

Birth order and sibship size as independent risk factors for asthma, allergy, and eczema

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This study was carried out to disentangle the independent relations of birth order and sibship size with the presence of asthma, allergy and eczema. In a retrospective study, 700 families in the Netherlands were selected with index children born in 1988–90. Data were extracted from reports of health examinations at the age of 6 years of these children and their siblings. Birth order, and not sibship size, appeared to be a strong risk factor for allergy (excluding eczema). Children with higher birth order had a lower risk of allergy compared with first-borns (adjusted odds ratios: 0.43, 0.26 and 0.05 for second-, third- and fourth- or higher borns, respectively; $p < 0.0001$). Allergy including eczema also had a significant relation with birth order ($p = 0.01$). For asthma there appeared no clear relation with birth order. For asthma a non-significant relationship with sibship size (adjusted for birth order) was found ($p = 0.06$): first-born children in small sibships were more at risk than those in larger sibships. For allergy and eczema no such trend was observed. In conclusion, birth order is inversely related to the risk of allergy, independent of the size of the sibship.

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The prevalence of asthma and allergy has increased during the past decades and much effort has been put into identifying risk factors for these disorders, including elements of western lifestyle. Golding and Peters were the first to describe the protective effect of sibship size for eczema and hay fever (1). Since 1986 many studies have demonstrated a lower prevalence of atopic disease in large families (2). There has been much speculation on the mechanism underlying this 'sibling effect'. According to the hygiene hypothesis, a reduced opportunity of cross-infection in small families could increase the risk of hay fever (3, 4). Also, pre-natal mother–child interactions might be different after multiple births (5, 6).

The proportion of allergy cases attributable to the sibling effect is approximately 30% (2). Hence, identification of the underlying mechanism is potentially important. However, different definitions of the sibling effect have been used, relating allergy to the number of older siblings, birth order, family size, the number of younger

siblings and sibship size. Several definitions are (almost) equivalent: the number of older siblings and birth order are equivalent, because birth order equals the number of older siblings plus one; sibship size parallels family size; and sibship size minus the number of younger siblings equals the number of older siblings plus one. Therefore it suffices to study the role of birth order and sibship size as risk factors for atopic disease. However, it is difficult to disentangle the effects of these two factors (7). In any random sample of individuals the two variables are strongly correlated, and including them both into a regression model would not yield a definite answer, unless both effects are assessed within families. To examine all children in a family at a fixed age in a prospective study would be difficult because maturation of the increasing sibship may take a long time. Therefore, we performed a retrospective study investigating within families the independent role of birth order and sibship size as determinants for asthma, allergy and eczema at the age of 6 years.

Methods

Study area and population

In the Netherlands all children fall under the auspices of a Municipal Health Service, which invites them for health examinations by a physician at the age of 6 years. Parents are requested to fill out a questionnaire with details on their child's health. Reports of these examinations are stored in a file together with the questionnaire and data from birth up to the last examination in secondary school, including letters from specialists after referrals. Files are kept at the Service for about 25 years. We focused on the municipality of Zwijndrecht, a town south of Rotterdam with over 40,000 inhabitants. From the files of the Municipal Health Service of Zwijndrecht, 700 families with at least two children with a written report of a check-up at the age of 6 years were randomly selected. At least one of the children in the family had to be born in 1988, 1989 or 1990.

Sample size calculation

We assumed a prevalence of allergy of 10% in first-born children and 5% in their siblings. In order to detect this difference with a power of 0.80 and $\alpha = 0.05$ a sample size of 700 families was required.

Data extraction

From the files the following data were extracted: current asthma, allergy, eczema [as recorded by the physician who did the check-up; in the questionnaire or mentioned in letter(s) from a paediatrician/pulmonologist], current medication, birth order, sibship size, date of birth, gender, date of check-up, year of birth of the mother, postal code, country of birth of the parents, occupation of the bread-winner, atopic disorders of the parents, diphtheria tetanus pertussis poliomyelitis (DTPP) vaccination status and duration of breast-feeding.

