

Letter to the Editor

Sibship and risk of asthma in a total population: A disease comparative approach

To the Editor:

Asthma is one of the most common chronic diseases in childhood and adolescence. There is a great body of evidence that younger siblings have a protective effect against asthma or atopic manifestations, such as hay fever, atopic eczema, and allergic sensitization.^{1,2} Different explanatory mechanisms have been discussed. One hypothesis is that older siblings promote early infections in childhood and repeated infections protect against atopic disorders.³ Another hypothesis is related to the intrauterine environment or interpregnancy interval because closely spaced pregnancies allow less time for recovery from any immunosuppressive effect,⁴ and yet another is that the risk is related to report bias, although the difference in health care-seeking behavior in first-born children as opposed to younger siblings could also be the case. Effects of sibship or interpregnancy intervals have also been seen for other diseases, such as some neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD)⁵ and type 1 diabetes,⁶ and a comparative disease approach has been requested.⁷

The aim of this study was to estimate the association between sibship characteristics and the subsequent diagnosis of asthma, bronchitis and respiratory tract infection, type 1 diabetes mellitus, gastroenteritis, and ADHD. We also aimed to test the potential effect of interpregnancy interval to second-born children as a measure of the intrauterine environment.

Through linkage of the Swedish Medical Birth Registry and the Multi-Generation Registry, we identified a cohort of first-born and second-born singleton children in Sweden from January 1, 1996, to January 1, 2002, in families with only full siblings.

Asthma and other disease outcomes were measured during 1 year (2008), when the children were 6 to 12 years of age, to capture prevalence of the chronic diseases (asthma, type 1 diabetes mellitus, and ADHD) and tendency to catch and search medical care for infections. In total, 314,477 children were identified after exclusions.

Disease outcomes were extracted from the Swedish National Patient Register (NPR) and the Swedish Prescribed Drug Register (SPDR). For asthma, diabetes, and ADHD, we used diagnoses from the NPR, dispensed medication in the SPDR, or both. For asthma medication, 2 or more dispensings of any of the drugs were required. The outcomes of lower respiratory tract infection, upper respiratory tract infection, bronchitis/bronchiolitis, and gastroenteritis were based solely on information from the NPR.

The children were classified as being either (1) first-born children with no siblings, (2) first-born children with at least 1 sibling, or (3) second-born children at the start of 2008. Second-born children were further categorized by time between their birth and that of their older sibling (<2, ≥2-4, and ≥5 years) to capture the length of the interpregnancy interval and immunosuppressive effects in the intrauterine environment.

The potential confounders of sex; birth weight; maternal age at delivery; prepregnancy body mass index (BMI); smoking during pregnancy; information on maternal and paternal education; cohabitation of the parents on December 31, 2007; and parental history of the outcome diseases were obtained from the Medical Birth Register, the longitudinal integration database for health insurance and labor market studies (LISA by Swedish acronym), the NPR, and the SPDR.

We used logistic regression to estimate odds ratios (ORs) of the association between sibling status and each of the diseases. The reference group was first-born children with siblings. Robust SEs were used to account for familial clustering of observations. Both crude and adjusted estimates are reported together with 95% CIs for all models. Additional analyses were done with second-born children further categorized by time between their birth and that of their older sibling. Details on study design, definition of exposure and outcome, and statistical analyses are provided in this article's Online Repository at www.jacionline.org.

The study was approved by the regional ethical review board in Stockholm, Sweden.

