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Objective sleep quality and metabolic risk in healthy weight children results from the randomized Childhood Adenotonsillectomy Trial (CHAT)

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Abstract

Background We hypothesized that cardiopulmonary coupling (CPC) sleep quality reflects cardiovascular and cardiometabolic health, in healthy weight children.

Methods Retrospective signal analysis of existing ECG data utilizing CPC, FDA cleared, software as medical device (SaMD). ECG signals were extracted from baseline polysomnography studies in the prospective Childhood Adenotonsillectomy Trial database, multicenter, single-blind, randomized controlled trial of 5.0–9.9-year-old children identified with obstructive sleep apnea syndrome without severe hypoxemia. Healthy weight was defined as age- and gender-specific BMI in the 5th–85th percentile range and overweight above the 85th percentile. The cohort was stratified based on CPC sleep quality Index (SQI) defined as high sleep quality (SQI ≥ 80) or low sleep quality (SQI < 60). Cardiovascular, cardiometabolic, quality of life, and cognition were compared between the sleep quality groups.

Results Healthy weight children with low sleep quality had more fragmented sleep with significantly higher arousal index (10.0 ± 4.3 vs.7.2 ± 3.1; $p = 0.00$) and $eLFC_{BB}$ (12.4 ± 4.9 vs. 0.9 ± 1.0; $p < 0.001$) CPC indicator of sleep fragmentation, higher average heart rate during sleep (84.5 ± 10.6 vs. 79.4 ± 7.1; $p = 0.03$) and worse insulin/glucose ratio (1.7 ± 1.6 vs. 1.1 ± 1.1; $p = 0.03$) and fasting insulin levels (7.9 ± 7.2 vs.5.3 ± 5.5; $p = 0.05$) when compared to healthy weight children with high sleep quality. SQI significantly correlates with average heart rate during sleep, insulin and triglyceride levels; for a unit increase in SQI, there is 0.154 unit decrease in average heart rate during sleep, 0.109 unit in insulin levels and 0.332 unit in triglyceride levels, respectively.

Conclusion CPC sleep quality offers insights into pediatric sleep and how it affects cardiovascular and cardiometabolic health. ECG is simple signal to collect, which makes this method practical for testing sleep, over multiple nights, and on multiple occasions providing information on sleep dynamics not possible before.

Trial registration NCT00560859

Keywords Children · Cardiovascular risk · Cardiometabolic risk · Sleep quality · Cardiopulmonary coupling

Introduction

Short and/or poor sleep in childhood increases risk of cardiovascular and cardiometabolic disease that may negatively affect the child's long-term health [1, 2]. Prior studies looking at this subject matter have primarily focused on sleep duration rather than sleep quality and have included overweight and/or obese children [3–5]. Most current publications are based on subjective self-reporting, known to inaccurately estimate both sleep quantity and quality and many include small sample sizes [6, 7]. Less information is available on how sleep quality affects cardiometabolic risk in healthy weight children.

Data Registry Childhood Adenotonsillectomy Study for Children with OSAS (CHAT)

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Methods for measuring sleep in children vary in level of accuracy, convenience, and cost. Patient's history, questionnaires, and physical examination alone are not reliable enough to accurately identify sleep quantity, quality, and pathology [8]. The gold standard for sleep evaluation in children is polysomnography (PSG) which is typically conducted in a clinical environment. PSG is a simultaneous and multivariate assessment of sleep parameters, including sleep duration, sleep staging, and generates an arousal index. Although PSG is considered the most accurate method to measure sleep [9], against which other measures are typically tested [10, 11], the method is extremely expensive, inconvenient, and challenging for children. PSG typically provides only one night of information, which unlikely reflects the child's natural sleep in their home environment [12].

Alternative methods that are commonly used to measure sleep parameters such as overnight oximetry and actigraphy are limited in their capacity to provide accurate measure of sleep quality and sleep quantity. Overnight oximetry provides no information about sleep quality or quantity. Oximetry in children is also less helpful than in adults as children have less collapsible upper airways and compensate for narrowing or partial obstruction of the airway by activation of upper airway muscles secondary to increased central ventilatory drive and therefore are less likely to have oxygen desaturations [13, 14]. Actigraphy has been shown to both over- and underestimate wake after sleep onset, thus providing a poor estimate of sleep disruptions when compared to PSG [10, 11]. Given the important role of sleep for healthy development, these constraints compromise the ability to objectively measure sleep quality in children. As inadequate sleep quality and/or quantity adversely affects both physical and mental health in children, simple and effective ambulatory methods to objectively and accurately measure sleep quality, quantity, and pathology would be clinically useful [7, 15, 16].

Cardiopulmonary coupling (CPC) [16–20] is a method to measure sleep duration, sleep quality, and sleep pathology derived from analyzing ECG signal collected during sleep. CPC is evidence-based software as a medical device (SaMD) coupling heart rate variability (HRV) and ECG-derived respiration (EDR). The method is Food Drug Administration (FDA) cleared, Health Insurance Portability and Accountability Act (HIPAA) compliant to establish sleep quality and evaluate sleep disorders to inform or drive clinical management. CPC sleep quality correlates well with delta sleep measured from the surface EEG, supporting the link between cortical EEG electrical activity and autonomic brain stem mediated cardiorespiratory functions [19, 20]. The method has previously been described in detail [16–20].

