Sleep and Breathing (2019) 23:645–650
https://doi.org/10.1007/s11325-018-1768-6

PEDIATRICS • ORIGINAL ARTICLE

Association between REM sleep and obstructive sleep apnea in obese and overweight adolescents

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Received: 24 August 2018 / Revised: 27 November 2018 / Accepted: 4 December 2018 / Published online: 15 December 2018

Abstract

Purpose Overweight and obese children have demonstrated reduced rapid eye movement (REM) sleep, affecting energy balance regulation and predisposition to weight gain. Obstructive sleep apnea (OSA) is a known cause of decreased REM sleep. The purpose of this study is to examine the association between the percentage of REM sleep, BMI *z*-score, and OSA severity in overweight and obese adolescents.

Methods We performed a cross-sectional study of 92 (43% female) overweight and obese adolescents (13–17 years old) who underwent overnight polysomnography (PSG) at Children's Hospital Los Angeles between 2010 and 2017.

Results The average Body Mass Index (BMI) *z*-score was 2.27 ± 0.47, with 71% having BMI *z*-score ≥ 2. REM% during PSG was 15.6 ± 6.8, and obstructive apnea-hypopnea index was 17.1 ± 24.3. The distribution across categories of OSA severity was 27% none (≤ 1.5 events/h), 24% mild (> 1.5–5 events/h), 8% moderate (> 5–10 events/h), and 41% severe (> 10 events/h). REM% was not associated with BMI *z*-score, either on univariate or multivariate regression with adjustment for age, gender, and apnea-hypopnea index (AHI). When subdivided into OSA categories, a 1-unit increase in BMI *z*-score was associated with a 5.96 ($p = 0.03$) increase in REM% in mild OSA and an 8.86 ($p = 0.02$) decrease in REM% in severe OSA. There was no association between BMI *z*-score and REM% in none and moderate OSA.

Conclusion Among overweight and obese adolescents, BMI *z*-score was associated with decreased REM% in severe OSA and unexpectedly increased REM% in mild OSA, but there was no association in none or moderate OSA.

Keywords Adolescents · Obesity · Obstructive sleep apnea · Rapid eye movement

Introduction

Obstructive sleep apnea (OSA) and obesity, both known to have adverse cardiovascular, metabolic, and neuropsychological consequences [1], continue to increase in epidemic proportions in most industrialized countries [2–4].

Previous studies have shown that short sleep duration is linked to the development of obesity and this relationship may be mediated by endocrine and metabolic changes, particularly the balance of ghrelin (associated with ratings of hunger) and leptin (associated with appetite) [4–6]. More recently, studies show that overweight and obesity risk in children and adolescents are not only associated with short sleep duration but also with changes in sleep architecture [6, 7]. Specifically, Liu et al. [6] attributed the increased overweight risk in children and adolescents to reduced REM sleep. In a study of healthy adults, Olson et al. also demonstrated that an increased percentage of REM sleep predicted a greater overnight change in leptin and a consequent decrease in morning leptin. Further, the investigators also showed that those with highest percentage of REM had lower morning leptin levels. In their cohort of patients, the authors did not find a relationship between sleep duration and leptin levels. Hence, an increased REM is needed to maintain lower leptin levels which would predict lower appetite and decreased risk of obesity [8].

REM sleep may affect energy balance via multiple pathways that include regulation of feeding behaviors, food preferences, appetite, and metabolism [9]. Gonnissen et al. [10] found that reduced REM in healthy men resulted in weight

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gain and positive energy balance due to a decrease in subjective feeling of "fullness," possibly through a shift in waking blood insulin and glucagon-like peptide-1 concentrations. In mice, a causative link was found between REM sleep reduction, medial prefrontal cortex activity (known to participate in mediating reward anticipation), and highly palatable foods [11]. REM sleep deprivation was also found to increase caloric intake via increased expression of pro-inflammatory cytokines (TNF-α, IL 6) which are known to participate in the molecular mechanism of insulin resistance [12].

Children with obesity are at risk for OSA. OSA is broadly recognized as a cause of decreased REM sleep [13–15].

To our knowledge, there is limited research describing the association between OSA and REM sleep specifically in overweight and obese patients.

