole offspring (Table 1).

In a further step of analysis, the combined effect of parental atopy and number of younger or older siblings was estimated by adding interaction terms to the model including the main effects. No statistical importance could

Table 1. Odds ratios and 95% confidence intervals for atopic disorders from logistic regression model for the total number of offspring taking correlation within the offspring into account.

	Value	Number of subjects n (%)	Number of atopic children n (%)	Adjusted odds ratio*	95% confidence intervals	χ^2 for trend†
Number of older siblings	0	1440 (54.5)	337 (23.4)	1	(Reference)	
	1	1154 (36.5)	220 (19.1)	0.82	0.64–1.04	
	2	423 (13.4)	71 (16.8)	0.82	0.59–1.18	
	3+	148 (4.7)	11 (7.4)	0.40	0.19–0.83	6.55 ($P = 0.01$)
Number of younger siblings	0	1440 (54.5)	257 (17.9)	1	(Reference)	
	1	1154 (36.5)	257 (22.3)	0.94	0.75–1.18	
	2	423 (13.4)	85 (20.1)	0.74	0.54–1.02	
	3+	148 (4.7)	40 (27.0)	1.14	0.70–1.85	0.07 ($P = 0.79$)
Gender	Male	1569 (49.6)	315 (20.1)	1	(Reference)	
	Female	1596 (50.4)	324 (20.3)	1.02	0.85–1.22	
Maternal atopy	–	2276 (71.9)	374 (16.4)	1	(Reference)	
	+	889 (28.1)	265 (29.8)	2.05	1.68–2.50	
Paternal atopy	–	2444 (77.2)	401 (16.4)	1	(Reference)	
	+	721 (22.8)	238 (33.0)	2.42	1.96–2.97	
Age of child (years)	≤ 3	307 (9.7)	24 (7.8)	1	(Reference)	
	4–6	479 (15.1)	93 (19.4)	2.79	1.68–4.63	
	7–10	1798 (56.8)	392 (21.8)	2.89	1.77–4.72	
	11–18	459 (14.5)	103 (22.4)	3.00	1.72–5.23	
	> 19	122 (3.9)	27 (22.1)	3.13	1.51–6.46	
Educational level	Low	972 (30.7)	159 (16.4)	1	(Reference)	
	Medium	931 (29.4)	193 (20.7)	1.22	0.95–1.56	
	High	1262 (39.9)	287 (22.7)	1.27	0.99–1.62	
Age of mother at birth of child (years)	≤ 20	242 (7.6)	46 (19.0)	1	(Reference)	
	21–25	949 (30.0)	212 (22.3)	1.19	0.81–1.73	
	26–30	1174 (37.1)	248 (21.1)	1.10	0.74–1.62	
	≥ 31	800 (25.3)	133 (16.6)	0.86	0.55–1.33	

*Odds ratios are adjusted by multiple logistic regression to all factors shown in the table. † χ^2 test for trend (d.f. = 1) from logistic regression model.

Table 2. Odds ratios and 95% confidence intervals for atopic disorders from logistic regression model with interaction terms for the combined effect of paternal atopy and number of older siblings.

	Number of subjects <i>n</i> (%)	Number of atopic children <i>n</i> (%)	Adjusted odds ratio*	95% confidence intervals	χ^2 for trend†
<i>Paternal atopy: number of older siblings</i>					
0:0	1122 (35.5)	207 (18.4)	1	(Reference)	
0:1	888 (28.1)	133 (15.0)	0.82	0.63–1.06	1.51
0:2	322 (10.2)	51 (15.8)	0.97	0.67–1.40	(<i>P</i> = 0.22)
0:3+	112 (3.5)	10 (8.9)	0.64	0.31–1.33	
1:0	318 (10.0)	130 (40.9)	2.87	2.18–3.78	
1:1	266 (8.4)	87 (32.7)	2.11	1.52–2.92	13.38
1:2	101 (3.2)	20 (19.8)	1.29	0.74–2.23	(<i>P</i> = 0.0002)
1:3+	36 (1.1)	1 (2.8)	0.15	0.02–0.98	
<i>Number of younger siblings</i>					
0	1440 (54.5)	257 (17.9)	1	(Reference)	
1	1154 (36.5)	257 (22.3)	0.98	0.78–1.23	0.001
2	423 (13.4)	85 (20.1)	0.78	0.57–1.08	(<i>P</i> = 0.97)
3+	148 (4.7)	40 (27.0)	1.20	0.75–1.92	
<i>Maternal atopy</i>					
–	2276 (71.9)	374 (16.4)	1	(Reference)	
+	889 (28.1)	265 (29.8)	2.09	1.71–2.54	

* Odds ratios are adjusted by multiple logistic regression to gender and age of child. † χ^2 test for trend (d.f. = 1) from logistic regression model.

