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Longitudinal Cardiovascular Outcomes of Sleep Disordered Breathing in Children: A Meta-Analysis and Systematic Review

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Objectives: The presence of sleep disordered breathing (SDB) is known to impact long-term cardiovascular morbidity in adults; however, the long-term effects in children are poorly understood. We aimed to systematically review and synthesize studies published to date on the long-term effects of SDB in children.

Study Design: Meta-analysis and systematic review using PubMed, CINAHL, Embase, and Scopus (all indexed years).

Methods: We searched for English-language articles containing original human data from prospective studies, with ≥7 participants, in children ≤18 years of age. Data regarding study design, demographics, clinical characteristics, outcomes, level of evidence, and risk of bias were obtained. Articles were independently reviewed by three investigators. Retrospective and cross-sectional studies were excluded.

Results: Of 1701 identified abstracts, 25 articles (combined n = 1418) were ultimately included. All studies reported longitudinal outcomes following treatment of SDB; 21 studies exclusively reporting outcomes after adenotonsillectomy. Therefore, studies were combined to objectively assess the effect of SDB treatment on cardiovascular outcomes. Although all cardiovascular parameters were within the normal range at baseline, at follow-up there was a significant decrease in mean pulmonary artery pressure, right ventricular end diastolic diameter, heart rate, mitral E/A ratio, and C-reactive protein. There was no significant change in interventricular septum thickness, left ventricular parameters (shortening fraction, systolic and end diastolic diameters, ejection fraction, posterior wall thickness, isovolumetric relaxation time), left atrial diameter, and aortic and pulmonary valve peak velocities.

Conclusions: Studies assessing the long-term cardiovascular effects of SDB in children are limited. The available literature indicates effects on autonomic function, right, and left heart function following treatment for SDB. However, well-designed, large-scale, prospective cohort studies (using standardized outcomes) are needed to better understand the relationship of cardiovascular morbidity in the context of pediatric SDB.

Keywords: sleep disordered breathing, obstructive sleep apnea, cardiovascular outcomes, children.

INTRODUCTION

The estimated prevalence of pediatric obstructive sleep apnea (OSA) is 1% to 5% with peak prevalence occurring between 2 and 8 years of age. This disease can result in significant morbidity to multiple organ systems.1 The effect of OSA on the cardiovascular system has been well characterized in adult longitudinal cohort studies such as the Sleep Heart Health Study2; however, pediatric studies are limited.3 In addition, many children are treated for OSA based upon the presence of sleep disordered breathing (SDB) symptoms, without formal diagnosis of OSA. While single-center, cross-sectional studies assessing the effect of SDB presence and treatment on cardiovascular outcomes exist, longitudinal studies are few. Currently available systematic reviews are limited by the number of outcomes reported or qualitative nature.4,5 One meta-analysis of cohort studies on echocardiographic findings in pediatric OSA.6 One limitation of this study is the sole inclusion of echocardiographic markers of cardiovascular disease, report of only four outcomes, and meta-analysis comparing OSA to controls without comparisons of outcomes before and after treatment for OSA. Therefore, our aim was to systematically review the literature regarding the long-term effects of SDB on cardiovascular outcomes in children and perform a meta-analysis of previously reported cardiovascular outcomes in the context of pediatric SDB.

MATERIALS AND METHODS

Study Selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations to perform this review (Figure 1). Studies were included if they evaluated changes in cardiovascular parameters at 2 or more time points, were prospective, contained an abstract, involved only patients ≤18 years, were published in English and included ≥7 subjects. We excluded review articles, animal studies, and articles without original data. For the meta-analysis section, we excluded studies with longitudinal outcomes measured <1 month or >1 year from the reported baseline. Studies documenting OSA or SDB were combined, given the limited number of studies assessing cardiovascular outcomes using echocardiography in children with polysomnogram confirmed OSA. Practice guidelines and review articles were reviewed to identify additional studies. This study was exempt from evaluation by the institutional review board.

Types of Outcome Measures

Our primary outcomes of interest were cardiovascular abnormalities measured by echocardiography or another validated test (electrocardiography, photoplethysmography, ultrasound)...
and serum biomarkers of endothelial function. Outcomes were organized in the following categories according to the function that was measured: autonomic dysfunction, endothelial function, right heart morphology and function, and left heart morphology and function.

**Data Sources and Study Selection**
With the help of a medical librarian, we searched PubMed, CINAHL, Embase, and Scopus on September 23, 2015, to identify relevant studies using combined key terms and exploded Medical Subject Headings (MeSH; Table 1).

Three investigators (R.S.A., S.L.I., and Z.E.) independently reviewed all identified titles, abstracts, and full-text articles. Disagreements were discussed and resolved by consensus. Outcomes were included in the meta-analysis if there were 2 or more studies, and the heterogeneity statistic ($\chi^2$) had a $p$ value $> .05$. For studies with incomplete results information, we contacted authors via e-mail for additional data (2 of 12 responded).
We calculated the mean differences (MD) and the 95% confidence intervals (CIs) and presented the results in forest plots. Outcomes reported by OSA severity were combined; weighted mean and pooled standardization were used for meta-analyses.

Statistical Analysis and Effect Size Calculation
We used the DerSimonian and Laird random effects model to calculate the summary post- and pre-intervention differences for SDB subjects who underwent adenotonsillectomy (T&A). Outcomes reported by OSA severity were combined; weighted mean and pooled standardization were used for meta-analyses. We calculated the mean differences (MD) and the 95% confidence intervals (CIs) and presented the results in forest plots.