Blinding

To avoid possible bias the researcher (RMD) classified children as being asthmatic, allergic or having eczema only if this was explicitly mentioned in the file by the physician who did the check-up or by a paediatrician or other specialist in a letter preserved in the file. In case of doubt the researcher consulted one of the Municipal Health Service's physicians who was blind for the risk factors under study.

Derived variables

The following variables were derived from data extracted from the files:

- Age of the mother at the time of delivery.
- Level of urbanization derived from the zip code (8). Because of the homogeneity of urbanization in the study area, two levels were recognized: heavily urbanized and moderately urbanized.
- Level of occupation using the classification system of the Dutch Statistical Office (9). Occupation was categorized into five levels: elementary, low, average, high, academic. In case of missing occupation, we estimated the level of occupation as follows: first (for all patients with known occupation) the mean income per bread-winner derived from the zip code (8) was used as predictor in a linear regression model with level of occupation as outcome variable (after checks of assumptions); for cases with 'occupation' missing the mean income per bread-winner was imputed from this linear equation.
- Country of origin; a dichotomy was used: both parents born in the Netherlands (yes/no).
- Season of birth divided in three categories: June–September, October–January and February–May (10–12).
- Breast feeding for 1 month or more. This cut-off point was chosen because it has been observed by Sears et al. (13) that children who were breastfed for <1 month have a risk of asthma and allergy similar to those who are not breastfed at all.

Statistical analysis

The independent relation of birth order and sibship size with asthma, allergy (including house-dust mite, pollen, furry pets, hay fever, rhinitis, excluding food allergy and eczema) eczema (including food allergy), allergy (including eczema/food allergy), and any atopic disorder (asthma, allergy, and/or eczema) was evaluated within families by means of logistic regression for repeated measurements (Generalized Estimating Equations) (14), families being the units of analysis, which takes correlation between family members into account (SAS PROC GENMOD). Analyses were performed both in univariate and multivariate models with adjustments for sibship size or birth order (depending on which model was applicable) and the subset of the following variables which changed the univariate point estimate by at least

10% (15): year of birth, season of birth, gender, age at the time of check-up, asthma, allergy and/or eczema of the parents, level of occupation of the bread-winner, age of the mother at the time of delivery, level of urbanization, country of origin and DTPP vaccination status. A two-sided p-value of 0.05 was considered significant. For the two main risk factors (birth order and sibship size) also tests for linear trend were performed. We performed the multivariate analyses both with and without 'breast-feeding for 1 month or more' in the model, as the causal pathway between breast-feeding and atopy is unclear, and may be in two directions: breast-feeding may have implications for the development of atopic disorder (13, 16), but children who are at risk of developing an atopic disorder are more likely to have been breast fed.

The SPSS (version 10; SPSS Inc, Chicago, IL) and SAS (version 6.12; SAS Institute Inc, Cary, NC) programs were used for all analyses.

Results

Data were obtained of 1961 children from 700 families. For 1727 of these children (88%) a health check-up file was available. The average age at which the health check-up was performed was 5.9 years (s.d. 0.6 years). Two hundred and forty-six children (14%) reported

at least one of the atopic disorders under study. Allergy has a strong relation with birth order: adjusted odds ratios 0.43, 0.26 and 0.05 for second-, third- and fourth- or higher borns, respectively (first-borns reference category); p-value for trend <0.0001. Only sibship size was included in the multivariate model. Also allergy according to the more comprehensive definition (including eczema and food allergy) showed a clear relation with birth order (adjusted odds ratios 0.47, 0.35 and 0.39, p-value for trend = 0.01). The odds ratio for birth order four and higher is somewhat raised because of more eczema in this category). For asthma there appeared no clear inverse relation with birth order. For none of the five outcome variables did addition of sibship size to the