Hypothesizing that low CPC sleep quality negatively affects cardiovascular and cardiometabolic health in healthy weight children with OSAS, we analyzed ECG signal from PSG data in the Childhood Adenotonsillectomy Study (CHAT). The CHAT database includes children with polysomnography (PSG) confirmed OSAS and information on metabolic risk, a combination of elevated blood pressure, waist circumference, elevated glucose and insulin levels, triglycerides, low and high-density lipoprotein levels (HDL), quality of life, and cognition. To test our hypothesis, we stratified healthy weight children from the CHAT cohort based on CPC sleep quality index (SQI) into three categories, low SQI ($SQI < 60$), moderate SQI ($60 \leq SQI < 80$), and high SQI ($SQI \geq 80$). SQI, a summary index incorporating sleep quality, sleep fragmentation, and sleep pathology, is presented on a scale of 0–100. SQI provides an easily understandable measure distinguishing between high and low sleep quality irrespective of type of pathology [17, 18], with normative values available for both pediatric and adult sleep [21–23].

Methods

Study design

CHAT is a multicenter prospective, controlled and single-blinded study conducted across seven academic sleep centers in the USA. Methodology [24] and primary results of the trial's neurocognitive outcomes were previously reported [25]. Participants, 1244 habitually snoring children age 5.0–9.9, recruited from pediatric sleep centers, pediatric otolaryngology clinics, general pediatric clinics, and the general community all underwent a baseline PSG test. Institutional review board approval was obtained from each participating institution, children provided assent and parents provided written informed consent. This study is a secondary analysis of the baseline data from CHAT that randomized eligible children aged 5.0–9.9 diagnosed with OSAS based on outcome of PSG-sleep study to early adenotonsillectomy (eAT) vs. control group undergoing watchful waiting with supportive care (WWSC) and compared the two groups for progression of their diagnoses 7 months after intervention [24].

Participants

Included in the randomized trial are 453 children identified with OSAS defined as an obstructive apnea-hypopnea index ($AHI \geq 2$ events per hour or an obstructive apnea index ($OAI \geq 1$ event per hour. Exclusion criteria included severe OSAS ($OAI > 20$, $AHI > 30$, or oxyhemoglobin saturation of less than 90% for more than 2% of total sleep time, craniofacial or cardiac disorders, recurrent tonsillitis requiring surgical intervention, psychiatric or behavioral disorders (including attention-deficit/hyperactivity disorder), and extreme obesity (defined by a body mass index (BMI) > 2.99, BMI, z; score of relative weight adjusted for child age and sex). The CHAT study was registered at Clinicaltrials.gov (NCT00560859).

Flow of participants through the study is presented as supplemental material.

Study procedures/ interventions

Polysomnography

All children participating in the study underwent full-night PSG with study-certified technicians using standardized protocol following the American Academy of Sleep Medicine (AASM) guidelines [8]. Scoring was performed according to the AASM pediatric criteria by certified technologists blinded to all other study data at two central PSG reading centers. AHI was defined as sum of all obstructive and mixed apneas, plus hypopneas associated with 50% reduction in airflow and either greater than 3% desaturation or electroencephalographic arousal, divided by hours of total sleep time.

Cardiopulmonary coupling (CPC)

CPC is evidence-based, automated software as a medical device (SaMD, SleepImage®). The CPC technique is FDA cleared, HIPAA compliant and has been described in detail and published [19]. The method analyzes ECG signal collected during sleep, extracting and coupling heart rate variability (HRV) and ECG-derived respiration (EDR), generating an ECG-derived sleep spectrogram (Fig. 1) [17–19]. NREM sleep is presented as a bimodal structure of stable (high-frequency coupling, HFC) and unstable (low-frequency coupling, LFC) sleep. Stable sleep occurs during part of stage N2 and all of stage N3 NREM sleep and is associated with periods of stable breathing, increased delta power, and blood pressure dipping. Conversely, unstable sleep is characterized by variability of tidal volumes and non-dipping of blood pressure. Fragmented REM sleep has an LFC signature, while normal REM sleep and wake have very low-frequency coupling signature (vLFC). A subset of low-frequency coupling, termed elevated low-frequency coupling broad-band ($eLFC_{BB}$) defines fragmented sleep, periods of apneas-hypopneas, and arousals while elevated low-frequency coupling narrow-band ($eLFC_{NB}$) defines periodicity and presents apneas caused by respiratory dyscontrol [17–26].

CPC summarizes sleep duration, sleep stability (HFC), sleep fragmentation ($eLFC_{BB}$, CVHR, vLFC, sleep state transitions), and sleep pathology ($eLFC_{BB}$, $eLFC_{NB}$, SAI) in the SQI, presented on a scale of 0–100. The SQI provides a meaningful unit of measure to track changes in sleep quality over time, with expected values for both pediatric and adult sleep to distinguish between healthy sleep and sleep pathology [17, 18, 23]. Sleep apnea indicator (SAI) identifies and summarizes respiratory events during sleep. SAI is a marker of autonomic changes in heart rate during apneas and hypopneas that are expected to decrease as OSAS is successfully treated with healthy sleep patterns dominating [17, 18]. CPC analysis of ECG has previously been demonstrated as a sleep screening test for children with obstructive sleep apnea [27] and that stable sleep increases after adenotonsillectomy with decrease in elevated low-frequency coupling broad-band ($eLFC_{BB}$), a parameter measuring sleep-disordered breathing in tandem with AHI capturing treatment effect [28, 29]. Using the SQI with the SAI, $eLFC_{BB}$ and $eLFC_{NB}$, it is possible to identify the prevalence and severity of sleep-disordered breathing (SDB) and to categorize as obstructive, central or complex sleep apnea [17, 26]. CPC analysis was applied to pooled baseline ECG data from both intervention arms for both healthy weight and overweight children with available cardiometabolic, quality of life, and cognition measures. Studies with low ECG signal quality were rejected. CPC analysis is based on sleep periods as scored in the existing CHAT PSG studies and parameters are presented as percentages of this sleep period.

