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

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REVIEW

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 Em/Am 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.

Statement of Significance
Studies prospectively assessing the long-term effects of OSA including the effect of treatment (either medical or surgical) on cardiovascular parameters in children with obstructive sleep apnea are limited. Future prospective studies, utilizing polysomnography for diagnosis, are needed to better understand the effects of OSA on cardiovascular outcomes in 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 Study[2]; 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.[4–7] There is one meta-analysis of cohort studies on echocardiographic findings in pediatric OSA.[5] 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)

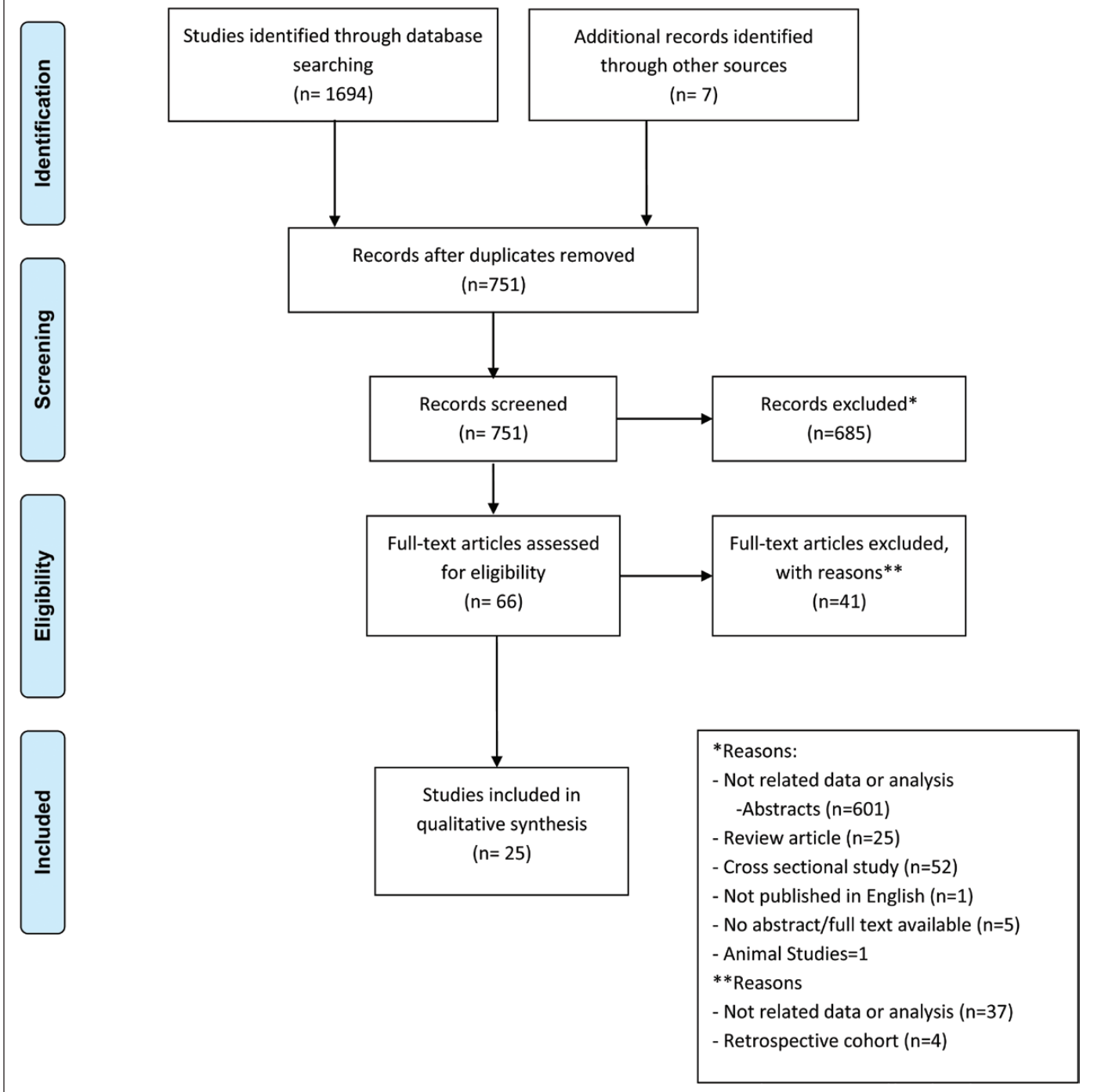

Figure 1—Flowchart for the identification of studies used in the systematic review and meta-analysis of the long-term cardiovascular outcomes of sleep disordered breathing (SDB) in children.

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 (χ^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).

