Sleep-Disordered Breathing and Blood Pressure in Children

A Meta-analysis

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Objectives: To estimate the risk of elevated blood pressure (BP) in children with obstructive sleep-disordered breathing (SDB) and to explore heterogeneity among published studies.

Data Source: PubMed database.

Study Selection: Pediatric cohort studies that investigated the relationship between SDB and BP.

Main exposure: Level of severity of SDB.

Main outcome measures: Elevated systolic and diastolic BP.

Results: During wakefulness, moderate to severe SDB was associated with 87% and 121% higher risk for elevated systolic and diastolic BP, respectively, compared with mild or no SDB, but the association was not statistically significant (random-effects odds ratio [OR], 1.87; 95% confidence interval [CI], 0.73-4.80; and random-effects OR, 2.21; 95% CI, 0.80-6.10, respectively). In terms of heterogeneity, reports of systolic BP were characterized by large heterogeneity (quantification heterogeneity metric [I²] = 53%), whereas studies recording diastolic BP had moderate heterogeneity (I² = 31%). During sleep, large heterogeneity was identified among studies regarding elevated systolic BP (I² = 54%), and the random-effects OR was 1.20 (95% CI, 0.29-5.02). No heterogeneity was detected regarding elevated diastolic BP (I² = 0%), although the fixed-effects OR was still not statistically significant (OR, 2.23; 95% CI, 0.61-8.16).

Conclusions: No evidence exists that moderate to severe SDB in childhood increases the risk of elevated BP, and there is heterogeneity among published reports. Large and methodologically rigorous investigations are needed.

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The term obstructive sleep-disordered breathing (SDB) has been used in the pediatric literature to describe episodes of intermittent partial or complete upper airway obstruction during sleep, whereas the relative concept in adult sleep medicine is obstructive sleep apnea syndrome.1 These episodes of upper airway obstruction result from the combination of increased upper airway resistance, mainly due to adenotonsillar hypertrophy, and decreased pharyngeal dilator muscle tone while the child is asleep.2,3 Primary snoring, upper airway resistance syndrome, obstructive sleep apnea-hypopnea, and mild, moderate, or severe SDB have been used in the literature to describe severity of intermittent upper airway obstruction during sleep.2-6 Although the presence of snoring and the apnea index or apnea-hypopnea index are part of the definition of these terms, specific cutoff values vary considerably from study to study.4,6 Evidence from large population studies6,10 that recruited adults indicates an association of elevated blood pressure (BP) with obstructive sleep apnea syndrome. Children with severe obstructive SDB may also have important consequences to the cardiovascular system. They can present with cor pulmonale and pulmonary hypertension,11 decreased right ventricle ejection fraction,12 increased left ventricle mass index,13 or decreased left ventricle diastolic function.14 Mechanisms responsible for these abnormalities have not been clarified, but sustained elevation of systemic arterial pressure could be one of them.

Although obstructive SDB related to adenotonsillar hypertrophy occurs often in children, the issue of a potential correlation between BP and severity of obstructive SDB remains unresolved.11 A few cohort studies15-16 with disparate estimates have been published, and currently conclusive data regarding the risk of elevated BP in children with intermittent up-

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per airway obstruction during sleep are inadequate. Some of the published pediatric reports suggest that the risk of elevated BP is high,\(^ {17}\) whereas others report moderate risk\(^ {16}\) or even absence of an association between the 2 conditions.\(^ {19}\) Moreover, in 1 investigation a negative correlation of diastolic BP during wakefulness with severity of SDB has been described.\(^ {5}\)

To provide an estimate of the risk of elevated BP in children with obstructive SDB, a meta-analysis of all available pediatric cohort studies on the subject was performed. Investigations of patients 18 years or younger with snoring, apneas, and difficulty breathing associated with adenotonsillar hypertrophy were included in the present meta-analysis. A pooled estimate of the risk of elevated BP expressed as an odds ratio (OR) was calculated, and the heterogeneity among studies and the existence of bias were explored. An effort was made to emphasize the inconsistent use of nomenclature in the currently available literature regarding terms that characterize severity of intermittent upper airway obstruction during sleep.

