Pediatric Sleep Apnea

Implications of the Epidemic of Childhood Overweight

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Over the last 30 years, the prevalence of overweight across all pediatric age groups and ethnicities has increased substantially, with the current prevalence of overweight among adolescents estimated to be approximately 30%. Current evidence suggests that overweight is modestly associated with obstructive sleep apnea syndrome (OSAS) among young children, but strongly associated with OSAS in older children and adolescents. The rising incidence of pediatric overweight likely will impact the prevalence, presentation, and treatment of childhood OSAS. The subgroup of children who may be especially susceptible include ethnic minorities and those from households with caregivers from low socioeconomic groups. OSAS, by exposing children to recurrent intermittent hypoxemia or oxidative stress, may amplify the adverse effects of adiposity on systemic inflammation and metabolic perturbations associated with vascular disease and diabetes. When these conditions manifest early in life, they have the potential to alter physiology at critical developmental stages, or, if persistent, provide cumulative exposures that may powerfully alter long-term health profiles. An increased prevalence of overweight also may impact the response to adenotonsillectomy as a primary treatment for childhood OSAS. The high and anticipated increased prevalence of pediatric OSAS mandates assessment of optimal approaches for preventing and treating both OSAS and overweight across the pediatric age range. In this Pulmonary Perspective, the interrelationships between pediatric OSAS and overweight are reviewed, and the implications of the overweight epidemic on childhood OSAS are discussed.

Keywords: sleep apnea; childhood obesity; childhood overweight

PEDIATRIC OBSTRUCTIVE SLEEP APNEA SYNDROME: OVERVIEW AND EPIDEMIOLOGY

Pediatric obstructive sleep apnea syndrome (OSAS) is a disorder in children characterized by repetitive episodes of upper airway obstruction, intermittent hypoxemia and hypercapnia, and snoring. Limited epidemiologic data suggest that the disorder affects 2 to 3% of middle-school children (1, 2), and as many as 13% of children aged 3 to 6 years (3). Prevalence may be two- to fourfold higher in vulnerable populations, such as in blacks and in children who were born preterm (1, 4), and symptoms of OSAS also appear to be increased in Hispanic children (5). Recent data suggest that OSAS is more common in children from poor neighborhoods (6). The chronic comorbidities associated with untreated pediatric OSAS include cognitive deficits, behavioral problems (inattention, hyperactivity, aggression, conduct problems, attention-deficit/hyperactivity disorder), mood impairments, excessive daytime sleepiness, impaired school performance, and poor quality of life (7–10). Untreated pediatric OSAS also has been associated with adverse cardiovascular and metabolic outcomes. Children with OSAS have higher levels of blood pressure, C-reactive protein (an inflammatory risk factor associated with cardiovascular disease) and increased insulin resistance, as well as left ventricular hypertrophy (11–15), suggesting that childhood OSAS also may increase the risk of developing severe chronic cardiovascular and metabolic conditions. However, these outcomes are also commonly observed in obesity, and the extent to which OSAS is an independent risk factor for these adverse cardiovascular and metabolic outcomes is uncertain. Despite the frequency and severity of OSAS during childhood, there are large knowledge gaps, including scant data that address causal pathways and population vulnerability to the disorder.

OSAS RISK FACTORS AND PATHOGENESIS: ASSOCIATIONS WITH OVERWEIGHT

Pediatric OSAS has both distinct and similar characteristics to adult OSAS. At all ages, narrowing and excessive collapsibility of the upper airway during sleep appears to be a common final pathway. In adults, airway compromise appears to be strongly related to male sex, ventilatory instability, and overweight (16). Three large epidemiologic studies have demonstrated that small changes in weight lead to changes in the apnea–hypopnea index (AHI) (17–20). Specifically, a 1% change in body mass index (BMI) has been estimated to lead to a 3% change in AHI (19), and a 10% increase in BMI increases incident OSAS by sixfold (17). Weight change appears to more strongly influence AHI level in men compared with women (17, 18, 20), and the effects of weight gain on increasing AHI level appear to be greater than the effects of weight loss on decreasing AHI (20). The mechanisms by which overweight acts as an OSAS risk factor in adulthood are probably multiple, but include adverse effects of overweight on lung mechanics and ventilation, as well as direct effects of overweight on airway size. The latter is supported by imaging studies showing an increase in parapharyngeal fat pads or visceral neck fat in adults with OSAS compared with control subjects (21, 22). This fat deposition is believed to alter pharyngeal size and shape, increasing the vulnerability of the upper airway to collapse.