Outcome measures

Healthy weight children defined as age- and gender-specific in the BMI range 5th–85th percentile and overweight in the BMI above 85th percentile were included in the analysis. Mean values for heart rate were obtained from PSG recordings by averaging ECG heart rate values across the sleep period. During a morning baseline exam, systolic and diastolic blood pressure was measured after a 10-min rest period, with the child sitting using calibrated sphygmomanometer with cuff size chosen based on the child's arm circumference.

Height was measured with calibrated wall-mounted stadiometer with the child in her/his stocking feet and weight was measured with research quality, calibrated digital scales. Blood was assayed for glucose and lipids (cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides), and fasting insulin levels. Developmental neuropsychological assessment (NEPSY) was applied for attention and executive function and pediatric quality of life (PedsQL) was assessed. SQI, a summary index of all CPC variables is provided. High sleep quality is defined as SQI ≥ 80 and low sleep quality as SQI < 60 at baseline, with moderate sleep quality defined between the two threshold markers [22]. SQI distribution in the cohort is summarized in Fig. 2. Differences in polysomnographic indices, cardiometabolic measures, quality of life, and cognition were compared between the sleep quality groups.

Statistical analysis

Outcome variables were compared between the three sleep quality groups. Continuous variables are presented as means

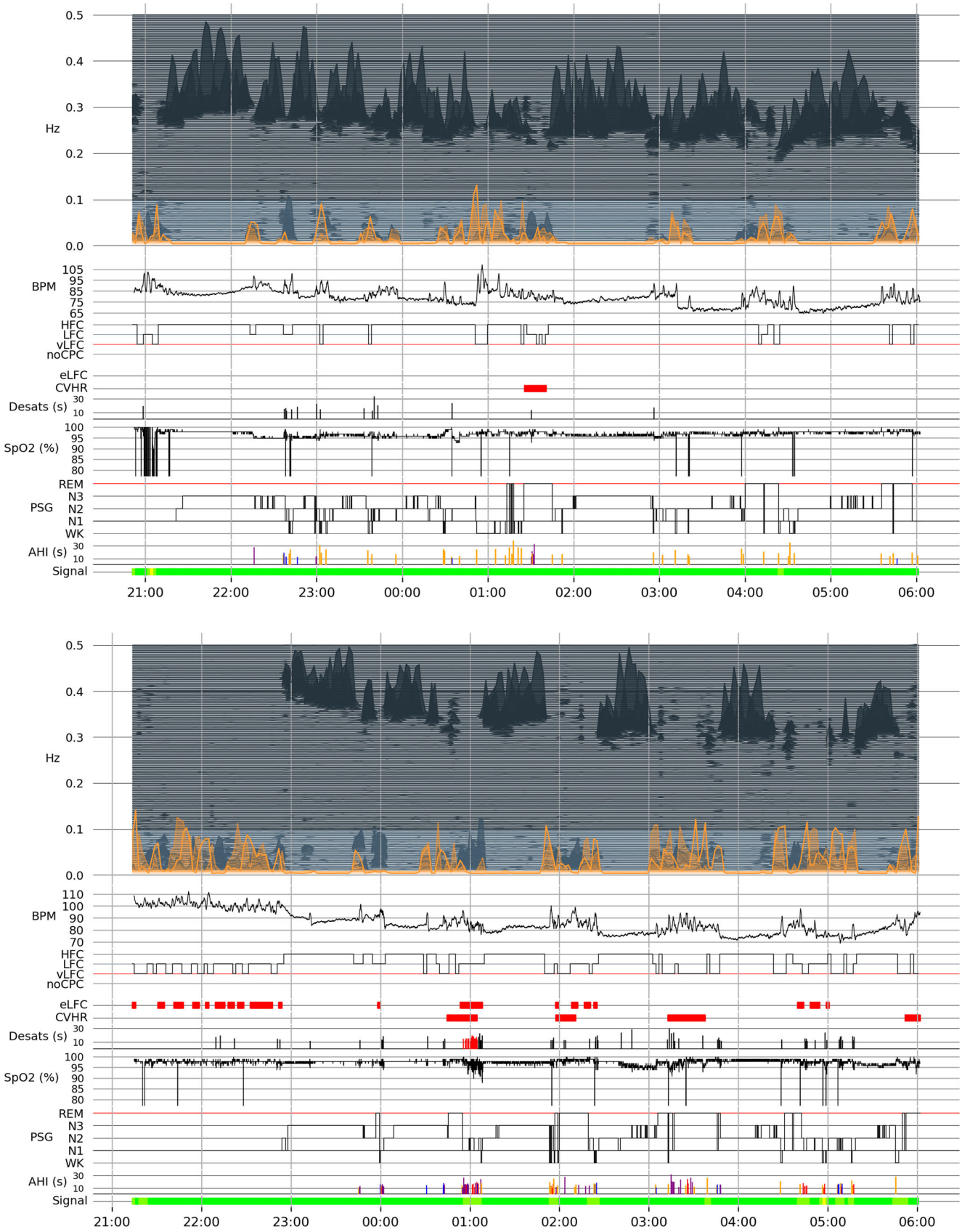
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Fig. 1 Sleep spectrograms and sleep data output, cardiopulmonary coupling, and polysomnography. Child with high sleep quality (above) vs. child with low sleep quality (below). Above: SQI = 89.0; SAI = 2.3; CVHR = 2.7; $eLFC_{BB}$ = 0.0%; $eLFC_{NB}$ = 0.0%; AHI = 1.2; ODI 3% = 1.6; average heart rate during sleep 78; blood pressure = 98/49 mmHg; fasting insulin = 3.3; fasting glucose = 4.5. Below: SQI = 49.8; SAI = 10.8; CVHR = 11.9%; $eLFC_{BB}$ = 16.5%; $eLFC_{NB}$ = 0.0%; AHI =11.8; ODI 3% = 14.2; average heart rate during sleep 84; blood pressure = 86/58; fasting insulin = 10.7 (μIU/ml); fasting glucose = 4.2 (mg/DL). The *X*-axis marks the timeline. *Y*-axis from top down; CPC sleep spectrogram; spectral presentation of the cardiopulmonary coupling (CPC) analysis. *x* = time; *y* = frequency, BPM, heart rate graph; CPC, hypnogram; eLFC, elevated low-frequency broad-band ($eLFC_{BB}$); elevated low-frequency narrow-band ($eLFC_{NB}$); CVHR, cyclic variation of heart rate; Desats, oxygen desaturations; SpO_2, oxygen saturation; polysomnography, (PSG) sleep staging; AHI scoring (obstructive (red); central (blue); mixed (black); hypopnea (purple); ECG, signal quality line

