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Lundkvist, Karin; Sundquist, Kristina; Li, Xinjun; Friberg, Danielle

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Familial Risk of Sleep-Disordered Breathing

Karin Lundkvist, MD[1*]; Kristina Sundquist, MD, PhD[2]; Xinjun Li, MD, PhD[2]; Danielle Friberg, MD, PhD[1]

[1]Department of Otorhinolaryngology, Karolinska Institutet, Stockholm, Sweden;

[2]Center for Primary Health Care Research, Lund University, Sweden

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Corresponding author: Dr. Karin Lundkvist, ENT Department, Karolinska University Hospital, Huddinge, Karolinska Institutet, CLINTEC, Stockholm, Sweden.
Phone +46 8 58586457. Fax +46 8 7467551. E-mail: karin.lundkvist@karolinska.se

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Contributor´s Statement Page

Karin Lundkvist, MD: Has contributed to conception and design, analysis and interpretation of data and drafting the article and final approval of the version to be published.

Kristina Sundquist, MD, PhD**:** Has contributed to conception and design, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Xinjun Li, MD, PhD: Has contributed to conception and design, analysis and interpretation of data and revising the article critically for important intellectual content and final approval of the version to be published.

Friberg, MD, PhD: Has contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Abstract

Objectives: To estimate the incidence of hospitalization for pediatric obstructive sleep apnea syndrome (OSAS) and/or sleep-disordered breathing (SDB) caused by adenotonsillar hypertrophy or tonsillar hypertrophy without infection, in children with parental OSAS.

Patients and method: Using the MigMed database at Lund University, hospital data on all children aged 0-18 in Sweden between 1997 and 2007, a total of 3 million individuals, were used to identify all first hospital admissions for the outcome variables OSAS and/or adenotonsillar or tonsillar hypertrophy. Next, individuals were categorized as having a mother or father with OSAS. Standardized incidence ratios (SIRs) with 95% confidence intervals (CI) were estimated for sons and daughters with parental OSAS. Offspring without parental OSAS were the reference group (SIR = 1).

Results: After accounting for socioeconomic status, age, and geographic region, the SIR of OSAS in sons with parental OSAS was 3.09 (95% CI 1.83–4.90), and in daughters 4.46 (95% CI 2.68–6.98). The SIR of adenotonsillar or tonsillar hypertrophy in offspring with parental OSAS was 1.82 (95% CI 1.54-2.14) in sons and 1.56 (95% CI 1.30–1.87) in daughters.

Conclusion: The study indicates a familial clustering of sleep-disordered breathing, which represents important information for clinicians.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a prevalent disease among adults and children, 2-4% [1] and 1-4%, respectively. Further, a recent epidemiological review based on questionnaires suggests that the prevalence of parent-reported symptoms of pediatric sleep-disordered breathing (SDB) is 4–11% [2].

OSA (Obstructive sleep apnea) is characterized by prolonged partial upper airway obstruction, intermittent complete or partial obstruction or both prolonged and intermittent obstruction that disrupts normal ventilation during sleep, normal sleep patterns or both [3,4]. OSAS also includes daytime symptoms. SDB is a wider concept with a spectrum of symptoms in which the milder forms comprise primary snoring and mouth breathing, often caused by nasal congestion and/or adenoid hypertrophy. The more severe forms of SDB comprise symptoms similar to the more strictly defined entity, pediatric OSAS, i.e., intermittent breathing pauses (apneas), snorts or gasps, and disturbed sleep. In younger children, the most common risk factor for the more severe form of SDB and OSAS is adenotonsillar hypertrophy [5], and surgical removal of adenoids and tonsils is the first treatment option. The complications of pediatric OSAS and SDB have in several studies shown to be similar; daytime neurobehavioral problems with impaired school performance and hypertension [6,7].

Previous epidemiologic studies on familial associations have indicated that genetic factors might constitute a risk factor for OSAS and SDB. In Sweden, the construction of large population-based patient registers led to a previous study by our group which showed, after accounting for socioeconomic status, age, geographic region, and period of diagnosis, an increased sibling risk of OSAS and SDB caused by adenotonsillar hypertrophy in children [8]. Understanding the familial risk of OSAS and or SDB will help clinicians to identify children at risk and offer opportunities for early intervention and treatment.