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

Database	MeSH terms
PubMed	("Blood Vessels"[mesh]) OR "Hypotension"[mesh]) OR "pulse"[mesh]) OR "Coronary Artery Disease"[mesh]) OR "Arrhythmias, Cardiac"[mesh]) OR "Stroke"[mesh]) OR "Hemodynamics"[mesh]) OR "Electrocardiography"[mesh]) OR "Atrial Function"[mesh]) OR "Heart Failure"[mesh]) OR "Nitric Oxide"[mesh]) OR "Hypertension, Pulmonary"[mesh]) OR ((((("Baroreflex"[mesh]) OR (("Pressoreceptors"[mesh]) OR Baroreceptor))))) OR "Chemoreceptor Cells"[mesh]) OR "Natriuretic Peptides"[mesh]) OR "Cardiac Output"[Mesh]) OR "Heart Rate"[Mesh]) OR "Echocardiography"[Mesh]) OR ((("Ventricular Dysfunction"[Mesh] OR "Ventricular Dysfunction, Right"[Mesh] OR "Ventricular Dysfunction, Left"[Mesh])))) OR "Ventricular Remodeling"[Mesh]) OR "Hypertension"[Mesh]) OR "Endothelium"[Mesh]) OR "Atherosclerosis"[Mesh]) OR ((("Autonomic Nervous System Diseases"[Mesh]) OR "Autonomic Nervous System"[Mesh])) OR "Blood Pressure"[Mesh]) OR "Cardiovascular System"[Mesh])) AND "Sleep Apnea Syndromes"[Mesh])) AND ((("Child"[Mesh]) OR "Adolescent"[Mesh]))) AND english[Language])) AND ("Longitudinal Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Long-term"[All Fields] OR "long term"[All Fields] OR "Epidemiologic Study Characteristics as Topic"[Mesh] OR "Clinical Trial" [Publication Type]) NOT "Cross-Sectional Studies"[mesh]
CINAHL	(MH "Blood Vessels+") OR (MH "Hypotension+") OR (MH "Hypertension+") OR (MH "Pulse+") OR (MH "Coronary Arteriosclerosis") OR (MH "Arrhythmia+") OR (MH "Stroke+") OR (MH "Hemodynamics+") OR (MH "Electrocardiography+") OR (MH "Heart Failure+") OR (MH "Nitric Oxide") OR (MH "Hypertension, Pulmonary+") OR (MH "Baroreflex") OR (MH "Chemoreceptor Cells+") OR (MH "Natriuretic Peptides+") OR (MH "Cardiac Output+") OR (MH "Heart Rate+") OR (MH "Echocardiography+") OR (MH "Ventricular Dysfunction+") OR (MH "Ventricular Dysfunction, Right") OR (MH "Ventricular Dysfunction, Left+") OR (MH "Ventricular Remodeling") OR (MH "Endothelium") OR (MH "Atherosclerosis") OR (MH "Autonomic Nervous System+") OR (MH "Autonomic Nervous System Diseases+") OR (MH "Blood Pressure+") OR (MH "Cardiovascular System+") ((MH "Prospective Studies+") OR (MH "Nonexperimental Studies") OR (MH "Case Control Studies+") OR (MH "Correlational Studies") OR (MH "Double-Blind Studies") OR (MH "Panel Studies+") OR (MH "Pseudolongitudinal Studies") OR (MH "Triple-Blind Studies") OR (MH "Single-Blind Studies") OR (MH "Experimental Studies+")) NOT (MH "Cross Sectional Studies")
EMBASE	'blood vessel'/exp OR 'hypotension'/exp OR 'pulse rate'/exp OR 'coronary artery disease'/exp OR 'heart arrhythmia'/exp OR 'cerebrovascular accident'/exp OR 'hemodynamics'/exp OR 'electrocardiography'/exp OR 'heart atrium function'/exp OR 'heart failure'/exp OR 'nitric oxide'/exp OR 'pulmonary hypertension'/exp OR 'pressoreceptor reflex'/exp OR 'chemoreceptor'/exp OR 'natriuretic factor'/exp OR 'heart output'/exp OR 'heart rate'/exp OR 'echocardiography'/exp OR 'heart ventricle function'/exp OR 'heart left ventricle function'/exp OR 'heart right ventricle function'/exp OR 'heart ventricle remodeling'/exp OR 'hypertension'/exp OR 'endothelium'/exp OR 'atherosclerosis'/exp OR 'autonomic neuropathy'/exp OR 'autonomic nervous system'/exp OR 'blood pressure'/exp OR 'cardiovascular system'/exp
Scopus	((TITLE-ABS-KEY (sleep apnea) AND TITLE-ABS-KEY (child OR adolescent) AND TITLE-ABS-KEY ("Blood Vessels" OR "Hypotension" 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 Diseases" OR "Autonomic Nervous System" 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"))

Data Extraction and Quality Assessment

For each study, we recorded the author, year of publication, study design, inclusion criteria, intervention, length of follow-up, and outcome. The level of evidence was determined according to the Center for Evidence-Based Medicine guidelines.[8] Triplicate evaluation of the Newcastle-Ottawa Scale for assessment of quality of nonrandomized studies in meta-analysis[9] was used (S-Table 2a). The Cochrane Collaboration tool for risk of bias[10] was used to evaluate randomized controlled trials (S-Table 2b).

Statistical Analysis and Effect Size Calculation

We used the DerSimonian and Laird[11] 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 χ^2 and I^2 statistics.[12] We classified heterogeneity based on the following I^2 threshold values: 0–40%: no significant heterogeneity; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; and 75–100%: considerable heterogeneity. For the χ^2 statistic, a p value of $< .05$ was considered statistically significant heterogeneity. If there was a substantial heterogeneity, the sources of heterogeneity were explored by removing studies with low methodological quality. For studies with significant heterogeneity, 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).[13,14]

RESULTS

Of the 1701 abstracts initially identified, 25 were included in the final review (n = 1418). The mean Newcastle Ottawa score was

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 susequently. We also performed a meta-analysis of studies comparing SDB cases versus nondiseased 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 asleep DBP at 6 months[18] and asleep SBP and DBP at 4 years after T&A[15] 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;$CI_{95\%}$ −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;$CI_{95\%}$0.00, 0.06]). Additionally, there were significant improvements in overnight baroreflex sensitivity,[18] BP variability,[15,18] asleep HR and HR variability,[16] 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[26], soluble CD40 ligand,[25] 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 in cICAM-1[30]. Four studies assessed change in C-reactive protein.[27,30–32] After removing sources of heterogeneity,[30] there was significant decrease in C-reactive protein at follow-up (Figure 19; [MD −0.41;$CI_{95\%}$ −0.48 to −0.35]).