and standard deviations (SD) with categorical variables as percentages. Multivariate analysis of variance (MANOVA), pairwise correlations, and ordinary least squares regression (OLS) was utilized to investigate differences in sleep quality between the groups. Statistical significance was rejected for *p* values greater than or equal to 0.05. Calculations were performed using Stata 15 (Stata version 15.1, StataCorp, College Station, TX) [30].

Results

Included in our main analysis are healthy weight (defined as age- and gender-specific BMI > 5th and BMI < 85th percentile). Subjects with defined ECG signal issues in the baseline data or missing cardiometabolic, quality of life, or cognitive data were excluded. Total of 174 healthy weight children were included, with high sleep quality, *n* = 35 (20%), with moderate sleep quality, *n* = 102 (59%), and with low sleep quality, *n* = 37 (21%), respectively. Baseline characteristics in anthropometric, cardiopulmonary coupling, polysomnographic, cardiovascular and cardiometabolic, quality of life, and cognition metrics are summarized in Table 1.

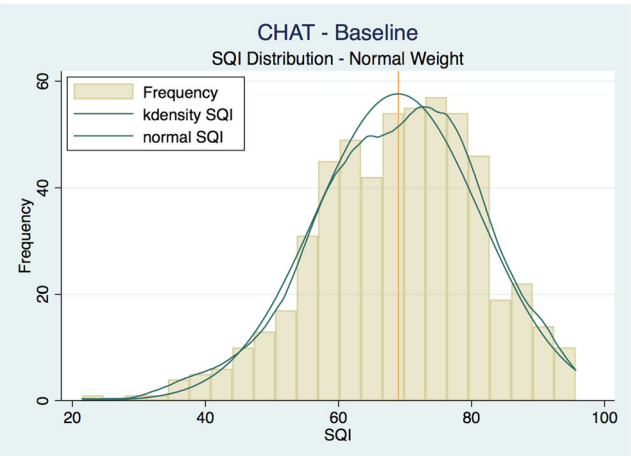

Fig. 2 Distribution of the sleep quality index (SQI). Baseline data of healthy weight children (*n* = 174) included in both intervention groups, early adenotonsillectomy (eAT), and watchful waiting with supportive care (WWSC)

Obstructive sleep apnea parameters As expected, when comparing the sleep quality groups of low and high sleep quality, there was a significant difference in both PSG measures of AHI 7.7 ± 6.5 vs. 4.8 ± 3.4, $p = 0.04$; $ODI_{3\%}$ 8.5 ± 8.1 vs. 4.2 ± 3.8, $p = 0.00$; arousal index 10.0 ± 4.3 vs. 7.2 ± 3.1, $p = 0.00$ and in CPC measures of SAI 6.4 ± 4.6 vs.1.1 ± 1.2, $p < 0.001$; $eLFC_{BB}$ 12.2 ± 4.9 vs. 0.9 ± 1.0, $p < .001$; $eLFC_{NB}$ 1.4 ± 1.4 vs.0.1 ± 0.4, $p < 0.001$, respectively.

Cardiovascular and cardiometabolic parameters Children with low sleep quality had higher average heart rate during sleep (84.5 ± 10.6 vs. 79.4 ± 7.1; $p = 0.03$) and insulin/glucose ratio (1.7 ± 1.6 vs.1.1 ± 1.1; $p = 0.03$). Average fasting insulin levels (7.9 ± 7.2 vs. 5.3 ± 5.5; $p = 0.05$) and triglyceride-HDL ratio (1.6 ± 0.7 vs. 1.2 ± 0.5; $p = 0.07$) trended negatively in children with low sleep quality.

Correlations of SQI and cardiovascular/cardiometabolic parameters Correlations between CPC variables and metabolic variables as well as key PSG variables within the subset of healthy weight children at baseline were calculated. SQI significantly correlated with the arousal index ($p < 0.003$), average heart rate during sleep ($p < 0.022$), triglyceride levels ($p < 0.019$), and triglyceride/HDL ratio ($p < 0.008$) (Table 2). Ordinary Least Square regression (OLS) results of SQI and insulin level demonstrated a 0.109 unit decrease in insulin level for a unit increase in SQI for healthy weight subjects, controlling for gender, race, and age. OLS models with the same independent variables of Triglyceride level and average heart rate during sleep demonstrated statistically significant effect of 0.332 and 0.154 unit decrease, respectively, for a unit increase in SQI (Table 3).