The present study represents a novel contribution, i.e., investigating the relationship between OSAS and or SDB with adenotonsillar or tonsillar hypertrophy, in children with parental OSAS.

The aim of this study was to estimate the risk of hospitalization during an 11-year period for pediatric OSAS and or SDB in the offspring of parents with a hospital diagnosis of OSAS. This risk was compared with that of offspring without parental OSAS. A further aim was to determine whether there were any differences by age or gender.

Material and Method

Outcome variables:

The total number of subjects and the incidence rate of hospital diagnosis of adult and pediatric OSAS, as well as pediatric adenotonsillar or tonsillar hypertrophy, were calculated for different age-groups, gender, period of diagnosis, region of residence and family income. Further, the standardized incidence ratios (SIRs, see below) of the pediatric diagnoses were calculated in offspring with a parent hospitalized for OSAS and compared with offspring to parents without hospitalization for OSAS.

Sweden has a social welfare system that comprises public primary and hospital health care for all individuals with a residence permit. To diagnose OSAS, sleep studies are required, i.e., full-night polysomnography (PSG), which represents a Golden standard. However, PSG is time-consuming, expensive, and not widely available in all countries. In Sweden, PSG is available but ambulant sleep apnea recordings or polygraphy (PG) is more widely used. It has been validated against PSG [9]. Sweden follows the definitions of OSAS according to the

American Academy of Sleep Medicine; i.e., an Apnea Hypopnea Index (AHI) of at least 5 is required in adults. There are no strictly defined criteria of OSAS in children. However, it has been proposed to represent an apnea-hypopnea index of more than 1 per sleep hour [4][10]. Fewer children than adults with symptoms of OSAS undergo sleep studies in Sweden; the ICD codes included below could therefore represent SDB in the children. Since SDB has no special diagnostic code, hospitalized children with such symptoms and suspected OSAS often get the code adenotonsillar hypertrophy or tonsillar hypertrophy instead. Such children are normally referred to an otorhinolaryngological clinic by a primary health care or hospital physician. They are mainly on hospital wards for surgical removal of adenotonsillar hypertrophy or, in fewer cases, for sleep studies. During the study period 1997-2007, around 80 % of the adenotonsillectomies due to SDB were performed at hospitals, according to The Swedish National Quality Register for tonsil surgery (Hessén Soderman AC, personal communication).

The reasons for hospitalization in adults are several; treatments with surgery or Continuous Positive airway Pressure, and also for sleep studies.

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, G 47.3, (2) hypertrophy of tonsils, J 35.1, or (3) hypertrophy of adenoids and tonsils, J 35.3, during the study period (1997-2007) in individuals aged 0-18 years. Children with a primary diagnosis of upper airway infections (acute tonsillitis, pharyngitis), or milder forms of SDB (only adenoid hypertrophy), were excluded.

The ICD-10 code of OSAS, G47.3, was also used in the parents.

Diagnostic codes at the individual level were retrieved from the Swedish Hospital Discharge Register in the MigMed2 database.

MigMed Research Database

Data used in this study were retrieved from the MigMed2 database, located at the Center for Primary Health Care Research, Lund University, Sweden. MigMed is a single, comprehensive database that has been constructed using several national Swedish data registers, including but not limited to, the Population Register, the Multigeneration Register, and the Swedish Hospital Discharge Register (1986–2007) [11-13]. Information from the various registers in the database was 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 each individual.

Since the database contains information from the Multigeneration register, it is possible to link more than 7.6 million index persons (person born in or after 1932 and registered in Sweden any time since 1961) with their biological parents, children, and siblings.

Explanatory Variables

Explanatory variables included gender, age at first hospital diagnosis of the outcome variable, 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 four categories based on the income level recorded by the taxation authorities.

Family income was provided by Statistics Sweden and was defined as the family income during the year of childbirth divided by the number of people in the mother's family. The

income parameter also took into consideration the ages of people in the family and used a weighted system whereby small children were given lower weights than adolescents and adults.