Test for overall effects were based on z-statistics and associated p values.

A heterogeneity test was performed by using the $\chi^2$ and $F$ statistics. We classified heterogeneity based on the following $F$ threshold values: 0–40%: no significant heterogeneity; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; and 75–100%: considerable heterogeneity. For the meta-analysis was not performed. All statistical analyses were conducted using the “metafor” package in R version 3.2.3 (R Core Team, Vienna, Austria).

RESULTS
Of the 1701 abstracts initially identified, 25 were included in the final review ($n = 1418$). The mean Newcastle Ottawa score was 3.2.3 (R Core Team, Vienna, Austria).

### Table 1—Search methodology for systematic review and meta-analysis of the long-term cardiovascular outcomes of SDB in children.

<table>
<thead>
<tr>
<th>Database</th>
<th>MeSH terms</th>
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<tbody>
<tr>
<td>PubMed</td>
<td>(&quot;Blood Vessels&quot;[mesh]) OR &quot;Hypotension&quot;[mesh]) OR &quot;pulse&quot;[mesh]) OR &quot;Coronary Artery Disease&quot;[mesh]) OR &quot;Arrhythmias, Cardiac&quot;[mesh]) OR &quot;Stroke&quot;[mesh]) OR &quot;Hemodynamics&quot;[mesh]) OR &quot;Electrocardiography&quot;[mesh]) OR &quot;Atrial Function&quot;[mesh]) OR &quot;Heart Failure&quot;[mesh]) OR &quot;Nitric Oxide&quot;[mesh]) OR &quot;Hypertension, Pulmonary&quot;[mesh]) OR (&quot;Baroreflex&quot;[mesh]) OR (&quot;Pressoreceptors&quot;[mesh]) OR Baroreceptor) OR &quot;Chemoreceptor Cells&quot;[mesh]) OR &quot;Natriuretic Peptides&quot;[mesh]) OR &quot;Cardiac Output&quot;[mesh]) OR &quot;Heart Rate&quot;[mesh]) OR &quot;Echocardiography&quot;[mesh]) OR ((&quot;Ventricular Dysfunction&quot;[mesh]) OR &quot;Ventricular Dysfunction, Right&quot;[mesh]) OR &quot;Ventricular Dysfunction, Left&quot;[mesh]) OR &quot;Endothelium&quot;[mesh]) OR &quot;Atherosclerosis&quot;[mesh]) OR (&quot;Autonomic Nervous System Disease&quot;[mesh]) OR &quot;Autonomic Nervous System&quot;[mesh]) OR &quot;Blood Pressure&quot;[mesh]) OR &quot;Cardiovascular System&quot;[mesh]) AND &quot;Sleep Apnea Syndromes&quot;[mesh]) AND (((&quot;Child&quot;[mesh]) OR &quot;Adolescent&quot;[mesh]) OR &quot;Long-term&quot;[mesh]) OR &quot;Long-term&quot;[All Fields] OR &quot;long term&quot;[All Fields] OR &quot;Epidemiologic Study Characteristics as Topic&quot;[mesh] OR &quot;Clinical Trial&quot;[Publication Type]) NOT &quot;Cross-Sectional Studies&quot;[mesh]</td>
</tr>
<tr>
<td>CINAHL</td>
<td>(MH &quot;Blood Vessels&quot;) OR (MH &quot;Hypertension&quot;) OR (MH &quot;Pulse&quot;) OR (MH &quot;Coronary Arteriosclerosis&quot;) OR (MH &quot;Arrhythmias&quot;) OR (MH &quot;Stroke&quot;) OR (MH &quot;Hemodynamics&quot;) OR (MH &quot;Electrocardiography&quot;) OR (MH &quot;Heart Failure&quot;) OR (MH &quot;Nitric Oxide&quot;) OR (MH &quot;Hypertension, Pulmonary&quot;) OR (MH &quot;Baroreflex&quot;) OR (MH &quot;Chemoreceptor Cells&quot;) OR (MH &quot;Natriuretic Peptides&quot;) OR (MH &quot;Cardiac Output&quot;) OR (MH &quot;Heart Rate&quot;) OR (MH &quot;Echocardiography&quot;) OR (MH &quot;Ventricular Dysfunction&quot;) OR (MH &quot;Ventricular Dysfunction, Right&quot;) OR (MH &quot;Ventricular Dysfunction, Left&quot;) OR (MH &quot;Endothelium&quot;) OR (MH &quot;Atherosclerosis&quot;) OR (MH &quot;Autonomic Nervous System&quot;) OR (MH &quot;Autonomic Nervous System Diseases&quot;) OR (MH &quot;Blood Pressure&quot;) OR (MH &quot;Cardiovascular System&quot;) OR (MH &quot;Prospective Studies&quot;) OR (MH &quot;Nonexperimental Studies&quot;) OR (MH &quot;Case Control Studies&quot;) OR (MH &quot;Correlational Studies&quot;) OR (MH &quot;Double-Blind Studies&quot;) OR (MH &quot;Panel Studies&quot;) OR (MH &quot;Pseudolongitudinal Studies&quot;) OR (MH &quot;Triple-Blind Studies&quot;) OR (MH &quot;Single-Blind Studies&quot;) OR (MH &quot;Experimental Studies&quot;) NOT (MH &quot;Cross-Sectional Studies&quot;)</td>
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<tr>
<td>EMBASE</td>
<td>&quot;blood vessel&quot;/exp OR &quot;hypotension&quot;/exp OR &quot;pulse rate&quot;/exp OR &quot;coronary artery disease&quot;/exp OR &quot;heart arrhythmia&quot;/exp OR &quot;cerebrovascular accident&quot;/exp OR &quot;hemodynamics&quot;/exp OR &quot;electrocardiography&quot;/exp OR &quot;heart atium function&quot;/exp OR &quot;heart failure&quot;/exp OR &quot;nitric oxide&quot;/exp OR &quot;pulmonary hypertension&quot;/exp OR &quot;pressor receptor reflex&quot;/exp OR &quot;chemoreceptor&quot;/exp OR &quot;natriuretic factor&quot;/exp OR &quot;heart output&quot;/exp OR &quot;heart rate&quot;/exp OR &quot;echocardiography&quot;/exp OR &quot;heart ventricle function&quot;/exp OR &quot;heart left ventricle function&quot;/exp OR &quot;heart right ventricle function&quot;/exp OR &quot;heart ventricle remodeling&quot;/exp OR &quot;hypertension&quot;/exp OR &quot;endothelium&quot;/exp OR &quot;atherosclerosis&quot;/exp OR &quot;autonomic neuropathy&quot;/exp OR &quot;autonomic nervous system&quot;/exp OR &quot;blood pressure&quot;/exp OR &quot;cardiovascular system&quot;/exp</td>
</tr>
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</table>
| Scopus    | ( TITLE-ABS-KEY ( sleep apnea ) AND TITLE-ABS-KEY ( child or adolescent ) AND TITLE-ABS-KEY ( "Blood Vessels" OR "Hypertension" OR "pulse" OR "Coronary Artery Disease" OR "Cardiac Arrhythmias" OR "Stroke" OR "Hemodynamics" OR "Electrocardiography" OR "Atrial Function" OR "Heart Failure" OR "Nitric Oxide" OR "Pulmonary Hypertension" OR "Baroreflex" OR "Pressoreceptors" OR Baroreceptor OR "Chemoreceptor Cells" OR "Natriuretic Peptides" OR "Cardiac Output" OR "Heart Rate" OR "Echocardiography" OR "Ventricular Dysfunction" OR "Ventricular Remodeling" OR "Hypertension" OR "Endothelium" OR "Atherosclerosis" OR "Autonomic Nervous System Disease" OR "Blood Pressure" OR "Cardiovascular System" ) ) ) AND ( "long term" OR "long-term" OR longitudinal OR prospective OR "follow up" OR "follow-up" OR "clinical trial" OR "randomized controlled trial" ) AND ( LIMIT-TO ( LANGUAGE , "English" ) )
8/9. All studies included adenotonsillectomy as an intervention, 21 exclusively. Of note, in four studies, a small proportion of each cohort was treated with medical management (CPAP, nasal steroids). 15-17 Details of the included studies are reported in Table 2. Key outcome measures that were consistent between studies are depicted in S-Tables 3a-d. A description of the cardiovascular outcomes reported in this review are provided in the Online Supplement. The mean ages ranged from 5 to 13 years for the SDB and control groups (those who did not undergo intervention). Sixteen studies used polysomnography to diagnose OSA, whereas nine diagnosed SDB clinically. The effect of SDB treatment on cardiovascular outcomes are meta-analyzed and reported subsequently. We also performed a meta-analysis of studies comparing SDB cases versus non-diseased controls. The results are depicted in the Online Supplement (S-Figure 1–8).