Table 1 shows the background characteristics of the study population. In total, 13.2% were first-born children without siblings, 42.8% were first-born children with siblings, and 44.0% were second-born children. First-born children were smaller at birth compared with second-born children, and there were differences in maternal age, smoking, parental education, and cohabitation between children with and without siblings. Children who had not yet had a sibling had higher odds of asthma (adjusted OR, 1.15; 95% CI, 1.08-1.22), diabetes (adjusted OR, 1.30; 95% CI, 1.09-1.56), gastroenteritis (adjusted OR, 1.55; 95% CI, 1.19-2.01), and ADHD (adjusted OR, 1.27; 95% CI, 1.14-1.43) compared with first-born children with siblings but no significant difference in odds of bronchitis/bronchiolitis and respiratory tract infections (Fig 1 and see Table E1 in this article's Online Repository at www.jacionline.org). Second-born children had lower odds of asthma and respiratory diseases compared with first-born children with siblings but with no significant differences in the odds of diabetes, ADHD, and gastroenteritis. Among second-born children, there was no clear difference in relation to the interpregnancy interval. Further details on Results and Discussion are provided in this article's Online Repository at www.jacionline.org.

The main finding of this study is that there is a difference in the prevalence of some common childhood outcomes in first-born children with or without siblings and second-born children. First-born children without siblings had higher odds of asthma, diabetes, gastroenteritis, and ADHD compared with first-born children with siblings. This might be related to health care-seeking behavior in families with only 1 child, reduced likelihood to have another child if the first has severe disease, or residual confounding caused by less advantaged social background in those without siblings or other differences in lifestyle. A recent meta-analysis on the association between sibship and diabetes reported a lower risk of childhood-onset type 1 diabetes with increasing birth order, which might reflect increased exposure to infections in early life in children born later.⁸ We also confirm that second-born children had lower odds of asthma and respiratory diseases compared with first-born children with siblings, but there

TABLE I. Child/family characteristics and outcome by sibling status in the study population (n = 314,477)

	First-born children without siblings,* no. (%)	First-born children with siblings, no. (%)	Second-born children, no. (%)
All	41,370 (13.2)	134,707 (42.8)	138,400 (44.0)
Sex			
Boy	20,969 (50.7)	69,559 (51.6)	71,260 (51.5)
Girl	20,401 (49.3)	65,148 (48.4)	67,140 (48.5)
Birth weight (g)			
≤2,999	7,740 (18.7)	19,663 (14.6)	11,896 (8.6)
3,000-3,499	13,864 (33.5)	45,032 (33.4)	37,586 (27.2)
3,500-3,999	13,085 (31.6)	47,294 (35.1)	53,450 (38.6)
4,000-4,499	5,244 (12.7)	18,333 (13.6)	27,677 (20.0)
≥4,500	1,215 (2.9)	3,763 (2.8)	7,328 (5.3)
Missing	222 (0.5)	622 (0.5)	463 (0.3)
Maternal age (y)			
<20	1,974 (4.8)	3,502 (2.6)	425 (0.3)
20-29	19,192 (46.4)	91,571 (68.0)	67,364 (48.7)
30-39	18,563 (44.9)	39,335 (29.2)	68,546 (49.5)
≥40	1,641 (4.0)	299 (0.2)	2,065 (1.5)
Maternal BMI (kg/m ²)			
<18.5	1,051 (2.5)	3,051 (2.3)	2,710 (2.0)
18.5-24.9	21,871 (52.9)	79,974 (59.4)	76,614 (55.4)
25.0-29.9	8,093 (19.6)	24,616 (18.3)	28,858 (20.9)
≥30	3,568 (8.6)	8,273 (6.1)	11,124 (8.0)
Missing	6,787 (16.4)	18,793 (14.0)	19,094 (13.8)
Family situation: parents living together			
No	18,146 (43.9)	17,419 (12.9)	26,739 (19.3)
Yes	21,428 (51.8)	115,897 (86.0)	109,540 (79.2)
Missing	1,796 (4.3)	1,391 (1.0)	2,121 (1.5)
Education level of mothers in 2004			
Elementary school	4,596 (11.1)	7,518 (5.6)	7,638 (5.5)
High school	22,125 (53.5)	67,302 (50.0)	72,614 (52.5)
College/university	14,034 (33.9)	59,508 (44.2)	57,482 (41.5)
Missing	615 (1.5)	379 (0.3)	666 (0.5)
Education level of fathers in 2004			
Elementary school	6,486 (15.7)	12,533 (9.3)	14,423 (10.4)
High school	22,592 (54.6)	72,069 (53.5)	75,289 (54.4)
College/university	11,084 (26.8)	49,222 (36.5)	47,310 (34.2)
Missing	1,208 (2.9)	883 (0.7)	1,378 (1.0)
Smoking during pregnancy			
Nonsmoker	30,414 (73.5)	114,859 (85.3)	118,186 (85.4)
1-9 Cigarettes/d	5,647 (13.7)	9,031 (6.7)	8,396 (6.1)
≥10 Cigarettes/d	2,301 (5.6)	2,856 (2.1)	3,537 (2.6)
Missing	3,008 (7.3)	7,961 (5.9)	8,281 (6.0)
Comorbidity†	8,388 (20.3)	25,168 (18.7)	23,736 (17.2)
Outcome variables			
Asthma	1,909 (4.6)	5,505 (4.1)	5,073 (3.7)
Bronchitis/bronchiolitis	33 (0.1)	104 (0.1)	72 (0.1)
Lower respiratory tract infection	64 (0.2)	216 (0.2)	140 (0.1)
Upper respiratory tract infection	485 (1.2)	1,376 (1.0)	1,086 (0.8)
Type 1 diabetes	208 (0.5)	554 (0.4)	596 (0.4)
Gastroenteritis	110 (0.3)	229 (0.2)	233 (0.2)
ADHD	658 (1.6)	1,308 (1.0)	1,262 (0.9)

