Autonomic Dysfunction: A Possible Pathophysiological Pathway Underlying the Association Between Sleep and Obesity in Children At-Risk for Obesity

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Abstract

While mounting evidence suggests that sleep plays an important role in the etiology of obesity, the underlying pathogenic pathways are complex and unresolved. Experimental sleep deprivation studies demonstrate sympathovagal imbalance, indicative of diminished parasympathetic activity and/or heightened sympathetic activity, is consequent to poor sleep. Further, obese children exhibit sympathovagal imbalance, particularly during the night, compared to non-obese children. The question remains whether sympathovagal imbalance is one potential pathophysiological pathway underlying the association between sleep and obesity. The aim of the present study was to examine whether sympathovagal imbalance contributed to the association between sleep and obesity in children. Participants included 564 children aged 10 to 12 years ($M = 11.67$, $SD = 0.95$; 43.5 % girls) from the QUALITY Cohort, a longitudinal study of children at-risk for the development of obesity. While children were at-risk due to confirmed parental obesity status, 57.7 % of children

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Conflict of interest None to disclose.

Author contributions The QUALITY Cohort Collaborative Group designed and coordinated the study and collected measurements at clinic visits. J.J.M. and P.P. planned the study design and analysis of the ECG recordings. D.C.J. performed the statistical analyses. D.C.J. and J.J.M. conceived the research question, interpreted the findings, and wrote the manuscript.

were of normal body mass index (5–85th percentile). Sleep duration, sleep timing, and sleep disturbances were based on child- and parent-report. Anthropometrics were measured for central adiposity (waist circumference) and body composition (body mass index, fat mass index). Sympathovagal imbalance was derived from heart rate variability spectral analyses. Estimated path coefficients revealed that sympathovagal imbalance partially contributed to the association between poor sleep (later bedtimes, sleep-disordered breathing) and obesity. These findings highlight the importance of better understanding sympathovagal imbalance and its role in the etiology and maintenance of obesity. Future research should consider investigating nocturnal sympathovagal balance in youth.

Keywords

Children; Obesity; Sleep; Heart rate variability; Sympathovagal imbalance; Autonomic dysfunction

Introduction

Childhood obesity is a global epidemic. Although recent data suggest the obesity prevalence may have plateaued, rates of childhood obesity are high and contribute to significant physical, psychological, and economic burden (Ogdon et al. 2012). Childhood obesity tracks into adulthood and confers risk for insulin resistance, impaired glucose tolerance, hypertension, and early precursors to cardiovascular disease (Knutson and van Cauter 2008). Mirroring these trends, shorter sleep duration has increased among youth, largely due to later bedtimes and unchanged rise times across these past decades (Knutson and van Cauter 2008). Further, worldwide studies estimate 20–30 % of children and 6–37 % of adolescents report problems related to prolonged sleep latency, difficulty initiating and maintaining sleep, frequent nocturnal awakenings, and poor quality sleep accompanied with significant daytime impairments (Beebe et al. 2007; Owens et al. 2000).

Numerous studies report an inverse association between sleep and obesity. Notably, sleep is a multidimensional construct, reflecting sleep duration, sleep patterns (e.g., bed time, weekend oversleep, phase shift), and sleep disturbances (e.g., fragmentation, disorders, quality; Jarrin et al. 2013). Cross-sectional studies reveal that shorter sleep duration, poor sleep quality, sleep disturbances, and a delayed sleep phase pattern are associated with larger body composition (e.g., body mass index, fat mass), greater central adiposity (e.g., waist/hip circumference), and increased obesity rates among both adults and youth (Beebe et al. 2007; Jarrin et al. 2013; Knutson 2012; Knutson and van Cauter 2008). Longitudinal studies provide pertinent information on the temporal nature of the association, with poor sleep (i.e., short sleep duration, sleep disturbances) preceding the development of obesity (Knutson 2012; Lumeng et al. 2007). Taken together, these cross-sectional and prospective findings provide convincing support of an association between sleep and obesity.

The pathogenic mechanisms underlying the association between sleep and obesity are not fully understood. Experimental research on the potential mechanisms underlying the association between sleep and obesity has largely focused on the role of hormones involved in appetite regulation. Laboratory sleep restriction studies demonstrate that sleep restriction

(e.g., 4 h of sleep for six nights) reduces leptin (appetite-suppressing hormone) and increases ghrelin (appetite-stimulating hormone), irrespective of energy intake and expenditure (Spiegel et al. 2004a, b). Further, induced sleep restriction, fragmented sleep, sleep disturbances, and lower sleep quality have been associated with increased cortisol levels in animals, adults, and children (El-Sheikh et al. 2008; Hairston et al. 2001; Spiegel et al. 2004a, b). While these hormones play an important role, it is likely that other pathogenic mechanisms associated with both sleep and obesity are involved.

The autonomic nervous system is an important contributor to coordinating energy homeostasis and plays a role in the pathophysiology of obesity (Peterson et al. 1998). Alteration of the sympathetic nervous system activity is widely assumed to promote the onset and development of obesity (Peterson et al. 1998; van Baak 2001). As such, autonomic dysfunction, or impaired cardiac autonomic modulation, is another plausible pathophysiological mechanism underlying the link between sleep and obesity (Spiegel et al. 2004a, b). Sympathovagal imbalance is a marker of autonomic dysfunction, characterized by sympathetic hyperactivity and/or parasympathetic withdrawal, typically derived from variability in heart rate (Task Force 1996). Autonomic dysfunction has been found to play a role in childhood obesity. Obese children exhibit sympathovagal imbalance and lower heart rate variability (HRV), compared with normal-weight children (Martini et al. 2001; Nagai et al. 2003; Riva et al. 2001). Children with greater body weight and diabetes mellitus have lower heart rate variability, compared to control children (Kaufman et al. 2007; Wawryk et al. 1997). Compared to normal-weight children, overweight and/or obese children show significant sympathetic hyperactivity and decreased parasympathetic functioning in response to non-invasive experimental autonomic tests (e.g., orthostatic test, Valsalva maneuver; Yakinci et al. 2000), especially during the night, even after controlling for sleep-disordered breathing and sleep apnea (Rabbia et al. 2003). Based on these results, autonomic alteration is evident and is likely an important etiologic factor of childhood obesity.

