

## CARDIOMETABOLIC IMPACT OF ADENOTONSILLECTOMY FOR CHILDHOOD SLEEP APNEA

# The Effect of Adenotonsillectomy for Childhood Sleep Apnea on Cardiometabolic Measures

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**Study Objectives:** Obstructive sleep apnea syndrome (OSAS) has been associated with cardiometabolic disease in adults. In children, this association is unclear. We evaluated the effect of early adenotonsillectomy (eAT) for treatment of OSAS on blood pressure, heart rate, lipids, glucose, insulin, and C-reactive protein. We also analyzed whether these parameters at baseline and changes at follow-up correlated with polysomnographic indices.

**Design:** Data collected at baseline and 7-mo follow-up were analyzed from a randomized controlled trial, the Childhood Adenotonsillectomy Trial (CHAT).

**Setting:** Clinical referral setting from multiple centers.

**Participants:** There were 464 children, ages 5 to 9.9 y with OSAS without severe hypoxemia.

**Interventions:** Randomization to eAT or Watchful Waiting with Supportive Care (WWSC).

**Measurements and Results:** There was no significant change of cardiometabolic parameters over the 7-mo interval in the eAT group compared to WWSC group. However, overnight heart rate was incrementally higher in association with baseline OSAS severity (average heart rate increase of 3 beats per minute [bpm] for apnea-hypopnea index [AHI] of 2 versus 10; [standard error = 0.60]). Each 5-unit improvement in AHI and 5 mmHg improvement in peak end-tidal CO<sub>2</sub> were estimated to reduce heart rate by 1 and 1.5 bpm, respectively. An increase in N3 sleep also was associated with small reductions in systolic blood pressure percentile.

**Conclusions:** There is little variation in standard cardiometabolic parameters in children with obstructive sleep apnea syndrome (OSAS) but without severe hypoxemia at baseline or after intervention. Of all measures, overnight heart rate emerged as the most sensitive parameter of pediatric OSAS severity.

**Clinical Trial Registration:** Clinicaltrials.gov (#NCT00560859)

**Keywords:** adenotonsillectomy, metabolism, obstructive sleep apnea syndrome, pediatrics

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## INTRODUCTION

Childhood Obstructive Sleep Apnea Syndrome (OSAS) affects 1% to 6% of young children, and is associated with a wide range of adverse health outcomes, including behavior problems and impaired growth.<sup>1</sup> In adult OSAS, cardiometabolic disorders, including hypertension, diabetes, coronary heart disease, heart failure, stroke, and atrial fibrillation, are widely recognized comorbidities and targets for intervention, with evidence that positive airway pressure (PAP) therapy may

improve insulin resistance and blood pressure control and reduce cardiovascular events.<sup>2–7</sup> In children, few studies have addressed the association between cardiometabolic dysfunction and OSAS<sup>8–25</sup> or the effect of OSAS treatment on outcomes such as blood pressure, lipids, and glucose metabolism. Some studies have demonstrated improvements in lipid profiles, liver function tests, C-reactive protein (CRP), apolipoprotein B, and blood pressure control after adenotonsillectomy (AT),<sup>26–30</sup> whereas other studies failed to show an effect of treatment.<sup>31,32</sup> These reports have been limited by nonrandomized and uncontrolled designs, and by relatively small sample sizes, long re-study intervals, and study of heterogeneous populations and wide age ranges.

We analyzed data from the Childhood Adenotonsillectomy Trial (CHAT), a randomized controlled multicenter study of health and behavioral outcomes in children with OSAS, randomized to early AT (eAT) or to Watchful Waiting with Supportive Care (WWSC). The primary results of the trial's neurocognitive outcomes were previously reported.<sup>33</sup> In this article, we report on the trial's secondary outcomes that addressed cardiometabolic health. We hypothesized that treatment

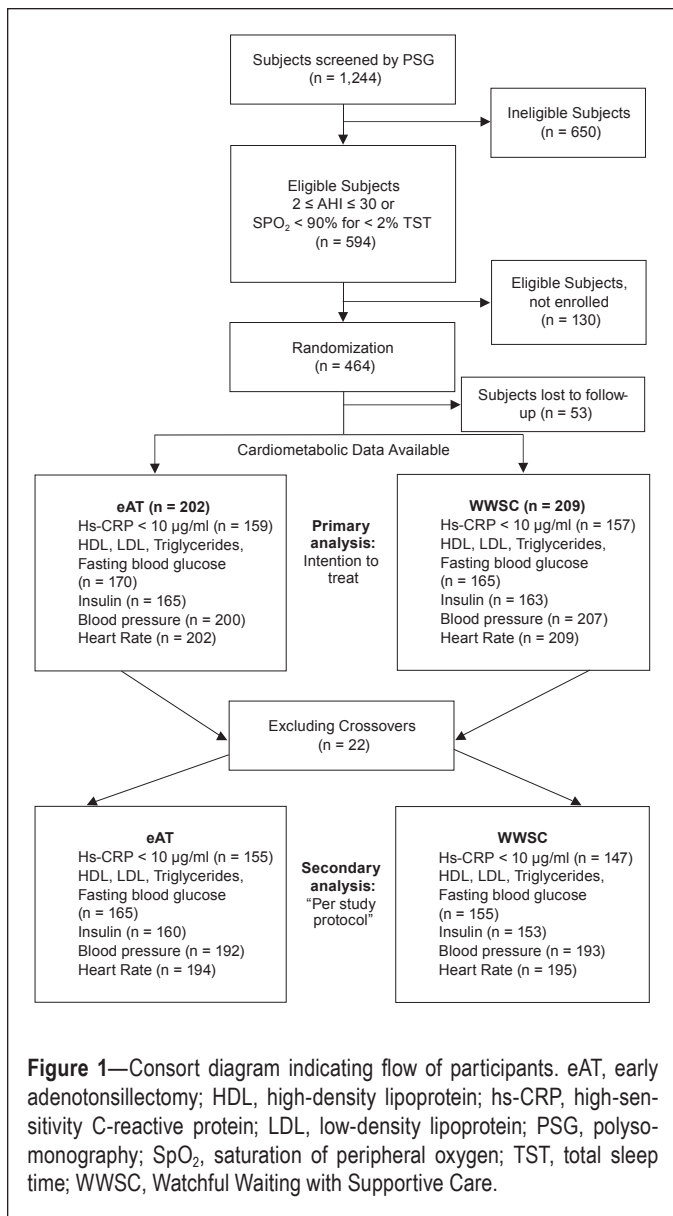
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**Figure 1**—Consort diagram indicating flow of participants. eAT, early adenotonsillectomy; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PSG, polysomnography; SpO<sub>2</sub>, saturation of peripheral oxygen; TST, total sleep time; WWSC, Watchful Waiting with Supportive Care.

