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Obesity and Altered Sleep: A Pathway to Metabolic Derangements in Children?

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Abstract

Obstructive sleep apnea (OSA) is a frequent disorder in children and is primarily associated with adenotonsillar hypertrophy., The prominent increases in childhood overweight and obesity rates in the world even among youngest of children have translated into parallel increases in the prevalence of OSA, and such trends will undoubtedly be associated with deleterious global health outcomes and life expectancy. Even an obesity phenotype in childhood OSA, more close to the adult type, has been recently proposed. Reciprocal interactions between sleep in general, OSA, obesity, and disruptions of metabolic homeostasis have emerged in recent years. These associations have suggested the a priori involvement of complex sets of metabolic and inflammatory pathways all of which may underlie increased risk for increased orexigenic behaviors and dysfunctional satiety, hyperlipidemia, and insulin resistance that ultimately favor the emergence of metabolic syndrome. Here, we will review some of the critical evidence supporting the proposed associations between sleep disruption and the metabolism-obesity complex. In addition, we will describe the more recent evidence linking the potential interactive roles of OSA and obesity on metabolic phenotype.

Over the last several decades, the prevalence and severity of overweight and obesity in children and adolescents have increased and led to the term "globesity". Some degree of deceleration in such trends has thankfully occurred most recently in several countries, and likely reflects the results of multiple public-driven efforts to reduce this epidemic. However, the overall world view is that the number of obese children will continue to rise and reach even more worrisome rates than current (Figure 1) [1-8]. Moreover, in a recently published review by Lobstein and colleagues [9], the authors concluded that in the USA, the average weight of a child has risen by more than 5 kg over the last three decades, and a third of the country's children are overweight or obese. Furthermore, some low-income and middle-

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income countries have reported similar or more rapid rises in child obesity, despite continuing high levels of undernutrition. Indeed, a rising prevalence of obesity in children from 42 million in 2013 to over 70 million in 2025 is anticipated in the African continent alone (see: http://www.who.int/end-childhood-obesity/facts/en/).

As a consequence of the increases in prevalence and severity of obesity, a corresponding increase in the prevalence of obesity-associated morbidities has occurred, and previously rare conditions such as the metabolic syndrome, cardiovascular disease, non-alcoholic liver steatosis, depression, and decreased quality of life have all begun to emerge, even among the youngest of children [10-15]. Importantly, childhood obesity does not only affect children when they are young, but also seems to impose long-lasting sequelae. For example, when comparing obese with non-obese children who were followed for a 22-year period, the presence of obesity alone independently predicted the long-term risks of diabetes or adulthood obesity [16].

In parallel with such alarming state of affairs, recent years, evidence has also started to emerge on the potentially important role of sleep and sleep disorders in either promoting, or aggravating obesity, and its attendant metabolic and cardiorespiratory complications. Conversely, the role of obesity in the pathophysiology of sleep disorders has also been advanced. Here, we will therefore review the evidence on the bilateral and mutual interactions linking sleep and disruption of metabolic homeostasis in children.

Obesity and Sleep

Societies in general, and more particularly technology-driven societies have rapidly transformed, and generated an increasingly demanding life pace [1]. This 24/7 lifestyle has in turn substantially altered sleep patterns and duration, not only in working adults but even in toddlers and children [17, 18]. The progressive decrements in sleep duration and sleep regularity have been accompanied by the aforementioned surge in the prevalence of childhood obesity, especially in the pubertal and post-pubertal period [19, 20]. In the last decade, arguments and evidence supporting a strong association between sleep duration and obesity have been put forth and corroborated across multiple studies in diverse populations from around the globe [21-26]. Concurrent with such epidemiological evidence, some of the biological pathways that underlie the strong association between sleep integrity and metabolic function have been partially elucidated. Such evidence would support that inadequate amounts of sleep will lead to endoplasmic reticulum stress in hypothalamic neurons, to alterations in some of the neuropeptides that regulate appetite, such as increased levels of ghrelin, reduced levels of leptin, and reduced central biological activity of orexin, all of which would then converge to increase food intake and reduce satiety [27-29] [30]. Under particular circumstances, the correlation of insufficient sleep with food desire and screen time emerges as being particularly prominent, especially among children and adolescents [23, 31-33]. Despite aforementioned comments, we should also note that although the overall data are supportive of an association between short sleep duration and increased risk for obesity, some studies have been somewhat conflictive for any of the age groups examined. For example, while multiple studies have identified a significant contribution of sleep duration to obesity risk in adults [34-37] such findings have not been