Autonomic dysfunction has also been linked to sleep, among both adults and children. Several studies have documented sympathovagal imbalance and parasympathetic withdrawal following experimental sleep deprivation. Among healthy adults, sympathovagal imbalance significantly increased 20 % after partial sleep deprivation (Zhong et al. 2005) and 15 % after total sleep deprivation (Tochikubo et al. 1996). Conversely, parasympathetic modulation significantly decreased 19 % after partial sleep deprivation (Tochikubo et al. 1996) and 22 % after total sleep deprivation (Zhong et al. 2005). Under partial sleep deprivation over six nights (e.g., 4 h sleep), healthy males evidenced significant increases in sympathovagal imbalance as compared to conditions of sleep recovery (Spiegel et al. 2004a, b). The increases in sympathovagal imbalance were particularly evident the following morning (9 a.m.–1 p.m.) and afternoon (1–5 p.m.) with 16–19 % increases, respectively. Thus, experimental manipulation of sleep duration suggests that greater autonomic dysfunction is associated with sleep loss.

In addition to sleep duration, sympathovagal imbalance is also relevant for other sleep disturbances. Among adults, sympathovagal imbalance is significantly associated with sleep fragmentation, sleep disorders (e.g., insomnia; Bonnet and Arand 2010), and subjective and objective reports of poor sleep quality (Tasali et al. 2008). Sympathovagal imbalance

significantly increased by 37 % and parasympathetic activation significantly decreased by 14 % after three consecutive nights of poor sleep quality (i.e., slow wave sleep suppression) in adults, even after controlling for breathing frequency, total sleep time, and total wake time (Tasali et al. 2008). Preliminary work in children has yielded parallel results.

Sleep deprived infants (i.e., no napping) showed twice as high sympathovagal imbalance compared to those in the napping condition (Franco et al. 2003). Children aged 9 years who slept 1 h less evidenced significantly higher sympathovagal imbalance and lower parasympathetic, compared to those with an additional hour of sleep (Rodríguez-Colón et al. 2011). Among clinical samples, children with obstructive sleep apnea evidenced a 9 % increase in sympathovagal imbalance and a 25 % reduction in parasympathetic activity the morning following an overnight polysomnography, compared to controls (Kwok et al. 2011). Similar results have been reported among children with sleep fragmentation (e.g., periodic leg movement), sleep-disordered breathing symptoms, and insomnia symptoms (e.g., difficulty initiating/maintaining sleep), even after adjusting for multiple covariates (Rodríguez-Colón et al. 2011; Walter et al. 2009). Taken together, evidence indicates poor sleep is associated with sympathovagal imbalance.

Current Study

Research evidence convincingly demonstrates that poor sleep is associated with childhood obesity. Numerous studies also have found that obese children and adolescents show significantly higher sympathovagal imbalance estimates than their normal-weight peers. Further, poor sleep adversely impacts a variety of physiological processes, including autonomic functioning. Poor sleep, via autonomic nervous system alterations, thus offers a plausible pathogenic role in the development of obesity. There is limited research examining the associations between sleep, obesity, and autonomic functioning among healthy pediatric samples or those at-risk for obesity. Given that sympathovagal imbalance is related with both sleep and obesity, it is proposed as one potential mediator of the association between sleep and the etiology of obesity.

The aim of the current study was to evaluate sympathovagal imbalance as a potential mechanism underlying the association between poor sleep and childhood obesity. This association was examined among healthy children who were at-risk for obesity, as at least one parent was obese. It was hypothesized that sympathovagal imbalance may underlie the association between poor sleep (shorter sleep duration, later bedtime, more sleep disturbances) and obesity (larger central adiposity, body composition), even after controlling for developmentally-relevant covariates.

Method

Study Sample

The study sample included children participating in the QUebec Adipose and Lifestyle InvesTigation in Youth (QUALITY) Cohort. The survey design and methods have been previously reported in detail (Lambert et al. 2011). Briefly, the aim of the QUALITY study was to investigate the natural history of excess weight and its related cardiometabolic

consequences among a large cohort of youth at-risk for the development of obesity. Inclusion criteria required at least one biological parent to have a BMI ≥ 30 kg/m² or waist circumference ≥ 102 cm (in men) and ≥ 88 cm (in women); there were no BMI or weight status inclusion criteria for children. Children were excluded if they had: (1) a previous diagnosis of type 1 or 2 diabetes, (2) a serious illness (e.g., renal failure, inflammatory bowel disease, cystic fibrosis), (3) a psychological condition or cognitive disorder that hindered participation in some or all of the study components, (4) were treated with anti-hypertensive medication or steroids, β -blockers, or thiazides, or (5) if they followed a highly restricted diet (<600 kcal/day; Lambert et al. 2011). All participants were Caucasian of Western European ancestry to reduce genetic admixture.

Baseline data (first visit; September 2005 to December 2008) were collected from 630 children aged 8–10 years. Of the original sample, 89.0 % ($n = 564$) completed the second visit (September 2008 to March 2011) when participants were aged 9–12 years. The present analyses are based on the second visit, when ECG data were recorded. Attrition was due to several reasons including refusal of the child to participate (18.2 %), family missed several appointments (9.0 %), family had no time, moved away, or could not be located (13.5 %), or other reasons not specified (59.0 %). No significant time differences were observed in anthropometric or socio-demographic measures (age, parental income, education measures) between children who participated at the second visit and those who did not return. The QUALITY study was approved by the ethics review board of Direction Santé Québec, Institut de la statistique du Québec, and CHU Sainte-Justine Hospital. Informed consent and assent were obtained by parents and children, respectively.