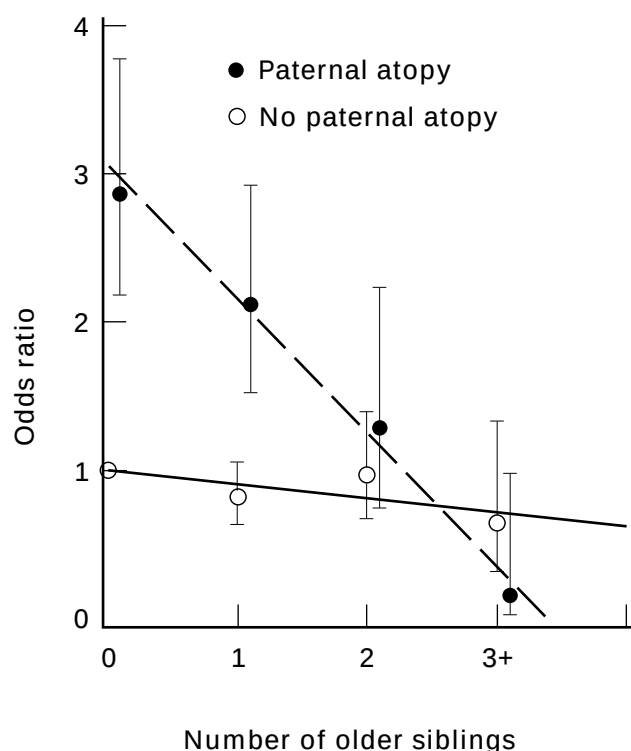


Fig. 1. Relative risk (odds ratios and 95% confidence intervals) of atopic disorders by number of older siblings after correction for other risk factors in a multivariate logistic regression analysis. The fitted slope of 'paternal atopy/number of older siblings' (dashed line) is significantly different from the fitted slope 'no paternal atopy/number of older siblings' (solid line), (χ^2 : 8.68, d.f. = 1, P = 0.003).

be shown for a combined effect of maternal atopy and both the number of younger and the number of older siblings (maternal atopy/younger siblings: χ^2 = 1.79, d.f. = 3, P = 0.62; maternal atopy/older siblings: χ^2 = 0.34, d.f. = 3, P = 0.95). Additionally no significant interaction of paternal atopy and the number of younger siblings was found (paternal atopy/younger siblings: χ^2 = 6.19, d.f. = 3, P = 0.10). In contrast, the combined effect of paternal atopy and the number of older siblings gained statistical significance (paternal atopy/older siblings: χ^2 = 11.3, d.f. = 3, P = 0.01) and was therefore considered in the final model. Accordingly the child's relative risk of atopic disorders was inversely associated with the number of older siblings only in the case of a paternal history of atopy (Table 2; trend for older siblings: χ^2 = 13.38, d.f. = 1, P = 0.0002). No such association occurred in the case of no paternal atopy together with the presence of having older siblings (Table 2; trend for older siblings: χ^2 = 1.51, d.f. = 1, P = 0.22). The relationship between a child's relative risk of atopic disorders and the number of older siblings in the case of paternal or no paternal atopy is

shown in Fig. 1. The trend for older siblings in the case of paternal atopy was significantly different from the trend for older siblings without a history of paternal atopy (χ^2 = 8.68, d.f. = 1, P = 0.003). The number of younger siblings was not related to the child's risk of atopy (Table 2; trend for younger siblings: χ^2 = 0.001, d.f. = 1, P = 0.97).