### Autonomic Dysfunction
Two studies assessed blood pressure in SDB children. 15,18 A significant decrease in sleep diastolic BP at 6 months 18 and asleep SBP and DBP at 4 years after T& A were reported. Changes in ambulatory BP parameters were not observed. Meta-analysis was not performed.

Three studies assessed awake heart rate (HR). 15,19,20 For the two studies included in the meta-analysis, there was a significant decrease in HR at follow-up (Figure 2; [MD −2.97; CI95% −5.18 to −0.77]). There was also a significant increase in RR interval (n = 3 studies 18,21,22; Figure 3; [MD 0.03; CI95% 0.00, 0.06]). Additionally, there were significant improvements in overnight baroreflex sensitivity, 18 BP variability, 15,18 asleep HR and HR variability, 18 and systolic and diastolic BP indices (in those with resolved SDB)23 after treatment.

### Endothelial Function
One study assessed endothelium-dependent, flow-mediated dilation (FMD) using ultrasound of the brachial artery; it reported a significant increase in FMD after AT in the surgical intervention group and no significant change after treatment with nasal steroids in the nonsurgical group. 24 One study used a modified hyperemic test after cuff-induced occlusion of the brachial artery, reporting a significant improvement in response after treatment with AT. 25 After AT, there was a significant decrease in endothelin-1, soluble CD40 ligand, NT-proBNP,27 and morning brain natriuretic peptide level, 28 an increase in circulating adropin concentration (in OSA children with endothelial dysfunction)29 and no significant change (Figure 8; [MD 1.90; CI95% −0.31 to 4.12]). In reviewing unique outcomes across studies, there were significant increases in RV ejection time, 42 time to peak velocity of pulmonary artery flow (TPV), 19 velocity–time integral of tricuspid flow (VTIt), and velocity–time integral of pulmonary flow (VTIta) 30 and a significant decrease in right ventricular isovolumetric relaxation time (IVRT) 15 and tricuspid regurgitation (TR). 15 There was no significant change in tricuspid full diastolic filling time, 33 tricuspid annular point systolic excursion, 44 RV isovolumetric contraction time (IVCt), 41 and tricuspid E/E´ (ratio of early tricuspid inflow to annular diastolic velocity). 12