Table 1. Data on 700 families with two or more children, one of which born in 1988–90

	n (%)
Sibship size (no. of children)	
2	368 (53)
3	210 (30)
4	73 (10)
5–9	49 (7)
Country of origin	
The Netherlands	606 (87)
Other	94 (13)
Mother atopic/asthmatic	
Yes	103 (15)
No	590 (84)
Unknown	7 (1)
Father atopic/asthmatic	
Yes	68 (10)
No	625 (89)
Unknown	7 (1)
Occupation level	
Elementary	23 (3)
Low	104 (15)
Average	467 (67)
High	73 (10)
Academic	33 (5)
Urbanization	
Heavily urbanized	339 (49)
Moderately urbanized	358 (51)
Unknown	3 (0)

Table 2. Data on the 1961 children in the study

	n (%)
Birth order*	
1	708 (36)
2	711 (36)
3	330 (17)
4	128 (7)
5–9	71 (4)
Year of birth†	
1969–75	17 (1)
1976–80	53 (3)
1981–85	270 (14)
1986–90	1085 (55)
1991–95	455 (23)
1996–2000	77 (4)
Unknown	4 (0)
Season of birth	
June–September	619 (32)
October–January	553 (28)
February–May	633 (32)
Unknown	156 (8)
Gender	
Male	1011 (52)
Female	944 (48)
Unknown	6 (0)
Age (years) of mother at delivery	
<26	400 (20)
26–30	809 (41)
31–35	567 (29)
>35	149 (8)
Unknown	36 (2)
Breast-feeding ≥1 month	
Yes	896 (46)
No	753 (38)
Unknown	312 (16)
DTPP vaccination	
Yes	1730 (88)
No	46 (2)
Unknown	185 (9)

*Inconsistencies within this variable and with sibship size are caused by multiple births and deceased children.

†Peak value in the category 1986–90 because index children were born in 1988, 1989, 1990.

Table 3. Data on health check-ups at age 6 years [mean (s.d.) = 5.9 (0.6)] in 1727 of the 1961 children included in the study

	n (%)
Health check-up file	
Available	1727 (88)
Not available	234 (12)
Data on 1727 children with available health check-up records	
Asthma	
Yes	153 (9)
No	1574 (91)
Allergy*	
Yes	77 (4)
No	1650 (96)
Eczema and food allergy	
Yes	106 (6)
No	1623 (94)
Allergy, incl. food allergy and eczema	
Yes	160 (9)
No	1567 (91)
Asthma and/or (food)allergy and/or eczema	
Yes	246 (14)
No	1481 (86)

*Including: hay fever, rhinitis, house dust mite allergy, pet allergy, excluding food allergy/eczema.

model substantially change the odds ratios for birth order. Table 1 lists the characteristics of the 700 families, Table 2 gives data on their 1961 children, and Table 3 presents data on the health examinations. Table 4 shows prevalences, odds ratios and adjusted odds ratios for asthma, allergy (without food allergy and eczema), eczema (including food allergy), allergy (including eczema/food allergy), and any atopic disorder, by birth order.

Sibship size was not strongly related to the outcome variables. Only asthma seems to be less prevalent in larger families (after adjustment for birth order, age of the mother and age at the time of the check-up), although the relationship is not

significant (p-value for trend: 0.06). For first-borns the prevalences of asthma were 10%, 7%, 6% and 3% in families with 2, 3, 4 and 5 or more children, respectively (data not in table). Table 5 presents results by sibship size.

Inclusion of breast-feeding in the multivariate model made no difference to these outcomes.

Discussion

It is generally assumed that birth order is a risk factor for allergy but as yet no within-family study has demonstrated its effect independent of sibship size. We found that birth order, but not sibship size, is a risk factor for allergy. Our data show no relationship between birth order and asthma; however, there seems to be a lower prevalence of asthma in larger families, especially after adjustment for birth order, implying that first-borns in small families have a higher prevalence of asthma than first borns in large families. An explanation for this phenomenon could be that parents decide not to plan for more children if a serious disease in their first child becomes manifest.

We found a risk of eczema and food allergy for children with birth order four and higher which was higher than the risk for birth order two and three. We wondered whether this might be due to a different awareness over time (of doctor or parents). We therefore checked whether there was a raised risk of (diagnosis of) eczema over time by considering the fraction of eczema reported for each year of check-up for first borns and for second borns separately. This did not reveal any time dependent pattern. We cannot explain our finding.