*No siblings at start of follow-up year (2008).

†Includes congenital malformations, neoplasm, metabolic disease, mental/behavioral disease, and diseases of the nervous, circulatory, digestive, and genitourinary systems.

Numbers shown are comorbidity before asthma.

was no significant difference in the odds of gastroenteritis, diabetes, and ADHD. It is likely that this is related to microorganism exposure³ or reduced health care-seeking behavior in parents used to viral infections in their second-born children, more comfortable with the disease, and less likely to seek evaluation or treatment.

Moreover, findings that there was no clear difference for inter-pregnancy intervals might argue for health care-seeking behavior rather than infectious burden or the intrauterine environment.^{3,4,9}

In conclusion, we have shown an association between sibship characteristics and subsequent diagnosis of asthma and other disease outcomes in a pattern that indicates an underlying

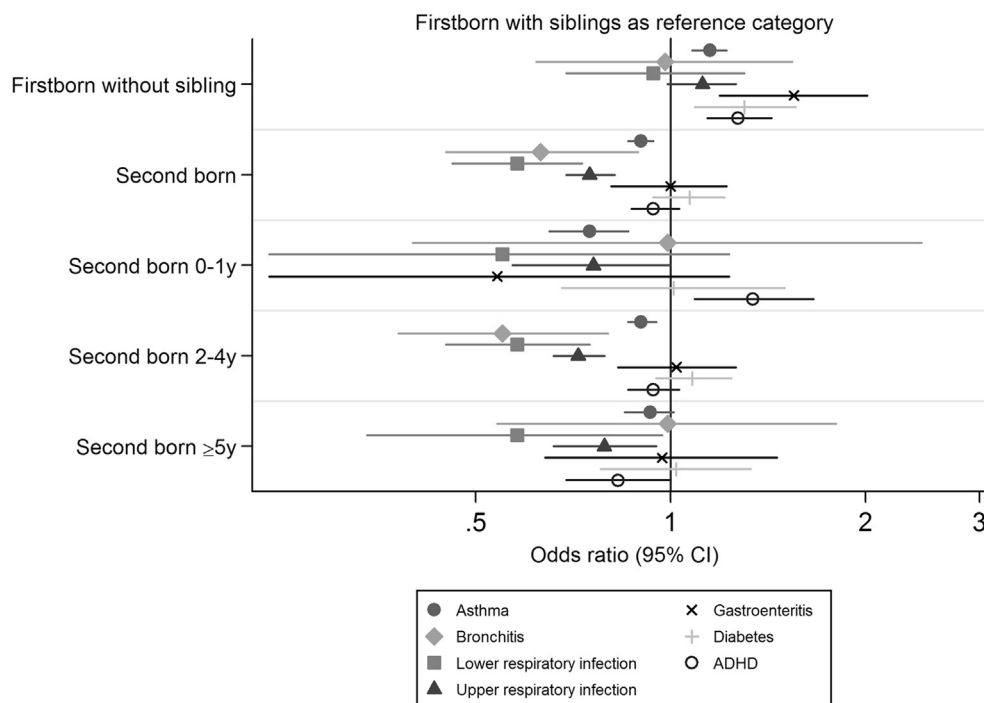


FIG 1. ORs and 95% CIs for the association between sibling status and disease outcomes in children 6 to 12 years of age. Second-born children were categorized according to interpregnancy interval (ie, years since birth of first-born sibling).

mechanism compatible with different health care-seeking behavior and microbial exposure.

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Catarina Almqvist, MD, PhD^{a,b}
Henrik Olsson, MSc^a
Tove Fall, VMD, PhD^c
Cecilia Lundholm, MSc^a

From ^athe Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ^bAstrid Lindgren Children's Hospital, Lung and Allergy Unit, Karolinska University Hospital, Stockholm, Sweden; and ^cthe Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden. E-mail: catarina.almqvist@ki.se.

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METHODS

Study population and design

To study the association between sibling status and disease outcomes, we identified a cohort of 6- to 12-year-old children in families with only full siblings. We used the Medical Birth Register, which contains data for 99% of all births in Sweden since 1973, to identify children who were either a woman's first or second child and born in Sweden from January 1, 1996, to January 1, 2002. The fathers were identified by means of linkage to