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 admission for the different outcome variables.

Statistical Analysis

Using the individual-level data in the MigMed2 database, the entire pediatric population of Sweden was sorted into 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 aged ≤18 years (the offspring) during the follow-up period. Next, the offspring was categorized as positive or negative for parental OSAS based on the presence or absence of the disorder in the mother and/or father. Offspring with diagnoses of OSAS and or adenotonsillar hypertrophy but without maternal and/or paternal hospitalization for OSAS was the reference group. The individual serial numbers described in the section on the MigMed2 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 dataset, i.e., for their first hospital diagnosis during the study period.

Person-years were calculated from the start of the 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, 2007. 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 (No) to the expected number of cases. The expected number of cases was calculated for age, gender, time period, region, and socioeconomic status-specific standard incidence rates derived from offspring lacking an affected parent. The test statistic χ^2 was used to calculate the probability (P value) of the SIR ratio between sons and daughters.

Ethical Considerations

This study was approved by the Ethics Committee of Lund University, Sweden.

Results

Descriptive characteristics of the study population and their parents

There were 34 933 children with diagnoses of OSAS and/or adenotonsillar or tonsillar hypertrophy and 23 413 parents with OSAS diagnoses during the study period (Table 1). Among the diagnosed children, 5.7 % had a first hospital diagnosis of OSAS. The majority of the children were 4-7 years old and 54.1 % were boys. The most common age at diagnoses among the parents was 50-59 years.

Pediatric OSAS and adenotonsillar or tonsillar hypertrophy was most common among families with low and middle low income, 42.5% and 34.9 %, respectively.

There were 153 children (7.6%) diagnosed with OSAS who were also diagnosed with adenotonsillar or tonsillar hypertrophy. There were no families with both parents affected by OSAS.

Gender and age-specific incidence rate of pediatric OSAS

Of the entire population (Table 2), a total of 1 167 sons and 841 daughters aged 0–18 years had a diagnosis of OSAS during the study period. The hospitalization rate was 10.5 per 100 000 person-years for sons, and 8.0 for daughters ($p < 0.001$), a significant gender difference. For those children with a parent affected with OSAS, the incidence rate for sons with OSAS was 26.1 per 100 000 person-years, and for daughters, 29.4, a non-significant gender difference.

Gender and age-specific incidence rate of adenotonsillar or tonsillar hypertrophy

Of the entire population (Table 2), a total of 17 747 sons and 15 178 daughters aged 0–18 years had a diagnosis of adenotonsillar or tonsillar hypertrophy. The rate was 159.1 per 100 000 person-years for sons and 143.8 per 100 000 person-years for daughters ($p < 0.001$), a significant gender difference.

For those children with a parent affected with OSAS, the incidence rate for sons with adenotonsillar or tonsillar hypertrophy was 219.0 per 100 000 person-years and, for daughters, 190.3, a non-significant gender difference.

The hospitalization rate for pediatric OSAS as well as adenotonsillar or tonsillar hypertrophy was significantly higher for offspring with parental OSAS compared to those without parental OSAS, among children below 8 years (Figures A and B).

Standardized incidence ratios (SIR) of pediatric OSAS and adenotonsillar or tonsillar hypertrophy

The overall SIR of pediatric OSAS among those with parental OSAS was 3.09 (95% CI, 1.83-4.90) in sons (Table 3) and 4.46 (95% CI, 2.68-6.98) in daughters (Table 4).

The overall SIR in children with adenotonsillar or tonsillar hypertrophy among those with parental OSAS was 1.82 (95% CI, 1.54-2.14) in sons, and 1.56 (95% CI, 1.30-1.87) in daughters.

Discussion:

The main finding of this study was that offspring with parental OSAS had a substantially higher risk of hospitalization for SDB, defined as pediatric OSAS or adenotonsillar or tonsillar hypertrophy than offspring without parental OSAS. The standardized incidence ratio was highest in the group with pediatric OSAS; 3.09 in sons and 4.46 in daughters.