Three other studies have investigated the relationship between birth order and atopy

Table 4. Atopic disorders by birth order: prevalences (%) and crude and adjusted (adj) odds ratios (OR) with 95% confidence intervals (CI_{95%})

Birth order	Asthma				Allergy (excl food allergy and eczema)				Food allergy and/or eczema				Allergy (incl. food allergy and eczema)				Any atopic disorder			
	%	OR	ORadj†	CI _{95%}	%	OR	ORadj‡	CI _{95%}	%	OR	ORadj§	CI _{95%}	%	OR	ORadj¶	CI _{95%}	%	OR	ORadj**	CI _{95%}
1*	8.7	1.00	1.00	—	7.4	1.00	1.00	—	8.1	1.00	1.00	—	13.4	1.00	1.00	—	16.3	1.00	1.00	—
2	8.9	1.02	0.82	0.52,1.29	3.4	0.43	0.43	0.26,0.70	4.9	0.58	0.62	0.37,1.05	6.9	0.47	0.47	0.31,0.71	12.8	0.74	0.71	0.49,1.02
3	9.0	1.14	0.85	0.46,1.61	2.5	0.29	0.26	0.11,0.59	4.3	0.46	0.44	0.18,1.05	6.5	0.41	0.35	0.18,0.68	12.6	0.74	0.66	0.38,1.15
4+	9.0	1.35	1.26	0.51,3.11	0.6	0.06	0.05	0.01,0.37	6.6	0.73	0.85	0.29,2.51	7.2	0.45	0.39	0.16,0.96	14.5	0.92	0.93	0.45,1.95
p-value for trend	0.99				<0.0001				0.18				0.001				0.36			

*Reference category.

†Adjusted for sibship size, year of birth, age at check-up, age mother at delivery.

‡Adjusted for sibship size.

§Sibship size, season of birth, diphtheria tetanus pertussis poliomyelitis (DTPP) vaccination, year of birth, age at check-up, age mother at delivery.

¶Adjusted for sibship size, year of birth, DTPP vaccination, age at check-up.

**Adjusted for sibship size, year of birth, season of birth, DTPP vaccination, age at check-up, atopy father, age mother at delivery, country of origin, urbanization.

Table 5. Atopic disorders by sibship size: prevalences (%) and crude and adjusted (adj) odds ratios (OR) with 95% confidence intervals (CI_{95%})

Sibship size	Asthma				Allergy (excl food allergy and eczema)				Food allergy and/or eczema				Allergy (incl. food allergy and eczema)				Any atopic disorder			
	%	OR	ORadj†	CI _{95%}	%	OR	ORadj‡	CI _{95%}	%	OR	ORadj§	CI _{95%}	%	OR	ORadj¶	CI _{95%}	%	OR	ORadj**	CI _{95%}
2*	10.2	1.00	1.00	—	4.8	1.00	1.00	—	5.9	1.00	1.00	—	9.4	1.00	1.00	—	15.5	1.00	1.00	—
3	7.8	0.73	0.68	0.41,1.11	4.2	0.89	0.99	0.55,1.80	5.8	0.98	0.88	0.51–1.49	8.5	0.89	0.92	0.59,1.42	12.2	0.75	0.71	0.48,1.06
4	8.4	0.81	0.63	0.32,1.23	4.4	0.92	1.59	0.70,3.60	7.1	1.23	1.20	0.57–2.54	10.2	1.10	1.34	0.74,2.42	15.6	1.01	0.95	0.57,1.59
5+	7.4	0.71	0.40	0.12,1.31	3.9	0.85	1.37	0.49,3.81	6.9	1.17	0.74	0.35–1.57	9.8	1.05	0.93	0.42,2.06	13.7	0.86	0.54	0.29,1.07
p-value for trend		0.06				0.34				0.77				0.77				0.11		

*Reference category.