Finally, we analyzed the baseline data including overweight children with low and high sleep quality (Table 4). When comparing health weight children with low sleep quality (SQI<60) with overweight children with high sleep quality (SQI≥80) the groups did not differ significantly in cardiometabolic measures or average heart rate during sleep. While overweight children had significantly higher average systolic blood pressure ($p = 0.01$) and C-reactive protein levels ($p = 0.02$). Comparing the low sleep quality groups of healthy weight and overweight children demonstrates a significant difference in both cardiovascular and cardiometabolic measures, average systolic blood pressure ($p < 0.001$), average diastolic blood

Table 1 Baseline characteristics of the 174 patients included in the ECG analysis, stratified based on sleep quality

	A. SQI < 60 ($n = 35$)	B. 60 ≤ SQI < 80 ($n = 102$)	C. SQI ≥ 80 ($n = 37$)	p (A vs. B)	p (A vs. C)
Characteristics					
Male (%)	54.3	56.9	52.8	0.98	0.48
African American (%)	34.3	41.2	52.8	0.36	0.07
Caucasian (%)	48.6	43.1	47.2	0.54	0.70
Other (%)	17.1	15.7	2.8	0.71	0.01
Medication for asthma (%)	22.9	16.7	19.4	0.76	0.51
Age (years)	6.3 (1.2)	6.1 (1.2)	6.3 (1.0)	0.59	0.93
BMI (kg/m2)	15.5 (1.2)	15.3 (1.3)	15.3 (1.1)	0.60	0.77
BMI z-score	− 0.1 (1.0)	− 0.3 (0.9)	− 0.2 (0.9)	0.74	0.93
Waist measurement (cm)	55.1 (4.5)	52.8 (4.0)	53.0 (3.5)	0.01	0.06
Polysomnographic measures					
Sleep duration	599.4 (75.1)	591.1 (69.6)	600.0 (96.1)	0.97	0.61
AHI	7.7 (6.5)	5.84 (5.2)	4.8 (3.4)	0.07	0.04
OAI	2.8 (3.2)	2.2 (2.76)	2.0 (2.0)	0.31	0.34
Arousal index	10.0 (4.3)	9.0 (3.1)	7.2 (3.1)	0.12	0.00
ODI 3%	8.5 (8.1)	5.1 (5.4)	4.2 (3.8)	0.01	0.00
Pct. sleep time SpO2 < 92%	0.4 (1.0)	0.3 (0.6)	0.3 (1.0)	0.24	0.61
Minimum O_2 saturation during sleep (%)	88.6 (4.2)	90.0 (4.4)	89.2 (7.7)	0.29	0.78
CPC-CVHR measures					
SQI	50.5 (7.1)	70.2 (5.7)	85.3 (4.2)	< 0.001	< 0.001
SAI	6.4 (4.6)	3.3 (4.1)	1.1 (1.2)	0.00	< 0.001
CVHR (%)	7.2 (5.2)	4.8 (5.1)	3.5 (3.5)	0.07	0.02
$eLFC_{BB}$ (%)	12.2 (4.9)	4.2 (2.8)	0.9 (1.0)	< 0.001	< 0.001
$eLFC_{NB}$ (%)	1.4 (1.4)	0.1 (0.4)	0.1 (0.4)	< 0.001	< 0 .001
Metabolic measures					
Average heart rate during sleep (bpm)	84.5 (10.6)	82.7 (8.2)	79.4 (7.1)	0.37	0.03
Average systolic blood pressure	94.5 (7.4)	93.2 (7.7)	94.5 (6.7)	0.36	0.84
Average diastolic blood pressure	60.0 (7.3)	59.3 (7.0)	60.7 (6.0)	0.58	0.83
Fasting insulin (μIU/ml)	7.9 (7.2)	4.3 (2.7)	5.3 (5.5)	< 0.001	0.05
Fasting glucose (mg/dl)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	0.66	0.83
Insulin/glucose ratio	1.7 (1.6)	0.9 (0.6)	1.1 (1.1)	< 0.001	0.03
Triglyceride-HDL ratio (mg/dL)	1.6 (0.7)	1.4 (0.7)	1.2 (0.5)	0.44	0.07
Triglyceride level (mg/dL)	72.9 (23.6)	68.2 (25.7)	60.6 (17.1)	0.77	0.14
Blood HDL level (mg/dL)	49.1 (10.9)	52.1 (10.8)	55.0 (13.8)	0.34	0.10
Blood LDL level (mg/dL)	91.8 (22.9)	86.4 (18.8)	86.7 (18.5)	0.32	0.32
C-reactive protein level (mg/mL)	0.8 (1.7)	2.5 (10.4)	0.5 (1.1)	0.40	0.87
Questionnaires					
PedQL parent total score	78.8 (14.0)	82.6 (12.7)	79.0 (14.2)	0.24	0.84
PedQL child total score	65.9 (13.1)	69.0 (15.0)	67.6 (13.0)	0.91	0.98
NEPSY: inhibition total score	8.4 (4.8)	7.5 (4.1)	7.9 (3.9)	0.38	0.70

Descriptive statistics were presented as means ± standard deviation (SD). BMI, body mass index (the weight in kilograms divided by the square of the height in meters); BMI z-score (relative weight adjusted for child age and sex); AHI, apnea/hypopnea index; ODI, oxygen desaturation index; SQI, sleep quality index; SAI, sleep apnea indicator; CVHR, cyclic variation of heart rate; $eLFC_{BB}$, elevated low-frequency coupling broad-band; $eLFC_{NB}$, elevated low-frequency coupling narrow-band; bpm, heart-beats per minute; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PedQL, pediatric quality of life questionnaire; NEPSY, neuropsychological assessment

pressure ($p = 0.02$), fasting insulin (p = 0.01), insulin/glucose ration (p = 0.01), triglyceride levels ($p = 0.02$), blood LDL level ($p = 0.03$), and C-reactive protein ($p = 0.01$).