### METHODS

#### SEARCH STRATEGY

PubMed was searched for English-language articles published before July 2006 using the following search criteria: ("apnea" or "sleep-disordered breathing" or "snoring") and ("children" and ("blood pressure" or "diastolic blood pressure" or "systolic blood pressure"). References cited in the retrieved articles were reviewed to identify additional published work not indexed by PubMed. Retrieved articles were evaluated by both of us to assess their appropriateness for inclusion in the meta-analysis. Abstracts, case reports, editorials, and review articles were excluded from further consideration. We reached a consensus about the inclusion or exclusion of original cohort studies.

#### DATA EXTRACTION

Blinded to study details, we independently abstracted data from each investigation, including study setting, cutoff values, validity of study design, and 2 × 2 contingency tables (SDB status and BP) that were necessary to calculate the ORs. Disagreements were resolved by discussing the full articles. Of all retrieved cohort studies, we included in the meta-analysis investigations that (1) recruited patients with obstructive SDB who were 18 years or younger (population sample or patients referred to the hospital for polysomnography); (2) assessed the association between BP and severity of obstructive SDB in study participants; and (3) provided enough information to allow calculation of ORs and 95% confidence intervals (CIs) for elevated BP. Severity of SDB presented in the published articles; those values for elevated BP was achieved by examining graphs of BP vs severity of SDB presented in the published articles; those values that were best at separating high and low BP were selected as cutoff limits.

Besides the availability of relevant published data, the corresponding investigators of each study were contacted and asked to provide data and cutoff values so that information could be standardized similarly across studies. They were also invited to comment on the methodological approach used for data extraction and interpretation of findings.

#### DATA SYNTHESIS

In the meta-analysis, the pooled (elevated systolic or diastolic BP during sleep and wakefulness) OR was estimated using fixed-effects (FE) (Mantel-Haenszel) and random-effects (RE) (DerSimonian and Laird) models.\(^ {20}\) The RE modeling assumes a genuine diversity in the results of various studies and incorporates a between-study variance to the calculations. Therefore, when heterogeneity exists among studies, the pooled OR is estimated using the RE model.\(^ {21,22}\)

Heterogeneity among studies was tested using the Q statistic, a weighted sum of squared deviations of individual study OR estimates from the pooled estimate.\(^ {23,24}\) When the ORs are homogeneous, Q follows a \(\chi^2\) distribution with \(r−1\) d.f. (r is the number of studies). Heterogeneity was also quantified by applying the quantification heterogeneity metric (\(I^2\)) (\(I^2=[Q−df]/Q\)), which is independent of the number of studies in the meta-analysis.\(^ {22,23,26}\) The \(I^2\) takes values between 0% and 100%, with higher values denoting greater degree of heterogeneity: \(I^2\) of 0% to 25% indicates no heterogeneity, \(I^2\) of 25% to 50% indicates moderate heterogeneity, \(I^2\) of 50% to 75% indicates large heterogeneity, and \(I^2\) of 75% to 100% indicates extreme heterogeneity. Heterogeneity was considered statistically significant if \(P<.10\).

Subgroup analysis was performed according to recruitment source of participants (hospital- vs population-based studies). Sensitivity analysis for studies that assessed the severity of SDB by methods other than polysomnography was performed. Sensitivity analysis examines the effect of excluding specific studies. Possible publication bias was tested by the Egger regression test for funnel plot asymmetry\(^ {27}\) and by the Begg-Mazumdar test that is based on the Kendall \(\tau\).\(^ {28,29}\) Analyses were performed using Compaq Visual Fortran with the IMSL library.\(^ {30,31}\)

### RESULTS

#### SEARCH RESULTS

The literature review identified 66 titles in PubMed that met the search criteria (Figure 1). Abstracts of these articles were reviewed, and 12 publications were judged to be potentially relevant. No further studies were iden-
CI was calculated accordingly. Three studies were hospital-based and 2 studies were population-based. In the 5 cohort studies, the OR for elevated systolic BP or diastolic BP during sleep and wakefulness ranged from 0.30 to 5.78 and from 0.44 to 7.5, respectively (Figure 1).