Measures

Anthropometrics—Anthropometric measures were taken following established protocols by a registered nurse, while participants were dressed in light clothing with shoes off. Using a standard measuring tape, waist circumference was measured midway between the lowest rib cage and the iliac crest; and hip circumference was measured at the widest part of the body, over the buttocks (World Health Organization 2008). Height was measured during maximal inspiration. Waist and hip circumferences and height were measured in duplicate, to the nearest 0.1 cm; if they differed by more than 0.5 cm, a third measure was taken. The mean of the two closest measures was used in data analyses. Only *waist circumference* was used as an index of central adiposity (similar results were observed for hip circumference; data not shown for parsimony).

Weight was measured to the nearest 0.2 kg with a spring scale tested daily for accuracy and calibrated against a set of standard weights. BMI was calculated as weight in kg divided by height in m². *BMI Z-scores* were determined using age- and sex-specific growth charts published by the U.S. Centers for Disease Control and Prevention (Ogdon et al. 2002). Overweight was defined as BMI in the 85th to <95 th percentile; obesity was defined as BMI in the ≥ 95 th percentile. While children were at-risk for obesity due to parental obesity, more than half were of normal weight status (57.7 %; BMI 5 to <85 th percentile).

Dual-energy X-ray absorptiometry (DEXA) scans, considered the gold standard in assessing obesity, were performed using DEXA, Prodigy Bone Densitometer System DFb14664 (GE

Lunar Corporation, Madison, WI, USA). Scan mode was based on weight guidelines provided by the manufacturer and each scan was analyzed using DEXA pediatric software version (Lunar Corporation). *Fat mass index* was derived from DEXA scans and calculated by dividing fat mass by the square of height (kg/m^2). BMI Z-scores and fat mass index were used as indices of overall body composition.

Sleep—Children's typical bed- and rise-times over the past week were obtained by self- and parent-report. *Sleep timing* refers to the bed- and rise-times reported by children (school days) and parents (usual/typical times). *Sleep duration* was calculated as the difference between bed- and rise-time. Aside from polysomnography derived sleep duration, this definition (i.e., calculated difference between bed- and rise-time) is deemed an acceptable sleep duration estimate because children easily understand it; it is considered more accurate compared to categorical responses, which are influenced by subjective interpretation; and, it has previously been moderately to strongly correlated with objective sleep actigraphy measures (rise-time $r = 0.45\text{--}0.99$; bedtime $r = 0.65\text{--}0.70$; Gaina et al. 2004; Matricciani 2013; Wolfson and Carskadon 1998).

Children's sleep habits were assessed using the Children's Sleep Habits Questionnaire (CSHQ; Owens et al. 2000). Parents answered 33 questions on their child's sleep habits and disturbances over the past week. Each question was rated on a 3-point scale that described the frequency (rarely, sometimes, usually) of sleep habits categorized into eight sleep disturbance subscales: sleep duration (e.g., my child sleeps too little), daytime sleepiness (e.g., my child seems tired), sleep-disordered breathing (e.g., my child snorts and gasps), sleep anxiety (e.g., my child is afraid of sleeping alone), sleep onset delay (e.g., my child falls asleep in 20 min), night awakenings (e.g., my child awakens more than once), bedtime resistance (e.g., my child struggles at bedtime), and parasomnias (e.g., my child sleepwalks). Items are summed to produce a score for each subscale and a total sleep disturbance score. *Sleep disturbances* was defined as the CSHQ total sleep disturbance score, which is heavily weighed on behavioral sleep problems (e.g., bedtime resistance); scores greater than 41 indicate clinically significant sleep disturbances (Owens et al. 2000). *Sleep-disordered breathing* was defined as its CSHQ subscale score; it is an index of non-behavioral sleep problems (e.g., snoring, sleep apnea). In sleep-disordered breathing, respiration is repeatedly disrupted, leading to frequent awakenings and micro-arousals that affect sleep quality. Sleep-disordered breathing has been postulated to uniquely contribute to increased fat deposits, particularly in abdominal regions (Björntorp 2001; Daniels et al. 1999; Drapeau et al. 2003). The CSHQ is well-established, has previously been used in children aged 4–17 years, distinguishes between healthy children and those with sleep disorders (sensitivity = 0.80; specificity = 0.72), and has demonstrated psychometric reliability (test–retest: $r = 0.62\text{--}0.79$; Beebe et al. 2007; Owens et al. 2000; Lewandowski et al. 2011; Wang et al. 2013). High internal consistency has been previously reported for the sleep-disordered breathing subscale ($\alpha = 0.93$; Owens et al. 2000).

Heart Rate Variability—Heart rate variability reflects beat-to-beat variation in heart rate, which is influenced by the simultaneous effects of both sympathetic and parasympathetic activity on the sinoatrial node (Berntson et al. 1997). Children wore pre-gelled silver

chloride electrocardiogram (ECG) electrodes in a modified Lead II configuration. The active electrode (and its derivative/dZ) was placed on the right clavicle next to the sternum over the first rib between the two collarbones. The second electrode was placed on the left mid-clavicular line at the apex of the heart over the ninth rib. The ground electrode was placed near the lowest possible right rib cage on the abdomen. Additional dZ electrodes were placed over the right fourth intercostal space at the sternal edge, the fifth intercostal space at the left axillary line, and on the sixth rib in the mid-clavicular line. Following a 20 min resting period, continuous ECG was recorded (8500 Marquette MARS Holter monitor; GE Marquette Medical Systems, Milwaukee, WI, USA) during the standardized clinic visit protocol.

Consistent with HRV measurement guidelines (Task Force 1996), each QRS complex was defined based on standard Marquette algorithms for QRS labeling, edited for artifacts, and further verified by review of a board-certified cardiologist. Artifact removal was based on a 20 % change from the previous signal as a criterion. Cubic spline interpolation method was used to replace data points where artifacts were identified or RR intervals were automatically excluded due to unreadable signals. A minimum of four acceptable R-peaks was required for spline interpolation to identify the continuous function between two central R-peaks. Next, input samples were linearly detrended, mean-centered, and tapered using a Hanning window. Finally, Fast Fourier Transformation spectral analyses, which transform ECG heart rate from beat-to-beat intervals to frequency power bands, were used to derive heart rate variability (HRV) variables. Frequency-domain HRV variables, including low frequency (LF, 0.04–0.15 Hz), high frequency (HF, 0.15–0.4 Hz), and their ratio (LF:HF), were calculated and expressed in absolute and natural log units. Psychometrics of heart rate variability measures in pediatric samples have been previously reported (Jarrin et al. 2012, 2014).