Table 2 Correlation coefficients of CPC metrics, PSG metrics and metabolic measures, *p* values in parenthesis

	SQI	SAI	CVHR (%)	$eLFC_{BB}$ (%)	$eLFC_{NB}$ (%)
AHI	− 0.125	0.253	0.218	0.068	0.07
	(0.1)	(0.001)	(0.004)	(0.371)	(0.362)
ODI 3%	− 0.201	0.225	0.19	0.132	0.069
	(0.008)	(0.003)	(0.012)	(0.082)	(0.366)
Arousal index	− 0.223	0.350	0.288	0.116	0.160
	(0.003)	(0.000)	(0.000)	(0.129)	(0.035)
Average heart rate during sleep (bpm)	− 0.174	0.129	0.053	0.161	− 0.058
	(0.022)	(0.091)	(0.489)	(0.034)	(0.449)
Average systolic blood pressure	0.007	− 0.007	0.021	0.009	0.011
	(0.925)	(0.932)	(0.788)	(0.905)	(0.883)
Average diastolic blood pressure	0.037	− 0.023	0.03	− 0.023	− 0.074
	(0.632)	(0.769)	(0.696)	(0.768)	(0.331)
Fasting insulin (μIU/ml)	− 0.108	0.007	− 0.059	0.151	0.195
	(0.21)	(0.935)	(0.493)	(0.078)	(0.023)
Fasting glucose (mg/dl)	− 0.109	− 0.053	− 0.041	0.152	− 0.008
	(0.195)	(0.535)	(0.629)	(0.072)	(0.927)
Triglyceride-HDL ratio (mg/dl)	− 0.221	0.092	0.016	0.135	0.019
	(0.008)	(0.275)	(0.854)	(0.109)	(0.826)
Triglyceride Level (mg/dL)	− 0.197	0.075	− 0.001	0.125	− 0.031
	(0.019)	(0.372)	(0.994)	(0.137)	(0.712)
Blood LDL level (mg/dL)	− 0.098	0.195	0.122	0.081	0.022
	(0.246)	(0.02)	(0.148)	(0.338)	(0.795)
Blood HDL level (mg/dL)	0.165	− 0.143	− 0.091	− 0.116	− 0.132
	(0.05)	(0.09)	(0.281)	(0.17)	(0.118)
C-reactive protein level (mg/mL)	0.034	− 0.024	− 0.052	− 0.039	− 0.057
	(0.694)	(0.779)	(0.543)	(0.649)	(0.508)
Insulin-glucose ratio	− 0.089	− 0.002	− 0.064	0.127	0.183
	(0.304)	(0.98)	(0.458)	(0.14)	(0.033)

AHI apnea/hypopnea index, *ODI* oxygen desaturation index, *bpm* heart-beats per minute, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol

Discussion

Our major findings from the analysis of baseline PSG recordings of children randomized to eAT or WWSC in the CHAT database using ECG-based CPC analysis are that healthy weight children with low sleep quality and OSAS have higher average heart rate during sleep and compromised insulin sensitivity when compared to healthy weight children with high sleep quality. With each unit increase of SQI a significant improvement was observed in average heart rate during sleep, insulin, and triglyceride levels. Comparing healthy weight children with low sleep quality and overweight children with high sleep quality, no significant difference was noted in average heart rate during sleep or cardiometabolic measures. Significant difference was documented when comparing healthy weight children with low sleep quality and overweight children with low sleep quality in both cardio metabolic and cardiovascular measures. The results supports our hypothesis that low sleep quality in childhood increases risk of cardiovascular and cardiometabolic disease, irrespective of weight and imply prognosis towards metabolic syndrome and weight gain in healthy weight children with low sleep quality, negatively affecting their long-term health prospects. With increasing variety of available wearable devices that record ECG data, this SaMD is a practical tool for multi-night testing in the child's natural sleeping environment, offering the opportunity to capture sleep dynamics. This simple approach also minimizes or eliminates the first night effect of sympathetic stimulation caused by the PSG testing, which previously has been identified as a challenging environment for children [31–33].

Early identification of low sleep quality to phenotype children that may benefit from timely and appropriate intervention could positively contribute to the child's future health prospects and quality of life. Further, the corollary may also hold true, where children with preserved sleep quality may require longitudinal observation and retesting rather than immediate intervention for their OSAS. Future studies are needed to

Table 3 Ordinary least squares regression

	Fasting insulin (μIU/ml)		Triglyceride level (mg/dl)		Average heart rate during sleep (bpm)	
	Coefficient	*p*	Coefficient	*p*	Coefficient	*p*
SQI	− 0.109	0.034	− 0.332	0.030	− 0.154	0.011
Male	0.656	0.385	− 2.538	0.516	− 5.008	0.000
African American	1.810	0.051	− 14.305	0.001	3.227	0.033
Race Other	− 0.001	0.999	− 3.365	0.548	− 1.000	0.647
Age (years)	0.221	0.498	1.641	0.327	− 1.322	0.032
Constant	10.296	0.045	88.100	0.000	102.791	0.000
	Prob > *F* = 0.0202		Prob > *F* = 0.0003		Prob > *F* = 0.000	
	R-squared = 0.1115		*R*-squared = 0.1338		*R*-squared = 0.1688	
	Root MSE = 4.4819		Root MSE = 22.511		Root MSE = 8.0144	

SQI on insulin level, triglyceride level, and average heart rate during sleep

Regression significance, *Root MSE* root mean-squared error

assess longitudinal associations of sleep quality, sleep quantity, and cardiovascular and cardiometabolic risk factors through repeated objective sleep recordings collected at multiple time points in the child's natural sleep environment.

With growing interest in the importance of identifying cardiovascular and cardiometabolic risk factors at an early stage in life [1, 2, 34, 35], our results indicate that the sleep period may offer additional information to identify children at increased risk. As the metabolic syndrome in childhood predicts adult cardiovascular disease and sleep duration and efficiency in children has been associated with adverse cardiovascular and cardiometabolic outcomes, improving sleep quality may be a potential target for prevention [1–3, 5, 36, 37]. Majority of current literature on this subject matter is focused on sleep duration rather than sleep quality and involves overweight and obese children. Obesity is strongly associated with cardiometabolic risk and has been reported [3]. Our analysis is more focused on healthy weight children, comparing high sleep quality (SQI ≥ 80) and low sleep quality (SQI < 60), to observe if sleep quality offers additional information in healthy weight children.