of OSAS in children by eAT would reduce systolic, diastolic, and mean resting blood pressure and heart rate during sleep and wakefulness; improve lipid profiles and glucose homeostasis; and lower levels of inflammatory markers. Secondly, we hypothesized that these parameters at baseline, as well as changes at follow-up, would correlate with indices of sleep disordered breathing (SDB) and sleep quality. Given the potential for subgroup differences in response to treatment, we also explored differences in groups stratified by race, OSAS severity, and body mass index (BMI).

## METHODS

### Study Sample

The design of the CHAT study has been previously described and the primary outcomes have been published.<sup>33–35</sup> In brief, children ages 5.0–9.9 y with polysomnography (PSG) confirmed OSAS (obstructive apnea-hypopnea index [AHI] ≥ 2 events/h or an obstructive apnea index [OAI] ≥ 1 event/h), a history of snoring, and considered to be surgical candidates for

adenotonsillectomy by an otolaryngologist were recruited from pediatric sleep centers/sleep laboratories, otolaryngology clinics, general pediatric clinics, and the general community from six clinical centers. Exclusion criteria included comorbidities, medications for psychiatric or behavioral disorders (including attention deficit hyperactivity disorder), recurrent tonsillitis, extreme obesity (defined by a body mass index > 2.99 for age group and sex, z-score) and severe OSAS (AHI ≥ 30, OAI ≥ 20 or oxyhemoglobin saturation of < 90% for > 2% of total sleep time). The study was approved by the Institutional Review Board of each institution. Informed consent was obtained from caregivers, and assent from children age 7 y or older. The study was registered at Clinicaltrials.gov (#NCT00560859). Figure 1 summarizes the flow of participants through the study.

### Interventions

Children were randomly assigned to eAT (surgery within 4 w after randomization) or a strategy of WWSC with reassessment for the need for surgery at 7 mo. All children/caregivers received information on sleep hygiene using standardized educational materials, were provided with saline nasal spray to be used as needed, and were evaluated and referred for treatment of comorbid conditions (e.g., asthma). Complete bilateral tonsillectomy and removal of obstructing adenoid tissue was performed by standard surgical techniques including cold dissection, monopolar electrocautery, coblation or microdebrider, with variation according to surgeon preference and not by patient characteristics. To ensure surgical uniformity across participating sites, intraoperative photographs were obtained on every 10<sup>th</sup> subject at each site, and were reviewed for adequacy of lymphoid tissue removal by the surgical quality control committee chair.

### Protocol

Each child underwent in-laboratory baseline and follow-up PSG by study-certified technicians, using similar sensors, and following American Academy of Sleep Medicine (AASM) pediatric guidelines for both acquisition and for scoring.<sup>36</sup> The PSGs were scored by registered sleep technicians who were specifically certified for this study after undergoing study-specific training and certification. Each PSG record was edited manually for muscle, movement, and electrical artifacts. A research clinic visit was scheduled soon after the baseline PSG, at which time certified research technicians and research nurses performed anthropometry, measured blood pressure, and obtained a fasting venous sample. Site investigators performed a physical examination. The investigators as well as CHAT study personnel involved with primary data collection were blinded to all study results. Only the study coordinator and the ear, nose, and throat surgeons were unblinded to the treatment group. Resting blood pressure was measured in triplicate after a 10-min rest period while sitting using a calibrated sphygmomanometer with a cuff size chosen based on the child's arm circumference. Resting heart rate was obtained during the physical examination. Height was measured with a calibrated wall-mounted stadiometer while the child was in his/her stocking feet; weight was measured with research quality, calibrated digital scales. All of these measurements were taken by CHAT certified site personnel in a standardized manner

according to written guidelines. Caregivers were asked to complete questionnaires addressing the child's medical, social, and family histories. Sleep duration was obtained from a parent-completed 7-day sleep diary. Fasting morning blood samples were drawn by venipuncture, processed and stored frozen until assayed in batch in a centralized laboratory (Laboratory for Clinical Biochemistry, University of Vermont, Burlington, VT). The median timing between baseline PSG and research clinic visit was 28 days. Time delays largely related to scheduling requirements (family, child, and staff availability.) Measurements were repeated approximately 7 mo after randomization following a protocol similar to that of the baseline examination.