Low Frequency HRV represents autonomic fluctuations associated with the regulation of vasomotor tone and blood pressure. Evidence from autonomic blockade studies suggests LF is a measure of both sympathetic and parasympathetic function (Cacioppo et al. 1994); recent findings suggest LF may reflect parasympathetic modulation or baroreflex function (Reyes Del Paso et al. 2013). *High Frequency HRV* represents the effects of respiration on heart rate, or respiratory sinus arrhythmia. Considerable evidence supports that HF is a measure of parasympathetic activity (Berntson et al. 1997; Cacioppo et al. 1994). *LF:HF ratio* is an index of sympathovagal balance, with higher estimates indicative of sympathovagal imbalance. Sympathovagal imbalance is extensively used as a marker of autonomic dysfunction, as it is considered an appropriate measure of sympathetic modulation based on microneurography and ganglionic blockade studies (Berntson et al. 1997; Diedrich et al. 2003; Pagani et al. 1997; Spiegel et al. 2004a, b; Task Force 1996); although this has been debated (Reyes Del Paso et al. 2013).

Physical Activity and Screen Time—Children completed the Seven Day Physical Activity Recall (Sallis et al. 1993). *Physical activity* was defined as the number of days during a typical school week in which they moderately or strenuously participated in sports, dance, or playing games (i.e., enough to feel hot, out of breath, make heart beat faster). Child-report measures of physical activity demonstrate high test–retest reliability ($r = 0.81$)

and moderate validity compared to heart rate monitoring ($r = .53$; Sallis et al. 1993). *Screen time* was defined as the total number of hours children reported they spent watching TV, using the computer or Internet, or playing videogames over the past week. Self-report estimates of screen time have previously demonstrated high test–retest reliability ($ICC = 0.98$) and validity ($ICC = 0.50–0.80$) among children (He et al. 2009).

Puberty—Sexual maturation was scored by a pediatric registered nurse according to Tanner descriptions for pre-pubertal, pubertal, and post-pubertal stages (Lambert et al. 2011; Marshall and Tanner 1969, 1970). Pre-pubertal stage criteria include no body hair growth, no menstruation or breast growth for girls, and no facial hair growth or deepening of the voice for boys. Pubertal stage criteria include any indication of body hair and breast growth and/or menstruation for girls, and any indication of facial hair growth and/or voice changes for boys. Post-pubertal stage criteria include complete body hair and breast growth, as well as menstruation for girls, and complete facial hair growth and voice changes for boys.

Tidal Volume—Tidal volume of breathing (natural volume of air inhaled and exhaled during spontaneous breathing; L/min) was measured using an indirect calorimetry standardized protocol (Wanger et al. 2005). Children wore an airtight facemask connected to a turbine volume measuring device (Oxycon-Pro, Jaeger) while seated and “breathing naturally” for 5 min to capture stable measures. Calibration of air volume (3 L syringe and automated) and air composition specific to the apparatus was completed prior to each test.

Procedure

During the scheduled visit, parents completed questionnaires (e.g., socio-demographics) and reported on child medication use in the last 2 weeks (e.g., antibiotics, pain/fever, colds/allergies) prior to data collection. Children completed questionnaires on their lifestyle habits (e.g., physical activity, screen time) while seated quietly. Anthropometrics were then measured by a pediatric registered nurse. Next, the nurse pre-cleaned the skin with rubbing alcohol swabs to minimize electrode resistance (<10 k Ω), prior to electrode placement. Continuous ECG was recorded during the clinic visit, which began in the morning between 07:00 and 09:00 and lasted an average of 3 h. During this time, participants were seated quietly while completing questionnaires and having biological measurements taken (e.g., blood pressure, blood draw). Then, the nurse removed the electrodes and Holter monitor. Finally, DEXA scans and indirect calorimetry tests were conducted to measure body composition and tidal volume of breathing.

Statistical Analyses

All data were double-entered and analyzed with IBM SPSS Statistics 21 software (SPSS, Inc., Chicago, IL). Data were retained as continuous to maximize statistical power and were checked for normality and linearity. The LF and HF distributions were skewed and thus, natural log-transformed (ln). To test the hypothesis that sympathovagal imbalance contributed to the association between poor sleep and childhood obesity, Preacher and Hayes’ (2008) bootstrapping macro method was used, which advances Baron and Kenny’s approach (1986). Similar to a linear regression framework, this method allowed for the estimation of the path coefficients for: (1) *Path A*: the total effect of sleep (independent

variable) on HRV (proposed contributory factor), (2) *Path B*: the direct effect of HRV on obesity (dependent variable), while controlling for sleep, (3) *Path C*: the total effect of sleep on obesity (without HRV), and (4) *Path C'*: direct effect of sleep on obesity, while controlling for HRV. Age, sex, puberty, screen time, physical activity, household income, parental education, heart rate, and tidal volume of breathing were included as covariates in all models.

Notably, sleep duration (parent-report), sleep timing, and sleep disturbances were not significantly associated with any HRV measures (i.e., *Path A*). Similarly, LF and HF were not significantly associated with any obesity measures (i.e., *Path B*); these variables were not included in the mediational analyses. Thus, mediational models included sleep duration (child-report), sleep timing, and sleep-disordered breathing (independent variables); LF:HF ratio (proposed contributory factor); and, waist circumference, BMI Z-score, and fat mass index (dependent variables).

Bias corrected bootstrapped confidence intervals (95 %, BcCI) were generated with 10,000 resamples and used to test for potential indirect effects of sleep on obesity through HRV (Preacher and Hayes 2008). A significant indirect effect was defined as the BcCI around the unstandardized coefficient not including zero (Preacher and Hayes 2008). This method was used as it is superior to SOBEL because it adjusts all paths for the possible influence of covariates not proposed to be indirect effects in the models, reduces type I error rates, increases statistical power, and does not assume a normal sampling distribution (Preacher and Hayes 2008). Alpha levels were set to 0.05 (two-tailed); Bonferroni corrections were applied as appropriate.

