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

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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 are undoubtedly 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 an increased risk for increased orexigenic behaviors and dysfunctional satiety, hyperlipidemia, and insulin resistance that ultimately favor the emergence of metabolic syndrome. Here, we review some of the critical evidence supporting the proposed associations between sleep disruption and the metabolism-obesity complex. In addition, we describe the more recent evidence linking the potential interactive roles of OSA and obesity on metabolic phenotype.
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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 this likely reflects the results of multiple public-driven efforts to reduce this epidemic. However, the overall worldview is that the number of obese children will continue to rise and reach even more worrisome rates than the current rate (Fig. 1).[1-8] Moreover, in a recently published review by Lobstein et al,[9] the authors concluded that in the United States, the average weight of a child has risen by more than 5 kg over the last 3 decades, and one-third of the country's children are overweight or obese. Furthermore, some low-income and middle-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 more than 70 million in 2025 is anticipated in the African continent alone (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, nonalcoholic 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 nonobese children who were followed up 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, in 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 therefore review the evidence on the bilateral and mutual interactions linking sleep and disruption of metabolic homeostasis in children.

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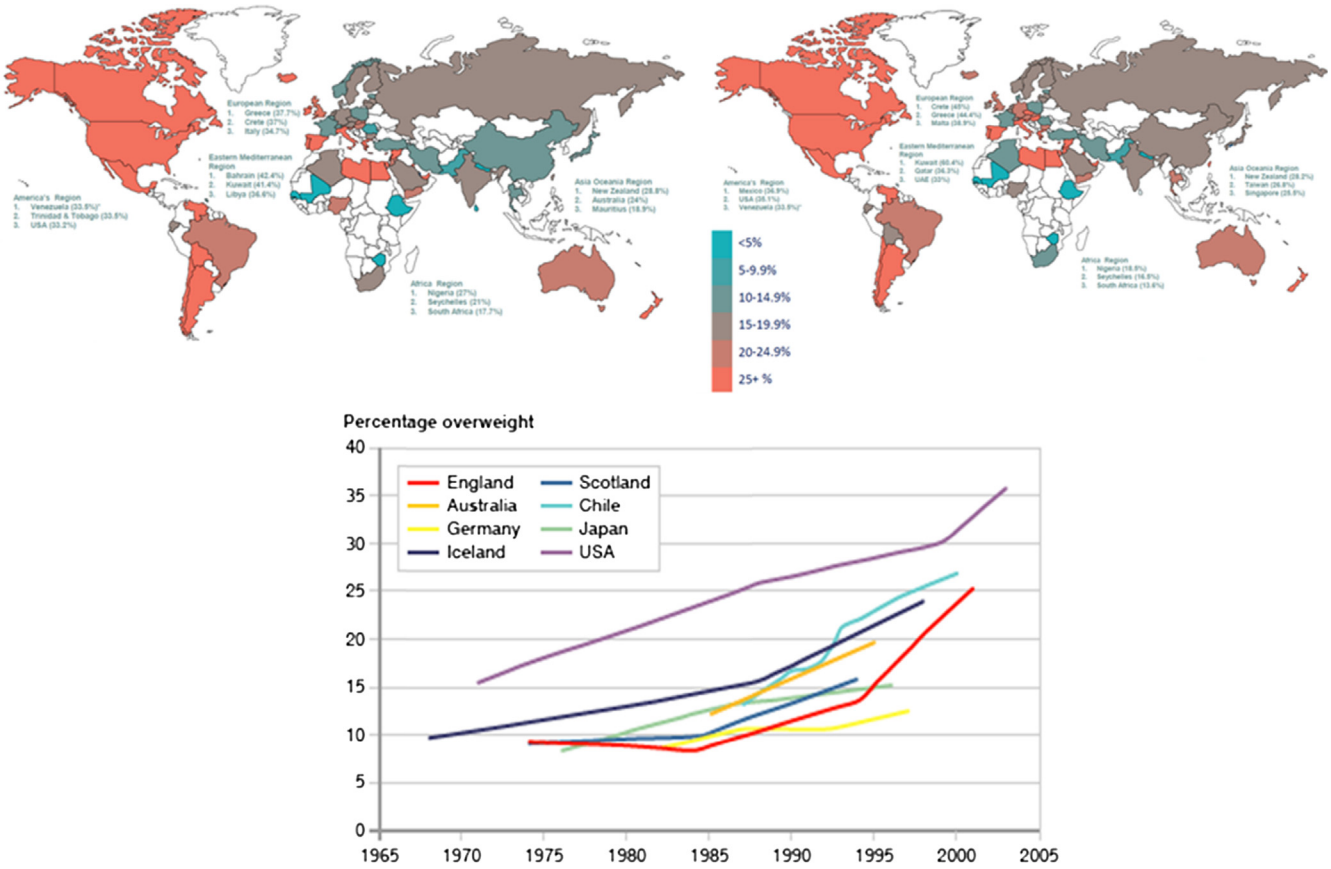