Additionally, a large number of children with adenotonsillar or tonsillar hypertrophy, one of the main etiologic factors for pediatric SDB and OSAS in young children, were included. The standardized incidence ratio was 1.82 in sons and 1.56 in daughters, i.e., lower than for OSAS, but still significantly increased. The present study has a novel approach to investigate familial aggregation; the use of hospital diagnosis, and the investigation of individual correlations between pediatric SDB and parental OSAS.

There were significant gender differences in the incidence rates of pediatric OSAS as well as adenotonsillar or tonsillar hypertrophy in the entire study population, with a higher rate in sons than in daughters. This is in accord with previous studies, which have shown that boys have a higher frequency of SDB than girls [2]. There were no significant gender differences in the incidence rates of these diagnoses in offspring with a parent affected with OSAS, which can be explained by the relatively fewer numbers of patients in this subgroup than in the entire population The categorization into different age groups in the present study showed that the highest incidence of SDB is in the group below 8 years. Other studies have shown similar results with a higher frequency of SDB in younger children [14]. In the present study, family income was investigated as an indicator of socioeconomic position. Pediatric OSAS and

adenotonsillar or tonsillar hypertrophy was most common among families with low or middle low income, 42.5% or 34.9 %, respectively. Canadian studies have also shown a correlation between socioeconomic status and pediatric SDB [15].

The association between pediatric and parental SDB/OSAS is in accord with an earlier study by Kalra et al. [16], who found a significant association between children and parents with habitual snoring. Previous epidemiologic studies conducted in different adult populations have also demonstrated familial aggregations of OSA [17,18]. The prevalence has varied quite a lot, from 21% in the Cleveland Family Study [18] to 84% in a Californian sample [19] among first-degree relatives of probands with OSAS. The Cleveland Study also reported that a person with a first-degree relative with OSAS has a 50% higher risk of having OSAS than an individual with no affected relatives [18]. Another study in Iceland reported a twofold risk in first-degree relatives [20]. Studies also including control samples showed that the odds ratio (OR) ranged from 2 to 46 [17, 18, 19]. It has been estimated that approximately 40% of the variance of the apnea-hypopnea index may be explained by familial factors [21].
Heredity might be an explanation for the increased familial risk as indicated by studies of adults and children [22]. Twin studies have shown a higher concordance for snoring between monozygotic twins than between dizygotic [23]. The genetics of OSA is probably multi-factorial. One of the factors is ethnicity, as the prevalence of SDB is higher among Afro-Americans [2]. Another factor is obesity, which is the most important risk factor for OSAS in adults. In children in Western countries, overweight and obesity are growing health problems. Obesity is considered to be inherited in a multi-factorial way [24]. Dayyat et al. suggest that OSA in obese children is a phenotypic variant of OSA closely resembling that in adults [25]. The authors also divide pediatric OSA into type I and type II. Type I is associated with marked lymphadenoid hypertrophy and an absence of obesity and is seen primarily in the

youngest children, and type II with obesity and an absence of lymphadenoid hypertrophy, resembling adult OSAS, and is seen primarily in older children.

Further, adenotonsillar or tonsillar hypertrophy might be inherited, and the size of the tonsils and adenoids increases from birth to adolescence with the greatest increase during the first years of life [26]. In a recent study by Khalyfa et al. [27], palatine tonsils in children were analyzed regarding gene expression to identify putative mechanistic pathways associated with tonsillar proliferation and hypertrophy in OSA. The authors found that phosphoserine phosphatase in tonsillar tissue played a role in hypertrophy in OSA children, but not in that derived from children with recurrent tonsillitis.

An additional genetic factor is facial growth and upper airway soft tissue (i.e., nasal obstruction). Bixler et al. have published data from the largest population-based sleep cohort, performed in American children aged 5–12. The authors concluded that, besides excess weight, nasal abnormalities (and not tonsil size) were statistically significant predictors of SDB in this age group [28]. Inflammation is also considered to be an important genetic factor, as inflammatory markers were up regulated in RNA studies of peripheral leukocytes in children with OSAS, which was not found in non-OSAS children [29].

