Sibling risk of Pediatric Obstructive Sleep Apnea Syndrome and Adenotonsillar Hypertrophy

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Objectives: To estimate sibling risk of hospitalization for children with sleep disordered breathing (SDB), diagnosed with (1) obstructive sleep apnea syndrome (OSAS), or (2) adenotonsillar hypertrophy in the total Swedish population.

Design, Setting, and Participants: Using the MigMed database at the Karolinska Institute, we divided the population of Sweden aged 0–18 years into sibling groups based on a shared mother and father and presence of a primary hospital diagnosis of OSAS or adenotonsillar hypertrophy for each individual born between 1978 and 1986, during the follow-up period 1997–2004. Individuals with at least one affected sibling were identified and the incidence rates were computed, using standardized incidence ratios (SIRs) with 95% confidence intervals (CIs). Reference groups were boys and girls with unaffected siblings of 2 or more.

Results: After accounting for socioeconomic status, age, and geographic region, boys with at least one sibling with OSAS had an increased risk of having OSAS (SIR, 33.2; 95% CI, 16.5–64.8), and in girls the SIR was 40.5 (19.4–81.4). For hypertrophy of the tonsils or hypertrophy of the adenoids and tonsils the corresponding SIRs were 4.53 (3.0–6.8) for boys and 4.94 (3.3–7.4) for girls.

Conclusions: The study indicates an increased sibling risk of sleep disordered breathing in children, which may be due to heritable genes and/or shared environment such as increased awareness among family members or referring doctors. Caregivers should ask parents if siblings have similar symptoms, and thus offer them early treatment.

Keywords: Heritability, population-based, sibling risk, sleep apnea, children

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inflammatory response. Apolipoprotein E (ApoE) epsilon4 allele was associated with not only increased odds of having SDB, but also with an increased risk for neurocognitive dysfunction, and polymorphisms involving more than one locus in the ApoE gene and its regulatory region were associated with OSA in Caucasian children.

In Sweden, there is a special hospital diagnostic code for OSAS. However, it is seldom used for children as they only occasionally undergo sleep studies, i.e., polysomnography at hospitals, with measurements of breathing, pulse oximetry, and/or transcutaneous carbon dioxide, can be performed. SDB has no special diagnostic code and therefore, children with symptoms and suspected OSAS get the code adenotonsillar hypertrophy instead. If a child previously has undergone adenoidectomy but still has symptoms, the code of hypertrophy of tonsils is used.

The construction of a large population-based patient register has led to the rapid development of genetic-epidemiological studies in Sweden. In addition, a recently published large-scale population-based study from our group has found that, after accounting for socioeconomic status, age, geographic region, and period of diagnosis, adults with at least one sibling who had a hospital diagnostic code of OSAS had a 3-fold increased risk of getting diagnosed with the same code during 8 years.

In the present study we included hospital data on all children in Sweden during the study period between 1997 and 2004, i.e., a total of 2.7 million individuals. The individual study population was siblings born in 1978 and onward. The use of hospital registry data eliminated recall bias. Recall bias is a potential problem when conducting case-control studies of familial risk because patients in the case group are prone to report a positive family history of the disease or other health problem being studied.

The main aim of this study was to define the familial risk of hospitalization for primary diagnostic codes of (1) OSAS and/or (2) suspected OSAS, with clinical signs of SDB and adenotonsillar hypertrophy, in Swedish children less than 19 years of age. A further aim was to determine whether there were any differences by age and gender.

METHODS

MigMed Research Database

Data used in this study were retrieved from the MigMed database, located at the Center for Family and Community Medicine at the Karolinska Institute in Stockholm. MigMed is a single, comprehensive database that has been constructed using several national Swedish data registers, including, but not limited to, the Total Population Register, the Multigeneration Register, and the Swedish Hospital Discharge Register (1986–2004). Information from the various registers in the database is linked at the individual level via the national 10-digit civic registration number assigned to each person in Sweden for his or her lifetime. Prior to inclusion in the MigMed database, civic registration numbers were replaced by serial numbers to ensure the anonymity of all individuals.