Therefore, we sought to examine the association between the percentage of REM sleep, BMI *z*-score, and OSA severity in overweight and obese adolescents.

Methods

We performed an observational retrospective cross-sectional study of 92 overweight and obese children and adolescents who had undergone polysomnography (PSG) at Children's Hospital Los Angeles from 2010 to 2017 for evaluation of sleep disordered breathing. This study was approved by the Children's Hospital Los Angeles institutional review board.

Inclusion criteria were children aged 13 to < 18 years diagnosed as overweight or obese (BMI *z*-score > 1) according to CDC percentile charts. Participants were otherwise healthy and were free of chronic lung disease, persistent asthma, craniofacial malformations, syndromic conditions, primary neuromuscular disorders, systemic or pulmonary hypertension, and medications that influence the length of REM period during sleep (e.g., selective serotonin reuptake inhibitors). All were referred for complaint of snoring. None were on positive airway pressure therapy, but some had adenotonsillectomy in the past.

Data were extracted from medical records and polysomnography reports. The following demographic data were collected: (1) age at the time of the PSG, (2) gender, (3) weight, height, BMI, BMI *z*-score, and weight percentile, based on age and gender, collected within 6 months of the PSG. Weight status (overweight/obese) was defined according to the BMI *z*-score. Overweight was defined as BMI *z*-score > 1. Obese was defined as BMI *z*-score > 2 [16, 17].

The following PSG variables were collected and analyzed based on AASM scoring guidelines: (1) N1, N2, N3 and REM period duration (represented as percent of TST), (2) sleep efficiency, (3) desaturation index, (4) arousal index, (5) peak endtidal CO_2 (mmHg), (6) obstructive apneas and mixed apneas, (7) central apneas, (8) obstructive hypopneas, and (9) obstructive apnea-hypopnea index (OAHI). OSA severity was categorized based on OAHI as follows: none (0–1.5 events/h), mild (> 1.5–5 events/h), moderate (> 5–10 events/h), and severe (> 10 events/h) [18].

Overnight polysomnography

Polysomnography was conducted at Children's Hospital Los Angeles (Los Angeles, California) in a quiet and dark room. PSG recordings were performed using Somnostar computerized polysomnography acquisition, audio/video, and storage system and included the following signals: electroencephalogram with electrode placement according to the 10–20 system (F3, F4, C3, C4, O1, O2) referenced to the contralateral mastoid, left and right electro-oculogram, chin electromyogram, left and right tibialis electromyogram, electrocardiogram, thermistor and nasal pressure cannula, thoracic and abdominal effort, peripheral oxygen saturation, snoring, and position sensors. Data were acquired and stored in digital format for subsequent analyses. Throughout the night, any meaningful behavior, such as general body movements and/or body position, was noted by trained personnel.

Sleep was staged and respiratory events were scored using the AASM Manual for Scoring Sleep and Associated Events [19]. Sleep and waking stages were visually scored in 30-s epochs and defined as stages N1, N2 and N3, stage R, and wakefulness (stage W). The pediatric criteria were used to score respiratory events. Obstructive apnea was defined as 90% drop in oro-nasal thermal sensor (or surrogate) for a duration of 2 breaths and is associated with the presence of respiratory effort throughout the entire period of absent airflow. Obstructive hypopnea was defined as 30% drop in the nasal pressure sensor for a duration of 2 breaths with concomitant 3% oxygen desaturation or arousal and is associated with snoring, increased inspiratory flattening of the nasal pressure, or thoracoabdominal paradox during the event. Only reported obstructive hypopneas were included in this study.