Results

Of the 564 participants who completed the second visit of the QUALITY study, participants were excluded for insufficient sleep data ($n = 5$) or incomplete ECG recordings ($n = 65$). Incomplete ECG recordings were due to incorrect use of Holter monitors ($n = 35$; 47.7 %), technical issues (e.g., battery died, $n = 20$; 30.8 %), or the child feeling ill/refusing to wear the monitor ($n = 14$; 21.5 %). Thus, the final sample size for the present analyses was 494. All ECG recordings were reviewed by a board-certified cardiologist; no cardiovascular pathology was identified (i.e., bradycardia, fibrillation, premature contraction).

All children were Caucasian, aged 11.67 years ($SD = 0.95$), of normal weight status (57.7 % BMI 5–85th percentile), and most were categorized as pre-pubertal status (64.8 %; see Table 1). The majority of children (95.0 %) did not take any over-the-counter or prescribed medications (e.g., cold, digestive, antibiotics, steroids, amphetamines, lipids, hypnotics) during the prior 2 weeks; none took medication for diabetes or hypertension. Three children were taking melatonin; because results were identical when analyses included and excluded these children, only data for the entire sample are presented. Children's anthropometric, sleep, and HRV measures are presented in Table 1. Briefly, based on self-report, children's typical bedtime was 20:53 ($SD = 0:38$) and they slept an average of ~ 9.5 h on school nights. Based on parent-report, children retired to bed on average at 20:51 ($SD = 1:05$), slept an

average of 10 h each night weekly, and 22.3 % of children exhibited clinically significant sleep disturbances (i.e., CSHQ total sleep disturbance score >41).

Hypothesis Testing

Path A: Independent Variable (Sleep) on Proposed Contributory Factor (Sympathovagal Imbalance)—Shorter sleep duration, later sleep timing, and more sleep-disordered breathing symptoms were significantly associated with higher sympathovagal imbalance (LF:HF ratio), while adjusting for covariates (see Table 2).

Path B: Proposed Contributory Factor on Dependent Variable (Obesity)—Higher sympathovagal imbalance (LF:HF ratio) was significantly associated with larger waist circumference, BMI Z-score, and fat mass index values in adjusted models (see Table 2).

Path C: Independent Variable on Dependent Variable—Later sleep timing and more sleep-disordered breathing symptoms were significantly associated with larger waist circumference, BMI Z-score, and fat mass index values in adjusted models (Table 2). Shorter sleep duration was also significantly associated with larger BMI Z-score and fat mass index values; further, a trend was observed between sleep duration and waist circumference ($p = 0.084$).

Path C': Direct Effect of Independent Variable on Dependent Variable—Higher sympathovagal imbalance (LF:HF ratio) partially contributed to the association between later sleep timing with larger waist circumference, BMI Z-score, and fat mass index values. Higher LF:HF ratio also partially contributed to the association between more sleep-disordered breathing symptoms with larger waist circumference, BMI Z-score, and fat mass index values (Fig. 1). After controlling for LF:HF ratio, a trend was observed between shorter sleep duration with larger BMI Z-score and fat mass index values ($p = 0.077$), but not with waist circumference (see Table 2).

To test the significance of the partial indirect effects of sympathovagal imbalance on sleep and obesity, bootstrapping analyses were conducted. Analyses concluded all indirect effects were significant, indicative that sympathovagal imbalance significantly partially contributed to the association between poor sleep (sleep timing, sleep-disordered breathing) with obesity (central adiposity, body composition; see Table 2).

Discussion

Obesity is a risk factor for multiple chronic diseases, disability, and premature mortality. Researchers continue to seek a better understanding of the pathogenesis of obesity. While mounting evidence suggests an association between sleep and obesity, the mechanisms underlying their association are complex and less clear. The aim of the present study was to investigate sympathovagal imbalance as one potential pathophysiological mechanism. The present study found preliminary support for the contributing role of sympathovagal imbalance in the concurrent association between poor sleep and childhood obesity. Namely, results were partly consistent with the hypotheses, such that LF:HF ratio significantly

contributed to the association between later sleep timing and more sleep-disordered breathing with larger central adiposity and body composition. Further, a trend was observed for LF:HF ratio partially contributing to the association between short sleep duration and the body composition indices, except for central adiposity. These findings are consistent with past research linking sleep-disordered breathing with obesity and sympathovagal imbalance (Hakim et al. 2012).

The paired associations between sleep, obesity, and sympathovagal imbalance were also consistent with previous research. First, among children in this at-risk sample, poorer sleep was associated with larger central adiposity and body composition. In other words, heavier youth reported shorter sleep duration, later bedtime, and endorsed more sleep-disordered breathing symptoms, even after adjusting for obesity-related covariates. These findings coincide with those previously reported (Beebe et al. 2007; Knutson 2012; Knutson and van Cauter 2008). Second, poorer sleep was associated with greater sympathovagal imbalance. Consistent with previous research (Rodríguez-Colón et al. 2011), children in the QUALITY Cohort with shorter sleep duration, later bedtime on school nights, and more sleep-disordered breathing, exhibited greater LF:HF ratio, indicative of greater sympathovagal imbalance. This association remained significant even after controlling for important developmentally-relevant covariates (e.g., puberty; Jarrin et al. 2014). While this association was evident with LF:HF ratio, the hallmark measure of sympathovagal imbalance, no association was observed for LF or HF measures. The lack of association with LF and HF may be attributable to daytime ECG recordings, as past studies report noticeable differences in sympathovagal imbalance during the night (Rabbia et al. 2003). Further, it is not necessarily the absolute levels of LF and HF that matter, but rather, their relative contribution to the *imbalance* that is critical and make LF:HF ratio a more sensitive measure of autonomic modulation (Berntson et al. 1997). Third, greater sympathovagal imbalance was associated with larger central adiposity and body composition, irrespective of covariates. These results corroborate past findings (Rodríguez-Colón et al. 2011) and support prospective evidence suggesting that sympathovagal imbalance at age 5.5 years was predictive of obesity 5 years later (Graziano et al. 2011). These observed paired associations also support sympathovagal imbalance as a plausible pathogenic pathway underlying the concurrent association between poor sleep and obesity in children.