CHARACTERISTICS OF INCLUDED STUDIES

Three studies provided BP data both during sleep and wakefulness, whereas in 2 reports, BP was measured only during wakefulness. In 1 investigation, adjusted ORs (by obesity and sleep efficiency) for high systolic and diastolic BP were reported. Since the 95% CIs for elevated systolic BP OR and diastolic BP OR were almost identical, the OR for overall high BP (either elevated systolic or diastolic BP) was estimated as the average of the systolic BP OR and diastolic BP OR, and the respective CI was calculated accordingly. Three studies were hospital-based and 2 studies were population-based.

In 1 report, the cutoff value for elevated BP was the 90th percentile from age-, height-, and sex-specific curves, whereas in a second investigation, elevated systolic or diastolic BP was defined using age-specific cutoff values derived from the published literature. In 2 publications, a BP index was calculated by the investigators to adjust for the effect of age, height, and sex on absolute BP values; the cutoff values of the BP index that were used to determine elevated systolic and diastolic BP were specified by us. Finally, for a fifth study, both an age index and absolute BP were provided; we used the mean absolute BP plus the standard deviation during wakefulness as the cutoff for high systolic or diastolic BP.

The values of polysomnography parameters used to separate patients with the most severe SDB from those with the least severe SDB or without SDB varied among investigations. In 1 report the limit was an apnea index of 1 episode per hour, and in 2 studies it was an apnea-hypopnea index of 10 episodes per hour or 5 episodes per hour. In a fourth study, a value of the respiratory disturbance index (apnea-hypopnea index) not stated in the article was used to form SDB severity groups (Table). One publication reported data during both rapid eye movement (REM) and non-REM sleep; the REM data were used in the meta-analysis, since it was not possible to combine data from REM and non-REM sleep. Furthermore, this is the stage of pediatric sleep with the highest frequency of obstructive apneas. In 1 study, a symptom questionnaire was administered to assess severity of obstructive SDB, and for this reason a sensitivity analysis was performed for that specific investigation.

STUDY HETEROGENEITY, POOLED ORS, AND PUBLICATION BIAS

In total, the 5 studies included 1149 participants, all of whom had BP measured during wakefulness, whereas 150 of them also had BP measured during sleep. The mean age of the patients varied from 5 to 12 years. In the 5 cohort studies, the OR for elevated systolic BP or diastolic BP during sleep and wakefulness ranged from 0.30 to 5.78 and from 0.44 to 7.5, respectively (Figure 2).

Large heterogeneity was identified among studies regarding elevated systolic BP during sleep (P = .11; I² = 54%), and the pooled RE OR was 1.20 (95% CI, 0.29-5.02). Lack of heterogeneity was found regarding elevated diastolic BP during sleep (P = .43; I² = 0%), but the pooled FE OR was still not statistically significant (OR, 2.23; 95% CI, 0.61-8.16). During wakefulness, moderate-to-severe SDB was associated with an 87% higher risk of elevated systolic BP and a 121% higher risk of elevated diastolic BP compared with mild or no SDB, but the association was not statistically significant; the OR for elevated systolic BP and 2.21 (95% CI, 0.80-6.10) for elevated diastolic BP. In terms of heterogeneity, reports of systolic BP during wakefulness were characterized by large heterogeneity (P = .07; I² = 53%), whereas studies recording diastolic BP had moderate heterogeneity (P = .22; I² = 31%). In sensitivity analysis, after exclusion of 1 study reporting BP during wakefulness, the pattern of results remained the same: for systolic BP during wakefulness, the RE OR was 1.89 (95% CI, 0.57-6.28) with large heterogeneity (P = .04; I² = 64%), and for diastolic BP, the RE OR was 2.05 (95% CI, 0.63-6.64) with moderate heterogeneity (P = .13; I² = 46%).