### Measurements

The PSG measures for this analysis consisted of AHI, expressed as the sum of all obstructive apneas plus hypopneas associated with > 3% desaturation or arousal per hour of sleep; oxygen desaturation index (ODI), defined as the number of oxyhemoglobin desaturations > 3% per sleep hour; peak end-tidal carbon dioxide (EtCO<sub>2</sub>); % total sleep time (TST) with EtCO<sub>2</sub> > 50 mmHg; oxygen saturation ≤ 92% of the TST, computed as the percentage of sleep time with oxygen saturation ≤ 92%; and proportion of sleep time in stages N2, N3, and rapid eye movement (REM). The average values of triplicate determinations for systolic and diastolic blood pressure were calculated and expressed as sex-, age-, and height-specific blood pressure percentiles.<sup>37</sup> BMI was calculated and converted to an age- and sex-adjusted BMI z-score based on the Centers for Disease Control and Prevention (CDC) growth charts (<http://www.cdc.gov/growthcharts/>). Weight was categorized based on percentiles for age and sex as follows: failure to thrive, < 5<sup>th</sup> percentile; normal, ≥ 5<sup>th</sup> and < 85<sup>th</sup>; overweight, ≥ 85<sup>th</sup> and < 95<sup>th</sup>; and obese, ≥ 95<sup>th</sup>.<sup>38</sup> Mean values for heart rate were obtained from PSG software (electrocardiogram or pulse oximeter) by averaging across the sleep period. Resting heart rate during wakefulness was determined by measurement of the radial pulse during a 1-min recording made during the morning research examination. Blood was assayed for glucose and lipids (cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides; Ortho Vitros Clinical Chemistry System 950/IRC instrument, Raritan, NJ), high sensitivity CRP [hs-CRP] (Siemens BNII analyzer, Deerfield, IL), and fasting insulin (Roche Elecsys 210 analyzer, Indianapolis, IN) levels. The interassay coefficients of variation were: glucose and lipids, < 2%; insulin, < 5%; high-sensitivity C-reactive protein (hs-CRP): 2.1–5.7%. Hs-CRP levels that were initially undetectable were repeated using a solid phase-based multiplex platform from Meso Scale Discovery (Gaithersburg, MD) (n = 156). Hs-CRP values exceeding 10 µg/mL, which likely indicate infection or acute illness, were excluded from analysis. Biochemical data were missing for approximately 20% of subjects due to specimen collection issues (child refusal, nonfasting state, inadequate blood draw). A comparison of these children to the remaining children with respect to age, sex, AHI value, and BMI-z-score indicated no differences according to missing data status.

### Statistical Analysis

Demographic, anthropometric, and cardiometabolic characteristics were summarized and compared between the groups utilizing analysis of variance (ANOVA) or chi-square

and Fisher exact tests. Cardiometabolic characteristics were also compared with published normative data in pediatric populations.<sup>39–41</sup> Unadjusted associations were assessed using Spearman correlation coefficients. Outcome measurements were hs-CRP, LDL cholesterol, HDL cholesterol, triglycerides, fasting blood glucose, fasting insulin, average heart rate during total sleep, REM sleep and non-REM sleep and during wake, and systolic and diastolic blood pressure percentile. Independent variables were treatment assignment (eAT, WWSC), AHI, ODI, peak EtCO<sub>2</sub>, EtCO<sub>2</sub> > 50 mmHg, oxygen saturation ≤ 92%, stage N1, N2, N3, and REM sleep. To address each of the study hypotheses, we conducted three series of analyses: The initial analysis assessed the association between sleep variables and cardiometabolic variables at baseline using multiple linear regression analysis. To evaluate the effect of intervention on cardiometabolic outcomes, we conducted an analysis of covariance (ANCOVA) for change in outcomes by treatment group. Finally, we used linear regression analysis to model the associations between changes in cardiometabolic outcomes in relationship to changes in indices of OSAS and sleep quality. Stratified analyses further explored groups defined by race, median baseline AHI, and median BMI z-score change. Analyses did not include total cholesterol or glucose homeostasis model assessment, because of their strong correlation with LDL cholesterol and insulin, respectively. All statistical models were adjusted for the trial's stratification variables: age (5 to 7 y of age vs. 8 to 9 y of age), race (African American vs. other), overweight/obesity status, and study site. Average heart rate during REM and non-REM sleep was only reported if results differed from average heart rate during total sleep. The primary analysis was an intention-to-treat analysis. Per-protocol analyses (i.e., excluding the 22 children who did not receive the assigned therapy) were performed, but not presented as they showed findings similar to the primary analysis. No corrections were made for multiple comparisons. Results are presented as mean ± standard deviation. All analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

### RESULTS

Characteristics for the analytic sample at baseline and by intervention group are shown in Table 1. Approximately half of the subjects were male and half were overweight or obese. Baseline anthropometric, sleep, and cardiometabolic characteristics were comparable across intervention groups. On average, compared with published normative data in pediatric populations, 7% of overall lipid levels, 8% of markers of glycemic control, and 3% of blood pressure values exceeded the normal range for age and sex.<sup>39–41</sup> Thus, although there was a high proportion of overweight or obese participants, relatively few participants had indices of cardiometabolic health that exceeded normative values. As reported before, over the intervention period, key measures of OSAS improved more while BMI z-score increased more in the eAT compared to the WWSC group.<sup>33,35</sup> (Table S1, supplemental material)

### Associations between Baseline PSG Indices and Study Outcomes

Adjusted linear regression analysis of the baseline data with cardiac parameters as the outcomes showed that AHI, ODI,