Data analysis

Statistical analysis was performed with Stata/IC 10.1 for Windows (StataCorp LP, College Station, TX, USA). Mean and standard deviation were calculated for continuous variables, with *t* tests used to compare values across subgroups (e.g., OSA severity). For categorical variables, proportions were calculated, with the use of chi-squared testing for comparisons across subgroups. Linear regression was used to examine the association between REM% and BMI *z*-score, with adjustment for potential confounders including OAHI, supine REM OAHI, and non-supine REM OAHI age, gender, and/or sleep efficiency. Regression analyses were performed for the entire study sample as well as within subgroups defined by

Table 1 Polysomnography variables

Polysomnographic variables	
PSG parameters	Mean ± Standard deviation
Sleep efficiency, %	82.9 ± 14
N1%	12.7 ± 11
N2%	48.6 ± 10.9
N3%	23.9 ± 9.9
REM%	15.6 ± 6.8
Desaturation index, #/h	16.09 ± 26
Peak endtidal CO_2 (mmHg)	50.4 ± 3.9
Arousal index, #/h	19.3 ± 21

PSG data for the entire study population

OSA severity categories and BMI *z*-score. p values < 0.05 were considered statistically significant.

Results

Patient demographics Ninety-two study subjects were included in this study, and 43% (40/92) were female. Seventy-one percent (65/92) were obese while 29% (27/92) were overweight. The distribution among OSA subgroups was 27% (25) none, 24% (22) mild, 8% (7) moderate, and 42% (38) severe. PSG findings are summarized in Table 1.

Table 2 presents the demographic and PSG findings according to OSA severity subgroups. BMI *z*-score was greater in the severe OSA subgroup, compared to no OSA and mild OSA (both $p < 0.001$) but not when compared to moderate OSA ($p = 0.20$). BMI *z*-scores compared between the other subgroups were not statistically different (all $p > 0.05$). REM% did not differ according to OSA severity group (all comparisons $p > 0.05$). There was no difference ($p = 0.40$) in REM% between those in the obese (BMI *z*-score > 2, 15.2 ± 0.9) vs. overweight (BMI *z*-score ≤ 2, 16.5 ± 1.1) subgroups.

Within OSA severity subgroups, unadjusted regression analyses showed that a 1-unit increase in BMI *z*-score was associated with a 5.05 ($p = 0.054$; 95% CI − 0.09, 10.2) increase in REM% in mild OSA and a 7.4 ($p = 0.03$; 95% CI − 14.0, − 0.8) decrease in REM% in severe OSA. There was no association between BMI *z*-score and REM% in the no OSA (− 0.1; 95% CI − 8.1, 7.9) or moderate OSA (− 1.2; 95% CI − 15.7, 13.2) subgroups (Fig. 1). Adjustment for age, gender, and OAHI produced similar results; a 1-unit increase in BMI *z*-score was associated with a 5.96 ($p = 0.03$; 95% CI 0.66, 11.3) increase in REM% in mild OSA and a 8.86 ($p = 0.02$; 95% CI 1.4, 16.3) decrease in REM% in severe OSA. Analyses using oxygen desaturation index in place of OAHI or adjustment for supine REM AHI or non-supine REM AHI showed similar results (data not shown).

Thus, the linear regression results evaluating the association between REM% and BMI *z*-score, with and without adjustment for OAHI, age, gender, and sleep efficiency only showed statistically significant associations for REM% and sleep efficiency (Table 3).

Discussion

This study shows that among overweight and obese adolescents, BMI *z*-score is associated with an increase in REM% in mild OSA and a decrease in REM% in severe OSA. There was no association among those without OSA and with moderate OSA, although the moderate OSA subgroup may have had insufficient sample size ($n = 7$).

Previous studies have shown associations between changes in sleep architecture (NREM and REM) with OSA and with obesity [7, 20, 21]. Specifically, Chamorro et al. [7] found reduced sleep time, sleep quality, decrease in N3, and decreased REM amount in 10-year-old overweight children. An inverse association between REM sleep and hunger exists and REM sleep might be the sleep stage most strongly associated with overweight in children and adolescents. REM sleep loss is associated with increased consumption of highly palatable foods such as fat and carbohydrates [10] and there is increased hunger with decreased REM [21], supporting a strong role of REM sleep in overweight and obesity in adolescents.

