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Increased inflammation from childhood to adolescence predicts sleep apnea in boys: A preliminary study

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ABSTRACT

While chronic systemic inflammation in obstructive sleep apnea (OSA) has been traditionally considered a consequence of intermittent hypoxia, several treatment studies targeting inflammation suggest that this process may precede the development of the disorder. A recent cross-sectional study in the Penn State Child Cohort (PSCC) revealed that inflammation largely mediates the association between visceral adiposity and OSA in adolescence. The purpose of this study was to examine for the first time whether, longitudinally, inflammation precedes OSA during this developmental period. A subsample of the PSCC with longitudinal sleep and inflammation data (n = 51) was included in this study. Participants underwent 9-h polysomnography (22:00–7:00), physical exam, and fasting morning blood draw at both time points. Plasma C-reactive protein (CRP) was measured via ELISA. At follow-up, visceral, subcutaneous, and total fat area were assessed via dual X-ray absorptiometry. Sex differences in body composition emerged in adolescence, with boys having more visceral adiposity than girls. Longitudinal increases in waist circumference from childhood to adolescence were associated with increases in CRP (ΔCRP) and follow-up CRP in boys, but not girls. Furthermore, in boys, ΔCRP was associated with higher follow-up apnea/hypopnea index (AHI). When ΔCRP was entered into a model predicting follow-up AHI, Δwaist circumference was no longer significant, indicating that inflammation largely explains the association between increasing central obesity and OSA severity. These preliminary findings, in a longitudinal, non-clinical sample of children developing OSA, suggest that inflammation derived from visceral adipose tissue precedes the development of the disorder, suggesting a potential causal mechanism.

1. Introduction

It is estimated that 1–4% of the general pediatric population (Bixler et al., 2008; Lumeng and Chervin, 2008) and 4–11% of adolescents (Spilsbury et al., 2015; Bixler et al., 2016) have obstructive sleep apnea (OSA), a prevalent sleep disorder characterized by obstruction of the upper airway during sleep despite breathing effort. While OSA in children is commonly thought to result from upper airway structural abnormalities, central obesity is increasingly recognized as a strong risk factor in children, adolescents, and adults (Bixler et al., 2008; Lumeng and Chervin, 2008; Shinohara et al., 1997; Vgontzas et al., 2000; Tauman and Gozal, 2006; Tsaoussoglou et al., 2010; Canapari et al., 2011). Importantly, the prevalence of OSA in adult men and women differs, with 17–24% of men and 5–9% of women demonstrating an apnea/hypopnea index (AHI) of five or more events per hour of sleep (Young et al., 1993; Bixler et al., 1998, 2001); these rates have recently increased between 14% and 55%, depending on the subpopulation studied, in conjunction with the obesity epidemic (Peppard et al., 2013).

Chronic systemic inflammation in OSA has been well-documented over the last two decades and correlates positively with apnea severity (Vgontzas et al., 2000). Traditionally, this inflammation has been largely considered a consequence of intermittent hypoxic episodes resulting from breathing pauses throughout the night (Ryan et al., 2005). Several treatment studies targeting inflammation, however, suggest that inflammation also precedes – and perhaps even plays a causal role – in the development of OSA. For example, compared to placebo, a three-week trial of the tumor necrosis factor alpha (TNFα) antagonist etanercept has been shown to reduce AHI in obese men with OSA (Vgontzas et al., 2004). Combined oral anti-inflammatory and intranasal

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corticosteroid treatment has also been demonstrated to largely normalize mild OSA in children (Kheirandish-Gozal et al., 2014). On the other hand, while the gold standard treatment, continuous positive airway pressure (CPAP) therapy, reliably reduces AHI, a recent large systematic review and meta-analysis of randomized controlled studies concluded that CPAP does not significantly alter levels of plasma inflammatory cytokines (Jullian-Desayes et al., 2015). Together, these findings suggest that inflammation may be more than simply a result of apnea, but rather also a cause and potential treatment target – though no longitudinal study has yet explored this hypothesis.

In adults, levels of proinflammatory cytokines are correlated positively with body mass index and, in particular, visceral adiposity (Vgontzas et al., 2000; Khaodhiar et al., 2004). Resident macrophages in visceral fat tissue secrete high levels of cytokines (Fain, 2006) as a result of adipocyte growth, oxidative stress, and endothelial damage (Wellen and Hotamisligil, 2003). Given that adult men tend to have at least twice as much visceral fat tissue as women (Wajchenberg, 2000) and are significantly more likely to present with OSA (Young et al., 1993; Bixler et al., 1998, 2001), inflammation again presents an enticing target. Indeed, a recent study in the general population Penn State Child Cohort demonstrated that inflammation strongly mediates, cross-sectionally, the association between visceral adiposity and OSA in adolescents, with 82% of the association explained by CRP levels (Gaines et al., 2016). No studies to date, however, have explored this association in a longitudinal sample.