†Adjusted for birth order, year of birth, diphtheria tetanus pertussis poliomyelitis (DTPP) vaccination, age at check-up, atopy mother, atopy father, age mother at delivery.

‡Adjusted for birth order, season of birth, DTPP vaccination, age at check-up, atopy mother, atopy father, age mother at delivery, country of origin, urbanization.

§Adjusted for birth order, season of birth, DTPP vaccination, age at check-up, atopy mother, atopy father, age mother at delivery, country of origin, urbanization, level occupation.

¶Adjusted for birth order, year of birth, DTPP vaccination, age at check-up, atopy mother, atopy father.

**Adjusted for birth order, season of birth, DTPP vaccination, age at check-up, atopy mother, atopy father, age mother at delivery, country of origin, urbanization, level occupation.

within families (17–19). Two of these (17, 18) selected families with at least one atopic child and did not consider the relationship between sibship size and atopy. The third study (19) evaluated the relationship between atopic disease and number of older siblings in a cross-sectional design, but evaluated children at different ages. After adjustment for other family characteristics (including ‘number of younger siblings’ which is almost equivalent to adjustment for sibship size), they found a protective effect of high birth order only in children with atopic fathers. Our data do not confirm this finding: the relationship in children of non-atopic fathers was even somewhat stronger than in children of atopic fathers.

In the Netherlands the proportion of first borns has risen from 27% in 1950 to 45% in 1990, whereas the proportion of fourth (and higher) borns was 31% in 1950 and 7% in 1990 (20). If we assume that the prevalences and odds ratios for allergy (excl. eczema/food allergy) found in this study apply to the period from 1950 to 1990 and that children without siblings (a category we did not consider) have the same risk as first-borns in larger sibships, the increase of allergy during these years due to this reduced family size would be 41%.

We considered it unlikely that breast-feeding is just a confounder. The causal path between atopy and breast-feeding is probably in two directions: breast-feeding may have implications for atopy (13, 16), but mothers of children at risk may be recommended to start or continue breast-feeding. Therefore, we analysed our data with and without ‘breast-feeding for at least 1 month’ in the multivariate model. Adjustment for breast-feeding resulted in similar odds ratios.

Breast-feeding appeared protective for asthma (6% vs. 12%) and for any atopic disorder (12% vs. 17%). Thus, if we could eliminate this ‘confounding by indication’, the protective effect might be even larger.

Misclassification

The data of this study are extracted from routinely collected records, and inaccurate reporting or underreporting of the disorders under study may have occurred. The prevalences of 9%, 4%, 6% and 14% for asthma, allergy, eczema and any atopic disease, respectively, suggest that there may be limited underreporting as higher prevalences have been published for the period most of the children in our study had their health examination (21, 22).

This does not necessarily invalidate our findings, as misclassification is unlikely to be differential, i.e. related to birth order or sibship size. An increased underreporting of disease with increasing birth order (the mother ‘getting used’ to diseases of her children) would explain the lower prevalence in children with higher birth order. However, results of an unpublished study conducted in 1998/1999 by physicians of the Municipal Health Service, where we extracted the data, suggest that there is no need for this concern (H. Aardoom personal communication, May 2002). They asked the accompanying parent of 400 children during the health check-up to fill out the ISAAC questionnaire for asthma symptoms (23). Self-reporting slightly increased with increasing birth order and increasing sibship size.

These routinely collected records inevitably have limitations. They did not provide informa-

tion on relevant conditions in the child's early life, apart from breast feeding. One can argue that these conditions usually do not change dramatically within families. On the contrary, a change in smoking habits or disposal of pets in case of an allergic first born cannot be excluded.

In conclusion, we demonstrated that birth order is inversely related to the risk of allergy, independent of the size of the sibship. However, it is still a question whether (within families) the reduced risk of later born children is because of an increased exposure to pathogens or to a with increasing parity changing pre-natal mother-child interaction. Further research is needed to detect which antenatal and/or environmental factors explain this relationship. The answer to this question could help us in the prevention of atopic disorders.

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