consistently reported [38], and could reflect either methodological issues in defining short sleep as compared to insufficient sleep [39]. In addition, multiple confounding factors that play a role in the propensity for obesity, are likely to start early in life, such that the associations between sleep and obesity may be lost later on when the surveys are conducted [40]. Furthermore, in a cross sectional and longitudinal study, Chaput and colleagues found that only those subjects manifesting short sleep duration, high disinhibition eating behavior, and low dietary calcium intake had significantly higher BMI compared to the reference category in both sexes. Indeed, over the 6-year follow-up period, these high-risk adult subjects were significantly more likely to gain weight and develop obesity [41] [42] [43].

Thus, to further clarify these issues, intervention trials aiming to establish whether prolongation of sleep will improve metabolic function and promote reduced weight gain, or even weight loss, have been initiated [44]. In children, a recent meta-analysis of the literature indicates that the strength of the association between sleep duration and obesity may actually be stronger in children and adolescents, and declines over time [38]; however, such association is not always present even in adolescents [45, 46]. In a longitudinal study, Caspedes and colleagues followed a cohort of children from 6 month till the age of seven, and found that chronic insufficient sleep from infancy to school-age was associated with higher mid-childhood metabolic risk. The best predictive risk score was derived from the mean of waist circumference, systolic blood pressure, HDL cholesterol, log-transformed triglycerides and HOMA-IR, and the independent contribution of sleep to the model was readily detectable [47]. Furthermore, some degree of predisposition for the existence of such association has been advanced, since sleep-associated changes in BMI appear to be primarily affecting those children whose BMI is already elevated [48]. Moreover, when looking at accompanying morbidities, sleep duration seems to have a major influence on the cardiovascular and cognitive aspects of those co-morbidities. In their most recent publication, Iglayreger and colleagues have shown that sleep duration inversely predicts cardiometabolic risk in obese adolescents, even when controlling for various measures of physical activity, anthropometry, and adiposity [49]. Conversely, longer sleep duration was also significantly associated with lower ambulatory systolic and diastolic blood pressure [50].

Despite the rather high number of studies exploring the sleep-obesity association the most important limitation of the vast majority of these studies in children is that they relied on subjective estimates of sleep duration [24, 51, 52]. Furthermore, the impact of the variability of sleep schedules on BMI trajectories was not explored, and the effects of specific sleep patterns on metabolic homeostasis in children are unknown, and somewhat precluded from investigation due to ethical concerns. Studies interrelating sleep duration and obesity are further hampered by the obstacles and inherent challenges of measuring sleep duration in a natural environment, such that most studies thus far have relied on parental reports. Parental reports however, will generally ‘overestimate’ the sleep duration of their children [53-55]. Out of all published studies, only 3 studies used actigraphy to record sleep but 2 of those limited such recordings to 24hr [21, 54]. We conducted a prospective and large scale cross-sectional study in which we found that in >300 community-dwelling healthy pre-pubertal children assessed with actigraphy for a week, sleep regularity was more prominently associated with both metabolic (insulin resistance) and inflammation (high-sensitivity C-

reactive protein) than sleep duration, even if a measurable effect was also detectable for those children with restricted sleep [56] . Thus, the scarcity of objective measures and of longitudinal studies and the disparity in age ranges across studies and within studies further generate another layer of complexities that restrict our ability to draw firm conclusions. For example, using similar literature review methodologies, Cappuccio et al. [53] approached the potential confounders in existing studies, e.g., gender proportions, sample size, sampling but applied a very different cut-off for defining 'short' sleep in children compared to the cut-off employed by Chen et al., i.e., ≤10 hours per night [21].

As with adults, the heterogeneity of the published associations between sleep duration and obesity reported in children range from absence of any association, to a negative linear trend or to an inverted U-shaped relationship. Such discrepancies may simply reflect sampling bias or over-controlling for certain variables. Notwithstanding, sleep duration and body weight are determined by a multitude of factors, including sociodemographic, socioeconomic, familial (e.g., family structure, overweight parent) and individual (e.g., health behavior, health status) [57, 58], and these factors need to be assessed and incorporated to enable more accurate adjustments for confounders and covariates in the interpretation of any future findings. Regardless of aforementioned limitations, the strength of the association between sleep duration with BMI is about 1.5 to 2-fold increase in the probability that decreased sleep duration will be present in children with increased BMI, will relative risks ranging from 1.15 to 11) [59, 60]. In this context, attempts to extend sleep in children are likely to fail, because both sleep regularity and sleep duration are established and relatively stable across long periods of time during childhood [61].