Accordingly, if only school children were included in the analysis (6–18 years of age, n = 2396), an inverse association between the child's relative risk of atopic disorders and the number of older siblings was observed only in the case of a history of paternal atopy (trend for older siblings: χ^2 = 8.65, d.f. = 1, P = 0.003; χ^2 for the combined effect of paternal atopy and number of older siblings: 5.13, d.f. = 1, P = 0.02). When analysing the data for the outcome variable 'hay fever and/or eczema', the results did not change substantially (trend for older siblings in the case of paternal atopy: χ^2 = 11.2, d.f. = 1, P = 0.0008; χ^2 for the combined effect: 7.0, d.f. = 1, P = 0.008).

Discussion

The data show that the number of older siblings is inversely correlated to the relative risk of atopic disorders (asthma, hay fever and eczema) within families, even if the information on the atopic conditions of the total number of offspring of the family is taken into account. In addition to previous reports, the data in this study suggest that having older siblings is negatively associated with the prevalence of atopic disease only for children with a history of paternal atopy. The inverse association of the relative risk of atopy and number of older siblings is consistent with previous findings [2,8,9]. Strachan emphasized the importance of birth order and speculated that infections in infancy could render the child less susceptible to allergic disease and hypothesized that early infections increased with sibship size, particularly in those with older siblings [2]. This hypothesis might be supported by *in vitro* studies which suggest that infections may stimulate the development of TH1 lymphocytes and prevent the proliferation of TH2 lymphocytes [10]. The protective effect of early infections might be attractive when explaining the importance of birth order. However, other biological factors should also be considered [4]. Since atopic fathers did not have fewer children than atopic mothers or non-atopic parents (data not shown), a genetic link between atopy and fertility is unlikely to explain the results. In more than 90% of cases the questionnaire was answered by the mother. Thus one could argue that mothers, if atopic, would overestimate the prevalence of atopic disorders in their offspring, which could result in a diminution of the so called sibling effect in the case of maternal atopy. However, this is unlikely since a decrease in the child's risk of atopy is also present in

the stratum with bilateral (maternal and paternal) parental atopy (data not shown).

Since the odds ratio for paternal atopy is slightly higher than for maternal atopy ($P=0.27$), the possibility that a mild history of paternal atopy was under-reported by the mothers cannot be excluded. Such a mild history of paternal atopy could be less related to the child's outcome than a severe history. Regarding maternal atopy, the estimated effect might be 'diluted' by reporting of mild cases. However, these speculations could not explain why the relative risk of atopic disorders is reduced with the number of older siblings only in the case of paternal atopy.

In a recent report asthma was suggested to be related to family size [1], but others did not support these findings [8,11]. This could explain the weaker trend with family size in the case of maternal atopy. However, the results did not alter substantially if the data was analysed for the outcome variable 'hay fever and/or eczema'. It is more likely that this observation can be interpreted as a combined effect of paternal atopy and sibship size on the development of atopic disease. Thus, paternal atopy could be the supposition for a strong protective factor of the surrogate variable 'number of older siblings', whereas maternal atopy appears not to be a permissible factor for the sibling effect. On the basis of data from this study the possibility remains that sibship size is also effective in the offspring of atopic mothers and in the offspring of parents without atopic history. However, if existent, the magnitude of the so called sibling effect appears to be much stronger in children of atopic fathers. A higher effectiveness of maternally derived factors could hypothetically have caused a diminution of the sibling effect in the case of maternal atopy. This is plausible since linkage studies have suggested an imprinting of maternal atopy genes [12–14]. Moreover, pre-natal immunological interactions between mother and child could be relevant [15]. Additionally, in samples of newborns [16–18], maternal but not paternal atopy was highly associated with cord blood IgE concentration, a marker suggested to be associated with the risk of atopic disorders [19,20]. Since genetic risk might be more pronounced in the offspring of atopic mothers [21–24], it appears plausible that the genetic risk is reduced by the so called sibling effect only in the offspring of atopic fathers.

In conclusion, data from this study indicate a strong inverse association between atopic disease and number of older siblings in the offspring of atopic fathers. This finding reinforces the importance of birth order and suggests that the so called sibling effect is subject to different parental disposition, which might also influence the child's risk of developing atopic disorders. Taking interactions of paternal atopy and number of older siblings into account, further investigations are needed to interpret the biological cause of the surrogate variable 'number of siblings'.

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