### Left Heart Morphology and Function
Three studies assessed LV diastolic function (mitral E/A ratio). 17,34,35 After removing sources of heterogeneity, 35 there was no significant change in mitral E/A ratio at follow-up (Figure 9; [MD 0.09; CI95% −0.22 to 0.40]). The two studies reporting mitral Em/Am ratio showed a significant increase (Figure 10; [MD 0.73; CI95% 0.63 to 0.84]). 35,35 Five studies assessed left ventricle shortening fraction (FS). 19,34,35,40,42 There was no significant change in FS (Figure 11; [MD −0.15; CI95% −0.25 to 0.16]). The four studies reporting left ventricular end-systolic and end-diastolic diameter (LVSd and LVDD) showed no significant change in either LVSD (Figure 12; [MD 0.01; CI95% −0.08 to 0.09]) 34,35,40,42 or LVDD (Figure 13; [MD −0.06; CI95% 0.15 to 0.04]) 35,35,41,42 with treatment. Two studies reported left ventricle myocardial performance index (LVMPi) 41,42; both reported a significant decrease in LVMPi at follow-up. Meta-analysis was not performed.

Three studies assessing left atrial diameter (LA) showed no significant change (Figure 14; [MD 0.03; CI95% −0.06 to 0.12]). 34,40,42 Analysis of two studies showed no significant change in either LV ejection fraction (Figure 15; [MD −0.26; CI95% −3.02 to 2.50]) or aortic valve peak velocity (Figure 16; [MD 1.70, CI95% 1.66 to 5.06]). 34,35 The two studies assessing left ventricle posterior wall thickness (LVp) also showed no significant change (Figure 17; [MD −0.21, CI95% −0.56 to 0.14]). 35,40 Three studies reported left ventricular...
Table 2—Summary of included studies in the systematic review and meta-analysis summarizing the cardiovascular outcomes following treatment of SDB in children.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design/ evidence level</th>
<th>No.</th>
<th>Age, years</th>
<th>Inclusion</th>
<th>PSG</th>
<th>Intervention</th>
<th>Interval pre/post</th>
<th>Outcome</th>
<th>Results</th>
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<tbody>
<tr>
<td>Abd El-Moneim et al.</td>
<td>2009</td>
<td>Prospective cohort (II)</td>
<td>30 cases</td>
<td>5 (2.5, 12)</td>
<td>SDB with AH</td>
<td>No</td>
<td>A</td>
<td>36 (30-52) days</td>
<td>Tricuspid E/A ratio</td>
<td>No control group</td>
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<td>TPV</td>
<td>↑</td>
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<tr>
<td>Amin et al.</td>
<td>2005</td>
<td>Prospective case control (III)</td>
<td>9 cases/ 9 controls</td>
<td>12.3 (3.9)</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT+</td>
<td>12 months</td>
<td>Mitrail E/A ratio</td>
<td>SDB &lt; controls</td>
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<td>Apostolidou et al.</td>
<td>2008</td>
<td>Prospective case control (III)</td>
<td>58 cases/ 17 controls</td>
<td>6.4 (3.3)</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT</td>
<td>5.8 ± 2.9 months</td>
<td>CRP</td>
<td>pre AT= controls</td>
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<td>Systolic BP Index</td>
<td>pre AT= controls</td>
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<td>Diastolic BP index</td>
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<td>Attia et al.</td>
<td>2010</td>
<td>Prospective case control (III)</td>
<td>42 cases/ 45 controls</td>
<td>5 (3.14)</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT</td>
<td>6.4 ± 0.56 months</td>
<td>RVDd</td>
<td>pre AT&gt; controls, post= controls</td>
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<td>Tricuspid E/A ratio</td>
<td>pre AT &lt; controls (mod-severe OSA), post= controls</td>
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<td>LVMI (gm/m2)</td>
<td>pre AT=controls, post= controls</td>
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<td>Year</td>
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<td>Results</td>
<td>SDB vs. controls</td>
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<tr>
<td>Baumert et al.</td>
<td>2011</td>
<td>Prospective case control (III)</td>
<td>40 cases/ 40 controls</td>
<td>7.5 (2.7)</td>
<td>ATH with OSA</td>
<td>Yes AT</td>
<td>6 mo (29.2 + 5.9 wks)</td>
<td>RR interval ‡</td>
<td>Pre AT≈ controls, post AT≈ controls</td>
<td>↑</td>
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<tr>
<td>Chan et al.</td>
<td>2015</td>
<td>Prospective case control (III)</td>
<td>63 cases/ 63 controls</td>
<td>10.3 (2.9)</td>
<td>ATH with OSA</td>
<td>Yes AT⁺</td>
<td>6 months</td>
<td>FMD of brachial artery</td>
<td>Pre AT≈ controls, post AT≈ controls</td>
<td>↑</td>
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<tr>
<td>Cincin et al.</td>
<td>2014</td>
<td>Prospective case control (III)</td>
<td>30 cases/ 30 controls</td>
<td>7.86 (3.83)</td>
<td>SDB with ATH</td>
<td>No AT</td>
<td>6 months</td>
<td>mPAP</td>
<td>pre AT≈ controls</td>
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**Table 2—Continued**
### Table 2—Continued