Figure 1 Prevalence trends in pediatric overweight and obesity around the world in girls (left upper panel) and boys (right upper panel), as well as yearly trends from 1965-2005 in different countries. (Modified from: http://www.worldobesity.org/ and https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/295685/07-926A3-obesity-international.pdf.)

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 in not only working adults but even 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 postpubertal 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 epidemiologic 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 leads to endoplasmic reticulum stress in hypothalamic neurons and 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.[27-30] 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 the 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, although 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 methodological issues in defining short sleep as compared with 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 et al found that only those subjects manifesting with short sleep duration, high disinhibition eating behavior, and low dietary calcium intake had significantly higher body mass index (BMI) when compared with that in the reference category in both the genders. Indeed, over the 6-year follow-up period, these high-risk adult subjects were significantly more likely to gain weight and develop obesity.[41-43]

Thus, to further clarify these issues, intervention trials aiming to establish whether prolongation of sleep improves metabolic function and promotes 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 et al followed up a cohort of children from 6 months till the age of 7 years and found that chronic insufficient sleep from infancy to school age was associated with higher midchildhood metabolic risk. The best predictive risk score was derived from the mean of waist circumference, systolic blood pressure, high-density lipoprotein cholesterol, log-transformed triglycerides, and homeostasis model assessment-estimated insulin resistance, 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, as 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 comorbidities. In their most recent publication, Iglayreger et al[49] have shown that sleep duration inversely predicts cardiometabolic risk in obese adolescents, even when controlling for various measures of physical activity, anthropometry, and adiposity. 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 effect 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 owing 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. However, parental reports generally "overestimate" the sleep duration of their children.[53-55] Of all published studies, only 3 studies used actigraphy to record sleep, but 2 of those limited such recordings to 24 hours.[21,54] We conducted a prospective and large-scale cross-sectional study in which we found that in >300 community-dwelling healthy prepubertal 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 with 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, for example, gender proportions, sample size, and sampling, but they applied a very different cut-off for defining "short" sleep in children when compared with the cut-off used by Chen et al,[21] that is, ≤ 10 hours per night.

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 overcontrolling for certain variables. Notwithstanding, sleep duration and body weight are determined by a multitude of factors, including sociodemographic, socioeconomic, familial (eg, family structure and overweight parent), and individual (eg, health behavior and 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 the aforementioned limitations, the strength of the association between sleep duration and BMI is approximately 1.5- to 2-fold increase in the probability that decreased sleep duration will be present in children with increased BMI, with relative risks ranging from 1.15-11.[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 they further propagate and induce structural and metabolic alterations in other organs, including skeletal muscle and the liver. Indeed, obesity is closely linked with 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 into consideration, Bonuck et al re-examined the effect of sleep-disordered breathing (SDB) and sleep duration in a large cohort of children who were 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 who are 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 is associated with potentially serious clinical consequences. Considerable insights into the nature and frequency of such morbidities and their underlying mechanisms have emerged in the last 2 decades.[66-71] 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 SDB 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, ie, sleep fragmentation), and at the low end of the severity spectrum, a condition that has been termed either primary or habitual snoring (ie, habitual snoring in the absence of apneas, gas exchange abnormalities, and 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 et al[84] examined risk factors for SDB in children aged 2-18 years and found that the risk among obese children was increased 4-5 fold. 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 the 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 intrathoracic 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 promotes physical inactivity,[103] particularly in those children who are 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 (IL)-6, IL-18, plasminogen activator inhibitor-1, monocyte chemoattractant protein-1, matrix metalloproteinase-9, adiponectin, apelin C, leptin, and osteocrin. We found overall significant decreases in monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, matrix metalloproteinase-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 when compared with 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, it may change its composition and lead to increased translocation of bacterial lipopolysaccharides (LPSs) 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 LPSs from the gut. Recently, a controlled study compared the levels of plasma LBP in 219 obese and nonobese participants; the nonobese controls (no OSA) had the lowest levels of LBP, and the presence of obesity without OSA was associated with significant LBP increases. Nevertheless, nonobese children with OSA exhibited increased LBP levels, with obese children with OSA demonstrating the highest LBP levels of all the 4 groups. Furthermore, LBP was independently associated with BMI 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, that is, surgical adenotonsillectomy, is fraught with a much higher failure rate in obese children,[125,126] although preliminary evidence would suggest that weight loss is associated with beneficial effects on OSA severity.[93] However, the effect 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 earlier, there is an overlapping issue that merits short mention. For example, obese children are at a high risk for attention deficit hyperactivity disorder.[127-129] Similarly, obesity has been implicated in reduced cognitive performance in children.[130] Coincidentally, we showed more than 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 attention deficit hyperactivity disorder as well as neurocognitive deficits and sleep restriction, sleep disorders (eg, 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]