Because the database contains information from the Multigeneration Register, it is possible to link more than 10 million index persons (persons born in or after 1932 and registered in Sweden any time since 1961) with their biological parents. The latest version of the Multigeneration Register, which has been incorporated in the MigMed database, includes supplementary data from church records on index persons domiciled in Sweden between 1947 and 1961, including information about biological parents, children, siblings, and adoptions. This population includes both first and second generation immigrants. We have no data on ethnicity or country of birth.

Outcome Variables

The 10th revision of the International Classification of Diseases (ICD-10) was used to identify all first hospital admissions for the outcome variables: (1) OSAS, (2) hypertrophy of tonsils, (3) hypertrophy of adenoids and tonsils, or (4) only hypertrophy of adenoids, during the study period (1997–2004) in individuals aged 0–18 years. ICD-10 code G47.3 was used to define OSAS, J 35.1 to define hypertrophy of tonsils, and J 35.3 to define hypertrophy of both adenoids and tonsils. Also, J 35.2 to define hypertrophy of adenoids was used, but as such children often have milder forms of SDB and seldom have suspected OSAS, the results are only showed in figures, not in tables. Children with primary diagnosis of upper airway infections (acute tonsillitis, pharyngitis) were excluded in the present study.

Diagnostic codes at the individual level were retrieved from the Swedish Hospital Discharge Register in the MigMed database. Sweden has a social welfare system that includes public primary and hospital health care for all individuals. During the study period, most children with suspected OSAS would have been referred to an otorhinolaryngologic clinic by a primary health care or hospital physician. The patients in the present study were mainly on hospital wards because of symptoms of SDB and suspected OSAS; for surgical removal of adenotonsillar hypertrophy, or, in rare cases, hospitalized for sleep studies. There are only a few private hospitals in Sweden, and the Swedish Hospital Discharge Register includes data from these hospitals, as well as from the public hospitals. However, some older children undergo ambulant sleep studies and therefore are not included in the present study. In addition, the routines for the overnight studies vary between different regions and hospitals in Sweden, which we have partly accounted for in the present analysis (see below).

Explanatory Variables

Explanatory variables included gender, age at first hospital diagnosis of the outcome variable in question, socioeconomic status (defined as family income), and geographic region of residence (i.e., in most cases geographic region of hospitalization). Family income was divided into 3 categories based on the income level registered by the taxation authorities.

Geographic region was divided into large cities (cities with a population of more than 200,000, i.e., Stockholm, Gothenburg, and Malmö), Southern Sweden, and Northern Sweden. Geographic region was included as an explanatory variable to adjust for possible differences between geographic regions in Sweden with regard to hospital admissions for the 3 outcome variables.
Statistical Analysis

Using the individual-level data in the MigMed database, the entire pediatric population of Sweden was sorted into sibling groups (families) based on a shared mother and father. The database was then used to determine the presence or absence of a primary hospital diagnosis of pediatric OSAS or hypertrophy of the tonsils, or hypertrophy of the adenoids and tonsils, in each individual during the follow-up period. Next, individuals were categorized as positive or negative for sibling OSAS, or hypertrophy of the tonsils, or hypertrophy of the adenoids and tonsils, based on the presence of the disorder in at least one of their siblings. Individuals without siblings were excluded from the analysis. The individual serial numbers described in the section on the MigMed research database were used to check that those with hospital diagnoses of pediatric OSAS, or hypertrophy of the tonsils, or hypertrophy of the adenoids and tonsils appeared only once in the data set, i.e., for their first hospital diagnosis during the study period.

Person-years were calculated from the start of follow-up on January 1, 1997, to hospitalization for OSAS, or hypertrophy of the tonsils, or hypertrophy of the adenoids and tonsils, death, emigration, or the end of the study on December 31, 2004. Age-specific incidence rates (defined as first hospitalization rates during the study period) were calculated for the whole follow-up period. The results are shown as standardized incidence ratios (SIRs) with 95% confidence intervals (CIs). SIRs were calculated as the ratio of the observed to the expected number of cases for age, gender, time period, region, and socioeconomic status. Sibling risks were calculated separately for boys and girls categorized as positive for the disease in question in at least one of their siblings compared with boys or girls characterized as negative for sibling OSAS, or hypertrophy of the tonsils, or hypertrophy of the adenoids and tonsils, using the cohort methods as described in a study by Hemminki et al. Briefly, we defined a cohort of individuals with at least one affected sibling and computed the incidence rates in this cohort over the study period. In a family with two or more affected siblings, each affected individual is included in the cohort (as the sibling of an affected individual).