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<th>Author</th>
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<th>PSG</th>
<th>Intervention</th>
<th>Interval pre/post</th>
<th>Outcome</th>
<th>Results</th>
<th>SDB vs. controls</th>
<th>SDB at follow-up</th>
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<td>Crisalli et al.</td>
<td>2012</td>
<td>Prospective case control (III)</td>
<td>133 cases/ 61 controls</td>
<td>9.4 (2.2)</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT</td>
<td>6 weeks and 6 months</td>
<td>Awake SBP</td>
<td>pre AT = controls</td>
<td>≈</td>
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<td>Awake DBP</td>
<td>pre AT = controls</td>
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<td>Asleep SBP</td>
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<td>Asleep DBP</td>
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<td>BRS</td>
<td>severe OSA &lt; controls</td>
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<td>BPV</td>
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<td>Goldbart et al.</td>
<td>2010</td>
<td>Prospective case control (III)</td>
<td>90 cases</td>
<td>19 (7) months</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT</td>
<td>3 months</td>
<td>CRP</td>
<td>Not reported</td>
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<td>NT-proBNP</td>
<td>pre AT &gt; controls</td>
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<td>Gorur et al.</td>
<td>2001</td>
<td>Prospective case control (III)</td>
<td>33 cases/ 33 controls</td>
<td>6.3 (2.1)</td>
<td>SDB with ATH</td>
<td>No</td>
<td>AT</td>
<td>6 months</td>
<td>RV/IVCT</td>
<td>pre AT = controls</td>
<td>≈</td>
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<td>LVSd</td>
<td>pre AT = controls, post AT = controls</td>
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<td>LVDd</td>
<td>pre AT &gt; controls, post AT = controls</td>
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<td>IVS</td>
<td>pre AT &gt; controls, post AT = controls</td>
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<td></td>
<td>FS</td>
<td>pre AT = controls, post AT = controls</td>
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<td>Author</td>
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<td>No.</td>
<td>Age, years</td>
<td>Inclusion</td>
<td>PSG</td>
<td>Intervention</td>
<td>Interval pre/post</td>
<td>Outcome</td>
<td>Results</td>
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<tr>
<td>Gozal et al.</td>
<td>2007</td>
<td>Prospective case control (III)</td>
<td>26 cases/ 8 controls</td>
<td>6.9 (0.6)</td>
<td>OSA with ATH</td>
<td>Yes</td>
<td>AT</td>
<td>4-6 months</td>
<td>LA</td>
<td>pre AT = controls, post AT = controls</td>
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<td>Gozal et al.</td>
<td>2013</td>
<td>Prospective case control (III)</td>
<td>35 cases/ 35 controls</td>
<td>7.2 (1.4)</td>
<td>OSA with ATH</td>
<td>Yes</td>
<td>AT</td>
<td>Not reported</td>
<td>LV IVRT</td>
<td>pre AT = controls, post AT = controls</td>
<td></td>
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<tr>
<td>Kaditis et al.</td>
<td>2011</td>
<td>Prospective cohort (II)</td>
<td>21 cases</td>
<td>7.1 (2.8)</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT</td>
<td>4.2±1.2 months</td>
<td>DT</td>
<td>pre AT &gt; controls, post AT = controls</td>
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<tr>
<td>Kheirandish-Gozal et al.</td>
<td>2006</td>
<td>Prospective cohort (II)</td>
<td>20 cases</td>
<td>7.3 ± 1.9</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT</td>
<td>10-14 weeks</td>
<td>VE</td>
<td>pre AT = controls, post AT = controls</td>
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<tr>
<td>Martha et al.</td>
<td>2013</td>
<td>Case-Control prospective (III)</td>
<td>33 cases/ 10 controls</td>
<td>6.7</td>
<td>SDB with ATH</td>
<td>No</td>
<td>AT</td>
<td>2-24 wks post op</td>
<td>LVPW</td>
<td>pre AT = controls, post AT = controls</td>
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<tr>
<td>Moghaddam et al.</td>
<td>2011</td>
<td>Prospective case control (III)</td>
<td>55 cases/ 55 controls</td>
<td>3 to 11</td>
<td>SDB with ATH</td>
<td>No</td>
<td>AT</td>
<td>6 months</td>
<td>VA</td>
<td>pre AT = controls, post AT = controls</td>
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<tr>
<td>Naiboglu et al.</td>
<td>2008</td>
<td>Prospective case control (III)</td>
<td>39 cases/ 20 controls</td>
<td>5.7 (1.9)</td>
<td>SDB with ATH</td>
<td>No</td>
<td>AT</td>
<td>6 months</td>
<td>LogBNP</td>
<td>↑</td>
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<tr>
<td>Pac et al.</td>
<td>2005</td>
<td>Prospective case control (III)</td>
<td>28 cases/ 35 controls</td>
<td>7.3 (2.9)</td>
<td>SDB with ATH</td>
<td>No</td>
<td>AT</td>
<td>1 month</td>
<td>Mitral E/A ratio</td>
<td>↑ (PH group only)</td>
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Table 2—Continued
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<th>Author</th>
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<th>Age, years</th>
<th>Inclusion</th>
<th>PSG</th>
<th>Intervention</th>
<th>Interval pre/post</th>
<th>Outcome</th>
<th>Results</th>
<th>SDB vs. controls</th>
<th>SDB at follow-up</th>
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<tbody>
<tr>
<td>Quante et al.</td>
<td>2015</td>
<td>Prospective RCT (III)</td>
<td>202</td>
<td>7 (4)</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT</td>
<td>7 months</td>
<td>Awake HR</td>
<td>No control group</td>
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<td>Talipinar et al.</td>
<td>2011</td>
<td>Prospective cohort (II)</td>
<td>37</td>
<td>6.8 (2.9)</td>
<td>ATH with SDB</td>
<td>No</td>
<td>AT/A/T</td>
<td>3-4 months</td>
<td>Endothelin-1</td>
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<td>Ugur et al.</td>
<td>2008</td>
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<td>29 cases/ 26 controls</td>
<td>6.7 (2.4)</td>
<td>ATH with OSA</td>
<td>Yes</td>
<td>AT/T</td>
<td>6 months</td>
<td>Mitral Em/Am ratio</td>
<td>pre AT&gt; control, post AT= control</td>
<td>↑</td>
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<tr>
<th>Author</th>
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<th>No.</th>
<th>Age, years</th>
<th>Inclusion</th>
<th>PSG</th>
<th>Intervention</th>
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<tr>
<td>Vlahandonis et al.</td>
<td>2013</td>
<td>Prospective case control (III)</td>
<td>40 cases/20 controls</td>
<td>12.9 (0.3)</td>
<td>SDB</td>
<td>Yes</td>
<td>AT/T*</td>
<td>4 years</td>
<td>Awake DBP</td>
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<td>Vlahandonis et al.</td>
<td>2014</td>
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<td>40 cases/20 controls</td>
<td>12.9 (0.3)</td>
<td>SDB</td>
<td>Yes</td>
<td>AT/T*</td>
<td>4 years</td>
<td>BRS</td>
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<td>Vlahandonis et al.</td>
<td>2014</td>
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<td>AT/T*</td>
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<td>Yilmaz et al.</td>
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<td>52 cases/33 controls</td>
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<td>SDB with ATH</td>
<td>No</td>
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<td>mPAP</td>
<td>pre AT reversal</td>
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↑ or ↓ indicates significant increase or decrease respectively. ≈ no significant difference. t**:detailed data obtained from author.