A further explanation of our findings is the increased medical awareness of SDB over time among both caregivers and the general population. The environment may also be a risk factor for SDB, e.g., parental smoking and low maternal education [30].

The present study has some weaknesses; only a few children undergo polysomnography or other objective sleep studies in Sweden; the diagnoses of OSAS in the children are therefore most often clinical. However, the use of hospitalization data suggests that we have included children with more severe symptoms of SDB and suspected OSAS, as children with milder

forms more often undergo surgery without hospitalization. In addition, most children in our study population were not diagnosed with OSAS; only 5.7% had this diagnosis whereas 94.3% had adenotonsillar or tonsillar hypertrophy without infection.

The use of hospital data suggests that we may also have included adult patients with a more severe OSAS. Furthermore, the database does not contain data on individual risk factors such as overweight, tonsil size and facial developmental factors. Data on physical examinations or ethnicity are also lacking. However, in a study from 2002 and 2008 of 4-year old children from the northern part of Sweden, the prevalence of overweight was approximately 15 % among girls and 20 % among boys [31]. In 2008, the Swedish population consisted of 14 % immigrants (born outside Sweden). The majority was from Finland, Iraq, and the former republic of Yugoslavia, and therefore we consider that most of the participants in the present study were Caucasians [32]. Our study was not able to take account of early environmental factors such as nutritional status in early life or passive smoking.

The present study has several strengths; the study population included a well-defined open cohort, the entire population of Sweden less than 19 years linked to their parents. It was possible to track the records of every person for the whole follow-up period because of the civic registration number assigned to each individual in Sweden. Additionally, the data in the Swedish Hospital Discharge Register is remarkably complete; in 2001 the main diagnosis was missing in only 0.9% and the national civic registration number in 0.4% of hospitalizations. Furthermore, the quality of the multigenerational part of the MigMed database is very high and includes information about children, siblings, parents, and adoptions for index persons born in 1932 and onward and domiciled in Sweden any time between 1947 and 2007. We have also adjusted for geographic and socioeconomic factors. Finally, the use of hospital register data eliminated recall bias, which is a potential problem with other study designs.

Conclusion

The study indicates a familial clustering of sleep-disordered breathing, findings that are useful for health professionals. Future studies could examine the possible interactions between hereditary and environmental factors.

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Table 1. Total number of cases of obstructive sleep apnea syndrome (OSAS), hypertrophy of tonsils or hypertrophy of adenoids and tonsils in offspring (aged 0 to 18 years) and OSAS in parent

	Offspring		Parent	
	No.	%	No.	%
Total cases	34933		23413	
OSAS	2008	5.7	23413	
Hypertrophy of tonsils or hypertrophy of adenoids and tonsils	32925	94.3		
Gender				
Males	18914	54.1	18158	77.6
Females	16019	45.9	5255	22.4
Age at diagnosis in offspring (years)				
0-3	6812	19.5		
4-7	17423	49.9		
8-12	6487	18.6		
13-18	4211	12.1		
Age at diagnosis in parents (years)				
<40			1950	8.3
40-49			4030	17.2
50-59			8102	34.6
60-69			6246	26.7
70-79			2707	11.6
>=80			378	1.6
Period of diagnosis (years)				
1997-1999	11470	32.8	8594	36.7
2000-2002	8993	25.7	6640	28.4
2003-2005	8937	25.6	5155	22.0
2006-2007	5533	15.8	3024	12.9
Region of residence				
Big cities	9756	27.9	8975	38.3
Southern Sweden	16369	46.9	10147	43.3
Northern Sweden	8808	25.2	4291	18.3
Family income				
Low income	14839	42.5	5361	22.9
Middle-low income	12208	34.9	6460	27.6
Middle-high income	5849	16.7	6114	26.1
High income	2037	5.8	5478	23.4

Table 2. Gender and Age-specific incidence rates of hospital diagnosis of obstructive sleep apnea syndrome (OSAS), hypertrophy of tonsils and hypertrophy of adenoids and tonsils per 100.000 person-years in boys and girls aged 0-18 years