**Table 1**—Baseline characteristics of subjects.

Characteristic	eAT (n = 202)	WWSC (n = 209)	P
<b>Characteristic</b>			
Age, y	7.0 ± 1.4	7.0 ± 1.4	0.65
Male sex, n (%)	91 (45.0)	110 (52.6)	0.12
Race, African-American, n (%) <sup>a</sup>	108 (53.5)	110 (52.6)	0.87
Use of medication for asthma, n (%)	53 (26.2)	50 (23.9)	0.59
<b>Anthropometric Measures</b>			
BMI z-score	0.9 ± 1.4	0.8 ± 1.3	0.83
Overweight or obese (BMI ≥ 85 <sup>th</sup> percentile), n (%) <sup>b</sup>	97 (48.0)	97 (46.4)	0.74
Obese (BMI ≥ 95 <sup>th</sup> percentile), n (%) <sup>b</sup>	69 (34.2)	69 (33.0)	0.81
Failure to thrive (weight < 5 <sup>th</sup> percentile), n (%) <sup>b</sup>	8 (4.0)	7 (3.3)	0.74
<b>Cardiometabolic Measures<sup>c</sup></b>			
hs-CRP, µg/ml (range)	1.42 ± 1.93 (0.01–8.83)	1.14 ± 1.75 (0.01–9.02)	0.18
LDL cholesterol, mg/dl (range)	94.0 ± 23.1 (45.0–175.0)	92.9 ± 22.9 (29.0–155.0)	0.68
HDL cholesterol, mg/dl (range)	50.6 ± 12.4 (26.0–93.0)	50.3 ± 11.4 (26.0–87.0)	0.82
Triglycerides, mg/dl (range)	74.6 ± 31.7 (34.0–232.0)	75.6 ± 34.9 (31.0–240.0)	0.77
Fasting blood glucose, mg/dl (range)	81.7 ± 6.8 (61.0–117.0)	82.2 ± 7.7 (59.0–132.0)	0.56
Fasting insulin, µIU/mL (range)	8.73 ± 8.93 (0.53–57.98)	9.27 ± 10.24 (0.61–68.51)	0.61
Systolic blood pressure percentile	43.5 ± 24.5	47.1 ± 23.6	0.13
Diastolic blood pressure percentile	61.4 ± 21.6	62.2 ± 20.1	0.71
Average heart rate during sleep, bpm (range)	84.2 ± 9.3 (63.0–110)	83.5 ± 8.9 (63.0–105.0)	0.42

Descriptive statistics were presented as means ± standard deviation (SDS). P values were based on t-test for continuous variables or chi-square test for categorical variables. <sup>a</sup>Race reported by caregivers. <sup>b</sup>Overweight or obese was defined as a BMI in the 85<sup>th</sup> percentile or higher, obese as a BMI in the 95<sup>th</sup> percentile or higher, and failure to thrive as a BMI in less than the 5<sup>th</sup> percentile. <sup>c</sup>Number of subjects for cardiometabolic measures varied from 157 to 209 per group. BMI, body mass index; eAT, early Adenotonsillectomy; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; WWSC, Watchful Waiting with Supportive Care.

EtCO<sub>2</sub> > 50 mmHg, and stage N1 sleep were positively associated with average heart rate during total sleep, REM sleep, and non-REM sleep, but not with wake heart rate (Table 2). Specifically, an AHI of 2 versus 10 was associated with an average sleep heart rate-increase of 3 bpm (standard error [SE] = 0.60). Further adjustment for percentage of REM sleep had no effect on these associations (data not shown). Lower proportions of time in stages N2 and REM sleep and higher proportions of N1 and N3 were associated with higher average heart rate during sleep. There were no significant associations between sleep indices (stage N1, stage N2, stage N3, REM sleep, AHI, ODI, EtCO<sub>2</sub> > 50 mmHg, and oxygen saturation ≤ 92%) and systolic and diastolic blood pressure percentile.

Regarding metabolic outcomes, no associations were observed between various baseline sleep measures with LDL cholesterol, HDL cholesterol, hs-CRP, and fasting blood glucose other than for triglyceride level. Triglycerides level was positively associated with stage N3 ( $\beta = 0.735$ , SE = 0.23, P = 0.002,) and negatively with stage N2 sleep ( $\beta = -0.618$ , SE = 0.23, P = 0.009).

### Treatment Effect on Study Outcomes

Fasting LDL cholesterol, blood glucose, and insulin tended to increase during the study interval in both eAT and WWSC groups, whereas heart rate during sleep and systolic blood pressure percentile decreased. After adjusting for the trial's stratification factors, no significant intervention effect was observed for these cardiometabolic measures (Table 3). Additional

exploratory analyses were conducted to assess if there was subgroup differences in treatment response by race (black vs. other), baseline median AHI (4.7) and median BMI z-score change. These results also showed no treatment effect on cardiometabolic outcomes in any of these subgroups (data not shown).

### Follow-up Analysis of Associations between Change in Polysomnographic Indices and Change in Study Outcomes

Comparable associations between change in sleep measures and change in cardiac measures were observed in analysis of each intervention group separately. We found no interaction between treatment and any of the predictors (data not shown). Therefore, data from both groups were combined in subsequent multiple regression analysis modeling with the change in cardiac measures as the outcome, adjusting for age, race, baseline overweight/obesity status, sex, and study site. Positive associations between change in AHI, peak EtCO<sub>2</sub> and EtCO<sub>2</sub> > 50 mmHg with change in average heart rate were observed (Table 4). Similar findings were observed for ODI and oxygen saturation ≤ 92%. Specifically, each 5-unit improvement in AHI and 5 mmHg improvement in peak EtCO<sub>2</sub> were estimated to reduce heart rate during sleep by 1 and 1.5 bpm, respectively. We also observed similar associations for resting heart rate during wakefulness with AHI and ODI but not with peak EtCO<sub>2</sub> and EtCO<sub>2</sub> > 50 mmHg ( $\beta = 0.317$ , SE = 0.08, P = < 0.001 and  $\beta = 0.287$ , SE = 0.08, P = < 0.001, for AHI and ODI, respectively).