Abbreviations: ATH, adenotonsillar hypertrophy; AT, adenotonsillectomy; Aov Vel, aortic valve peak velocity; BNP, brain natriuretic peptide; cICAM-1, circulating intercellular adhesion molecule-1; CRP, C reactive protein; DBP, Diastolic blood pressure; E/A ratio, early to atrial filling velocity ratio; EF, ejection fraction; Em/Am ratio, ratio of peak early to late diastolic filling velocity; FMD, flow-mediated dilation of the brachial artery; FS, LV Shortening fraction; HR, heart rate; IVS, interventricular septum thickness; LVDd, Left ventricular end diastolic diameter; LVsd, LV end systolic diameter; LA, left atrial diameter; LV MPI, LV myocardial performance index; LVPW, left ventricle posterior wall thickness; LV IVRT, LV Isovolumetric relaxation time; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone brain natriuretic peptide; PASP, Pulmonary artery systolic pressure; PulvVel, pulmonary valve peak velocity; RVDd, Right ventricular end-diastolic diameter; RV MPI, RV myocardial performance index; SBP, Systolic blood pressure; SDB, sleep disordered breathing; T, tonsillotomy.

*Subjects received medical or surgical treatment.
**Figure 2**—Meta-analysis of studies on awake heart rate data comparing before (pre) versus after (post) intervention.

**Figure 3**—Meta-analysis of studies on RR interval data comparing before (pre) versus after (post) intervention.

**Figure 4**—Meta-analysis of studies on Tricuspid E/A ratio data comparing before (pre) versus after (post) intervention.

**Figure 5**—Meta-analysis of studies on mean pulmonary artery pressure (mPAP) data comparing before (pre) versus after (post) intervention.

**Figure 6**—Meta-analysis of studies on interventricular septum thickness (IVS) data comparing before (pre) versus after (post) intervention.

**Figure 7**—Meta-analysis of studies on right ventricular end diastolic diameter (RVDD) data comparing before (pre) versus after (post) intervention.

**Figure 8**—Meta-analysis of studies on pulmonary valve peak velocity comparing before (pre) versus after (post) intervention.

**Figure 9**—Meta-analysis of studies on mitral E/A ratio data comparing before (pre) versus after (post) intervention.
**Figure 10**—Meta-analysis of studies on mitral Em/Am ratio data comparing before (pre) versus after (post) intervention.

**Figure 11**—Meta-analysis of studies on shortening fraction (FS) data comparing before (pre) versus after (post) intervention.

**Figure 12**—Meta-analysis of studies on left ventricle end systolic diameter (LVSD) data comparing before (pre) versus after (post) intervention.

**Figure 13**—Meta-analysis of studies on left ventricle end diastolic diameter (LVDD) data comparing before (pre) versus after (post) intervention.

**Figure 14**—Meta-analysis of studies on left atrial dimension (LA) data comparing before (pre) versus after (post) intervention.

**Figure 15**—Meta-analysis of studies on left ventricle ejection fraction (EF) data comparing before (pre) versus after (post) intervention.

**Figure 16**—Meta-analysis of studies on aortic valve peak velocity (Aov) data comparing before (pre) versus after (post) intervention.

**Figure 17**—Meta-analysis of studies on left ventricle posterior wall thickness (LVPW) data comparing before (pre) versus after (post) intervention.
isovolumetric relaxation time (LV IVRT). After removing the source of heterogeneity, there was no significant change at follow-up (Figure 18; [MD 3.50, CI (−2.16 to 9.16)]. One study showed a decrease in LV mass (indexed to BSA), while another reported no significant change in LV mass (indexed to height). One study reported a significant decrease in LV ET. Changes in mitral E/E', deceleration time, LV peak filling velocity, LA contraction velocity, and LV IVCT were not observed with treatment in individual studies.