Pathophysiology of Sympathovagal Imbalance

The present findings provide new knowledge about the role of a sympathovagal imbalance as a potential pathogenic pathway through which poor sleep may lead to obesity in children. Extant literature also provides increasing support for the pathophysiology of sympathovagal imbalance having a contributing role in this association. Sleep disturbances are associated with nocturnal arousals, which enhance sympathetic activity, leading to increases in urinary catecholamine levels, heart rate, blood pressure, and sympathovagal imbalance among adults and youth (Ekstedt et al. 2004; Knutson and van Cauter 2008; Spiegel et al. 2004a, b; Tochikubo et al. 1996; Zhong et al. 2005). For example, individuals with clinical sleep disorders (e.g., sleep apnea, insomnia) evidence elevated heart rate, reduced parasympathetic activity (Bonnet and Arand 2010), and progressive increases in sympathetic activity over time during sleep and wakefulness (Hakim et al. 2012).

In addition to sleep disturbances, sleep timing also seems to play an instrumental role in sympathovagal balance, as HRV is influenced by circadian rhythm. Circadian misalignment (i.e., phase shift, sleeping at inappropriate times) may disrupt the circadian function of the autonomic nervous system (Haqq et al. 2011). Delayed sleep phase patterns (i.e., later bed- and rise-times) are associated with reduced HRV (Jarrin et al. 2014), as well as greater BMI in children and adolescents (Jarrin et al. 2013; Olds et al. 2011). While delayed sleep phase patterns are typical during adolescent development, children as young as 8 years with later bedtimes also have an increased risk of obesity (Jarrin et al. 2013; Olds et al. 2011). In fact, there is evidence that the transition into phase delay associated with adolescence is occurring earlier, which corresponds with the increasingly earlier onset of puberty (Roenneberg et al. 2004; Tonetti et al. 2008).

Sympathetic activation influences hormone production and adipose tissue. Pharmacologic sympathetic blockade increases leptin levels, and after acute treatment with catecholamines, decreases circulating leptin (Rayner and Trayhurn 2001). Moreover, the autonomic nervous system innervates white adipose tissue, with parasympathetic input increasing adipose mass and sympathetic input decreasing fat mass via reduced differentiation and cell proliferation (Fliers et al. 2003). Although this seems counterintuitive, white adipose tissue releases significant cytokines and hormones (e.g., leptin, adiponectin, resistin, tumour necrosis factor- α) that regulate energy expenditure, appetite, and satiety (Fliers et al. 2003). In other words, as an indirect result of sympathetic overactivation, hormones that curb the development of obesity are not produced. Further, distribution of adipose tissue (i.e., visceral vs. subcutaneous) is influenced by differential activity of the autonomic nervous system (Fliers et al. 2003). For example, abdominal visceral fat in males is associated with sympathetic activation, while subcutaneous fat is not (Alvarez et al. 2004).

McEwen and colleagues have postulated that poor sleep is a major stressor that activates the stress response system, and if chronic, may cause progressive wear and tear, or allostatic overload (Danese and McEwen 2012). While individuals often do not report feeling stressed under conditions of sleep loss, physiological evidence suggests otherwise (Spiegel et al. 2004a, b). Chronic stress activation (e.g., frequent nocturnal awakenings) can lead to negative alterations in the autonomic (e.g., sympathovagal imbalance), endocrine (e.g., cortisol), and immune systems; and, it has been suggested these negative alterations exert enduring effects on aging and health (Danese and McEwen 2012). Yet, the results of the present study and past research indicate these sorts of physiological dysregulations can be observed during childhood and adolescence. Given that these associations are evident and emerging at a young age provides new insight and suggests that it may not require chronic activation or long exposures to accelerate and exaggerate pathophysiology. Relatedly, duration of obesity has been suggested to influence autonomic cardiovascular control, with greater sympathovagal imbalance observed among children who recently developed obesity (Rabbia et al. 2003).

The effect sizes of the contributing role of sympathovagal imbalance on sleep and obesity in the present study are significant, yet small (2–3 %), suggesting that myriad factors are likely also involved in this complex regulatory system. Most endocrine organs are sensitive to changes in sleep, which in turn may lead to the pathophysiological consequences that

promote obesity, including changes in appetitive hormones, cortisol, and insulin sensitivity (Knutson and van Cauter 2008; Knutson 2012; Spiegel et al. 2004a, b). Compared to sleep extension, sleep restriction leads to significant reductions in leptin (−18 %), increases in ghrelin (+28 %) and ghrelin:leptin ratio (+71 %), as well as increased hunger (+24 %) and appetite ratings (+23 %) for calorie-dense carbohydrate rich foods, even when energy intake and expenditure are kept constant (Spiegel et al. 2004a, b). Thus, these experimental findings suggest one alternative explanation that disruptions in sleep may lead to substantial alterations in leptin and ghrelin, and thus, energy intake.

There is also evidence that suggests metabolism may be more influenced by sleep timing, rather than sleep duration (Scheer et al. 2009). In other words, obtaining sleep at one's natural/ideal point in their circadian rhythm may have a larger impact than the actual length of sleep obtained. Further, children and adolescents with delayed sleep phase patterns are susceptible to overeating, have less moderate-to-vigorous physical activity, and have high screen time, compared to those with non-delayed sleep phase patterns (Olds et al. 2011). As another alternative explanation, delayed sleep phase patterns may merely increase exposure to obesogenic environments (i.e., missed breakfast, greater sedentary behavior, more time awake at night to consume foods). Together, these findings raise important future research questions about the pathogenesis of the association between sleep, obesity, and autonomic dysfunction.