Summary

The prevalence and severity of obesity in children and adolescents has dramatically increased worldwide along

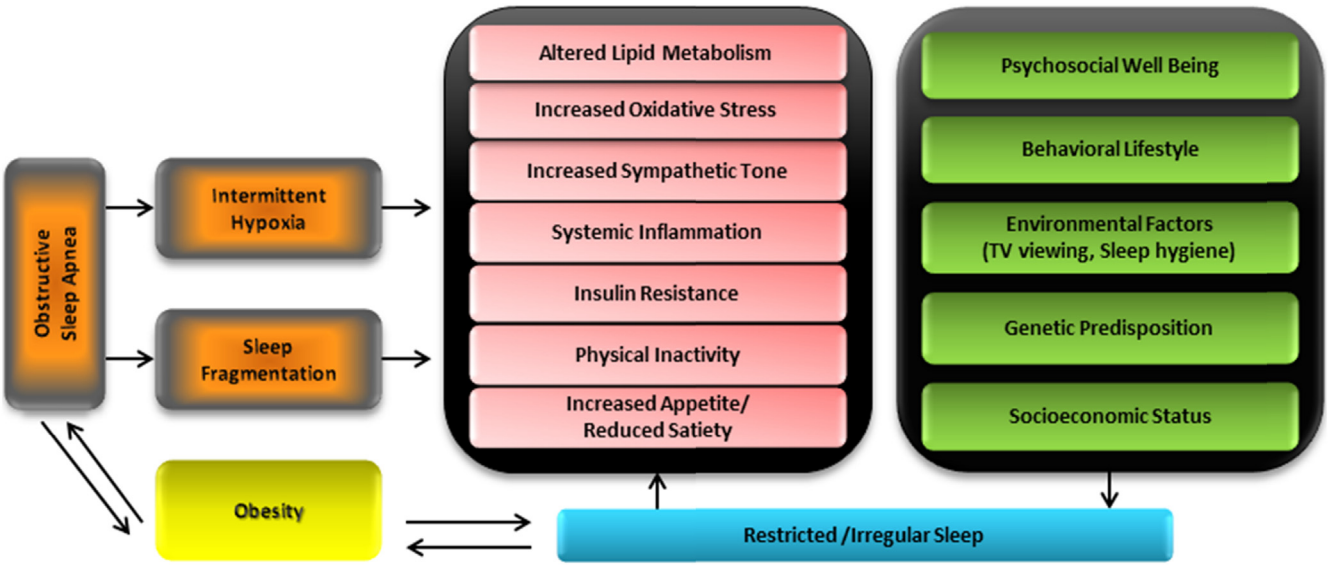

Figure 2 Schematic diagram illustrating the convergence and interdependence of alterations in sleep duration and regularity and perturbations in sleep associated with OSA into multiple processes that promote obesity and vice versa. (Color version of figure is available online.)

with obesity-associated morbidities particularly affecting the metabolic and cardiovascular systems. The role of sleep habits, for example, duration and regularity, and their effect on accelerated weight accrual mechanisms is slowly emerging, but the picture is far from complete. Similarly, obesity and OSAS appear to contribute to the initiation and progression of each other, possibly via their shared effects on the recruitment and potentiation of inflammatory pathways (Fig. 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 also have the potential to slow down the progression of the rampant obesity epidemic that affects humans everywhere.