An increased proportion of time in stage 3 sleep from baseline to follow-up was associated with reduction in systolic

**Table 2**—Associations of baseline cardiac parameters with sleep measures.

Outcome	Explanatory Variable								
	AHI	Stage N1	Stage N2	Stage N3	REM Sleep	EtCO <sub>2</sub> > 50 mmHg	ODI 3	Oxygen Sat ≤ 92%	Sleep Duration by Diary Report
Resting heart rate during wakefulness									
Beta	0.16	0.23	-0.001	0.04	-0.32	0.06	-0.10	-0.18	0.28
SE	0.10	0.14	0.08	0.08	0.14	0.04	0.09	0.22	0.48
P value	0.12	0.10	0.99	0.64	0.02	0.11	0.28	0.42	0.56
Average heart rate asleep									
Beta	0.37	0.26	-0.15	0.14	-0.22	0.06	0.41	0.26	-0.37
SE	0.08	0.10	0.06	0.06	0.10	0.03	0.06	0.16	0.35
P value	< 0.001	0.01	0.01	0.02	0.03	0.02	< 0.001	0.10	0.29
Heart rate NREM sleep									
Beta	0.38	0.33	-0.17	0.12	-0.19	0.06	0.42	0.18	-0.41
SE	0.08	0.11	0.06	0.06	0.11	0.03	0.07	0.17	0.37
P value	< 0.001	0.003	0.01	0.06	0.08	0.04	< 0.001	0.31	0.27
Heart rate REM sleep									
Beta	0.37	0.20	-0.13	0.14	0.22	0.07	0.40	0.38	-0.30
SE	0.07	0.1	0.06	0.06	0.1	0.03	0.06	0.16	0.34
P value	< 0.001	0.04	0.03	0.02	0.02	0.005	< 0.001	0.02	0.37
Systolic blood pressure percentile									
Beta	-0.02	0.17	0.02	0.07	-0.41	-0.12	-0.23	-0.48	-1.48
SE	0.21	0.28	0.17	0.17	0.28	0.07	0.18	0.45	0.97
P value	0.92	0.54	0.91	0.68	0.14	0.10	0.20	0.28	0.13
Diastolic blood pressure percentile									
Beta	-0.21	0.05	-0.12	0.18	-0.22	-0.03	-0.20	0.03	-1.64
SE	0.18	0.24	0.141	0.14	0.23	0.06	0.15	0.38	0.82
P value	0.24	0.82	0.41	0.21	0.34	0.60	0.18	0.94	0.05

Linear regression was used to assess the association of baseline cardiac measures outcomes and baseline sleep measures, adjusting for age, race (black vs. other), weight status (overweight or obese vs. nonoverweight), sex, and study site. AHI, apnea-hypopnea index; EtCO<sub>2</sub>, peak end-tidal carbon dioxide; NREM, nonrapid eye movement; ODI, oxygen desaturation index; REM, rapid eye movement; SE, standard error.

**Table 3**—Change of cardiometabolic measures from baseline to follow-up in the early Adenotonsillectomy compared to the Watchful Waiting with Supportive Care group.

Outcome	eAT			WWSC			Effect size	P
	Baseline	Follow-up	Change*	Baseline	Follow-up	Change*		
hs-CRP, µg/mL <sup>a</sup>	1.5 ± 2.0	1.4 ± 2.0	-0.1 ± 2.2	1.1 ± 1.6	1.4 ± 2.0	0.3 ± 2.0	-0.18	0.16
LDL, mg/dL <sup>b</sup>	93.3 ± 21.6	93.6 ± 22.8	0.3 ± 16.0	92.9 ± 22.0	93.7 ± 22.9	0.8 ± 17.4	-0.03	0.87
HDL, mg/dL <sup>c</sup>	50.7 ± 12.9	50.6 ± 14.1	-0.2 ± 9.6	51.4 ± 11.8	51.8 ± 12.3	0.4 ± 8.3	-0.06	0.64
Triglycerides, mg/dL <sup>d</sup>	70.0 ± 23.7	73.9 ± 31.4	3.9 ± 30.7	73.1 ± 33.0	73.1 ± 39.0	-0.1 ± 34.0	0.12	0.29
Fasting blood glucose, mg/dL <sup>e</sup>	81.4 ± 7.1	82.2 ± 7.6	0.8 ± 6.9	81.4 ± 6.0	82.0 ± 7.1	0.7 ± 7.1	0.01	0.88
Fasting insulin, µIU/mL <sup>f</sup>	8.1 ± 7.6	11.3 ± 13.2	3.2 ± 10.4	8.4 ± 9.0	9.2 ± 7.8	0.8 ± 10.0	0.24	0.06
Systolic blood pressure percentile	43.5 ± 24.6	42.9 ± 24.3	-0.6 ± 29.1	47.5 ± 23.6	45.7 ± 24.2	-1.8 ± 26.1	0.05	0.62
Diastolic blood pressure percentile	61.5 ± 21.5	62.6 ± 21.4	1.2 ± 26.2	62.6 ± 20.0	61.9 ± 22.2	-0.7 ± 24.5	0.07	0.47
Average heart rate during sleep, bpm	84.2 ± 9.3	82.3 ± 8.6	-2.0 ± 7.6	83.5 ± 8.9	82.2 ± 7.9	-1.4 ± 8.3	-0.08	0.39
Heart rate NREM sleep, bpm	82.6 ± 9.8	81.2 ± 9.5	-1.4 ± 8.1	82.1 ± 9.4	80.7 ± 8.1	-1.4 ± 8.6	-0.01	0.90
Heart rate REM sleep, bpm	85.7 ± 8.9	83.5 ± 8.2	-2.2 ± 7.3	85.0 ± 8.8	83.6 ± 8.2	-1.5 ± 8.0	-0.09	0.31
Resting heart rate during wakefulness	86.5 ± 12.4	83.7 ± 10.5	-2.8 ± 13.7	87.4 ± 10.5	85.6 ± 11.7	-1.8 ± 13.6	-0.07	0.53