Several proposed mechanisms explain the association between impaired sleep quality, sleep quantity, and metabolic risk factors. Curtailment of sleep causes a stress response with augmented autonomic activity increasing sympathetic output affecting the sleeping heart rate and the hypothalamus-pituitary-adrenocortical axis influencing metabolic processes. The cardiopulmonary coupling method characterizes sleep based on interaction of autonomic heart rate variability and respiratory oscillations for characterization of sleep quality summarized in the SQI, collectively reflecting autonomic nervous system (ANS) output during sleep. Reduced SQI indicates increased sympathetic activity and reduced parasympathetic activity during the sleep period [18, 38].

Overnight heart rate has previously been found to be the most sensitive parameter for determining severity of OSAS [8]. Higher average heart rate during sleep in healthy weight children with low sleep quality reflects more respiratory events, arousals, and increased sympathetic activity, contributing to increased metabolic risk [8, 38, 39]. Healty weight children with low sleep quality had significantly higher insulin/glucose ratio and fasting insulin compared to healthy weight children with high sleep quality and SQI was strongly correlated with triglyceride levels and triglyceride/HDL ratio. Compromised insulin sensitivity and lipid metabolism and increased average heart rate during sleep are all independent risk factors for atherosclerotic cardiovascular disease, echoing previously published data that compromised sleep efficiency is associated with increased metabolic risk starting early in childhood [1, 34, 35]. SQI is a summary index of all CPC parameters, and as expected is strongly correlated with the arousal index. SAI, a summary index reflecting autonomic cardiac responses to respiratory perturbations such as apneas and hypopneas, has a strong correlation with the arousal index and as expected correlates with AHI [18]. As children have less collapsible upper airways and are known to desaturate less makes detection of arousals vital when evaluating sleep disorders in children [13, 14].

Our analysis did not find a difference in sleep duration between the sleep quality groups. This may be explained by the highly controlled testing environment in the sleep laboratory and the single night testing protocol. Output of questionnaires and assessments of cognitive abilities did not differ when comparing healthy weight children with low and high sleep quality, which may indicate lack of reliability to retrace sufficient information for clinical evaluation in this age group [8].

Limitations to our analysis are that there is no control group and that the CHAT protocol only includes children with PSG confirmed OSAS as it was designed to test response to adenotonsillectomy and watchful waiting with supportive care based on changes in AHI. While these results present statistically significant relationships between SQI and metabolic

Table 4 Comparison of healthy weight children with low SQI < 60 (A) to overweight children with high SQI ≥ 80 (B) and low SQI < 60 (C), included in the ECG analysis and stratified based on sleep quality

	Healthy weight (A)	Overweight (B, C)			
	A.SQI < 60 (n = 35)	B. SQI ≥ 80 (n = 19)	C. SQI < 60 (n = 49)	p (A vs. B)	p (A vs. C)
Characteristics					
Male (%)	54.3	36.8	38.8	0.22	0.16
African American (%)	34.3	79.0	49.0	0.00	0.18
Caucasian (%)	48.6	15.8	34.7	0.02	0.74
Other (%)	17.1	5.3	12.2	0.21	0.11
Currently taking medication for asthma (%)	22.9	36.8	16.3	0.91	0.71
Age (years)	6.3 (± 1.3)	6.9 (± 1.7)	7.5 (± 1.5)	0.12	< 0.001
BMI (kg/m^2)	15.7 (± 1.2)	22.3 (± 4.0)	24.3 (± 4.2)	< 0.001	< 0.001
BMI z-score	0 .0 (± 0.9)	2 .0 (± 0.6)	2.2 (± 0.5)	< 0.001	< 0.001
Waist measurement (cm)	55.2 (± 4.6)	69.4 (± 11.2)	78 .0 (± 11.4)	< 0 .001	< 0.001
Polysomnographic measures					
Duration	610.7 (± 72.9)	605.5 (± 73.1)	603.3 (± 83)	0.80	0.67
AHI	7.7 (± 6.3)	6.8 (± 4.0)	8.2 (± 6.6)	0.57	0.72
OAI	2.8 (± 3.4)	2.1 (± 1.8)	1.9 (± 2.4)	0.38	0.15
Arousal index	10.0 (± 3.8)	8 .0 (± 4.4)	7.9 (± 2.8)	0.08	0.01
ODI 3%	8.5 (± 7.7)	7.6 (± 6.0)	10 (± 8.3)	0.65	0.40
Pct. sleep time SpO2 < 92%	0.5 (± 1.0)	0.8 (± 1.2)	0.9 (± 2.0)	0.48	0.36
Minimum O2 saturation during sleep (%)	88.4 (± 3.9)	88.5 (± 4.8)	87.4 (± 5.0)	0.92	0.32
Metabolic measures					
Average heart rate during sleep (bpm)	84.5 (± 10.8)	85.9 (± 10.7)	87.2 (± 9.6)	0.64	0.23
Average systolic blood pressure	94.9 (± 6.9)	101.9 (± 9.4)	103.0 (± 8.6)	0.00	< 0.001
Average diastolic blood pressure	60.3 (± 6.7)	63.6 (± 8.7)	64.0 (± 7.4)	0.13	0.02
Fasting insulin (μIU/ml)	7.9 (± 7.2)	9.4 (± 5.9)	15.4 (± 12.6)	0.46	0.01
Fasting glucose (mg/dl)	4.5 (± 0.4)	4.8 (± 0.8)	4.6 (± 0.3)	0.12	0.65
Insulin/glucose ratio	1.7 (± 1.6)	2.5 (± 2.1)	3.3 (± 2.6)	0.21	0.01
Triglyceride-HDL ratio (mg/dl)	1.5 (± 0.7)	1.7 (± 1.0)	2.2 (± 1.6)	0.49	0.05
Triglyceride level (mg/dL)	70.6 (± 23.9)	79.4 (± 38.2)	94.8 (± 50.2)	0.34	0.02
Blood HDL level (mg/dL)	49.2 (± 10.8)	50.9 (± 17.2)	49.1 (± 13.3)	0.69	0.98
Blood LDL level (mg/dL)	90.2 (± 23.1)	94.9 (± 24.2)	104.7 (± 28.0)	0.52	0.03
C-Reactive protein level (mg/mL)	0.8 (± 1.8)	2.6 (± 3.2)	3.6 (± 5.1)	0.02	0.01
Questionnaires					
PedQL parent total scale score	78.7 (± 13.7)	76.9 (± 14.2)	72.9 (± 17.6)	0.64	0.10
PedQL child total scale score	67.6 (± 12.9)	69.9 (± 17.0)	70.3 (± 15.8)	0.58	0.42
Nepsy: inhibition total error scaled score	8.5 (± 4.7)	6.1 (± 4.4)	7.3 (± 3.4)	0.07	0.19