Relative weights used to calculate the age-standardized incidence rates were based on the European standard population. We judged this standard population to be a precise choice because a study from 2002 found that the 1960 standard population (the Segi standard) was as precise as more recent standard populations in the calculation of age-standardized rates.

The test statistic $\chi^2$ was used to calculate the probability (P value) of the SIR ratio between gender and age.

Ethical Considerations

This study was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden.

RESULTS

A total of 854 boys and 627 girls aged 0–18 years had a first hospital diagnosis of pediatric OSAS during the study period (Table 1). The first hospitalization rates in the entire population were 10.3 per 100,000 person-years for boys and 8.0 per 100,000 person-years for girls (significant gender difference, $P = 0.014$). The incidence rate of boys with a sibling history of OSAS was 544.8 and for girls 462.8 (no significant gender difference, $P = 0.503$).

There were 23 children (8%) diagnosed with pediatric OSAS who were also diagnosed with hypertrophy of the tonsils, or adenoids and tonsils; data not shown.

A total of 13,656 boys and 11,648 girls aged 0–18 years had a first hospital diagnosis of hypertrophy of the tonsils, or hypertrophy of adenoids and tonsils. The first hospitalization rates in the entire population were 165.0 per 100,000 person-years for boys and 148.8 per 100,000 person-years for girls (significant gender difference, $P < 0.001$). The incidence rate for boys with a sibling history of hypertrophy of the tonsils or hypertrophy of the adenoids and tonsils was 861.6 and, for girls, 812.6 (no significant gender difference, $P = 0.185$).

In Table 2, the SIRs for the first hospitalization for OSAS, hypertrophy of the tonsils, or hypertrophy of adenoids and tonsils, among children with ≥ 1 sibling with the disorders are shown by age groups. The models are adjusted for all the explanatory variables simultaneously. The overall SIR of OSAS among those who had ≥ 1 affected sibling was 33.23 (95% CI, 16.54–64.84) for boys and 40.49 (95% CI, 19.44–81.35) for girls, compared with the reference group of those without a sibling history of the disorder, no significant gender differences. The overall SIR of hypertrophy of the tonsils, or hypertrophy of adenoids and tonsils, among those who had at least one affected sibling was 4.53 (3.01–6.79) for boys and 4.94 (3.27–7.44) for girls, compared with the reference group of those without a sibling history of these disorders, a significant gender difference, $P = 0.049$. Children with only hypertrophy of adenoids, had a SIR of 17.12 (95% CI, 8.33–34.04) in boys, and a SIR of 8.88 (95% CI, 3.33–21.5) in girls, not shown in the table.

Table 3 shows SIRs and the observed number with pediatric OSAS who had at least one sibling with pediatric OSAS by gender of the affected siblings. When a male sibling had pediatric OSAS, the risk (SIR) that a male sibling would also have the disorder was 30.80 (95% CI, 13.28–67.38) and that a female sibling would have the disorder was 36.65 (95% CI, 15.06–83.15). When a female sibling was affected the risk (SIR) that a male sibling would have OSAS was 38.83 (95% CI, 15.96–88.11) and that a female sibling would have the disorder was 42.70 (95% CI, 16.45–101.58).

In children with hypertrophy of the tonsils or hypertrophy of the adenoids and tonsils who had at least one sibling with hypertrophy of the tonsils or hypertrophy of the adenoids and tonsils, the results were: when a male sibling had the disorder, the risk (SIR) that a male sibling would also have it was 4.38 (95% CI, 2.86–6.72) and that a female sibling would have the disorder was 4.75 (95% CI, 3.06–7.33). When a female sibling was affected the risk (SIR) that a male sibling would have OSAS was 38.83 (95% CI, 15.96–88.11) and that a female sibling would have the disorder was 42.70 (95% CI, 16.45–101.58).