Descriptive statistics were presented as mean ± standard deviation. All P values were adjusted for age (5 to 7 y vs. 8 to 9 y), race (black vs. other), weight status (overweight or obese vs. nonoverweight), sex, and study site. \*Change is from baseline to follow-up. Normative range: <sup>a</sup>< 3 µg/mL; <sup>b</sup>1–5 y: Male: 40–128 mg/dL, Female: 62–128 mg/dL; 6–10 y: Male: 49–130 mg/dL, Female: 58–129 mg/dL; <sup>c</sup>1–5 y: Male: 26–64 mg/dL, Female: 29–72 mg/dL; 6–10 y: Male: 25–74 mg/dL, Female: 30–67 mg/dL; <sup>d</sup>1–5 y: Male: 44–157 mg/dL, Female: 42–155 mg/dL; 6–10 y: Male: 44–188 mg/dL, Female: 44–194 mg/dL; <sup>e</sup>60–100 mg/dL; <sup>f</sup>1–15 µIU/mL. eAT, early adenotonsillectomy; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NREM, nonrapid eye movement; REM, rapid eye movement; WWSC, Watchful Waiting with Supportive Care.

**Table 4**—Associations between changes from baseline to follow-up in cardiac measures and changes in corresponding sleep measures.

Cardiometabolic Marker*	Polysomnographic Measure*	$\beta$	SE	P
Systolic blood pressure percentile	AHI	0.03	0.17	0.85
	Stage N2	0.28	0.18	0.11
	Stage N3	-0.44	0.17	0.01
	REM sleep	0.16	0.29	0.58
	Sleep duration	-1.01	0.96	0.29
	Peak EtCO <sub>2</sub>	-0.29	0.37	0.43
	EtCO <sub>2</sub> > 50 mmHg	-0.10	0.08	0.18
	ODI 3	-0.04	0.16	0.81
	Oxygen saturation $\leq$ 92%	0.05	0.37	0.90
Diastolic blood pressure percentile	AHI	-0.20	0.15	0.19
	Stage N2	0.05	0.16	0.76
	Stage N3	-0.05	0.16	0.74
	REM sleep	0.18	0.27	0.51
	Sleep duration	-0.89	0.87	0.31
	Peak EtCO <sub>2</sub>	-0.46	0.33	0.16
	EtCO <sub>2</sub> > 50 mmHg	-0.05	0.07	0.45
	ODI 3	-0.11	0.15	0.47
	Oxygen saturation $\leq$ 92%	0.47	0.34	0.17
Average heart rate asleep	AHI	0.19	0.05	< 0.001
	Stage N2	-0.07	0.05	0.16
	Stage N3	0.02	0.05	0.64
	REM sleep	-0.08	0.08	0.34
	Sleep duration	-0.28	0.26	0.28
	Peak EtCO <sub>2</sub>	0.29	0.10	0.004
	EtCO <sub>2</sub> > 50 mmHg	0.05	0.02	0.02
	ODI 3	0.23	0.05	< 0.001
	Oxygen saturation $\leq$ 92%	0.30	0.11	0.006

Linear regressions were used to assess the association of change in cardiac measures outcomes with change in sleep measures from baseline to follow-up, adjusting for age, race (black vs. other), weight status (overweight or obese vs. nonoverweight), sex, and study site. \*Change from baseline to month 7. AHI, apnea-hypopnea index; EtCO<sub>2</sub>, peak end-tidal carbon dioxide; NREM, nonrapid eye movement; ODI, oxygen desaturation index; REM, rapid eye movement; SE, standard error.

blood pressure percentile. Further adjustment for percentage of REM sleep had no effect on these associations (data not shown).

No associations were observed between change in AHI, stage N2, stage N3, and REM sleep with any of the metabolic measures.

In an exploratory analysis assessing change in cardiometabolic parameters from baseline to follow-up within the 253 children who had “resolution of OSAS” (reduction in AHI to < 2 and apnea index to < 1), we found significantly increased levels of insulin and decreased heart rate (heart rate during sleep and resting heart rate during wakefulness) following intervention (P = 0.004 and P = < 0.001).