**DISCUSSION**

In this systematic review and meta-analysis, we evaluated the longitudinal cardiovascular changes reported for children with SDB/OSA. All included studies reported outcomes before and after treatment (primarily with T&A). Differences in outcomes in SDB/OSA children compared to controls at baseline were also ascertained and depicted in the supplement. Overall, we found that a number of measures improved after treatment, but the mean values both before and after treatment were typically within the normal range. After treatment (most commonly with T&A), these children had significant decreases in mPAP, RV Dd, awake HR, RV Dd, and C-reactive protein and significant increases in RR interval and mitral Em/Am ratio. These outcome parameters are markers for pulmonary hypertension (mPAP), LV diastolic function (mitral E/A), RV dysfunction (RV Dd), baroreflex function (RR interval and awake HR), and endothelial dysfunction (C-reactive protein). Although the synthesis of results is not definitively convincing for significant cardiovascular strain at baseline, the change following treatment may suggest that early signs of cardiovascular dysfunction may be present in these children. There is concern that childhood disruptions in the cardiovascular system may result in lifelong cardiovascular morbidity, although further work is necessary to better understand this relationship. It is important that we review currently available evidence carefully, as subtle (albeit non-significant) effects on cardiovascular parameters may be additive over time.

There is sufficient evidence to suggest that severe OSA in adults significantly increases the risk of cardiovascular disease, stroke, and all-cause mortality. Adults with SDB, regardless of severity, have a 2–3 time greater risk of developing hypertension at 4-year follow-up compared to controls. While the cardiovascular morbidity of OSA in children has been summarized previously, meta-analyses are limited by low level of evidence, as the majority of published studies are cross-sectional or retrospective, and available reviews are primarily qualitative in nature.

**Autonomic Dysfunction**

Obstructive events during sleep lead to increased sympathetic nervous system activation, which in turn may contribute to elevated BP. Pediatric cross-sectional studies show that primary snoring and SDB is associated with increased BP. Our results indicate that upon resolution of OSA, there was a significant decrease in nocturnal BP at 6-month and 4-year follow-up. Additionally, when evaluating the baseline characteristics of children included in this review, we found that when compared to controls, children with SDB had higher baseline nocturnal SBP and shorter RR interval (S-Figures 1–2). Carotid sinus and aortic arch stretch receptors modulate the baroreflex which is a feedback loop that regulates BP. Children with OSA have altered baroreceptor sensitivity (BRS) which improves with resolution of OSA. Although retrospective studies indicate HR variability is altered in children with SDB, prospective research is limited. The decrease in heart rate, improvements in overnight baroreflex sensitivity, BP variability, and heart rate variability, and systolic and diastolic blood pressure indices (in those with resolved SDB) at follow-up suggests an improvement in sympathetic imbalance after treatment of SDB.

**Endothelial Function**

OSA has also been linked to impaired endothelial function—a risk factor for atherosclerosis-related vascular disease. Moreover, treating OSA with CPAP has been shown to improve endothelial function. The majority of currently available pediatric evidence is cross-sectional in nature. When assessing endothelium-dependent FMD of the brachial artery, the gold standard in assessing endothelial function, OSA children have altered baroreceptor sensitivity (BRS) which improves with resolution of OSA. Although retrospective studies indicate HR variability is altered in children with SDB, prospective research is limited. The decrease in heart rate, improvements in overnight baroreflex sensitivity, BP variability, and heart rate variability, and systolic and diastolic blood pressure indices (in those with resolved SDB) at follow-up suggests an improvement in sympathetic imbalance after treatment of SDB.
C-reactive protein as a marker of inflammation in the context of metabolic consequences of OSA were not within the scope of this review. A comprehensive review of biomarkers related to OSA has been previously reported as well as a meta-analysis on the effects of T&A on C-reactive protein.

Right Heart Morphology and Function
Although the baseline values for mPAP and estimated pulmonary artery systolic pressure in the majority of studies were within normal range (<25 mm Hg) and the magnitude of changes after T&A were small, our results suggest that improvement may be seen shortly following intervention. Reducions in RVDd after intervention may indicate a decrease in RV dilation and improvement in RV reserve—although the magnitude of improvement reported was marginal. When compared to controls at baseline, we found that IVS thickness was significantly higher in SDB children (suggesting a potential effect on RV pressure overload), but no significant improvement was seen at follow-up. Although tricuspid E/A ratio did not change significantly at follow-up, it is difficult to determine whether the significant improvement in Em/Am ratio (albeit from a normal baseline) across individual studies represents normative changes over time or is suggestive of improvement in diastolic dysfunction after T&A. However, changes in RV ejection time, RV MPi, VTItv, VTItpa, TPV, RV ET, and RV IVRT observed in individual studies all suggest improvement in right heart morphology and function at follow-up. When evaluating the baseline characteristics of children included in this review, we found that when compared to controls, children with SDB had higher baseline mPAP, RVDd and IVS thickness, and lower tricuspid E/A ratio (S-Figures 3–6).