Obesity can lead to changes in metabolic profile by eliciting the accumulation of adipose tissue, a complex and active organ that is composed of connective tissue, adipocytes, and the subcutaneous vascular fraction, the latter containing cells of multiple lineages, such as endothelial cells, adipocyte progenitors, T cell lymphocytes, and macrophages. With increased adipocyte number and size, changes in adipocyte-derived hormones and in regional tissue perfusion and oxygenation lead to increased local oxidative stress and promote the recruitment of innate inflammatory cells and activation of complex mechanistic cascades abutting in major alterations in adipose tissue function. The conglomerate results of these events invoke the onset of insulin resistance and other metabolic derangements within adipose tissues. However, the latter perturbations are not restricted to adipose tissue, but further propagate and induce structural and metabolic alterations in other organs, including skeletal muscle and liver. Indeed, obesity is closely linked to fat storage in liver, and is nowadays considered as a major risk factor for the development of fatty liver disease [62]. Thus, the effects of sleep patterns on BMI z-score and metabolic markers could be difficult to reverse if interventions are not implemented early in life. Taking all those confounders in consideration, Bonuck and colleagues reexamined the effect of sleep disordered breathing (SDB) and sleep duration in a large cohort of children who was longitudinally monitored for 15 years; they found that both SDB and short sleep duration significantly and independently increased the odds of becoming overweight over time. Those findings underscore the potential importance of early identification and remediation of any sleep disturbance, as minimal as it may seem, as a potentially viable strategic approach for reducing childhood obesity. [63]. In summary, identification of children at risk during infancy and early

childhood by periodic assessments of sleep duration, regularity or onset of sleep disorders, along with prospective interventions aiming to prolong and regularize sleep in such children should provide us with more definitive answers as to the role of sleep in the context of BMI regulation and metabolic homeostasis during the formative childhood years.

Obesity and Obstructive Sleep Apnea Syndrome: Bad, Bad, and "Badder"

Childhood obstructive sleep apnea syndrome (OSAS) has now become widely acknowledged as a highly prevalent disorder affecting up to 5% of all children [64, 65], and associated with potentially serious clinical consequences. Considerable insights into the nature and frequency of such morbidities have emerged in the last 2 decades, and their underlying mechanisms [66-68] [69] [70, 71]. In parallel, the classic presentation of children with OSA as children with adenotonsillar hypertrophy and failure to thrive has now been widely and extensively replaced by a preponderance of patients being either overweight or obese [72]. OSA in children is characterized by recurrent events of partial or complete upper airway obstruction during sleep, resulting in disruption of normal gas exchange (intermittent hypoxia and hypercapnia) and sleep fragmentation. The clinical spectrum of obstructive sleep-disordered breathing includes frank OSA of varying severity, the upper airway resistance syndrome (traditionally associated with low frequency of obstructive apneic events and globally preserved normal oxygenation patterns, but evidence for increased respiratory-related arousals, i.e., sleep fragmentation), and at the low end of the severity spectrum, a condition that has been termed either primary or habitual snoring (i.e., habitual snoring in the absence of apneas, gas exchange abnormalities and/or disruption of sleep architecture). The prevalence of habitual snoring is much higher than that of frank OSA with ratios of 5:1 across most population studies [73-76]. In the vast majority of cases of OSA in children, hypertrophic tonsils and adenoids in the upper airway play a major role [77], that requires however the concurrent presence of alterations in structural and anatomical characteristics, protective reflexes and neuromuscular abnormalities of the upper airway. Thus, pediatric OSA is more common in those children with a positive family history of OSA, children with allergy, children born prematurely, in African American children, and in children with chronic upper and lower respiratory tract diseases [78-82].

Among the many risk factors of OSA in children, there is no doubt that obesity is by far the most important [83]. In a case-control study design, Redline and colleagues examined risk factors for sleep disordered breathing in children aged 2-18 years, and found that the risk among obese children was increased 4-5 fold [84]. More recently, a study by the same research group reported that obesity, but not habitual snoring, in middle childhood predicted adolescent OSAS, thereby suggesting that screening, preventing, and treating obesity in childhood should alleviate the risk of OSA [85]. Similar trends demonstrating increased risk of OSA among obese and overweight children have been reported worldwide [86-94]. Hence, childhood obesity is definitely associated with a higher risk for development of OSA.