the Multi-Generation Register, which contains information on biological and adoptive parents of Swedish residents born since 1932, to include only families with full siblings. Because the effect of sibship might be different in families with multiples, we excluded families with multiparous births. Families were also excluded if they contained adopted children or if mothers had immigrated to Sweden after 15 years of age to ensure that all their children were born in Sweden. Furthermore, we required all children to be alive and living in Sweden during follow-up in 2008. In total, 379,706 children were identified, and 314,477 remained after exclusions.

Asthma and other disease outcomes were measured during 1 year (2008), when the children were 6 to 12 years of age, to capture prevalent disease for the chronic diseases (asthma, type 1 diabetes mellitus, and ADHD) and tendency to catch and search medical care for infections.

Outcome definition

Disease outcomes were extracted from the NPR and SPDR. The Patient Register includes information on primary diagnoses, as well as up to 7 secondary diagnoses, from all inpatient hospital visits in Sweden since 1987, along with approximately 80% of all outpatient visits in specialist care in Sweden since 2001. All diagnoses since 1997 are registered according to the International Classification of Diseases, Tenth Revision (ICD-10). The SPDR includes all medication dispensed in Swedish pharmacies since July 1, 2005, as recorded by using the Anatomic Therapeutic Chemical classification system (ATC). For asthma, diabetes, and ADHD, we used both diagnoses from the NPR (ICD-10: J45-J46 for asthma, E10 for diabetes, and F90 for ADHD), dispensed medication in the SPDR (ATC: R03AC, R03BA, R03AK, and/or R03DC for asthma; A10A for diabetes; and N06BA for ADHD), or both. For asthma medication, 2 or more dispensings of any of the drugs were required. The SPDR can be used to reliably assess asthma^{E1} and type 1 diabetes^{E2} in this age group. The outcomes of lower respiratory tract infection (ICD-10: J09-J18), upper respiratory tract infection (ICD-10: J00-J06), bronchitis/bronchiolitis (ICD-10: J20-J22), and gastroenteritis (ICD-10: A09) were based solely on information from the NPR, either as a primary diagnosis or as one of the 2 first secondary diagnoses.