Right Heart Morphology and Function

Three studies assessed change in tricuspid E/A ratio (peak early filling to filling during atrial contraction).[19,33–35] After removing sources of heterogeneity,[19,33] there was no significant change in tricuspid E/A ratio at follow-up (Figure 4; [MD −0.02;$CI_{95\%}$ −0.08 to 0.04]. Two studies reported a significant increase in tricuspid Em/Am ratio (early to late diastolic myocardial velocity). Meta-analysis was not performed (p = .0006).[33,35] Six studies reported estimated mean pulmonary artery pressure (mPAP) using Mahan formula.[19,33,36–39] After removing sources of heterogeneity,[33,36,38] there was a significant decrease in mPAP (Figure 5; [MD −5.59;$CI_{95\%}$−7.19 to −3.99]). Two studies reported estimated pulmonary artery systolic pressure[33,35]; although neither reported the proportion of children with pulmonary hypertension, both showed a significant improvement at follow-up. Meta-analysis was not performed.

Three studies assessed interventricular septum thickness (IVS).[35,40] There was no significant change at follow-up (Figure 6; [MD −0.19;$CI_{95\%}$ −0.69 to 0.31]). Four studies assessed right ventricular diastolic diameter (RVDd).[19,40–42] After removing sources of heterogeneity,[41] there was a significant decrease in RVDd in the SDB group (Figure 7; [MD −0.12;$CI_{95\%}$ −0.20 to −0.03]. Two studies reported the right ventricular myocardial performance index (RVMPi)[33,42]; both showed a significant reduction (suggesting improvement) at follow-up. Due to heterogeneity between studies, meta-analysis was not performed. The two studies assessing pulmonary valve peak velocity showed no significant change at follow-up (Figure 8; [MD 1.90; $CI_{95\%}$−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(VTItv),[1]and velocity–time integral of pulmonary flow (VTIpa)[7] and a significant decrease in right ventricular isovolumetric relaxation time (IVRT)[15] and tricuspid regurgitation (TR).[43] There was no significant change in tricuspid full diastolic filling time,[34] 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; $CI_{95\%}$ −0.22 to 0.40]. The two studies reporting mitral Em/Am ratio showed a significant increase (Figure 10; [MD 0.73;$CI_{95\%}$0.63 to 0.84]).[33,35] Five studies assessed left ventricle shortening fraction (FS).[19,34,35,40,42] There was no significant change in FS (Figure 11; [MD −1.05, $CI_{95\%}$−2.25 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; $CI_{95\%}$−0.08 to 0.09])[34,35,40,42] or LVDd(Figure 13; [MD −0.06;$CI_{95\%}$−0.15 to 0.04])[34,35,41,42] 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;$CI_{95\%}$−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;$CI_{95\%}$−3.02 to 2.50]) or aortic valve peak velocity (Figure 16; [MD 1.70,$CI_{95\%}$−1.66 to 5.06]).[34,35] The two studies assessing left ventricle posterior wall thickness (LVpw) also showed no significant change (Figure 17; [MD −0.21,$CI_{95\%}$ −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.

Author	Year	Design/ evidence level	No.	Age, years	Inclusion	PSG	Intervention	Interval pre/post	Outcome	Results	
										SDB vs. controls	SDB at follow-up
Abd El-Moneim et al.	2009	Prospective cohort (II)	30 cases	5 (2.5, 12)	SDB with AH	No	A	36 (30-52) days	Tricuspid E/A ratio	No control group	↑
									FS		≈
									RVDd		↓
									Awake HR		≈
									mPAP		↓
									VTItv		↑
									VTIpa		↑
									TPV		↑
Amin et al.	2005	Prospective case control (III)	9 cases/ 9 controls	12.3 (3.9)	ATH with OSA	Yes	AT[a]	12 months	Mitral E/A ratio	SDB < controls	↑
Apostolidou et al.	2008	Prospective case control (III)	58 cases/ 17 controls	6.4 (3.3)	ATH with OSA	Yes	AT	5.8 ± 2.9 months	CRP	pre AT≈ controls	≈
									cICAM-1	pre AT≈ controls	≈
									Systolic BP Index	pre AT≈ controls	↑ in unresolved/ controls ↓ in resolved
									Diastolic BP index	pre AT≈ controls	↑ in unresolved/ controls ↓ in resolved
Attia et al.	2010	Prospective case control (III)	42 cases/ 45 controls	5 (3.14)	ATH with OSA	Yes	AT	6.4 +- 0.56 months	RVDd	pre AT> controls, post≈ controls	↓
									mPAP[a]	pre AT> controls, post≈ controls	↓
									PASP	pre AT> controls, post≈ controls	↓
									Tricuspid E/A ratio	pre AT < controls (mod-severe OSA), post≈ controls	↑
									LVMi (gm/m2)	pre AT>controls, post≈ controls	↓