Pediatric OSAS, similar to the adult syndrome, is associated with excessive collapsibility of the pharyngeal airway (23). Family studies have shown that OSAS aggregates within families; evidence of intergenerational transmission (24) suggests that

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common genetic risk factors operate in young and older individuals. However, there are notable differences in the presentation of OSAS and associated risk factors in adults and children. Unlike the male predominance of adult OSAS (25), in prepubertal children OSAS is estimated to be equally represented among males and females (1, 26), and, as described below, is most commonly associated with adenotonsillar hypertrophy and only weakly associated with overweight. Children with OSAS often have an anatomic predisposition to airway collapse, as evidenced by reduced upper airway dimensions detectable by acoustic reflectometry (27) as well as magnetic resonance imaging (28, 29). In children, the maximal airway narrowing corresponds to areas where the tonsils, adenoids, and soft palate overlap, and, at least in small study samples of predominantly young children, is not associated with parapharyngeal fat deposition (28). It is not known whether the lack of observed parapharyngeal fat is due to the small study samples of children, most of whom were not overweight, that were studied or if body fat distribution in children infrequently involves deposition of fat in the upper airway area. These imaging findings are consistent with the observation that adenotonsillar enlargement, not obesity, is the most commonly recognized risk factor for OSAS among children (30). It is also consistent with craniofacial and lymphoid growth patterns: young children have relatively small pharyngeal dimensions and large amounts of lymphoid tissue, jointly compromising the airway.

Pediatric OSAS, possibly more so than the adult syndrome, also is associated with respiratory allergies and with asthma or asthma symptoms (4, 31). The bases for these associations are unclear but may include the following: associated nasal disease and increased nasal resistance causing increased negative pressure swings, inducing pharyngeal collapse; generalized (upper and lower) airway inflammation and narrowing; and common genetic mechanisms. Obesity is associated with both asthma and with OSAS, and may partly, but not fully, explain the observed associations between asthma and OSAS (31).

How important is overweight as a childhood OSAS risk factor? Data from the Cleveland Family Study, which included children aged 4 to 18 years, indicate that children who are overweight are at a 4.6-fold increased risk for sleep apnea than children who are normal weight (4). In contrast, in a cohort of children aged 8 to 11 years, the odds ratio for OSAS given overweight was only 1.3 (95% confidence interval, 0.55, 3.10) (1). A follow-up study of a sample of children from the latter cohort assessed at ages 13 to 16 years, however, showed a remarkably different pattern, with an odds ratio for overweight greater than 9.0 (S.R., unpublished). Although further analyses are needed to more precisely examine the age dependency of the associations between OSAS and overweight, the marked differences in this cohort studied 4 years apart appear attributable to the ages of the sample at each visit: there was a weak association with obesity in prepubertal children and a strong association in adolescents. This pattern is consistent with reports from a variety of populations showing generally weaker associations between overweight and indices of OSAS (including reported snoring) in younger as compared with older pediatric samples (3, 32–34). Although three studies of children younger than 13 years reported no difference in levels of BMI between snorers or children with sleep-related desaturation compared with children without evidence of OSAS (3, 32, 33), two other studies of adolescents reported that body weight or central obesity was a strong predictor of snoring (34, 35). One notable example, however, of a study reporting a strong association between obesity and pediatric OSAS in younger children is from China. In this study of 90 children, aged 7 to 11 years, OSAS was identified in 32.6% of children who were overweight as compared with 4.5% of their normal-weight peers (36). This study was particularly interesting because it also demonstrated that overweight was associated both with adenoid hypertrophy and velopharyngeal narrowing, suggesting that overweight may increase susceptibility to OSAS through several different causal pathways. Other data have demonstrated that Asian individuals are at increased risk for OSAS at lower levels of BMI than individuals of European descent (37), possibly due to differences in body fat composition or to craniofacial features (38). Thus, young Chinese children may be more susceptible to the effects of overweight than children of other ethnic groups. Further research aimed at elucidating the relative differences in overweight as an OSAS risk factor in younger compared with older children and among ethnic groups may identify important developmental and genetic determinants for risk factors that modify the influence of overweight as an OSAS risk factor.