For asthma, diabetes, and ADHD, we used diagnoses from the NPR, dispensed medication in the SPDR, or both. Thus the use of an appropriate drug in the SPDR would qualify a child for a disease category, even if they did not appear in the NPR, and children who only had an appropriate diagnosis in the NPR without medication in the SPDR were still classified as having a diagnosis. Numbers on the overlap between asthma diagnosis in the NPR and medication in the SPDR have been thoroughly displayed in a recent validation study.^{E1} All prescribed drugs have been registered in the SPDR from 2005 onward, and our outcomes were all measured in 2008, when the SPDR register had full coverage.

Exposure classification

The children were classified as being either (1) first-born children with no siblings, (2) first-born children with at least 1 sibling, and (3) second-born children at the start of 2008. Second-born children were further categorized by time between their birth and that of their older sibling (<2 years, ≥2-4 years if ≥2 years but <5 years, or ≥5 years) to capture the length of the interpregnancy interval and immunosuppressive effects in the intrauterine environment.

Covariates

Child characteristics of sex and birth weight and maternal characteristics of age at delivery, prepregnancy maternal BMI, and smoking during pregnancy were retrieved from the Medical Birth Register. Information on

maternal and paternal education in 2004 and cohabitation of the parents on December 31, 2007, was obtained from the longitudinal integration database for health insurance and labor market studies (LISA by Swedish acronym) held by Statistics Sweden. Parental history of the outcome diseases were extracted by using the same registers, diagnostic codes, and ATC codes as for the corresponding outcomes in the children. Parental history of the disease was defined as ever having the corresponding diagnosis registered in the NPR in 2001-2008 or drugs in the SPDR from July 1, 2005, to December 31, 2008, from the start of the registers until the end of follow-up.

Statistical analysis

We used logistic regression to estimate ORs of the association between sibling status and each of the diseases. The reference group was first-born children with siblings. Robust SEs were used to account for familial clustering of observations.

Both crude estimates and estimates adjusted for maternal age at delivery, prepregnancy maternal BMI, smoking during pregnancy, maternal and paternal education as a proxy for socioeconomic status, and familial history of the corresponding outcome disease, are reported together with 95% CIs for all models. Additional analyses were done with second-born children further categorized by time between their birth and that of their older sibling.

The study was approved by the regional ethical review board in Stockholm, Sweden.

RESULTS

Table I shows the background characteristics of the study population. In total, 13.2% were first-born children without siblings, 42.8% were first-born children with siblings, and 44.0% were second-born children. In both cohorts the first-born children with and without siblings were smaller at birth compared with the second-born children. Compared with the children with siblings (both first- and second-born children), parents of the children without siblings were more often living apart during pregnancy and had lower education, and the mothers were younger and more often smoked during pregnancy.

DISCUSSION

The main finding of this study is that there is a difference in the risk of some common childhood outcomes in first-born children with or without siblings and second-born children. We confirm that second-born children have higher risk of asthma and respiratory tract infections in early life but lower risk of later asthma. First-born children without siblings compared with those with younger siblings have reduced risk of milder respiratory tract infections but not pneumonia in early life and later have an increased risk of asthma, type 1 diabetes, and ADHD. Some of these findings might be assigned to increased microbial pressure in children with siblings or parental health care-seeking behavior and decisions made by health care providers, which is of public health significance.

The strengths of this study include (1) a population- and register-based longitudinal study design in a unified health care environment with recording in medical registers of a well-defined cohort in Sweden; (2) prospectively collected information on full sibship and maternal background factors, which precludes recall bias; (3) ascertainment of asthma by applying predetermined asthma criteria to the NPR (covers all inpatient and approximately 80% of all outpatient visits in specialist care) and SPDR (full coverage of all dispensed

asthma medication) and other outcomes^{E1} along with a comparative disease approach; and (4) assessment of risks in a cohort with established family pattern. In addition, we had reasonable statistical power, and the results are generalizable to the general population.