Strengths, Limitations, and Future Recommendations

This study had four strengths and limitations that merit discussion. First, the sample was a unique strength of the study, as it was comprised of a large cohort of children at-risk for developing obesity, based on confirmed parental overweight status. The QUALITY Cohort sample provided an exceptional opportunity to explore the research question of the possible role of sympathovagal imbalance in a targeted, vulnerable sample. While 57.7 % of the at-risk children were of normal weight status, their average BMI values were higher than those reported for same-age girls (21.27 vs. 18.5) and boys (21.02 vs. 18.3) in a national population-representative survey (NHANES 2009–2010; Ogdon et al. 2012). They also had a shorter sleep duration (−26 min) and later bed-time (+10 min), compared to children in a provincially representative study within Québec; there were no differences in sleep-disordered breathing symptoms (Laperge et al. 2011). Finally, they had LF:HF ratio values comparable to overweight and obese children in previous studies (Rodríguez-Colón et al. 2011). It is postulated that among samples of obese children, similar findings or stronger associations may be observed. Indeed, compared to controls, obese children exhibit significantly more sleep disturbances (Beebe et al. 2007) and greater LF:HF ratio (Rabbia et al. 2003; Rodríguez-Colón et al. 2011). Incidentally, only Caucasian children participated in the QUALITY Cohort, which limits generalizability of the results to other populations.

Second, the findings are limited by the cross-sectional data, which precludes examination of sympathovagal imbalance as a true mediator in the association between sleep and childhood obesity. It is important that these findings be replicated and extended with longitudinal, prospective designs or experimental studies to elucidate the temporal nature of this complex, and possible causal association. Because experimental sleep-restriction studies with children

and adolescents pose practical limitations and concerns with ecological validity, it will be pertinent for researchers to triangulate findings across methodological designs (experimental, cross-sectional, prospective). Future researchers should consider other factors that may contribute to these associations as causal variables, mediators, and/or moderators. It would also be prudent to evaluate this association with diverse samples (e.g., weight status, race). Despite these constraints, the present cross-sectional findings were robust, even after adjusting for multiple comparisons (i.e., Bonferroni correction) and when controlling for developmentally-relevant covariates, including age, sex, puberty, screen time, physical activity, household income, parental education, heart rate, and tidal volume breathing.

Third, the use of subjective measures of sleep provided insufficient information about circadian alignment, sleep architecture, sleep efficiency, or sleep disorders. Notably, subjective measures are necessary to assess sleep quality, as objective sleep measures fail to capture one's perception of how restorative sleep is for them. Further, child- and parent-reported subjective sleep measures have established reliability and validity; and, it is recognized that multiple informants provide unique information essential for comprehensive sleep assessment within pediatric samples (Lewandowski et al. 2011; Matricciani 2013; Owens et al. 2000). Nevertheless, future researchers should incorporate objective measures of sleep (e.g., actigraphy, polysomnography) to assess additional sleep dimensions (e.g., wake after sleep onset; REM activity, apnea index). Relatedly, recommended use of actigraphy (i.e., accelerometers) would also have the added benefit of objective assessment of physical activity and sedentary behavior.

Fourth, objective measurement of obesity and autonomic functioning was conducted using equipment recognized as the medical gold-standard, following standardized methodological procedures. Specifically, fat mass index was derived from DEXA scans, waist and hip circumference were based on the World Health Organization recommended protocol (World Health Organization 2008), and heart rate variability was assessed using Holter monitors, in accordance with established guidelines (Task Force 1996). Of note, the use of LF:HF ratio as an index of sympathovagal imbalance has been debated (Reyes Del Paso et al. 2013); other measures (e.g., plasma/urinary catecholamines, pre-ejection period) and techniques (e.g., impedance cardiography, pharmacological blockade, microneurography) can be used to derive indices of autonomic dysfunction. While the present study only recorded ECG during the morning, future researchers may wish to consider 24 h or night-time recordings, as previous studies have observed a more prominent nocturnal decrease in parasympathetic activity and sympathetic hyperactivity in obese children (Rabbia et al. 2003).

Conclusion

The present findings provide new information about how poor sleep may lead to childhood obesity. Sympathovagal imbalance significantly contributed to the association between poor sleep (later sleep timing, sleep-disordered breathing) and obesity (central adiposity, body composition), among a sample of children at-risk for obesity. Trends were also observed for this association with sleep duration. These findings are of particular interest because the association between sleep, obesity, and sympathovagal imbalance appears to be emerging at a young age. This holds promise for future research considering mechanisms and lifecourse

trajectories and further highlights the importance of better understanding the complex pathophysiological mechanisms that may contribute to the etiology and maintenance of obesity. The observed effect sizes were small and significant, suggesting that other putative pathogenic mechanisms and potential contributory factors should also be considered. Importantly, these findings emphasize clinical recommendations for good sleep hygiene among children and adolescents to ensure they are getting adequate sleep, both in terms of quantity and quality. Future researchers should use longitudinal designs with objective measures of sleep, obesity, and sympathovagal imbalance to evaluate the temporal and possible causal nature of this association.

Acknowledgments

This work was partly supported by the Canadian Institutes of Health Research (J. McGrath OCO-79897, MOP-89886, MSH-95353; D.C. Jarrin BO512201). The QUALITY Cohort is funded by the Canadian Institutes of Health Research (M. Henderson #MOP-119512; M. Lambert #OHO-69442, #NMD-94067, #MOP-97853), the Heart and Stroke Foundation of Canada (#PG-040291), and Fonds de la recherche en santé du Québec. Dr. Marie Lambert (July 1952–February 2012), pediatric geneticist and researcher, initiated the QUALITY Cohort. Her leadership and devotion to QUALITY will always be remembered and appreciated. Sincere thanks to the dedicated QUALITY Cohort staff, especially Catherine Pelletier (Coordinator), Ginette Lagacé, Natacha Gaulin-Marion, and Hugues Charron, without whom this research would not be possible. Finally, we are grateful to all the families that participate in the QUALITY Cohort.

Abbreviations

BMI	Body mass index
CSHQ	Children's Sleep Habits Questionnaire
DEXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
FFT	Fast Fourier Transform
HF	High frequency
LF	Low frequency

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Biographies

Dr. Denise C. Jarrin received her Ph.D. in health psychology from Concordia University. Her research program focuses on psychophysiological and psychosocial correlates of sleep disturbances. Specifically, in autonomic dysfunction of the stress response system (measured by heart rate variability), and its link with sleep and health outcomes, including obesity.