Table 2—*Continued*

Author	Year	Design/ evidence level	No.	Age, years	Inclusion	PSG	Intervention	Interval pre/post	Outcome	Results	
										SDB vs. controls	SDB at follow-up
									Mitral Em/Am ratio	Pre AT < controls, post AT≈ controls	↑
									Tricuspid Em/Am ratio	Pre AT< controls, post AT≈ controls	↑
									LV MPI	Pre AT>controls, post AT≈ controls	↓
									RVMPI	Pre AT>controls, post AT≈ controls	↓
Baumert et al.	2011	Prospective case control (III)	40 cases/ 40 controls	7.5 (2.7)	ATH with OSA	Yes	AT	6 mo (29.2 + - 5.9 wks)	RR interval‡	Pre AT≈controls, post AT≈ controls	↑
Chan et al.	2015	Prospective case control (III)	63 cases/ 63 controls	10.3 (2.9)	ATH with OSA	Yes	AT[a]	6 months	FMD of brachial artery	Pre AT<controls, post AT≈ controls	↑
Cincin et al.	2014	Prospective case control (III)	30 cases/ 30 controls	7.86 (3.83)	SDB with ATH	No	AT	6 months	mPAP	pre AT> controls	↓
									LVDd	pre AT≈ controls	≈
									LVSd	pre AT≈ controls	≈
									FS	pre AT≈ controls	≈
									RVDd	pre AT≈ controls	≈
									LVMPI	pre AT≈ controls	↓
									RVMPI	pre AT> controls	↓
									LA	pre AT≈ controls	≈
									Mitral E/E'	pre AT≈ controls	≈
									LV IVCT	pre AT≈ controls	≈
									LV IVRT	pre AT≈ controls	↓
									LV ET	pre AT≈ controls	↓

Table 2—*Continued*

Author	Year	Design/ evidence level	No.	Age, years	Inclusion	PSG	Intervention	Interval pre/post	Outcome	Results	
										SDB vs. controls	SDB at follow-up
									Tricuspid E/E'	pre AT≈ controls	≈
									RV IVCT	pre AT≈ controls	≈
									RV IVRT	pre AT≈ controls	↓
									RV ET	pre AT< controls	↑
									TAPSE	pre AT≈ controls	≈
Crisalli et al.	2012	Prospective case control (III)	133 cases/ 61 controls	9.4 (2.2)	ATH with OSA	Yes	AT	6 weeks and 6 months	Awake SBP	pre AT ≈ controls	≈
									Awake DBP	pre AT≈ controls	≈
									Asleep SBP		**↓(severe OSA)**
									Asleep DBP		**↓(severe OSA)**
									Asleep RR	pre AT ≈ controls	≈
									BRS	severe OSA < controls	↑
									BPV		↓
Goldbart et al.	2010	Prospective case control (III)	90 cases	19 (7) months	ATH with OSA	Yes	AT	3 months	CRP	Not reported	↓
									NT-proBNP	pre AT> controls	↓
									TR		↓
Gorur et al.	2001	Prospective case control (III)	33 cases/ 33 controls	6.3 (2.1)	SDB with ATH	No	AT	6 months	RVDd	pre AT> controls, post AT ≈ controls	
									LVSd	pre AT≈ controls, post AT ≈ controls	
									LVDd	pre AT> controls, post AT ≈ controls	
									IVS	pre AT> controls, post AT ≈ controls	
									FS	pre AT≈ controls, post AT ≈ controls	

Table 2—*Continued*

Author	Year	Design/ evidence level	No.	Age, years	Inclusion	PSG	Intervention	Interval pre/post	Outcome	Results	
										SDB vs. controls	SDB at follow-up
									LA	pre AT≈ controls, post AT ≈ controls	
									LV IVRT	pre AT≈ controls, post AT ≈ controls	
									DT	pre AT> controls, post AT ≈ controls	
									VE	pre AT≈ controls, post AT ≈ controls	
									LVPW	pre AT≈ controls, post AT ≈ controls	
									VA	pre AT≈ controls, post AT ≈ controls	
Gozal et al.	2007	Prospective case control (III)	26 cases/ 8 controls	6.9 (0.6)	OSA with ATH	Yes	AT	4-6 months	Modified hyperemic test	pre AT< controls, post AT≈ controls	↑
Gozal et al.	2013	Prospective case control (III)	35 cases/ 35 controls	7.2 (1.4)	OSA with ATH	Yes	AT	Not reported	Adropin level	OSA/EF+ <OSA/ EF-<control	**↑ in EF+,≈ in EF-**
Kaditis et al.	2011	Prospective cohort (II)	21 cases	7.1 (2.8)	ATH with OSA	Yes	AT	4.2+-1.2 months	RR interval		**↑ (except stage 1)**
									logBNP		↑
Kheirandish-Gozal et al.	2006	Prospective cohort (II)	20 cases	7.3 ± 1.9	ATH with OSA	Yes	AT	10-14 weeks	CRP	No control group	↓
Martha et al.	2013	Case-Control prospective (III)	33 cases/ 10 controls	6.7	SDB with ATH	No	AT	2-24 wks post op	mPAP		**↓ (PH), ≈ (Non PH)**
Moghaddam et al.	2011	Prospective case control (III)	55 cases/ 55 controls	3 to 11	SDB with ATH	No	AT	6 months	mPAP		**↓ (PH group only)**
Naiboglu et al.	2008	Prospective case control (III)	39 cases/ 20 controls	5.7 (1.9)	SDB with ATH	No	AT	6 months	mPAP	pre AT> control, post AT≈ controls	↓
Pac et al.	2005	Prospective case control (III)	28 cases/ 35 controls	7.3 (2.9)	SDB with ATH	No	AT	1 month	Mitral E/A ratio	pre AT≈ control	≈
									Tricuspid E/A ratio	pre AT≈ control	≈