References

1. Lobstein T, Baur L, Uauy R: Obesity in children and young people: A crisis in public health. Obes Rev 5:4-104, 2004
2. Magarey AM, Daniels LA, Boulton TJ: Prevalence of overweight and obesity in Australian children and adolescents: Reassessment of 1985 and 1995 data against new standard international definitions. Med J Aust 174:561-564, 2001
3. Oza-Frank R, Hade EM, Norton A, et al: Trends in body mass index among Ohio's third-grade children: 2004-2005 to 2009-2010. J Acad Nutr Diet 113:440-446, 2013
4. Smith SM, Craig LC, Raja AE, et al: Growing up before growing out: Secular trends in height, weight and obesity in 5- –6-year-old children born between 1970 and 2006. Arch Dis Child 98:269-273, 2013
5. Broyles S, Katzmarzyk PT, Srinivasan SR, et al: The pediatric obesity epidemic continues unabated in Bogalusa, Louisiana. Pediatrics 125:900-905, 2010
6. Claire Wang Y, Gortmaker SL, Taveras. EM: Trends and racial/ethnic disparities in severe obesity among US children and adolescents, 1976-2006. Int J Pediatr Obes 6:12-20, 2011
7. Edwards KL, Clarke GP, Ransley JK, et al: Serial cross-sectional analysis of prevalence of overweight and obese children between 1998 and 2003 in Leeds, UK, using routinely measured data. Public Health Nutr 14:56-61, 2011
8. Ogden CL, Flegal KM, Carroll MD, et al: Prevalence and trends in overweight among US children and adolescents, 1999-2000. J Am Med Assoc 288:1728-1732, 2002
9. Lobstein T, Jackson-Leach R, Moodie ML, et al: Child and adolescent obesity: Part of a bigger picture. Lancet 2015 [Epub ahead of print]
10. Barlow SE, Dietz WH: Obesity evaluation and treatment: Expert Committee recommendations. The Maternal and Child Health Bureau, Health Resources and Services Administration and the Department of Health and Human Services. Pediatrics 102:E29, 1998
11. Biro FM, Wien M: Childhood obesity and adult morbidities. Am J Clin Nutr 91:1499s-1505s, 2010
12. Daniels SR, Arnett DK, Eckel RH, et al: Overweight in children and adolescents: Pathophysiology, consequences, prevention, and treatment. Circulation 111:1999-2012, 2005
13. Luepker RV, Jacobs DR, Prineas RJ, et al: Secular trends of blood pressure and body size in a multi-ethnic adolescent population: 1986 to 1996. J Pediatr 134:668-674, 1999
14. Singer C, Stancu P, Cosoveanu S, et al: Non-alcoholic Fatty liver disease in children. Curr Health Sci J 40:170-176, 2014
15. Than NN, Newsome PN: A concise review of non-alcoholic fatty liver disease. Atherosclerosis 239:192-202, 2015
16. Liang, Y, Hou, D, Zhao X, et al. Childhood obesity affects adult metabolic syndrome and diabetes. Endocrine 2015.
17. Krueger PM, Friedman EM: Sleep duration in the United States: A cross-sectional population-based study. Am J Epidemiol 169: 1052-1063, 2009
18. Mindell JA, Meltzer LJ, Carskadon MA, et al: Developmental aspects of sleep hygiene: Findings from the 2004 National Sleep Foundation Sleep in America Poll. Sleep Med 10:771-779, 2009
19. Ogden CL, Carroll MD, Kit BK, et al: Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. J Am Med Assoc 307:483-490, 2012
20. Wang Y, Beydoun MA: The obesity epidemic in the United States—Gender, age, socioeconomic, racial/ethnic, and geographic characteristics: A systematic review and meta-regression analysis. Epidemiol Rev 29:6-28, 2007
21. Chen X, Beydoun MA, Wang Y: Is sleep duration associated with childhood obesity? A systematic review and meta-analysis. Obesity (Silver Spring) 16:265-274, 2008
22. Fatima Y, Doi SA, Mamun AA: Longitudinal impact of sleep on overweight and obesity in children and adolescents: A systematic review and bias-adjusted meta-analysis. Obes Rev 16:137-149, 2015