Subgroup analyses for hospital-based studies during wakefulness produced no significant association for both systolic and diastolic BP; for systolic BP, the RE OR was 1.36 (95% CI, 0.35-5.22) with large heterogeneity (P = .09; I² = 59%), and for diastolic BP, the RE OR was 1.39 (95% CI, 0.34-5.61) with moderate heterogeneity (P = .19; I² = 40%). Of interest, heterogeneity was lacking among the population-based studies (P = .44 for systolic BP and P = .99 for diastolic BP, I² = 0%), and the pooled ORs (during wakefulness) were significant: for systolic BP, the FE OR was 3.24 (95% CI, 1.19-8.78), and for diastolic BP, the FE OR was 6.28 (95% CI, 1.74-23.03).
was 4.74 (95% CI, 1.36-16.56). Nevertheless, these results were based only on 2 studies, and definitive conclusions cannot be drawn.

There was no evidence of publication bias ($P = .13$ for the Egger test and $P = .33$ for the Begg-Mazumdar test) during wakefulness (studies during sleep are included).

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Study Characteristics and Remarks</th>
<th>No. of Male (Female) Patients in Cohort/Age, y (Patient Group)*</th>
<th>High SBP, % of Patients With Moderate to Severe SDB vs Mild or No SDB</th>
<th>High DBP, % of Patients With Moderate to Severe SDB vs Mild or No SDB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcus et al,4 1998</td>
<td>United States</td>
<td>Hospital-based PSG BP measurement every 15 minutes during PSG, average of BP values Moderate to severe SDB if apnea index $&gt;1$ episode per hour High BP if greater than mean $+$ SD during wakefulness (defined by us)</td>
<td>67 (30)/5 ± 3 (moderate to severe SDB) and 8 ± 4 (mild or no SDB)</td>
<td>12.2 vs 11.5 while awake; 7.3 vs 7.7 while asleep</td>
<td>12.2 vs 7.7 while awake; 4.9 vs 3.8 while asleep</td>
</tr>
<tr>
<td>Kohyama et al,16 2003</td>
<td>Japan</td>
<td>Hospital-based PSG BP measurement every 15 minutes during PSG, average of BP values Moderate to severe SDB if apnea-hypopnea index $&gt;10$ episodes per hour High BP if (BP measured $-$ BP cutoff for hypertension) $&gt;30$ mm Hg (value defined by us)</td>
<td>23 (4)/4-11</td>
<td>71.4 vs 25 while awake; 57.1 vs 18.8 during REM sleep; 28.6 vs 12.5 during NREM sleep</td>
<td>85.7 vs 50 while awake; 57.1 vs 18.8 during REM sleep; 28.6 vs 12.5 during NREM sleep</td>
</tr>
<tr>
<td>Enright et al,17 2003</td>
<td>United States</td>
<td>Population-based PSG at home BP measurement in the evening before PSG Moderate to severe SDB if respiratory disturbance index above a certain value (not reported) High BP if $&gt;90$th percentile</td>
<td>239 (108)/6-11</td>
<td>OR adjusted by sleep efficiency, 4.57 (95% CI, 1.21-17.3)</td>
<td>OR adjusted by sleep efficiency and obesity, 4.75 (95% CI, 1.22-18.6)</td>
</tr>
<tr>
<td>Amin et al,5 2004</td>
<td>United States</td>
<td>Hospital-based PSG BP measurement every 15 minutes for 24 hours, average of BP values Moderate to severe SDB if apnea-hypopnea index $&gt;5$ episodes per hour High BP if (BP measured $-$ BP at 95th percentile) $&gt;100$/BP at 95th percentile $&gt;5$% (value defined by us)</td>
<td>60 (24)/10.8 ± 3.5</td>
<td>50 vs 63.2 while awake/18.2 vs 31.6 while asleep</td>
<td>9.1 vs 18.4 while awake; 4.5 vs 5.3 while asleep</td>
</tr>
<tr>
<td>Kaditis et al,19 2005</td>
<td>Greece</td>
<td>Population-based SDB severity assessed by symptom questionnaire BP measurement in the morning Moderate to severe SDB if snoring present $&gt;3$ nights per week during the last 6 months High BP if above certain cutoff values used by Kohyama et al16</td>
<td>760 (352)/1-18</td>
<td>4 vs 2 while awake</td>
<td>0 vs 0.1 while awake</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; NREM, non–rapid eye movement; OR, odds ratio; PSG, overnight polysomnography; REM, rapid eye movement; SBP, systolic blood pressure; SDB, sleep-disordered breathing.