Table 2—*Continued*

Author	Year	Design/ evidence level	No.	Age, years	Inclusion	PSG	Intervention	Interval pre/post	Outcome	Results	
										SDB vs. controls	SDB at follow-up
									FS	pre AT≈ control	≈
									IVS	pre AT≈ control	≈
									LVSd	pre AT≈ control	≈
									LVDd	pre AT≈ control	≈
									LVPW(end-systolic)	pre AT≈ control	≈
									LVPW(end-diastolic)	pre AT≈ control	≈
									LA	pre AT≈ control	≈
									EF	pre AT≈ control	≈
									Mitral FDT	pre AT≈ control	≈
									Tricuspid FDT	pre AT> control	≈
									Ao_v Vel	pre AT≈ control	≈
									Pul_v Vel	pre AT≈ control	≈
Quante et al.	2015	Prospective RCT (III)	202 cases	7 (4)	ATH with OSA	Yes	AT	7 months	Awake HR	No control group	↓
Talipinar et al.	2011	Prospective cohort (II)	37 cases	6.8 (2.9)	ATH with SDB	No	AT/A/T	3-4 months	Endothelin-1	No control group	↓
									CRP		≈
Ugur et al.	2008	Prospective case control (III)	29 cases/ 26 controls	6.7 (2.4)	ATH with OSA	Yes	AT/T	6 months	Mitral Em/ Am ratio	pre AT> control, post AT≈ control	↑
									Tricuspid Em/Am ratio	pre AT> control, post AT≈ control	↑
									FS	pre AT≈ control	≈
									IVS	pre AT≈ control	≈
									LVSd	pre AT≈ control	≈
									LVDd	pre AT≈ control	≈
									PASP	pre AT> control	↓

Table 2—*Continued*

Author	Year	Design/ evidence level	No.	Age, years	Inclusion	PSG	Intervention	Interval pre/post	Outcome	Results	
										SDB vs. controls	SDB at follow-up
									LVPW	pre AT≈ control	≈
									EF	pre AT≈ control	≈
									LVMi (gm/m)	pre AT≈ control	≈
									RVDd (cm/m)	pre AT≈control	≈
									LV IVRT	pre AT≈ control	≈
									Mitral E/A ratio	pre AT≈ control	≈
									Tricuspid E/A ratio	pre AT≈ control	≈
									Aortic valve peak velocity	pre AT≈ control	≈
									Pulmonary valve peak velocity	pre AT≈ control	≈
Vlahandonis et al.	2013	Prospective case control (III)	40 cases/ 20 controls	12.9 (0.3)	SDB	Yes	AT/T[a]	4 years	Awake DBP	SDB> controls	≈
							T&A in 9 children		Awake SBP	SDB> controls	≈
							T in 1		Asleep DBP	SDB> controls	↓
							Nasal steroid in 1		Asleep SBP	SDB> controls	↓
							Combination in 1		HR	followup≈ controls	≈
Vlahandonis et al.	2014	Prospective case control (III)	40 cases/ 20 controls	12.9 (0.3)	SDB	Yes	AT/T [a]	4 years	BRS		**↑ (resolved OSA group)**
									BPV		↓
Vlahandonis et al.	2014	Prospective case control (III)	40 cases/ 20 controls	12.9 (0.3)	SDB	Yes	AT/T [a]	4 years	HRV		↓
Yilmaz et al.	2005	Prospective case control (III)	52 cases/ 33 controls	7.7 (2.5)	SDB with ATH	No	AT	5 months	mPAP	pre AT> control	↓

↑ or ↓indicates significant increase or decrease respectively, ≈ no significant difference, ǂdetailed 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; LVMPi,LV myocardial performance index; LVpw, left ventricle posterior wall thickness; LVIVRT, 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 valve peak velocity; RVDd, Right ventricular end-diastolic diameter; RVMPi, RV myocardial performance index; SBP,Systolic blood pressure; SDB, sleep disordered breathing; T, tonsillectomy.
[a]Subjects received medical or surgical treatment.

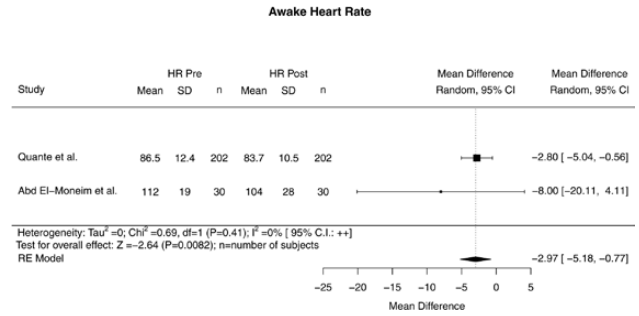

Figure 2—Meta-analysis of studies on awake heart rate data comparing before (pre) versus after (post) intervention.

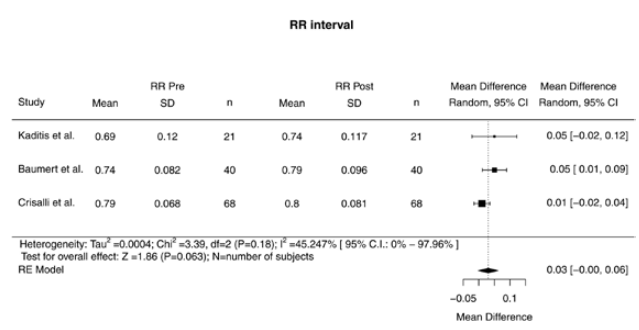

Figure 3—Meta-analysis of studies on RR interval data comparing before (pre) versus after (post) intervention.

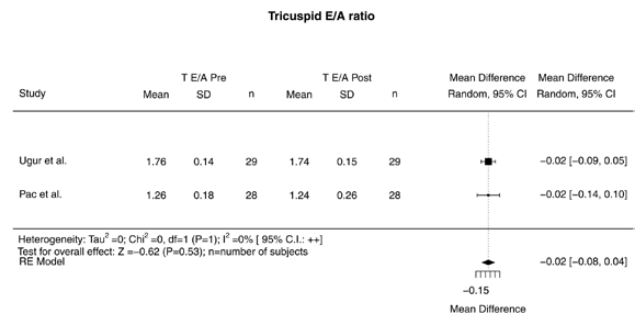

Figure 4—Meta-analysis of studies on Tricuspid E/A ratio data comparing before (pre) versus after (post) intervention.