## DISCUSSION

In this large, randomized controlled trial of eAT for PSG-confirmed childhood OSAS, we found that eAT compared to the WWSC group did not result in a significant change in

fasting glucose, insulin, lipids, hs-CRP, blood pressure or heart rate over a 7-mo intervention period in children ages 5 to 9 y, the majority of whom had normal cardiometabolic parameters at baseline examination. We also did not observe significant correlations between polysomnographic indices and cardiometabolic variables other than an association between measures of OSAS severity (AHI, ODI, EtCO<sub>2</sub>) and heart rate in sleep (particularly REM sleep). We also observed that over the 7-mo intervention period, improvements in measures of oxygen saturation and end tidal CO<sub>2</sub> levels were associated with decreases in heart rate during sleep. Wake heart rate also improved in association with improved AHI and ODI. These results indicate that of all the measured cardiometabolic parameters, relatively simple indices of average heart rate during wakefulness and sleep were sensitive to OSAS severity. We also observed several interesting associations between N3 sleep and cardiometabolic parameters. In particular, increases in stage N3 sleep over the intervention period were associated with decreases in systolic blood pressure. However, the positive correlation between stage N3 sleep and triglyceride level was unexpected and of unclear significance.

Animal, adult, and pediatric studies implicate intermittent hypoxemia and sleep fragmentation in the pathogenesis of OSAS-related dysregulation of blood pressure, autonomic function, inflammation, and glucose and lipid metabolism.<sup>9,17–23,42–45</sup> Because children with severe hypoxemia were excluded from our study, it is possible that the lack of a significant effect of eAT on cardiometabolic outcomes reflects the modest level of hypoxemia in the CHAT sample. Our findings are not inconsistent with the limited and observational literature, which has shown variable cardiometabolic effects of treatment in children with OSAS. A study of 62 obese and nonobese children with OSAS reported significant improvements in serum lipid profiles and CRP after surgical removal of hypertrophic tonsils and adenoids in the entire cohort. However, significant improvements of insulin were only present in obese children.<sup>26</sup> Another small study found that children with resolution of OSAS (either by AT, positive pressure ventilation, or spontaneously) experienced a small but significant decrease in total cholesterol levels. However, no changes in insulin, glucose, triglycerides, or HDL cholesterol could be shown, whether or not treatment occurred.<sup>27</sup> Li et al.<sup>46</sup> demonstrated a significant reduction of CRP following treatment (AT, nasal corticosteroids, or positive pressure ventilation) in 16 children with OSAS, whereas lipid profiles remained unchanged. Similar to the findings of two other studies, we could not find a significant association between severity of OSAS with levels of fasting insulin and glucose.<sup>47,48</sup> Shamsuzzaman et al.<sup>24</sup> found that ODI rather than AHI was associated with increased insulin resistance in children with OSAS, an interesting result that could not be replicated in our study. One study on long-term outcomes of children with OSAS of whom 29% were treated with either AT, nasal steroids or a combination of treatments, including a nonsnoring control group, revealed that improvement of SDB (spontaneously or as a result of treatment) was associated with improved baroreflex control of blood pressure. However, there was no difference in either wake or overnight systolic blood pressure in the control, resolved, and unresolved groups at follow-up, which is in line with our study results.<sup>29</sup> In

contrast to our study, most prior research reported on patients with more severe OSAS, were not randomization trials, and did not robustly consider potential confounders.

In contrast to a null effect of eAT on cardiometabolic outcomes, we observed that improvement in AHI (or ODI or EtCO<sub>2</sub>) and increased stage N3 sleep in the intervention period was associated with reduction in heart rate and systolic blood pressure, respectively. The more significant associations observed for changes in PSG parameters than an effect of intervention per se (eAT vs. WWSC) may reflect the fact that there was within-group heterogeneity in changes in OSAS severity over the intervention period. In particular, 46% of children in the WWSC group had resolution of their OSAS and 21% of the eAT group had persistence of OSAS at follow-up, potentially reducing the between-group differences for the surgical and control arms.<sup>33</sup> Furthermore, the eAT group gained more weight than the WWSC group,<sup>35</sup> and weight gain may have confounded other treatment effects. Consistent with this notion, insulin sensitivity as measured by fasting insulin and glucose showed a trend toward worsening in the eAT group compared to the WWSC group at follow-up, and in fact was significantly increased in the subgroup in whom OSAS was resolved.

The sensitivity of change in heart rate to improvement in OSAS indices across the study period was consistent with the results of the baseline analysis showing that higher AHI, ODI, and EtCO<sub>2</sub> were each associated with higher heart rate. Heart rate has been described to be elevated in association with respiratory disturbances.<sup>2,30,49</sup> Recently, Walter et al.<sup>25</sup> comprehensively investigated nocturnal autonomic function in school children with SDB. In all sleep stages, children with moderate to severe OSAS had significantly higher heart rates compared with the control group. Moreover, children with SDB showed a significant lower heart rate variability during sleep than control children without SDB.<sup>25</sup> In another study, Muzumdar et al.<sup>30</sup> showed a significant reduction in heart rate during sleep in association with a reduction in AHI after adenotonsillectomy with a decrease in sympathetic balance as demonstrated by heart rate variability. It has been proposed that an accelerated heart rate induced by sympathetic nervous system over activity is responsible for the reported risk of long-term cardiovascular events and all-cause mortality.<sup>50,51</sup> Our results extend those reports by showing that OSAS is associated not only with heart rate measures during sleep as well as during wakefulness, albeit changes are small.

Increase in stage N3 sleep (also known as slow wave sleep; SWS) from baseline to post intervention was associated with a decrease in systolic blood pressure percentile. Stage N3 sleep is when parasympathetic tone is highest and sympathetic tone the lowest, corresponding to the stage when heart rate and blood pressure decline. In adults, decreased SWS has been linked to incident hypertension in older men.<sup>52</sup> In children, support for a relationship between blood pressure and SWS can be found in a recent study from Hannon et al.<sup>53</sup> that reported an association between decreased amounts of REM and N3 sleep with greater morning blood pressure in obese adolescents.