In the context of obesity, upper airway narrowing and increased collapsibility could result from fatty infiltration of upper airway structures and tongue, and subcutaneous fat deposits in the anterior and lateral cervical regions also exerting collapsing forces [95, 96]. Obesity

may also affect ventilatory capacity through mass loading of the respiratory system [97]. Increased adipose tissue in the abdominal wall and cavity as well as surrounding the thorax increases the global respiratory load, and reduces intra-thoracic volumes and diaphragm excursion, particularly when in the supine position, all of which may result in decreased oxygen reserve and increased work of breathing during sleep. Finally, obesity can be accompanied by poor quality sleep, which may raise the threshold for arousal and therefore prolong the duration of upper airway collapse and its consequences [98].

Conversely, the presence of OSA could promote or aggravate obesity and associated morbidities. OSA is associated with daytime sleepiness [99-102] and sleepiness will promote physical inactivity [103], particularly in those children at risk for obesity, such that it should not be surprising that the degree of daytime sleepiness is exaggerated in obese children with OSA [104]. There is also compelling evidence that OSA promotes the initiation and propagation of both localized and systemic inflammatory processes, such that similar to obesity, OSA is currently viewed as a chronic low-grade inflammatory disease [105-112], In this setting, OSA and obesity may interact and potentiate each other and thus amplify their adverse consequences [113-117]. Recently, in a community based study we aimed to examine the effects of adenotonsillectomy in obese children with polysomnographically diagnosed OSAS, on plasma levels of inflammatory and metabolic markers including interleukin-6 (IL-6), IL-18, plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinase-(MMP-9), adiponectin, apelin C, leptin and osteocrin. We found overall significant decreases in MCP-1, PAI-1, MMP-9, IL-18 and IL-6, and increases in adropin and osteocrin plasma concentrations occurring after surgery and normalization of the polysomnography, reflecting the reversibility of the inflammatory activity after OSA treatment [118]. The same trends were also found when measuring similar markers in obese children with OSA, compared to obese non-OSA children [119]. The restricted cluster of systemic inflammatory changes further indicates the importance of treatment of OSA to prevent the comorbidity effects of obesity and sleep apnea. [118]. Moreover, another inflammatory connection between obesity and sleep apnea has been recently explored: the gut microbiome. This uniquely important ecological community is not only a major homeostatic regulator, but if perturbed may change its composition and lead to increased translocation of bacterial lipopolysaccharides (LPS) across the gut epithelium into the systemic circulation. Under such circumstances, altered gut microbiota could lead to obesity and metabolic dysfunction [120-122]. Similarly, gut microbiota could be perturbed by the presence of OSA and trigger inflammation [123]. LPS-binding protein (LBP) serves as a surrogate marker of underlying low-grade endotoxemia by LPS from the gut. Recently, a controlled study compared the levels of plasma LBP in 219 obese and non-obese participants, the non-obese controls (no OSA) had the lowest levels of LBP, and the presence of obesity without OSA was associated with significant LBP increases. Nevertheless, non-obese children with OSA exhibited increased LBP levels, with obese children with OSA demonstrating the highest LBP levels of all four groups. Furthermore, LBP was independently associated with body mass index and with measures of OSA severity as well as with metabolic dysfunction, particularly insulin resistance as indicated by the homeostasis model assessment of insulin resistance [124]. Those findings prompt us to postulate that disrupted sleep and other factors facilitating

obesity such as a high-fat diet may disrupt the gut microbiome and lead to increased systemic LPS levels with resultant inflammation, promoting downstream metabolic dysfunction .

Although the bidirectional interactions between OSA and obesity appear to be irrefutable, well-controlled interventional trials aiming to assess the implications of treating one of the disorders to ameliorate the other are only starting to emerge. There is now little doubt that the usual treatment of OSA, i.e., surgical adenotonsillectomy, is fraught with a much higher failure rate in obese children [125, 126], while preliminary evidence would suggest that weight loss is associated with beneficial effects on OSA severity [93]. However, the impact of treating OSA on obesity propensity or on metabolic dysfunction is yet to be fully explored.