Although in some cases OSAS simply may be a manifestation of a single risk factor (e.g., tonsillar hypertrophy or overweight) operating to compromise airway size, the variable responses to OSAS therapy and heterogeneity of disease presentation (30, 39, 40) suggest that it is probably more common that several anatomic and physiological risk factors interact to influence individual susceptibility to recurrent episodes of upper airway collapse. Thus, in young children with small airway dimensions, relatively little pharyngeal fat but large amounts of lymphoid tissue may manifest as a strong OSAS risk factor (41). However, in older children and adolescents, lymphoid hypertrophy may be less prominent and fat deposition patterns may more closely parallel that in adults. In thinner children or adults, the influence of craniofacial structure or of comorbidities that influence ventilatory instability may predominate as risk factors. Additional research is needed to quantify the association of individual risk factors with OSAS, and the interactions among risk factors, and to address how such associations vary across the pediatric age range. Such data would be potentially useful in developing better strategies for screening and risk stratification.

OVERWEIGHT: EPIDEMIOLOGY AND RISK FACTORS

"Overweight" for children ages 2 to 19 is defined as at or above the 95th percentile of BMI for age, and "at risk for overweight" is defined as at or above the 85th and below the 95th percentile of BMI for age according to the National Center for Health Statistics/Centers for Disease Control and Prevention (CDC) (42). The CDC has reported significant increases in the prevalence of overweight among children of all ages in the past two to three decades. From the 1988–1994 to the 1999–2000 NHANES (National Health and Nutrition Examination) survey, the prevalence of overweight for children ages 2 to 5 years increased from 7 to 10% (43, 44). Among adolescents, the prevalence of overweight tripled from 5 to 15% from the late 1970s to 2000, with 30% of adolescents considered to be at risk for overweight or already overweight. Childhood overweight is especially high among minority children, especially among girls, with 17% of non-Hispanic black girls aged 6 to 17 years considered to be overweight (43). In both children and adults, the relative contribution of overweight as a risk factor of OSAS is likely to increase as the population becomes heavier.

The contributing causes of childhood overweight are multifactorial and beyond the scope of this commentary. Numerous biological, psychological, and social factors are plausible contributors to the obesity epidemic. Characteristics of the environment, the child, as well as the parents and family contribute to variation in the weight of children. Parental overweight has been found to be the strongest factor in predicting childhood overweight from birth to age 9.5 years (45). Children who are overweight

with at least one obese parent have the highest risk of being overweight as adults (46). This relationship likely reflects the importance of both genetic and shared environmental factors. Approximately 5 to 25% of the variance in weight may be related to genetic variability (47, 48), and more than 100 genes, many associated with thermogenesis, appetite regulation, and insulin sensitivity, have been shown to be associated with BMI or with the aggregation or inheritance patterns of BMI in families (49). Parental lifestyle behaviors, such as dietary intake and physical activity levels, also influence their children's behaviors, and thus their risk for overweight (37–39). Parental practices during mealtimes also may play a role in the development of childhood overweight. Less parental monitoring of children's food selections relates to greater consumption of nonnutritious foods and higher caloric content of meals (50). Parental diet and overweight may be particularly relevant to childhood OSAS. As reviewed earlier, overweight is strongly associated with adult OSAS. OSAS also shows strong familial aggregation (24), with evidence that children with OSAS are more likely to have a parent with OSAS than are unaffected children (40). Parents with OSAS, who are often overweight, may promote overeating and other behaviors that could contribute to overweight, and consequently OSAS, in their children.