*Age is presented as mean ± SD or range.
with those during wakefulness). Nevertheless, this result might not be reliable because the number of included studies was relatively small. In 3 studies, selection bias occurred because participants were habitual snorers referred to sleep disorders laboratories for polysomnography. It is conceivable that those participants had more severe obstructive SDB compared with other children with snoring in the community.

**COMMENT**

**MAIN FINDINGS**

Although population studies in adults have provided strong evidence regarding an association between obstructive sleep apnea and hypertension, it is unclear whether such a correlation is active in childhood. Overall, the present meta-analysis revealed a lack of association between systolic or diastolic BP and SDB and also identified moderate to large heterogeneity among studies. Results between measurements during sleep and wakefulness were consistent. Although the risk of elevated diastolic BP in children with moderate to severe SDB was twice the risk of elevated systolic BP, the previous association did not achieve statistical significance. Subgroup analysis produced a significant association only when the population-based studies were considered. Since only 2 such articles have been published, inferences cannot be taken for granted.

**STRENGTHS AND WEAKNESSES OF THE STUDY**

The strength of the present analysis is based on the aggregation of data from the published reports. For this reason, more information is available for estimating the strength of a potential association between disturbance of respiration during sleep and BP. Non-English, non-indexed, and nonpublished studies in the literature were not reviewed; thus, bias could have been introduced. Studies with significant results are more likely to be published, especially in English-language indexed journals, whereas studies with negative findings are more likely to be published in a local journal, which is often nonindexed. It has been reported that studies published in non-English journals show lower methodological quality. Juni and colleagues have shown that exclusion of published studies in languages other than English may not affect pooled estimates.

An effort was made for consistent inclusion criteria regarding study participants from different reports, although this effort was limited by the methodological characteristics of the individual studies. For example, the study...
by Kwok et al\textsuperscript{18} was not included in the analysis because it compared children with mild SDB with healthy controls (no SDB). In addition, in the study by Kwok et al, polysomnography was performed for cases but not for controls.

A quality assessment of the included studies was avoided, since it has been shown\textsuperscript{38} that quality does not affect the magnitude of effects in published studies, and thus quality measures do not necessarily explain heterogeneity. However, some controversy exists in the literature about whether variations in study quality are an important source of heterogeneity.\textsuperscript{34,39} In addition, the use of composite scales for assessing quality is problematic in meta-analysis.\textsuperscript{38-41} In the present study, an analysis of individual components (subgroup analysis) of study quality and heterogeneity or sensitivity analysis, for those components that were considered important, was adopted.\textsuperscript{20,34} The only measures of quality that could have affected heterogeneity are the study design (population or hospital based); the use of polysomnography, which is confounded with the hospital-based studies; and activity status (sleep or wakefulness). However, the number of studies is small for this type of analysis, and the results should be interpreted with caution. Moreover, meta-regression techniques were not adopted because we were limited by the number of studies.\textsuperscript{40}

**METHODOLOGICAL CHARACTERISTICS OF INDIVIDUAL STUDIES**

Some specific characteristics of the individual studies that might have decreased the power of the meta-analysis to detect a significant association of BP with SDB need to be mentioned. Variable definitions of severity of SDB and elevated BP potentially contributed to the large heterogeneity among published investigations. All included publications\textsuperscript{4,5,16,19} except for 1\textsuperscript{17} were designed to assess the potential correlation of BP values with severity of SDB and not the risk of elevated BP according to the apnea-hypopnea index. Use of correlation analysis as a statistical method made comparisons among different investigations difficult.