Descriptive statistics were presented as means ± standard deviation (SD). BMI, body mass index (the weight in kilograms divided by the square of the height in meters); BMI z-score (relative weight adjusted for child age and sex); AHI, apnea/hypopnea index; ODI, oxygen desaturation index; SQI, sleep quality index; bpm, heart-beats per minute; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PedQL, pediatric quality of life questionnaire; NEPSY, neuropsychological assessment

risk in this population, SQI is not solely focused on sleep apnea. Future studies should fine-tune optimal cut-points for SQI and SAI and investigate long-term associations between objective sleep quality and metabolic risk factors. This requires more comprehensive data collection with a control group of healthy children with high sleep quality, collected over multiple nights on both weekdays and weekends. Sleep quantity is important for metabolic risk [3, 31], which is more realistically reflected if the sleep test is done repeatedly over multiple nights in the child's normal sleep environment. As this data collection was conducted under highly controlled testing environment in a sleep laboratory, impact of sleep quantity is likely underestimated as sleep quality and sleep quantity have collective impact on cardiovascular and cardiometabolic health. This analysis though has a number of significant strengths. The sample size is large including racially diverse group of 5.0–9.9-year-old children.

Rigorous data collection provides various sleep, cardiovascular and cardiometabolic, quality of life, and cognitive outcomes. The differences in racial representation in children between the sleep quality groups are likely a reflection of the sample rather than a true difference; however, this will also require further evaluation.

In summary, SQI provides information on augmented autonomic response during sleep. Healthy weight children with low sleep quality presented higher average heart rate during sleep, less insulin sensitivity, and compromised lipid profiles, when compared to healthy weight children with high sleep quality. Overweight children with low sleep quality had significantly worse cardiovascular and cardiometabolic profile when compared to healthy weight children with low sleep quality. These results indicate that cardiovascular and cardiometabolic risk factors develop in childhood and may be better captured by additionally measuring sleep quality than only through assessing weight group differences. Objective sleep quality and quantity information collected repeatedly over time will improve understanding of pediatric sleep health, effects of sleep curtailments, and may improve intervention strategies and interventions that are appropriate to reduce metabolic risk in children. The advantages of using CPC-derived variables is that the method being SaMD, is defined by data acquisition characteristics that may make clinical use and research in children more accessible than previously possible. This simple and flexible method offers objective and fully automated output for measuring and tracking sleep quality, quantity, and pathology over time to identify sleep disorders and track therapy efficacy. Use of this method warrants further investigation through childhood development, especially given reduced cost and suitability compared with polysomnography that is not available for multi-night testing or in the child's natural sleeping environment.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

The study protocol was approved by the Institutional Review Board of all sites participating in the study, specific for that site and recruitment procedures met the local HIPAA rules. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants or their caretakers included in the study.

Conflict of interest Mr. Hilmisson is a Data Analyst for MyCardio LLC. SleepImage is the brand name of MyCardio LLC, a privately held entity. MyCardio LLC is a licensee of the CPC algorithms, a method to use ECG to identify sleep quality and sleep apnea, from the Beth Israel Deaconess Medical Center, Boston, MA, USA.

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Dr. Magnusdottir is a medical director of MyCardio LLC, with a partial ownership. SleepImage is the brand name of MyCardio LLC, a privately held entity. MyCardio LLC is a licensee of the CPC algorithms, a method to use ECG to identify sleep quality and sleep apnea, from the Beth Israel Deaconess Medical Center, Boston, MA, USA.

Abbreviations AT, adenotonsillectomy; AASM, American Academy of Sleep Medicine; ANS, autonomic nervous system; AHI, apnea-hypopnea index; BMI, body mass index; CPC, cardiopulmonary coupling; CVHR, cyclic variation of heart rate; CHAT, Childhood Adenotonsillectomy Trial; EDR, electrocardiogram-derived breathing; ECG, electrocardiogram; EEG, electroencephalogram; $eLFC_{BB}$, elevated low-frequency broad-band; $eLFC_{NB}$, elevated low-frequency narrow-band; HRV, heart rate variability; HDL, high-density lipoprotein; HFC, high-frequency coupling; LFC, low-frequency coupling; MANOVA, multivariate analysis of variance; NEPSY, neuropsychological assessment test; NREM, non-rapid eye movement sleep; ODI, oxygen desaturation index; OSAS, obstructive sleep apnea syndrome; OLS, ordinary least squares regression; PedQL, pediatric quality of life; PSG, polysomnography; REM, rapid eye movement sleep; SAI, sleep apnea indicator; SE, standard error; SQI, sleep quality index; SWS, slow-wave sleep; TG, triglyceride; vLFC, very low-frequency coupling

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