There were no families with > 2 siblings affected with OSAS. However, there were families with > 2 siblings affected with hypertrophy of the tonsils or hypertrophy of the adenoids and tonsils. Boys and girls with no affected sibling were used as a reference. For 64 boys, the SIR was 96.63 (52.61–174.59)
for having the disorder and, for 47 girls, it was 77.92 (40.47–146.63); there was no significant gender difference, P = 0.26; data not shown in table.

We also performed an additional analysis, to calculate age differences, in order to investigate the effect of environmental factors on sibling risk. Large age differences indicate less shared environment and vice versa. The children were divided in 2 groups: <4 years old and ≥4 years old. There was no significant age difference in pediatric OSAS between 25 younger boys, SIR of 41.18 (18.82–86.08), and 12 older boys, SIR of 23.71 (8.62–58.75), P = 0.11. For the few number of girls with OSAS, there was a significant age difference between 23 younger girls, SIR of 56.33 (25.22–119.71), and 8 older girls, SIR of 22.38 (6.76–62.68), P = 0.02. However, in children with hypertrophy of the tonsils or hypertrophy of the adenoids and tonsils, there were only small, non-significant age differences; data not shown in table.

**DISCUSSION**

The sibling risk of pediatric OSAS was extremely high in the present study, with an incidence ratio of 33.2 in boys and 40.5 in girls in children who had at least one sibling with an OSAS diagnosis. We also included children with SDB and suspected OSAS with adenotonsillar hypertrophy, which is the main cause of pediatric OSAS. The familial risk of OSAS was much higher than in the group with adenotonsillar hypertrophy, the incidence ratio being 4.5 in boys and 4.9 in girls. However, the increase was highly significant and the numbers of children were much larger than in OSAS. The gender-specific ratio showed similar increases, as well as the ratios for boys and girls with one, two, or more affected siblings. There were significant gender differences in the first hospitalization rates in the entire study population with a higher rate for OSAS in boys than girls, as well as for hypertrophy of lymphoid tissue in boys compared to girls. This is in accordance with previous studies, which have shown that boys have a higher frequency of SDB than girls. There was no significant gender difference in the incidence rate of OSAS among those with a sibling history of OSAS, which was in contrast to adenotonsilar hypertrophy, in which a statistically significant gender difference was found; the SIR in girls was 4.9 compared to 4.5 in boys. However, this small gender difference is probably of minor clinical importance.

The results of the current study, with sibling aggregation of pediatric SDB are consistent with those of previous studies, i.e., the Cleveland Family Study investigated predictors of sleep disordered breathing in 577 children with a mean age of 10 years. Ten percent of the children had at a mean of 5 years previously undergone tonsillectomy and/or adenoidectomy. An independent risk factor for SDB in these children was, besides obesity and black race, a high familial risk (related to an affected proband). It suggested that there are both shared and unshared genetic factors underlying susceptibility to OSA and obesity and that the genetic determinants of obesity may be modulated by the severity of apnea.

A recently published study by our group on adult OSAS was conducted using the same methods as in the present study. We showed an increased risk in males with at least one sibling who had OSAS with a SIR of 3.4 in males and 3.2 in females for having OSAS. To the best of our knowledge, these are the only

<table>
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<th>Age at diagnosis (y)</th>
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**Table 1—Age-Specific Incidence Rates of Obstructive Sleep Apnea Syndrome, Hypertrophy of Tonsils and Hypertrophy of Adenoids and Tonsils Per 100,000 Person-Years in Boys and Girls Aged 0–18 Years**