	Entire population					With a parent affected with OSAS				
	Son		Daughter		Gender difference	Son		Daughter		Gender difference
Age at diagnosis (years)	No.	Incidence rates	No.	Incidence rates	P value	No.	Incidence rates	No.	Incidence rates	P value
0-3	4202	196.6	2610	128.9	<0.001	31	417.5	19	271.1	0.140
4-7	10000	439.4	7423	342.8	<0.001	89	852.1	61	625.6	0.063
8-12	3160	101.3	3327	112.3	<0.001	19	98.3	28	154.2	0.129
13-18	1552	42.9	2659	78.1	<0.001	30	94.5	34	114.5	0.441
All	18914	169.6	16019	151.7	<0.001	169	245.1	142	219.8	0.337
OSAS	1167	10.5	841	8.0	<0.001	18	26.1	19	29.4	0.719
Hypertrophy of tonsils or hypertrophy of adenoids and tonsils	17747	159.1	15178	143.8	<0.001	151	219.0	123	190.3	0.250

Table 3. Standardized incidence ratios and observed number of cases of obstructive sleep apnea syndrome (OSAS), hypertrophy of tonsils or hypertrophy of adenoids and tonsils in sons, showed by age groups

Age at diagnosis (years)	Father with OSAS				Mother with OSAS				Parent with OSAS			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
0-3	28	**2.04**	**1.36**	**2.96**	3	1.79	0.34	5.29	31	**2.01**	**1.37**	**2.86**
4-7	79	**2.10**	**1.67**	**2.62**	10	1.99	0.95	3.67	89	**2.09**	**1.68**	**2.57**
8-12	17	1.08	0.63	1.73	2	0.90	0.09	3.32	19	1.06	0.64	1.65
13-18	27	**2.47**	**1.62**	**3.59**	3	1.64	0.31	4.86	30	**2.35**	**1.58**	**3.36**
All	151	**1.94**	**1.64**	**2.27**	18	1.67	0.99	2.65	169	**1.90**	**1.63**	**2.21**
OSAS	17	**3.37**	**1.96**	**5.41**	1	1.28	0.00	7.36	18	**3.09**	**1.83**	**4.90**
Hypertrophy of tonsils or hypertrophy of adenoids and tonsils	134	**1.84**	**1.54**	**2.18**	17	1.70	0.99	2.74	151	**1.82**	**1.54**	**2.14**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval

Bold type: 95% CI does not include 1.00.