In baseline analyses, stages N1 and N3 sleep were positively associated with heart rate while stages N2 and REM sleep were negatively associated with heart rate. Although speculative, it

is possible that these associations reflect differences in homeostatic drive (i.e., resulting in more N3 sleep when studied in the laboratory) in some of the children who may be sleep deprived and have elevated sympathetic tone. Because sleep architecture changes and cardiometabolic function changes with puberty, it is also possible that pubertal influences may have confounded this association.<sup>54,55</sup> Although our analysis controls for age and sex and analyzed children younger than 9 y, there is a trend for earlier puberty, especially among African Americans who constituted a majority of our sample.<sup>56</sup>

This study has a number of significant strengths, including its large sample, inclusion of a racially diverse group, randomized design, and rigorous collection of measurements. However in the interpretation of our findings, several limitations must be considered. First, cardiometabolic parameters were assessed on only two time points, 6 to 7 mo apart. Measurement variability could bias the findings toward the null. It is possible that associations between cardiometabolic parameters and sleep indices may be stronger or weaker at later time points. Second, findings are applicable to children with mild to moderate levels of OSAS and should not be generalized to children who are markedly hypoxemic. Furthermore, results should not be generalized to primary snorers or those with upper airway resistance syndrome. Finally, analyses were not subject to correction for multiple comparisons, so that the likelihood of false positive findings is increased. The analyses in this paper were secondary to the primary results of the CHAT study, and thus require future independent replication.

In summary, this study evaluated the effect of eAT for OSAS on cardiometabolic parameters using a randomized controlled design. In contrast to our expectations, changes in levels of glucose, lipids, insulin, CRP, blood pressure, and heart rate were not different between eAT and WWSC groups. However, we identified the potential sensitivity of heart rate as an index of OSAS severity and a measure of responsiveness to OSAS improvement. We also identified a negative association between N3 sleep and lower blood pressure, a finding previously reported in adults. Because elevated heart rate and blood pressure are associated with increased cardiovascular risk, our results support further research aimed at clarifying the role of OSAS and its treatment of cardiovascular health of children.

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## SUPPLEMENTAL MATERIAL

**Table S1**—Change of sleep measures and BMI z-score from baseline to follow-up in the early Adenotonsillectomy compared to the Watchful Waiting with Supportive Care group.

Outcome	eAT			WWSC			Effect Size	P
	Baseline	Follow-up	Change*	Baseline	Follow-up	Change*		
AHI, events/h	6.9 ± 5.7	1.6 ± 3.0	-5.3 ± 6.2	6.6 ± 5.6	5.9 ± 10.1	-0.7 ± 9.5	-0.57	< 0.001
Stage N1, % TST	8.6 ± 4.2	6.8 ± 3.2	-1.8 ± 3.8	8.8 ± 4.2	8.4 ± 4.7	-0.4 ± 4.7	-0.32	0.001
Stage N2, % TST	41.2 ± 7.5	44.5 ± 7.2	3.3 ± 8.2	41.4 ± 7.9	42.8 ± 7.0	1.4 ± 7.8	0.24	0.02
Stage N3, % TST	31.4 ± 7.3	30.0 ± 7.0	-1.4 ± 8.2	31.8 ± 7.7	30.9 ± 6.7	-0.8 ± 7.7	-0.07	0.47
REM sleep, % TST	18.8 ± 4.2	18.6 ± 3.9	-0.1 ± 4.8	18.1 ± 4.4	17.9 ± 4.2	-0.2 ± 4.9	0.004	0.85
Peak EtCO <sub>2</sub> , mmHg	55.3 ± 3.8	54.2 ± 3.6	-1.1 ± 4.3	54.1 ± 3.8	54.4 ± 4.2	0.3 ± 4.9	-0.31	0.008
EtCO <sub>2</sub> > 50 mmHg, % of TST	12.0 ± 19.9	7.3 ± 14.6	-4.7 ± 20.8	9.0 ± 19.1	9.5 ± 18.5	0.5 ± 24.5	-0.23	0.07
ODI 3, events/h	7.4 ± 6.9	2.9 ± 3.7	-4.6 ± 7.1	6.8 ± 6.3	6.3 ± 10.4	-0.5 ± 9.3	-0.49	< 0.001
Oxygen saturation ≤ 92%, % TST	0.6 ± 1.3	0.3 ± 2.2	-0.3 ± 2.5	0.7 ± 3.5	0.6 ± 3.3	-0.2 ± 4.6	-0.04	0.77
Sleep duration, h/day	9.4 ± 1.3	9.4 ± 1.3	-0.1 ± 1.5	9.6 ± 1.4	9.6 ± 1.3	0.0 ± 1.8	-0.05	0.66
BMI z-score	0.9 ± 1.4	1.2 ± 1.2	0.3 ± 0.4	0.8 ± 1.3	1.0 ± 1.3	0.2 ± 0.4	0.30	0.003

Descriptive statistics were presented as mean ± standard deviation. All P values were adjusted for age (5 to 7 years of age vs. 8 to 9 years of age), race (black vs. other), weight status (overweight or obese vs. non-overweight), gender and study site. \*Change is from baseline to follow-up. AHI, apnea-hypopnea index; BMI, body mass index; eAT, early adenotonsillectomy; ODI, oxygen desaturation index; REM, rapid eye movement; WWSC, Watchful Waiting with Supportive Care.