Since linear regression analysis was the main statistical method of evaluating the association between BP and SDB, we had to define elevated BP. This task was performed using either absolute BP values\textsuperscript{4} or measurements adjusted by age and sex (BP index).\textsuperscript{5,16} Comparing absolute BP values in childhood may be inefficient when they are not adjusted for patient age, sex, and height. However, it was not possible to derive a cutoff value for the BP index from all included studies. Consistent definitions of severity of SDB and of high BP would most likely decrease heterogeneity between reports and would increase the possibility to document a significant risk of elevated BP in children with moderate to severe SDB.

Last but not least, assessment of the severity of SDB and frequency of BP recording differed among reports. The largest of all investigations\textsuperscript{4} used an SDB symptom questionnaire to evaluate severity of SDB, whereas in all other reports\textsuperscript{4,5,16,17} study patients underwent polysomnography. Exclusion of the former publication and sensitivity analysis did not alter the pattern of results. In the second largest study, BP was measured at home in the evening before polysomnography,\textsuperscript{17} whereas Marcus et al\textsuperscript{4} and Kohyama et al\textsuperscript{17} recorded BP every 15 minutes during polysomnography. In contrast, Amin et al\textsuperscript{4} monitored BP every 15 minutes for 24 hours. Finally, Kaditis et al\textsuperscript{4} measured BP at school in the morning.

As a result of these described differences in study methods, in some publications BP measurements collected at certain points of time were entered in the analysis,\textsuperscript{17,19} and in others the average of repeated BP values recorded during several hours was used. Because of the previous methodological differences, BP during wakefulness had slightly different meaning in different studies. In some, it referred to wakefulness at night\textsuperscript{4,16} and in others to wakefulness during both the night and day.\textsuperscript{5} In addition, in the investigation by Kohyama et al,\textsuperscript{16} BP data were reported during wakefulness, REM sleep, and nonREM sleep. Only wakefulness and REM sleep data were entered in the meta-analysis because it was difficult to combine BP measurements from the 2 stages of sleep. Although SDB in childhood occurs mainly during REM sleep,\textsuperscript{33} exclusion of BP data collected during non-REM sleep is another limitation of this meta-analysis.

**PATHOPHYSIOLOGIC MECHANISMS AND CLINICAL IMPLICATIONS**

Speculations have been made regarding the potential pathophysiologic mechanisms responsible for BP elevation related to SDB and regarding the clinical significance of high BP. Hypoxia and microarousals due to intermittent upper airway obstruction during sleep most likely lead to sympathetic nervous system activation and elevated BP.\textsuperscript{42,43} Accumulating evidence suggests that similar to adults,\textsuperscript{44} obstructive SDB in children is associated with abnormalities that may predispose them to future cardiovascular morbidity. Except for changes in cardiac structure and function,\textsuperscript{3,14} several studies indicate that SDB in childhood is correlated with reduced arterial distensibility,\textsuperscript{18} chronic inflammation,\textsuperscript{6,45,46} and metabolic disturbances.\textsuperscript{37}

**CONCLUSIONS**

According to results of the present meta-analysis, no evidence exists of elevated BP, especially systolic BP, in children with the most severe disturbance of respiration during sleep. However, the conclusions so far are based on relatively small numbers of cases recruited in a few studies, and for this reason any inferences must be done cautiously. The published reports are heterogeneous in terms of methods and participants’ inclusion criteria. In conclusion, the potential relationship between BP and SDB still remains an unresolved issue. Large, rigorous, population-based studies that will assess the risk of elevated BP in groups of children with progressively increasing severity of SDB measured by polysomnography are urgently needed. A consensus on nomenclature describing the severity of obstructive SDB by scientific societies with an interest in pediatric sleep medicine will greatly facilitate this task.
REFERENCES