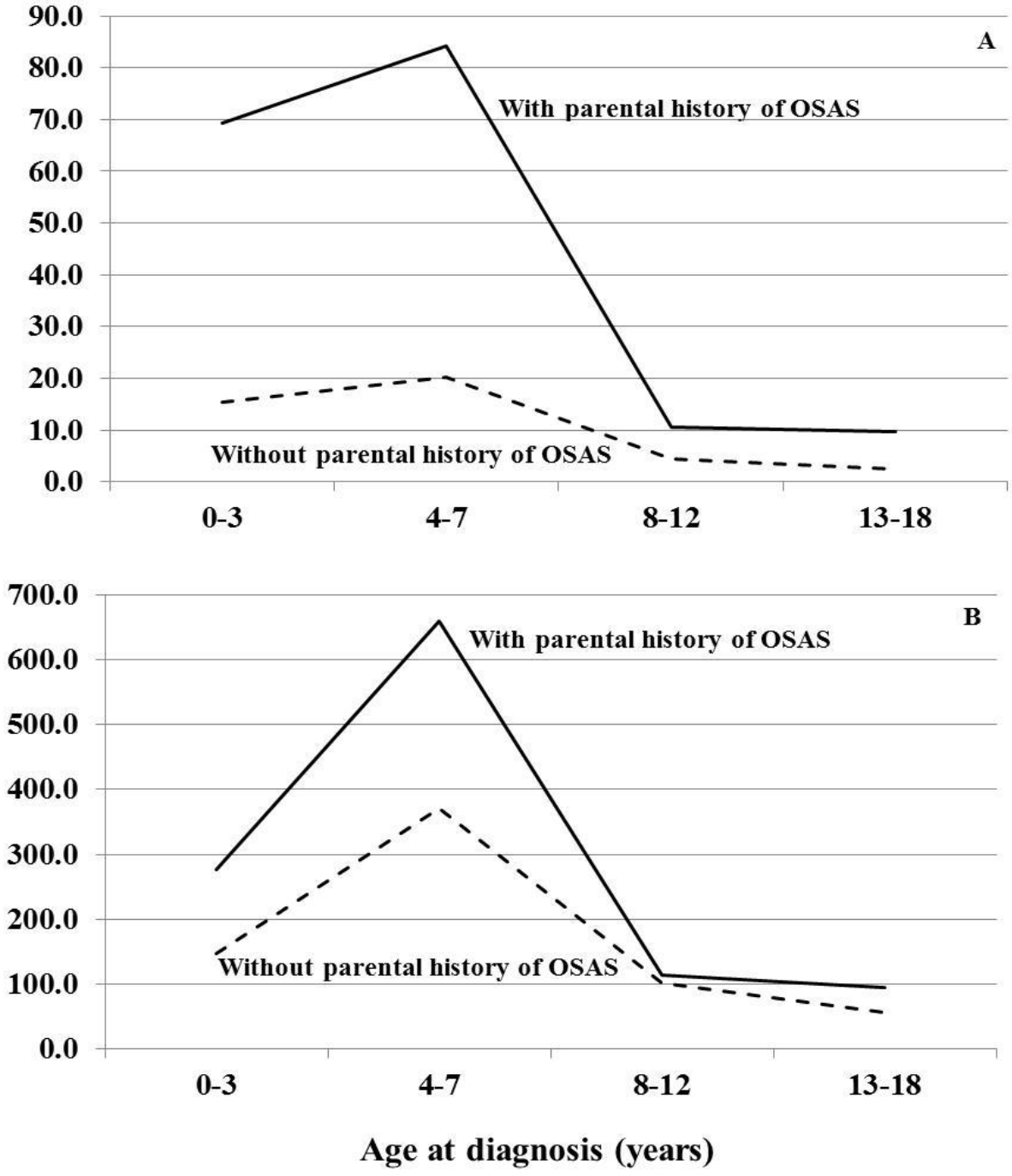
Table 4. Standardized incidence ratios and observed number of cases of obstructive sleep apnea syndrome (OSAS), hypertrophy of tonsils or hypertrophy of adenoids and tonsils in daughters, showed by age groups

Age at diagnosis (years)	Father with OSAS				Mother with OSAS				Parent with OSAS			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
0-3	15	1.72	0.96	2.85	4	**4.48**	**1.16**	**11.58**	19	**1.98**	**1.19**	**3.10**
4-7	59	**2.07**	**1.58**	**2.68**	2	0.61	0.06	2.25	61	**1.92**	**1.47**	**2.47**
8-12	22	1.27	0.79	1.93	6	2.68	0.96	5.86	28	1.43	0.95	2.07
13-18	27	1.42	0.94	2.07	7	2.31	0.91	4.78	34	**1.55**	**1.07**	**2.16**
All	123	**1.68**	**1.39**	**2.00**	19	**2.01**	**1.21**	**3.15**	142	**1.71**	**1.44**	**2.02**
OSAS	16	**4.27**	**2.43**	**6.95**	3	**5.89**	**1.11**	**17.42**	19	**4.46**	**2.68**	**6.98**
Hypertrophy of tonsils or hypertrophy of adenoids and tonsils	107	**1.54**	**1.26**	**1.86**	16	**1.79**	**1.02**	**2.91**	123	**1.56**	**1.30**	**1.87**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval

Bold type: 95% CI does not include 1.00.

The hospitalization rate per 100.000 person years in different age groups, Fig A, for OSAS and, Fig B, for adenotonsillar and tonsillar hypertrophy



A. The hospitalization rate for pediatric OSAS in offspring with and without parental history of OSAS

B. The hospitalization rate for children with adenotonsillar hypertrophy in offspring with and without parental history of OSAS. Note the significant differences between children who have parents with or without OSAS, especially among the children aged 4–7 years.