Characteristics of one's neighborhood (i.e., the built environment) have been associated with physical activity levels, nutritional intake, and overweight (51). Decreased physical activity from reduced formalized physical activity school programs as well as food manufacturing and marketing programs (e.g., big portion sizes, fast food, high-fructose corn syrup) have been suggested as explanations for the overweight epidemic and have served as targets for potential public health interventions (52). Child behavior, temperament, and sleeping habits also have been implicated as potential contributors (36, 43, 55–58).

DOES OSAS CONTRIBUTE TO RISK OF CHILDHOOD OVERWEIGHT?

Many behaviors associated with OSAS also have been associated with risk of childhood overweight (Table 1). Thus, one can speculate that OSAS may be a risk factor for childhood overweight, operating through behavioral mechanisms. A growing body of data indicates that snoring and even modest levels of OSAS are associated with a range of behavioral disturbances, such as increased externalizing and hyperactive-type behaviors (7, 53). Behavioral problems have been presumed to be manifestations of sleep fragmentation, sleep deprivation, and/or intermittent hypoxemia. A causal role for OSAS in the development of behavioral problems in children is suggested by data from uncontrolled studies of improved daytime functioning and behavior after treatment of OSAS (54, 55), suggesting that these deficits may be, at least in part, reversible. Behavioral problems associated with OSAS are similar to those associated with risk of overweight. Children who demonstrate high levels of anger/frustration or clinically meaningful behavior problems have an increased risk of becoming overweight (45, 56). A study of 755 children between the ages of 8 to 11 years in the 1998 National Longitudinal Survey of Youth showed that children with clinically meaningful behavior problems had an increased risk of being overweight or becoming overweight (56). The magnitude of this relationship was similar to previously recognized risk factors of maternal overweight and race (i.e., being African American or Hispanic rather than white). A prospective study that followed 150 children from birth to 9.5 years of age found that child temperament (e.g., anger/frustration) and tantrums over food were among the primary risk factors for overweight (45). However, no study has yet directly linked behavioral risk factors as mediating factors explaining potential causal associations between childhood OSAS and overweight. Nonetheless, it is plausible to suggest a cycle of disease susceptibility, whereby increased externalizing behavior leads to overweight, resulting in OSAS, which further may exacerbate behavioral problems that increase risk of overweight.

Severity of overweight also may be exacerbated by effects of sleep apnea, such as reduced physical activity accompanying sleep apnea–associated mood and energy changes (57). In adults, reduced physical activity is associated with OSAS (58). The possible role of childhood OSAS on activity level and its effects on weight have not yet been studied.

TABLE 1. COMMON BEHAVIORAL AND DISEASE CORRELATES FOR PEDIATRIC OBSTRUCTIVE SLEEP APNEA SYNDROME AND OVERWEIGHT

Behavioral problems
• Low self-esteem
• Hyperactivity/impulse control
Metabolic dysfunction
• Abnormal glycemic control/insulin resistance
• Systemic inflammation
• Oxidative stress
Vascular disease
• Hypertension
• Cardiac hypertrophy
Other
• Gastroesophageal reflux
• Asthma

HEALTH OUTCOMES ASSOCIATED WITH OVERWEIGHT AND THEIR POSSIBLE EXACERBATION BY OSAS

Childhood overweight is not only a risk factor for behavioral problems and OSAS but also an early risk factor for much of adult morbidity and mortality (59). Overweight adolescents are at marked increased risk for overweight in adulthood. (46). The short- and long-term health consequences of overweight and later adult overweight include an array of chronic medical conditions. These include, but are not limited to, cardiovascular disease (e.g., dyslipidemia, hypertension) and endocrine problems (e.g., insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus) (59–62). Adverse effects of obesity appear to be due to an active role of adipose tissue in mediating cytokine, growth factor, and sex steroid levels (63), which interactively may modify the actions and secretion of insulin and the metabolism of fatty acids.