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The indication of tonsillectomy mainly was because of recurrent and/or chronic tonsillitis. We know from the diagnostic codes that the children in the present study underwent tonsillectomy primarily because of OSAS and adenotonsillar hypertrophy, and not tonsillitis. However, we cannot rule out the possibility that the children secondarily also had an acute infection, which may have worsened their SDB symptoms. The heritability for recurrent and/or chronic tonsillitis and hypertrophy of lymphoid tissue is probably different, which makes it difficult to compare the results. Unfortunately, we did not have enough statistical power to perform a twin study of the Swedish children. However, recent genetic studies of both adult and pediatric patients studies that have investigated family risks in siblings with a history of medically verified OSAS or in children with adenotonsillar hypertrophy. The increased risks for OSAS and also the main causes of pediatric OSAS, adenotonsillar hypertrophy, could be an expression of genetic or shared environmental mechanisms. However, the results from the present study cannot differ between these mechanisms. The influence of heritability has been investigated in a twin-study from 1991, using questionnaires. The persons had undergone childhood tonsillectomy from 1939 to 1964 and the heritability factor varied between 29% to 82%. Their study has a recall bias and was performed during a time era when the indication of tonsillectomy mainly was because of recurrent and/or chronic tonsillitis. We know from the diagnostic codes that the children in the present study underwent tonsillectomy primarily because of OSAS and adenotonsillar hypertrophy, and not tonsillitis. However, we cannot rule out the possibility that the children secondarily also had an acute infection, which may have worsened their SDB symptoms. The heritability for recurrent and/or chronic tonsillitis and hypertrophy of lymphoid tissue is probably different, which makes it difficult to compare the results. Unfortunately, we did not have enough statistical power to perform a twin study of the Swedish children. However, recent genetic studies of both adult and pediatric patients.
with OSAS indicate that genetic mechanisms do play an important role.\textsuperscript{14-18} Future studies will probably clarify this.

Possible environmental factors are the increased medical awareness of SDB over time, both among parents and doctors. It is likely that parents who have one child with symptoms of SDB are more prone to seek evaluation for a sibling, even if the symptoms in the sibling are milder. Also the referring doctors may influence the sibling incidence, as the awareness and personality differs between doctors. There were only small age differences in the present study which indicate that the children had more shared environment.

There are weaknesses in the present study. Firstly, there are no strict definitions of adenotonsillar hypertrophy and SDB. In addition, few children undergo polysomnography or other sleep studies in Sweden, which make the diagnosis more uncertain. On the other hand, the use of only hospitalization data (leading either to sleep studies or adenotonsillectomy), suggest that we have included children with more severe symptoms of SDB, and suspected OSAS. Children with only hypertrophy of adenoids often have milder symptoms of SDB, and therefore did we only present results from those in figures and not in the tables. On the other hand, the increased sibling risks were similar in all investigated groups. Secondly, children with milder forms of SDB more often undergo surgery on both private and public ambulatory wards without hospitalization. The fact that we have only calculated the SIR of siblings with hospital diagnosis and compared it with a group of siblings without hospital diagnosis means that we can have missed children with milder forms of non-hospitalized OSAS and/or adenotonsillar hypertrophy. However, this is a non-differential bias, as it most likely affected both investigated groups equally. Thirdly, we had no data on individual risk factors for pediatric OSAS, such as obesity or craniofacial abnormalities. In a register that includes an entire population, it is not feasible to include individual data on weight, height, ethnicity and other individual risk factors for OSAS. However, the children were primarily hospitalized for OSAS, or adenotonsillar hypertrophy, the main etiological factors to OSAS, which increases the possibility that the diagnoses are valid. Fourthly, our study was not able to take account of early environmental factors, such as nutritional status early in life.

The present study has several strengths: the study population included a well-defined open cohort, the entire pediatric population of Sweden. Additionally, the data in the Swedish Hospital Discharge Register are very complete. In 2001, the main diagnosis was missing in 0.9% and the national civic registration number in 0.4% of hospitalizations.\textsuperscript{22} Finally, the quality of the multigenerational part of the MigMed database is very high, and it includes information about parents, children, siblings, and adoptions for index persons born in 1932 and onward and domiciled in Sweden at any time between 1947 and 2004.

The experience and knowledge of pediatric OSAS varies markedly in society at large, among both the population and caregivers. It is a serious disorder, with impairments both in the quality of life and in cognitive functions, as well as a significant risk of cardiovascular complications.\textsuperscript{1} Environmental or hereditary risk factors may explain the observed familial clustering seen in the present study.

Caregivers who investigate children with clinical signs or symptoms of SDB should ask their family members about similar signs or symptoms in siblings. If the answers are positive, these children should be sent to an ear nose throat specialist for further examination and treatment.

**ABBREVIATIONS**

OSAS - obstructive sleep apnea syndrome
SDB - sleep disordered breathing
SIR - standardized incidence ratio
CI - confidence interval

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**DISCLOSURE STATEMENT**

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