Left Heart Dynamics and Function
Cross-sectional studies suggest that SDB is associated with elevated BP in children and linked to higher left ventricular mass and left ventricular diastolic dysfunction. The E/A ratio is a measure of diastolic function. Although baseline values for mitral E/A ratios were normal (>1), there was a significant increase in Em/Am ratio with treatment without a significant change in E/A ratio. Since assessment of Em/Am using Tissue Doppler Imaging is a more sensitive marker of diastolic dysfunction compared to E/A ratio assessment using traditional echocardiography, these findings suggest that more sensitive tools may be needed to detect these subtle changes in children. Although cross-sectional data suggests LV hypertrophy in children with SDB, the two studies reporting LV mass at follow-up reported conflicting results. Uğur et al. reported no significant change at follow-up, while Attia et al. reported a significant decrease in LVMi (indexed to BSA) at follow-up. Although cohorts from both studies were of similar age and nonobese, indexing left ventricular mass to height may be more sensitive in detecting LVH. LVMPi is a sensitive diagnostic and prognostic indicator of both systolic and diastolic dysfunction; both studies reporting it showed a decrease with treatment as well as significant elevations at baseline when compared to controls. Changes in other markers of left sided dysfunction such as LVDd, LV EF, LA, LVPw LV IVRT, LVSd and FS were not observed. Among the studies reported in this review, we found that when compared to controls, SDB children had higher baseline LVMPi and lower mitral E/A ratio (S-Figures 7–8).

In summary, although the majority of cardiovascular parameters in children with SDB are within the normal range at baseline, treatment has significant impact on markers of cardiovascular strain such as mean pulmonary artery pressure, right ventricular end diastolic diameter, HR, and mitral Em/Am ratio. Since cardiovascular effects are additive over time, these results suggest that earlier diagnosis of SDB (and subsequent treatment) may prevent long-term cardiac morbidity. We did not find any significant changes in interventricular septum thickness, left ventricular parameters (shortening fraction, systolic and end diastolic diameters, ejection fraction, posterior wall thickness, isovolumetric relaxation time), left atrial diameter, and aortic and pulmonary valve peak velocities. Given the paucity of available data, it is difficult to conclude what cardiovascular parameters are most sensitive and relevant for this patient population. Certainly, more robust studies involving larger sample sizes may be more revealing. For example, in order to design a randomized controlled trial with equal numbers assigned to the treated and control group, one will need 72, 356, and 12 subjects in each group (total of 144, 712, and 24 subjects) to detect a significant postintervention difference in mPAP, RV Dd, and mitral Em/Am ratio, respectively, to achieve 80% power at significance level of 0.05. For a pre–post design in which subjects serve as their own control, samples of 38, 180, and 8 will achieve 80% power respectively for detecting significant pre- and post-treatment difference in mPAP, RV Dd, and mitral Em/Am ratio at a significance level of 0.05.

LIMITATIONS
Our study had several limitations. The literature regarding longitudinal changes in cardiovascular parameters is limited, and there is significant heterogeneity in diagnostic modalities and outcomes reported. Standards regarding reporting of echocardiogram parameters exist although have not been consistently used for research in this context. Some notable examples of this are the inconsistent use of z-scores and the different methods of indexing left ventricular mass by body size across studies. This hinders qualitative comparisons across studies. Moreover, only sixteen studies reported diagnosis of OSA based on polysomnography (the gold standard), while clinical symptoms and questionnaires were used to identify SDB in the remainder. Of the 16 studies documenting OSA with polysomnography, only 3 reported echocardiogram findings (1 study only reporting one outcome). Outcomes assessed across studies were not sufficient enough to separately consider these studies for quantitative analysis. Also, details regarding the severity of OSA, as well as improvement in polysomnogram parameters after treatment, were not consistently reported. Additionally, several demographic parameters such as gender, ethnicity, and obesity may have contributed to heterogeneity of outcomes (and potential confounding of results) and were not able to be controlled for in our analysis. Obesity is a known major risk factor for cardiovascular disease, and it is key that this be factored for when performing research studies pertaining to cardiovascular risk of SDB. In pediatrics, the variability in terminology and metrics...
used to define obesity (body mass index [BMI], BMI percentile, and BMI z-score) further complicates comparison across studies. Six studies did not report BMI data; three reported absolute BMI values; two reported BMI percentiles; six reported BMI z-scores; two specifically reported excluding children with BMI > 29; one reported excluding those with BMI z-score > 2.9; and one reported body surface area instead of BMI data. Despite these limitations, our review provides a comprehensive synthesis and evaluation of the available literature regarding longitudinal changes in cardiovascular parameters in children with OSA, reporting the largest collection of cardiac outcomes meta-analyzed to date.

CONCLUSION
Although cross-sectional studies in children show that SDB is associated with significant cardiovascular comorbidities, well-designed and long-term prospective studies are limited. The currently available literature indicates that SDB impacts sympathetic activity, right, and left heart function. Moreover, the treatment of SDB may result in a reduction in cardiovascular strain. Well-designed, large-scale, prospective cohort studies (using standardized outcomes) are needed to better understand the relationship of cardiovascular morbidity and SDB.

Gaps
1. There is limited information regarding the long-term impact of OSA on cardiovascular morbidity in children, and this literature is fraught with heterogeneity.
2. Studies prospectively assessing the effect of treatment (either medical or surgical) on cardiovascular parameters in children with obstructive sleep apnea are limited.
3. Information regarding appropriate outcome measures to assess cardiovascular morbidity associated with pediatric OSA is necessary.
4. Prospective studies, utilizing polysomnography for diagnosis, are needed to better understand the effects of complete vs. partial treatment of OSA on cardiovascular parameters in children.

REFERENCES


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SUPPLEMENTARY MATERIAL
Supplementary Material is available at SLEEP online.

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