Table 2 Demographic and polysomnography findings according to OSA severity

	No OSA ($n = 25$)	Mild OSA ($n = 22$)	Moderate OSA (n = 7)	Severe OSA ($n = 38$)
Age (years)	15.2 ± 1.1	14.5 ± 1.4	14.6 ± 1.3	14.9 ± 1.4
Gender (% female)	68%	50%	43%	24%
BMI *z*-score	2.02 ± 0.32	2.11 ± 0.51	2.29 ± 0.66	2.51 ± 0.35
OAHI	0.7 ± 0.4	2.8 ± 1.0	8.2 ± 1.8	37.7 ± 26.6
REM%	16.4 ± 6.0	17.0 ± 6.2	15.4 ± 8.3	14.2 ± 7.4

Demographic and relevant polysomnography findings according to OSA severity subgroups (*OSA* obstructive sleep apnea, *BMI* body mass index, *AHI* apnea-hypopnea index, *REM* rapid eye movement)

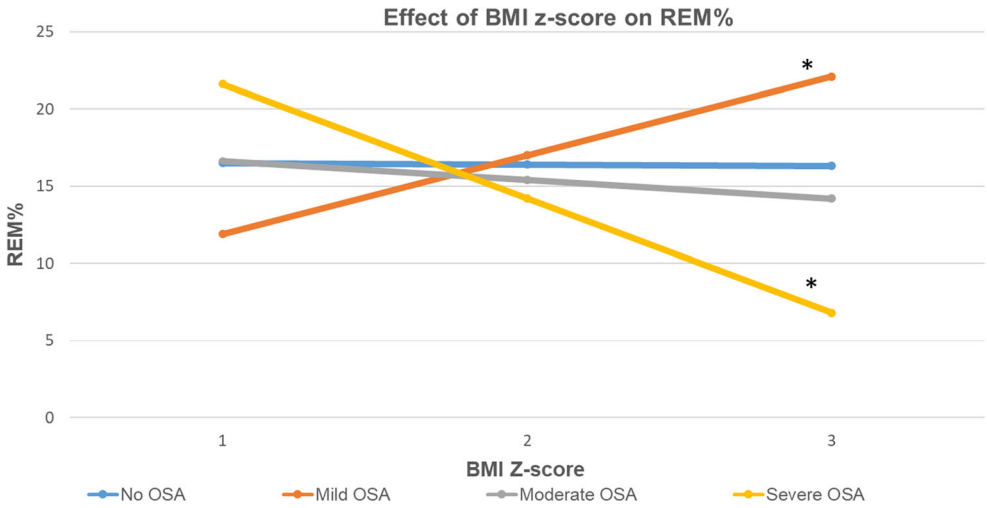

Fig. 1 Unadjusted regression analyses show the effect of BMI *z*-score on REM% in different OSA severity subgroups (asterisk marks statistical significance). BMI, body mass index; REM, rapid eye movement; OSA, obstructive sleep

Jalilioghader et al. [20] compared sleep architecture and OSA in obese children with and without metabolic syndrome and demonstrated that sleep architecture changes (among them, decreased REM) are most likely a direct result of OSA severity. Redline et al. demonstrated decreased REM percentage in adults with more severe OSA but with average BMI of 28.5 ± 5.4 kg/m^2. Our study also showed decreased REM in those with severe OSA supporting previous studies showing an inverse association between REM and OSA severity in obese individuals, suggesting that REM percent is modifiable when OSA is treated.

Our study is unique in that it shows differential relationship between REM sleep percent and the severity of OSA. We found that REM% is significantly affected in obese and overweight adolescents at the ends of the spectrum of OSA but not in those without OSA or with moderate OSA. There was decreased REM in those with severe OSA while there was increased REM in those with mild OSA. Durdik et al. [22] showed no change in REM% but lower N3 and higher N1 percentage in children with mean age 5.25 ± 1.39 years with the common phenotype of childhood OSA (long face, narrow palate, adenotonsillar hypertrophy). Our study population was comprised of adolescents with the mean age of 14.9 ± 1.3 years, and a mean BMI *z*-score of 2.27 ± 0.47, resembling the "adult" phenotype of OSA (obesity, increased neck circumferences). This difference in ages of our cohorts might also explain our findings of REM sleep duration changes in different OSA categories. We also found reduced N3 stage but unlike Durdik et al., normal N1 stage percent. (Table 1).