Dr. Jennifer J. McGrath is the Director of the Pediatric Public Health Psychology Laboratory and an Associate Professor at Concordia University in Montreal. She examines the impact of health inequalities and how stress, socioeconomic status, environment, and behavior among children and adolescents increase risk for cardiovascular disease during adulthood.

Dr. Paul Poirier's research interests include cardiomyopathy associated with diabetes and obesity, metabolic syndrome, autonomic functioning, and the role of exercise and dietary behavior in diabetes and obesity.

The QUALITY Cohort Collaborative Group comprises specialists in pediatrics, endocrinology, cardiology, genetics, nutrition, biochemistry, vascular imaging, health psychology, social sciences, kinesiology, dentistry, epidemiology, biostatistics, and public health. The main interest of this research team is to increase understanding of the natural history of cardiovascular disease risk factors and Type 2 diabetes in children, which in turn will help program planners design effective health promotion and disease prevention interventions.

Fig. 1.

Path diagram of indirect and direct effects. *Path values* represent unstandardized regression coefficients. *Values outside parentheses* represent total effect of sleep (Children's Sleep Habits Questionnaire sleep-disordered breathing) on central adiposity (waist circumference), prior to inclusion of sympathovagal imbalance (LF:HF ratio). *Value in parentheses* represents the direct effect, from bootstrapping analyses, of sleep on central obesity after sympathovagal imbalance is included. ** $p < .01$; *** $p < .001$

Table 1

Socio-demographics, anthropometric, sleep, and heart rate variability measures

	Mean (<i>n</i>)	SD (%)
Socio-demographics		
Age (years)	11.67	0.95
Sex (males)	(279)	(56.5 %)
Anthropometrics		
Waist circumference (cm)	71.85	11.91
Hip circumference (cm)	85.72	10.93
Body mass index percentile	68.79	28.68
Body mass Z-score	1.08	0.70
Fat mass index (kg/m ²)	6.26	3.57
Body weight status ^a		
Underweight (< 5th percentile)	(10)	(2.0 %)
Normal (5 to < 85th percentile)	(285)	(57.7 %)
Overweight (85 to < 95th percentile)	(75)	(15.2 %)
Obesity (≥ 95th percentile)	(124)	(25.1 %)
Sleep measures		
Sleep duration (min)		
Child-report	588.02	42.10
Parent-report	594.44	40.82
Bed-time (hr:min)		
Child-report	20:53	0:38
Parent-report	20:51	1:05
Rise-time (hr:min)		
Child-report	06:41	0:31
Parent-report	06:48	0:38
Sleep disturbances total ^b (range 17–58)	37.83	5.51
Sleep-disordered breathing ^b (range 1–8)	3.25	0.71
Heart rate variability		
Low frequency (LF)		
ms ²	1,463.47	1,077.28
ln	7.08	0.63
High frequency (HF)		
ms ²	923.49	679.78
ln	6.55	0.78
LF:HF ratio	1.85	0.95

ln natural log transformation^aBMI percentiles based on age- and sex-specific distributed values of Centers for Disease Control^bSubscales of Children's Sleep Habits Questionnaire

Table 2

Estimated path coefficients and bootstrapped confidence intervals

	B (SE)	p	95 % BcCI
Path A: Sleep on sympathovagal imbalance			
Sleep duration	−0.05 (0.02)	0.030 *	—
Sleep timing	0.05 (0.02)	0.042 *	—
Sleep-disordered breathing	0.10 (0.03)	0.001 **	—
Path B: Sympathovagal imbalance on obesity			
Waist circumference	4.53 (1.35)	0.000 ***	—
BMI Z-score	0.26 (0.11)	0.010 *	—
Fat mass index	0.94 (0.41)	0.016 *	—
Path C: Sleep on obesity			
Sleep duration			
Waist circumference	−1.01 (0.58)	0.084 +	—
BMI Z-score	−0.10 (0.05)	0.043 *	—
Fat mass index	−0.36 (0.18)	0.042 *	—
Sleep timing			
Waist circumference	1.43 (0.63)	0.023 *	—
BMI Z-score	0.15 (0.05)	0.004 **	—
Fat mass index	0.56 (0.19)	0.003 **	—
Sleep-disordered breathing			
Waist circumference	4.23 (0.79)	0.000 ***	—
BMI Z-score	0.37 (0.06)	0.000 ***	—
Fat mass index	1.17 (0.23)	0.000 ***	—
Path C': Sleep on obesity with sympathovagal imbalance			
Sleep duration			
Sleep duration on waist circumference	−0.78 (0.58)	0.179	−0.538, −0.045
Sleep duration on BMI Z-score	−0.09 (0.05)	0.077 +	−0.038, −0.001
Sleep duration on fat mass index	−0.32 (0.18)	0.077 +	−0.142, −0.003
Sleep timing			
Sleep timing on waist circumference	1.17 (0.62)	0.061 +	0.067, 0.599
Sleep timing on BMI Z-score	0.14 (0.05)	0.007 **	0.001, 0.041
Sleep timing on fat mass index	0.51 (0.19)	0.008 **	0.004, 0.156
Sleep-disordered breathing			
Sleep-disordered breathing on waist circumference	3.79 (0.79)	0.000 ***	0.112, 1.019
Sleep-disordered breathing on BMI Z-score	0.35 (0.06)	0.000 ***	0.001, 0.067
Sleep-disordered breathing on fat mass index	1.11 (0.24)	0.000 ***	0.003, 0.259

All models include covariates: age, sex, puberty, screen time, physical activity, household income, parental education, heart rate, and tidal volume breathing. Statistical significance after Bonferroni correction ($p = .005$) are indicated by bolded values
BMI body mass index, *BcCI* bias corrected bootstrapped confidence intervals for indirect effects

⁺
 $p < .09$;

^{*}
 $p < .05$;

^{**}
 $p < .01$;

^{***}
 $p < .001$