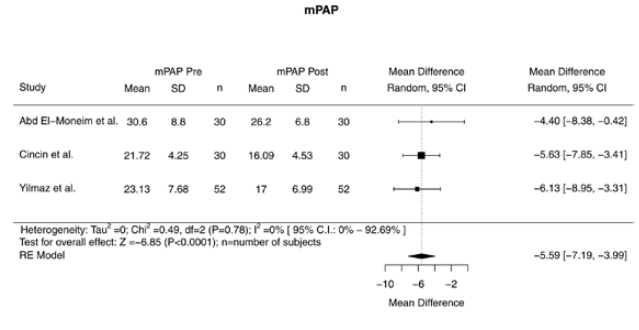

Figure 5—Meta-analysis of studies on mean pulmonary artery pressure (mPAP) data comparing before (pre) versus after (post) intervention.

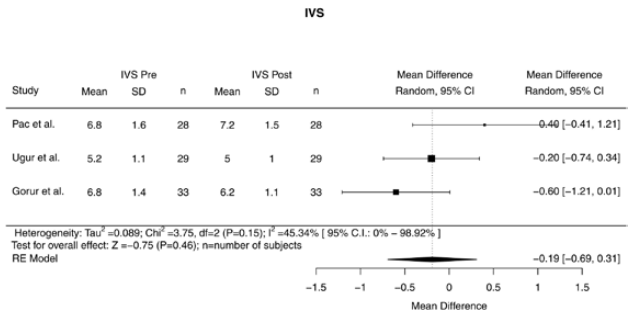

Figure 6—Meta-analysis of studies on interventricular septum thickness (IVS) data comparing before (pre) versus after (post) intervention.

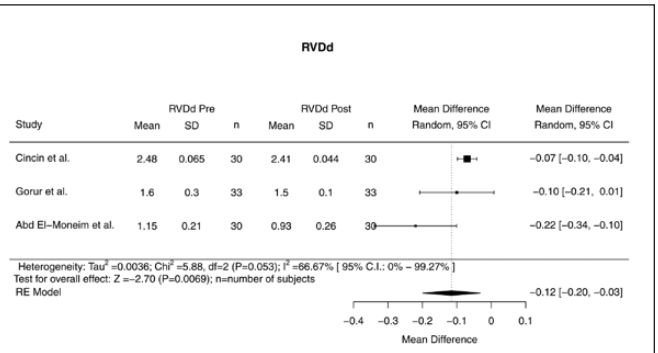

Figure 7—Meta-analysis of studies on right ventricular end diastolic diameter (RVDd) data comparing before (pre) versus after (post) intervention.

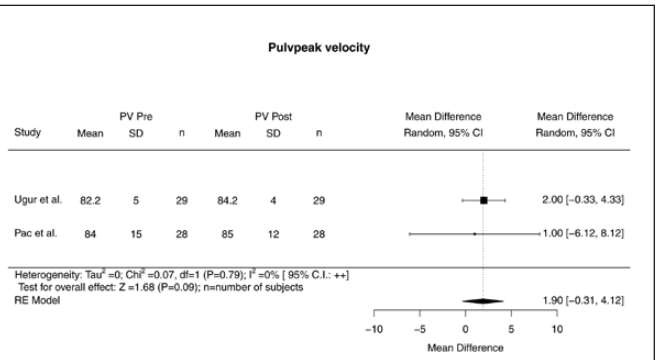

Figure 8—Meta-analysis of studies on pulmonary valve peak velocity comparing before (pre) versus after (post) intervention.

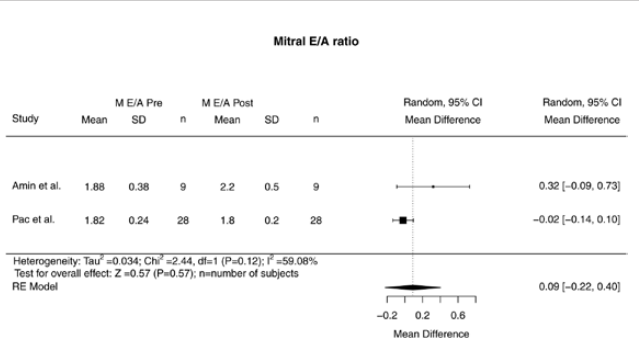

Figure 9—Meta-analysis of studies on mitral E/A ratio data comparing before (pre) versus after (post) intervention.

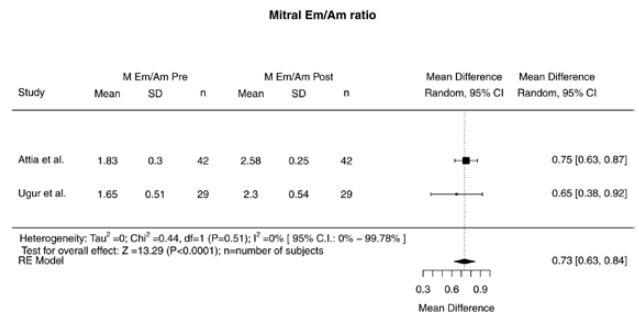

Figure 10—Meta-analysis of studies on mitral Em/Am ratio data comparing before (pre) versus after (post) intervention.