Emerging data suggest that OSAS leads to a pattern of cardiovascular and metabolic perturbations similar to obesity, including abnormalities in glycemic control and up-regulation of inflammatory cytokines (15, 64, 65). These effects are believed to be responses to chronic intermittent hypoxemia and oxidative stress, leading to the generation of reactive oxygen species, stimulation of various inflammatory cytokines, and endothelial dysfunction (66–69). Such effects appear to be relevant to pediatric patients with OSAS, as evidenced by studies showing elevations in inflammatory mediators in children with sleep-disordered breathing (15, 65, 70). Thus, childhood OSAS may exacerbate the effects of simple overweight by augmenting risk of insulin resistance and vascular disease. If these conditions persist over many years, they may cause cumulative stresses resulting in a wide range of morbidities throughout life.

IMPACT OF OVERWEIGHT ON APPROACHES TO OSAS TREATMENT

A rise in the prevalence of overweight may influence, at a population level, the response to surgery performed for OSAS. The

most common treatment for childhood OSAS is adenotonsillectomy. Improving the patency of the upper airway with surgery directed at removing lymphoid tissue, however, may be relatively less effective in overweight children who also suffer obesity-related upper airway compromise or ventilatory control and/or lung mechanical dysfunction (71). It is possible that children who are overweight have a pattern of OSAS that is similar to that of adults, and is thus less responsive to surgery. It is not known whether overweight children respond to adenotonsillectomy in the same way as normal-weight children.

Historically, many children undergoing adenotonsillectomy were underweight, and weight gain after surgery often was a beneficial effect (72, 73). However, weight gain after adenotonsillectomy occurring in overweight children, or children at risk for overweight, could produce an unintended exacerbation of OSAS. Changes in energy balance after adenotonsillectomy (i.e., possibly related to improved appetite after removal of obstructive lymphoid tissue, neuroendocrine changes, or decreased energy expenditure associated with reduced work of breathing [72]) may cause increased weight gain, resulting in one risk factor (tonsillar hypertrophy) to be replaced with another (overweight). Substantial weight gain after adenotonsillectomy has been reported in a study of 45 children undergoing surgery for OSAS; z scores for weight increased after surgery in 58% of the children who were overweight before surgery (74).

Additionally, adenotonsillectomy in morbidly obese children is associated with greater perioperative risk than in normal-weight children (75).

Research on the effectiveness of adenotonsillectomy in children representative of a broad range of weights will be of crucial importance as the prevalence of children who are overweight continues to rise. Because some data suggest that a history of adenotonsillectomy is a risk factor for OSAS, and adenotonsillectomy may contribute to additional weight gain, it seems prudent to consider the role of strategies for treating and preventing childhood overweight among children who have had an adenotonsillectomy.

SHORT SLEEP: AN ADDITIONAL CULPRIT LINKING OVERWEIGHT AND OSAS

Short sleep is a recently recognized risk factor for both adult and childhood overweight. In a sample of 1,024 adults in the Wisconsin Sleep Cohort Study, elevations in BMI were observed among individuals who usually sleep fewer than 6 hours (76). In this cohort, short sleep duration also was associated with abnormalities in appetite regulatory hormones (i.e., low leptin and elevated ghrelin), independent of BMI. Experimental acute sleep curtailment among adults has also been associated with increased hunger and appetite and hormonal abnormalities (77). Shorter sleep times in children have been associated with overweight in cross-sectional and longitudinal studies (78–81). These studies have generally shown equivalent or greater risk estimates for overweight associated with short sleep compared with traditional overweight risk factors (snacking behavior, TV watching, activity level).