The study should also be interpreted within its limitations. We were not able to assess other exposures, such as day care or farming households. Previous studies have reported that the protective effect of sibship appears strongest for children who entered day care between the ages of 6 and 12 months^{E3}; however, in Sweden the majority of children are older than 1 year (median, 18 months) at the start of day care.^{E4}

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TABLE E1. ORs and 95% CIs for the cohort aged 6 to 12 years for the association between disease outcomes in 2008 and sibship status

	Crude OR (95% CI)	Adjusted OR (95% CI) [†]
Asthma		
First-born children with sibling	1.00	1.00
First-born children without siblings [‡]	1.14 (1.08-1.20)	1.15 (1.08-1.22)
Second-born children	0.89 (0.86-0.93)	0.90 (0.86-0.94)
<2 y*	0.81 (0.71-0.92)	0.75 (0.65-0.86)
2-4 y	0.90 (0.86-0.93)	0.90 (0.86-0.95)
≥5 y	0.91 (0.84-0.99)	0.93 (0.85-1.01)
Bronchitis/bronchiolitis		
First-born children with sibling	1.00	1.00
First-born children without siblings [‡]	1.03 (0.70-1.53)	0.98 (0.62-1.54)
Second-born children	0.67 (0.50-0.91)	0.63 (0.45-0.89)
<2 y*	0.99 (0.44-2.26)	0.99 (0.40-2.44)
2-4 y	0.60 (0.43-0.84)	0.55 (0.38-0.80)
≥5 y	0.94 (0.54-1.65)	0.99 (0.54-1.80)
Lower respiratory tract infection		
First-born children with sibling	1.00	1.00
First-born children without siblings [‡]	0.96 (0.73-1.28)	0.94 (0.69-1.30)
Second-born children	0.63 (0.51-0.78)	0.58 (0.46-0.73)
<2 y*	0.64 (0.31-1.29)	0.55 (0.24-1.23)
2-4 y	0.62 (0.49-0.78)	0.58 (0.45-0.75)
≥5 y	0.68 (0.44-1.07)	0.58 (0.34-0.97)
Upper respiratory tract infection		
First-born children with sibling	1.00	1.00
First-born children without siblings [‡]	1.15 (1.04-1.28)	1.12 (0.99-1.26)
Second-born children	0.77 (0.71-0.83)	0.75 (0.69-0.82)
<2 y*	0.77 (0.60-1.00)	0.76 (0.57-1.00)
2-4 y	0.75 (0.69-0.81)	0.72 (0.66-0.79)
≥5 y	0.87 (0.74-1.02)	0.79 (0.66-0.95)
Type 1 diabetes		
First-born children with sibling	1.00	1.00
First-born children without siblings [‡]	1.22 (1.04-1.44)	1.30 (1.09-1.56)
Second-born children	1.05 (0.93-1.18)	1.07 (0.94-1.21)
<2 y*	0.99 (0.70-1.42)	1.01 (0.68-1.50)
2-4 y	1.05 (0.93-1.18)	1.08 (0.95-1.24)
≥5 y	1.08 (0.86-1.35)	1.02 (0.78-1.33)
Gastroenteritis		
First-born children with sibling	1.00	1.00
First-born children without siblings [‡]	1.57 (1.25-1.97)	1.55 (1.19-2.01)
Second-born children	0.99 (0.83-1.19)	1.00 (0.81-1.22)
<2 y*	0.53 (0.25-1.11)	0.54 (0.24-1.23)
2-4 y	1.02 (0.85-1.24)	1.02 (0.83-1.26)
≥5 y	0.98 (0.68-1.42)	0.97 (0.64-1.46)
ADHD		
First-born children with sibling	1.00	1.00
First-born sibling without siblings [‡]	1.65 (1.50-1.81)	1.27 (1.14-1.43)
Second-born children	0.94 (0.87-1.01)	0.94 (0.87-1.03)
<2 y*	1.55 (1.28-1.87)	1.34 (1.09-1.66)
2-4 y	0.90 (0.83-0.98)	0.94 (0.86-1.03)
≥5 y	0.91 (0.77-1.06)	0.83 (0.69-1.00)

*Second-born children were categorized according to interpregnancy interval (ie, years since birth of first-born sibling).

[†]Adjusted for maternal age, maternal BMI, smoking during pregnancy, family history of asthma, and parental education level.[‡]No siblings at start of follow-up year (2008).