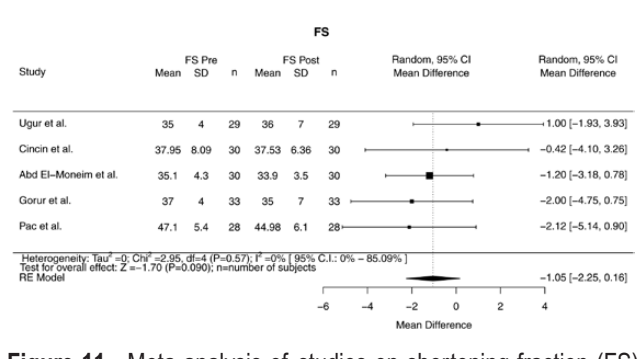

Figure 11—Meta-analysis of studies on shortening fraction (FS) data comparing before (pre) versus after (post) intervention.

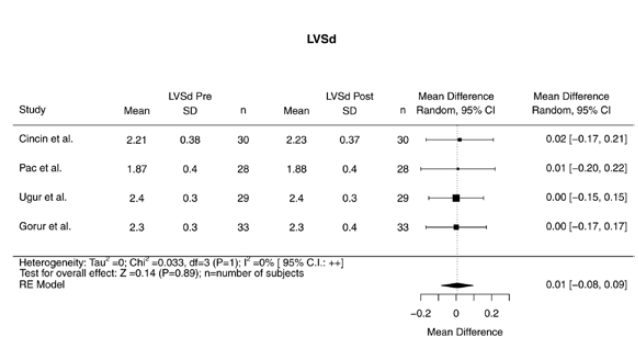

Figure 12—Meta-analysis of studies on left ventricle end systolic diameter (LVSd) data comparing before (pre) versus after (post) intervention.

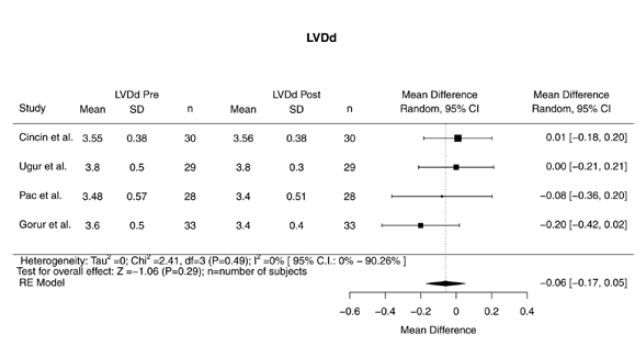

Figure 13—Meta-analysis of studies on left ventricle end diastolic diameter (LVDd) data comparing before (pre) versus after (post) intervention.

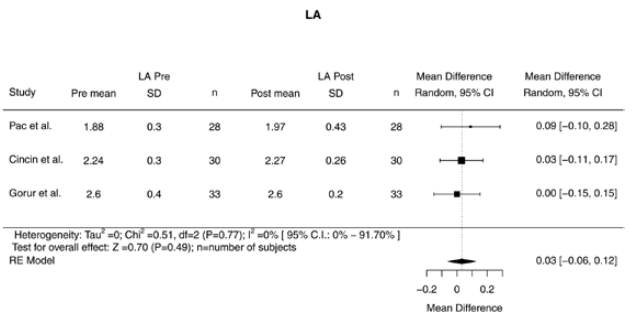

Figure 14—Meta-analysis of studies on left atrial dimension (LA) data comparing before (pre) versus after (post) intervention.

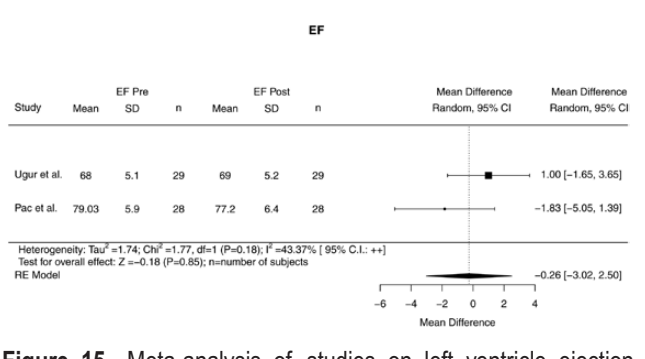

Figure 15—Meta-analysis of studies on left ventricle ejection fraction (EF) data comparing before (pre) versus after (post) intervention.

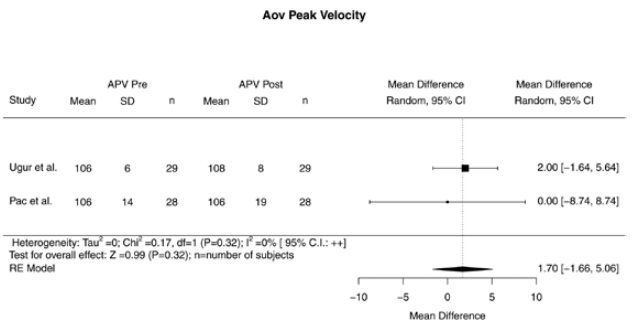

Figure 16—Meta-analysis of studies on aortic valve peak velocity (Aov) data comparing before (pre) versus after (post) intervention.