Because sleep deprivation may accompany OSAS, it is possible that OSAS indirectly has contributed to the rise in overweight. Conversely, shorter sleep may be causally linked to overweight, which then increases OSAS risk. Therefore, sleep deprivation, OSAS, and overweight may interact, exacerbating the severity and effects of each condition. More than 33% of adolescents get less than the recommended 9 hours of sleep (82). In addition, short sleep due to late sleep times was fivefold more likely in African-American boys than in other groups (83). This is particularly worrisome because children and adolescents who sleep less are more likely to become overweight.

CONCLUSIONS

In summary, although the current evidence suggests that overweight is only modestly associated with OSAS among young children, the rising prevalence of childhood overweight is likely to increase the prevalence of childhood OSAS and the proportion of cases of OSAS attributable to overweight. Data from the Wisconsin Sleep Cohort show both a rise in overweight and a rise in OSAS, with overweight explaining more than 30% of the attributable risk for OSAS, and a much larger percentage of risk in younger women (84). The increased prevalence of childhood overweight over the last decade (44) also may be expected to result in a concomitant rise in OSAS in older children and adolescents, and possibly in younger children. Disease burden may be particularly great in populations also at risk for overweight, such as ethnic minorities, who may also be at increased risk for OSAS because of craniofacial or soft tissue characteristics, other genetic factors, or environmental factors associated with socioeconomic class. A rise in overweight may also broadly impact the response to therapy for OSAS.

Although it is well recognized that public health needs will rise with the increasing prevalence of overweight among children, the potentially synergistic adverse health effects due to concomitant OSAS has not been considered. The interacting pathophysiologies and pathoetiologies of these conditions may create a "perfect storm." Each condition likely increases the expression of, as well as the severity and comorbidity of, the other condition, and may impact treatment approaches. OSAS may contribute to behavioral problems that predispose to weight gain. In addition, OSAS, by exposing children to recurrent intermittent hypoxemia and/or oxidative stress, may amplify the adverse effects of adiposity on systemic inflammation and metabolic perturbations associated with vascular disease and diabetes. When these conditions manifest early in life, they have the potential to alter physiology at critical developmental stages, or, if persistent, provide cumulative exposures that may powerfully alter long-term health profiles. The subgroup of children who may be especially susceptible include ethnic minorities and those from households with caregivers from low socioeconomic groups, which are groups historically at risk for poor medical outcomes.

The high and anticipated increased prevalence of pediatric OSAS mandates assessment of optimal approaches for preventing and treating both OSAS and childhood overweight across the range of population subgroups, with consideration of how each condition may be modified in the presence of the other. Such strategies could include the following: (*1*) establishment of "best practices" for optimizing sleep habits of children by incorporating sleep hygiene guidance into behavioral interventions that promote healthy lifestyles, with a particular focus on high-risk groups as mentioned previously; (*2*) evaluation of the cost-effectiveness of alternative approaches for OSAS screening and diagnosis in children and consideration of the role of surgical versus nonsurgical interventions for treatment of pediatric OSAS in children who are overweight; and (*3*) increasing awareness of the role of OSAS in the etiology of childhood overweight and related conditions among primary care practitioners and the general public. In this way, public health efforts should be duly targeted to both OSAS and childhood overweight due to the potential combined impact (i.e., synergistic effects) of both conditions. Research needs include work at evaluating the efficacy of behavioral sleep interventions to aid in the prevention and treatment of childhood overweight. For young children as well

as adolescents, such interventions could include sleep subcomponents involving increased parental monitoring and supervision of sleep-related behaviors; goal-setting for nighttime rituals, established bedtimes and sleep duration; positive reinforcement of goal attainment (e.g., rewards/incentives established for getting to bed early); and problem solving regarding decreasing barriers to getting adequate sleep. Furthermore, studies of sleep disorders in children may provide a means to identify early pathogenic steps in the development of childhood overweight and chronic health problems, to better define the etiologic role of OSAS in the pathogenesis of metabolic and cardiovascular conditions, and to more conclusively identify high-risk subgroups that would most benefit from early intervention.

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