Given the well-characterized sex differences in central obesity and OSA prevalence, the association of visceral adiposity with inflammation, and evidence that inflammation may precede the development of OSA, we explored the longitudinal mechanisms underlying the development of incident OSA in a general population sample of children transitioning to adolescence. We hypothesized that OSA severity in adolescence was associated with (a) increases in waist circumference since childhood, particularly in boys, (b) elevations in proinflammatory cytokines since childhood, and (c) that increases in inflammation during this developmental period largely explain the association between accumulating central obesity and sleep apnea severity.

2. Methods

2.1. Participants

The study participants comprised a subsample of the Penn State Child Cohort (PSCC) – a representative general population sample of 700 children (ages 5–12 years) – who served as healthy controls (AHI < 2) in a study exploring inflammation and metabolic abnormalities in children with OSA (Tsaoussoglou et al., 2010). Of n = 82 participants who were approached and gave a blood sample during childhood, n = 51 returned an average of 8.4 years later as adolescents as part of their follow-up visit (Bixler et al., 2008, 2009). All participants have complete longitudinal sleep data and provided fasting morning blood samples. Importantly, the 51 participants in the present study did not differ from the rest of the PSCC participants (n = 649) in terms of baseline age (9.14 ± 0.23 years vs. 9.17 ± 0.08 years, respectively, p = 0.905), BMI percentile (63.19 ± 4.17 vs. 63.13 ± 1.14, p = 0.989), sex distribution (41.2% boys vs. 53.3% boys, p = 0.071), nor ethnic minority distribution (15.70% minority vs. 20.20% minority, p = 0.284).

Written informed consents were obtained from participants 18 years and older. Assent was sought for those younger than 18 years, and consent was obtained from their parents or legal guardians. All research protocols were reviewed and approved for compliance with the policy of the human subjects Institutional Review Board at Penn State University College of Medicine.

2.2. Sleep laboratory protocol

At both baseline and follow-up time points, all participants underwent a 9-h, single-night polysomnography (PSG) recording in a sound-attenuated, light- and temperature-controlled room with a comfortable, bedroom-like atmosphere (Fig. 1). Each subject was continuously monitored from 22:00 h until 7:00 h using 14-channel recordings of electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG). Respiration was monitored via nasal pressure (Pro-Tech PTAF Lite; Mukilteo, WA), thermocouple (Salter Labs; Lake Forest, IL), and thoracic/abdominal strain gauges (Model 1312, Sleepmate Technologies; Midlothian, VA). Hemoglobin oxygen saturation (SpO2) was assessed using a pulse oximeter placed on the index finger (Model 3011 Xpod, Nonin Medical, Inc.; Plymouth, MN). Snoring sounds were monitored via a sensor attached to the throat. All data were recorded using Twin Recording & Analysis software (Grass-Telefactor; West Warwick, RI). Visual sleep stage scoring was conducted by a registered polysomnography technologist according to standardized criteria (Rechtshaffen and Kales, 1968). Apnea/hypopnea index (AHI; number of apneas and hypopneas summed per hour) was ascertained. An apnea was defined as a cessation of airflow with a minimum duration of 5 s (for those aged < 16 - years) or 10 s (for those $\geq$ 16 years at follow-up) and an associated out-of-phase strain gauge movement; a hypopnea was characterized by a reduction of airflow by approximately 50% with an associated decrease in SpO2 of at least 3% or an associated EEG arousal (Iber et al., 2007).

2.3. Physical assessment

During their baseline and follow-up visits in the laboratory (Fig. 1), all participants underwent a physical examination, during which height (stadiometer Model 242, SECA Corp.; Hanover, MD), weight (Model 758C, Cardinal Manufacturing; Webb City, MO), and waist circumference (via tape measure) were recorded according to Centers for Disease Control (2011) criteria. Body mass index (BMI) was calculated (in kg/m^2) and converted to a percentile according to a formula based on the Centers for Disease Control's (2009) sex-specific BMI-for-age growth charts. All participants were deemed to not have any active illness or infection at the time of their visit, nor did anybody have CRP values >10 mg/L. Participants identified their race/ethnicity from one of six options; "ethnic minority status" was re-defined as "non-white/Caucasian" for statistical purposes.

At follow-up, participants also underwent a dual-energy X-ray absorptiometry (DXA) scan using a Hologic Discovery W scanner (Hologic Inc.; Waltham, MA; 195 × 65 cm field of view) to obtain a precise measure of body fat. Regions of interest included visceral, subcutaneous, and total (visceral plus subcutaneous) adipose tissue area. These regions were identified by Hologic APEX 4.0 software (Hologic Inc.; Bedford, MA) and visually verified by an experienced investigator; detailed descriptions of these measures can be found elsewhere (Hologic, Inc., 2010; Kelly et al., 2010).

2.4. Blood draw and assay procedures

Upon awakening (7:00), blood samples were collected in EDTA-containing tubes, then spun for 10 min at 3000 RPM. Plasma was aliquoted into cryotubes and stored at −80 °C until assayed. High-sensitivity C-reactive protein (CRP) was measured via enzyme-linked immunosorbent assay (ELISA; R&D Systems; Min-