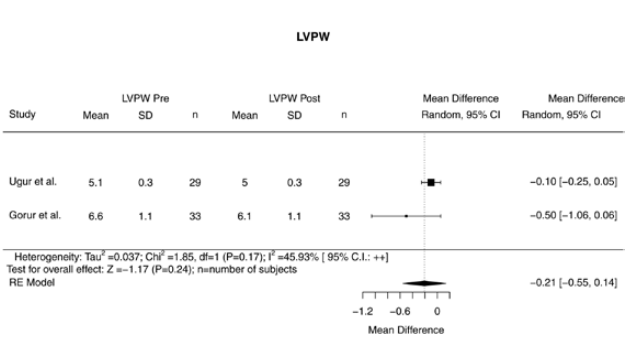

Figure 17—Meta-analysis of studies on left ventricle posterior wall thickness (LVPW) data comparing before (pre) versus after (post) intervention.

isovolumetric relaxation time (LV IVRT).[35,40,42] After removing the source of heterogeneity,[42] there was no significant change at follow-up (Figure 18; [MD 3.50,$CI_{95\%}$ −2.16 to 9.16]). One study showed a decrease in LV mass (indexed to BSA),[41] while another reported no significant change in LV mass(indexed to height).[35] One study reported a significant decrease in LV ET[42]. Changes in mitral E/E',[15] deceleration time,[40] LV peak filling velocity,[33] LA contraction velocity,[11] and LV IVCT[45] 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, RVDd, awake HR, RVDd, 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 (RVDd), 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.[46] It is important that we review currently available evidence carefully, as subtle (albeit non-significant) effects on cardiovascular parameters may be additive over time.

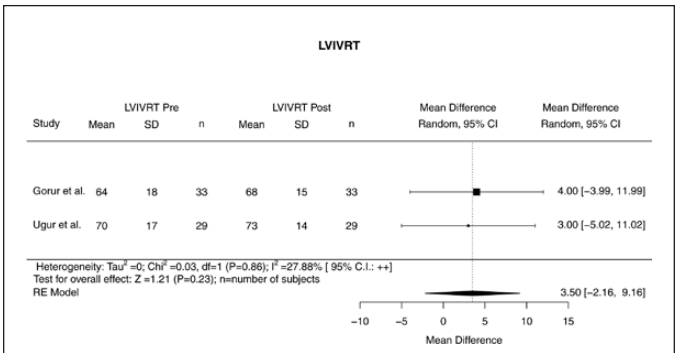

Figure 18—Meta-analysis of studies on left ventricle isovolumetric relaxation time (LVIVRT) data comparing before (pre) versus after (post) intervention.

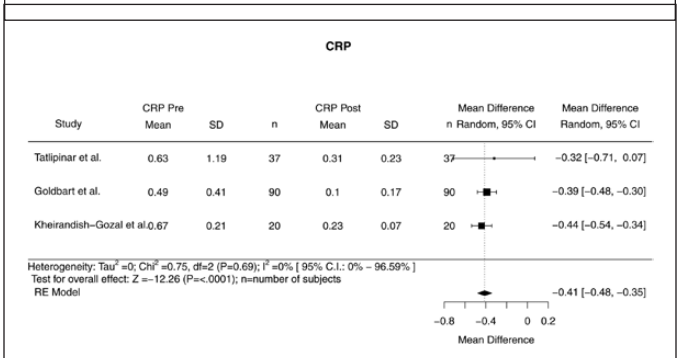

Figure 19—Meta-analysis of studies on c-reactive protein (CRP) data comparing before (pre) versus after (post) intervention.

There is sufficient evidence to suggest that severe OSA in adults significantly increases the risk of cardiovascular disease, stroke, and all-cause mortality.[47–49] Adults with SDB, regardless of severity, have a 2–3 time greater risk of developing hypertension at 4-year follow-up compared to controls.[50] While the cardiovascular morbidity of OSA in children has been summarized previously,[51,52] meta-analyses are limited by low level of evidence, as the majority of published studies are cross-sectional or retrospective,[4–7] and available reviews are primarily qualitative in nature.[53]

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.[44,45,54–57] Our results indicate that upon resolution of OSA, there was a significant decrease in nocturnal BP at 6-month[18] and 4-year follow-up[58]. 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.[15,18,59] Although retrospective studies indicate HR variability is altered in children with SDB,[60,61] prospective research is limited.[16] The decrease in heart rate, improvements in overnight baroreflex sensitivity,[18] BP variability[15,18] and heart rate variability,[16] and systolic and diastolic blood pressure indices (in those with resolved SDB)[23] 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.[62,63] Moreover, treating OSA with CPAP has been shown to improve endothelial function.[64] The majority of currently available pediatric evidence is cross-sectional in nature.[65–69] When assessing endothelium-dependent FMD of the brachial artery, the gold standard in assessing endothelial function,[70] OSA children have lower values compared to controls at baseline, with reversal of these changes after AT[24]. Measuring endothelial function with a modified hyperemic test after cuff-induced occlusion of the brachial artery yields similar results suggesting an improvement in endothelial function after OSA treatment.[25] Prospective studies reporting serum biomarkers reflective of endothelial function provide further support that associations in the context of OSA exist and improvement occurs after treatment. C-reactive protein (CRP) is a marker of inflammation and a potentially useful biomarker of cardiovascular morbidity. Studies reporting

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[71] as well as a meta-analysis on the effects of T&A on C-reactive protein.[72]

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. Reductions 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, VTIpa, 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.[17,22,73] 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,[74] the two studies reporting LV mass at follow-up reported conflicting results. Ugur 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, RVDd, 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, RVDd, 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 quantitative 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[34,38,39,75–77]; three reported absolute BMI values[35,41,78]; two reported BMI percentiles[79,80]; six reported BMI z-scores[20,28,30,43,58,81]; two specifically reported excluding children with BMI > 29[41, 82]; one reported excluding those with BMI z-score > 2.99[20]; and one reported body surface area instead of BMI data.[83] 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.

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SUPPLEMENTARY MATERIAL

Supplementary Material is available at *SLEEP* online.

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