Sleep, Sleep Apnea, Obesity, Cognition and Behavior

Beyond the metabolic consequences of altered sleep and obesity interactions reviewed above, there is an overlapping issue that merits short mention. For example, obese children are at high risk for attention deficit hyperactivity disorder (ADHD) [127-129]. Similarly, obesity has been implicated in reduced cognitive performance in children [130]. Coincidentally, we showed over 15 years ago that OSA is associated with reduced academic performance that can be long-lasting if left untreated [131, 132], and further uncovered substantial associations between sleep disorders such as OSA or disrupted sleep and behavioral and cognitive functioning that appear to include BMI as a significant component of a mediation model [133]. Thus, complex relationships and interdependencies have emerged between behavioral pathologies resembling ADHD as well as neurocognitive deficits and both sleep restriction, sleep disorders (e.g., OSA) and obesity [134-138]. These areas clearly need to be incorporated into the metabolic implications of sleep, particularly when considering that impulsivity may lead to a propensity for eating disorders or obesogenic eating patterns [139].

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Summary

The prevalence and severity of obesity in children and adolescents has dramatically increased worldwide along with obesity-associated morbidities particularly affecting the metabolic and cardiovascular systems. The role of sleep habits, e.g., duration and regularity, and their impact on accelerated weight accrual mechanisms is slowly emerging but the picture is far from complete. Similarly, obesity and obstructive sleep apnea syndrome appear to contribute to the initiation and progression of each other, possibly via their shared effects on the recruitment and potentiation of inflammatory pathways (Figure 2). Future efforts aimed at intervention will undoubtedly shed increased light into the roles played by sleep in obesity. Irrespectively, we cannot afford to wait for the results of such studies, such that implementation of public health campaigns that promote the “3H”, healthy sleep, healthy food, and healthy exercise habits, particularly among children, will not only do no harm but have the potential to slow down the progression of the rampant obesity epidemic that affects humans everywhere.

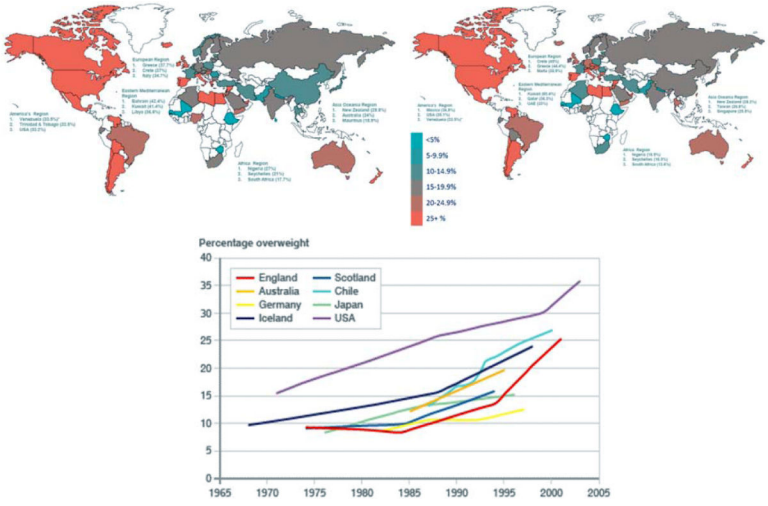

Figure 1.

Prevalence trends in pediatric overweight and obesity around the world in girls (left upper panel) and boys (right upper panel), as well as yearly trends from 1965 to 2005 in different countries.

Modified from: http://www.worldobesity.org/ and https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/295685/07-926A3-obesity-international.pdf

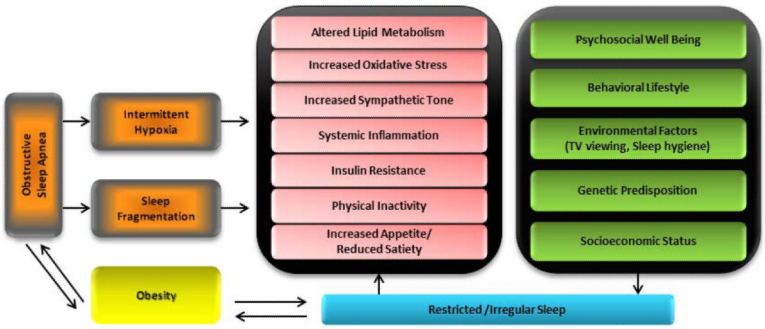

Figure 2.

Schematic diagram illustrating the convergence and interdependence of alterations in sleep duration and regularity and perturbations in sleep associated with OSA into multiple processes that promote obesity, and vice-versa.