Overweight and obesity are known risk factors for OSA [23]. It has been shown that the risk of OSA in children increases by 12% for each increase of 1 kg/m^2 of BMI above the mean [24]. Since OSA results in decreased REM sleep percentage [6, 25] and REM is important in regulating energy balance [26–28], these patients are caught in a vicious cycle of sleep deprivation, obesity, and OSA. Further, it has been shown that REM sleep deprivation causes a rebound effect of energy conservation and weight gain with consumption of highly palatable foods [11], adding to the detrimental effect of short REM on growth and development [9, 26].

This study has several limitations. First, a single night recording in the laboratory may alter sleep organization and architecture in some patients. A first night effect can partially explain the reduction in REM sleep percent. Our data shows that all groups, including those without OSA, had reduced REM indicating that if a first night effect was present, it likely affected the entire cohort in the same manner (Table 2). In addition, Marcus et al. [29] demonstrated that there is little clinically significant night-to-night variability in pediatric polysomnography and that a single polysomnographic night

Table 3 Regression results for association with REM% and BMI *z*-score, with and without adjustment for OAHI, age, gender, and sleep efficiency

BMI *z*-score	OAHI	Age (years)	Gender (female vs. male)	Sleep efficiency
− 1.68 ± 1.54				
− 1.15 ± 1.60	− 1.68 ± 1.54	− 0.58 ± 0.54		
− 1.01 ± 1.70	− 0.03 ± 0.03	− 0.59 ± 0.54	0.36 ± 1.55	
− 0.09 ± 1.50	− 0.05 ± 0.03	− 0.39 ± 0.47	0.13 ± 1.36	0.24 ± 0.05*
− 0.65 ± 1.48		− 0.34 ± 0.48	0.40 ± 1.37	0.23 ± 0.05*

Data represent estimates of association between variables with REM%. $p < 0.05$

* Statistical significance, $p < 0.05$

is an adequate measure of the OSAS in children. Since adolescents tend to have a delayed sleep phase, it is possible that the increase in REM in the mild OSA subgroup may represent a rebound effect related to the opportunity to sleep in the laboratory vs having a late bedtime at home. Second, anthropometric measurements of weight and height were measured only once in a range of up to 6 months before or after the sleep study. However, all measures were performed by trained personnel using the same scale and stadiometer, Certainly, a measurement closer to the sleep study would be desirable. Further information on other factors affecting OSA severity, i.e., ethnicity and sleep position, were not available in all patients in this cohort.

Our results highlight OSA severity as a modifiable risk factor for REM sleep reduction in overweight and obese adolescents and can be broadly applicable in the general pediatric overweight and obese population. Our study population included carefully selected group of obese adolescents free of comorbid conditions such as diabetes mellitus, nonalcoholic steatohepatitis, and other conditions related to obesity and were only receiving intermittent short-acting beta agonist and nasal steroid. These participants were referred for a sleep study by community pediatricians, sleep/pulmonary specialists, and obesity management clinics, hence remarkably representative of a general obese adolescent population.

Conclusion

In conclusion, this study shows that REM% decreased as weight increased in adolescents with severe OSA while those mild OSA had the opposite response and moderate OSA were not affected at all.

These findings indicate that OSA has a substantial role as a confounder and a potential modifiable risk factor for REM reduction and that the changes in REM percent might play an independent role in the mediation of obesity. The unexpected "counter-trend" in the mild OSA group merits further study to confirm these finding as well as to explore potential mechanisms. Future study of the trajectory of weight, sleep architecture, and OSA over time may help sort out causation and better elucidate the relationships between these entities.

Funding This work was supported in part by the National Institutes of Health (NIH) grants HL090451 and EB001978, University of Southern California Center for Transdisciplinary Research on Energetics and Cancer grant TREC U54 CA 116848, and grant M01 RR00047 and RO1-HL-105210 from Children's Hospital Los Angeles General Clinical Research Center.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was approved by the Children's Hospital Los Angeles institutional review board.

Informed consent Informed consent was waivered by the Children's Hospital Los Angeles institutional review board for all individual participants included in the study.

Abbreviations AASM, American Academy of Sleep Medicine; BMI, body mass index; CDC, centers for disease control and prevention; NREM, non rapid eye movement; OAHI, obstructive apnea-hypopnea index; OSA, obstructive sleep apnea; PSG, polysomnography; REM, rapid eye movement

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