23. Franckle RL, Falbe J, Gortmaker S, et al: Insufficient sleep among elementary and middle school students is linked with elevated soda consumption and other unhealthy dietary behaviors. Prev Med 74:36-41, 2015
24. Marshall NS, Glozier N, Grunstein RR: Is sleep duration related to obesity? A critical review of the epidemiological evidence. Sleep Med Rev 12:289-298, 2008
25. Miller AL, Lumeng JC, LeBourgeois MK: Sleep patterns and obesity in childhood. Curr Opin Endocrinol Diabetes Obes 22:41-47, 2015
26. Taheri S, Thomas GN: Is sleep duration associated with obesity—Where do U stand? Sleep Med Rev 12:299-302, 2008
27. Mavanji V, Teske JA, Billington CJ, et al: Elevated sleep quality and orexin receptor mRNA in obesity-resistant rats. Int J Obes 34:1576-1588, 2010
28. Weiss R, Bremer AA, Lustig RH: What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci 1281:123-140, 2013
29. Zheng H, Berthoud HR: Neural systems controlling the drive to eat: Mind versus metabolism. Physiology 23:75-83, 2008
30. Cleator J, Judd P, James M, et al: Characteristics and perspectives of night-eating behaviour in a severely obese population. Clin Obes 4:30-38, 2014
31. Appelhans BM, Fitzpatrick SL, Li H, et al: The home environment and childhood obesity in low-income households: Indirect effects via sleep duration and screen time. BMC Public Health 14:1160, 2014
32. Falbe J, Davison KK, Franckle RL, et al: Sleep duration, restfulness, and screens in the sleep environment. Pediatrics 135:e367-e375, 2015
33. Sijtsma A, Koller M, Sauer PJ, et al: Television, sleep, outdoor play and BMI in young children: The GECKO Drenthe cohort. Eur J Pediatr 174:631-639, 2015
34. Buxton OM, Marcelli E: Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. Soc Sci Med 71:1027-1036, 2010
35. Hairston KG, Bryer-Ash M, Norris JM, et al: Sleep duration and five-year abdominal fat accumulation in a minority cohort: The IRAS family study. Sleep 33:289-295, 2010
36. Nishiura C, Noguchi J, Hashimoto H: Dietary patterns only partially explain the effect of short sleep duration on the incidence of obesity. Sleep 33:753-757, 2010
37. Taveras EM, Rifas-Shiman SL, Rich-Edwards JW, et al: Association of maternal short sleep duration with adiposity and cardiometabolic status at 3 years postpartum. Obesity (Silver Spring) 19:171-178, 2011
38. Nielsen LS, Danielsen KV, Sorensen TI: Short sleep duration as a possible cause of obesity: Critical analysis of the epidemiological evidence. Obes Rev 12:78-92, 2011
39. Grandner MA, Patel NP, Gehrman PR, et al: Problems associated with short sleep: Bridging the gap between laboratory and epidemiological studies. Sleep Med Rev 14:239-247, 2010
40. Monasta L, Batty GD, Cattaneo A, et al: Early-life determinants of overweight and obesity: A review of systematic reviews. Obes Rev 11:695-708, 2010

41. Chaput JP, Leblanc C, Perusse L, et al: Risk factors for adult overweight and obesity in the Quebec Family Study: Have we been barking up the wrong tree? Obesity (Silver Spring) 17:1964-1970, 2009
42. Chaput JP, McNeil J, Despres JP, et al: Short sleep duration as a risk factor for the development of the metabolic syndrome in adults. Prev Med 57:872-877, 2013
43. Chaput JP, Bouchard C, Tremblay A: Change in sleep duration and visceral fat accumulation over 6 years in adults. Obesity (Silver Spring) 22:E9-E12, 2014
44. Cizza G, Marincola P, Mattingly M, et al: Treatment of obesity with extension of sleep duration: A randomized, prospective, controlled trial. Clin Trials 7:274-285, 2010
45. Calamaro CJ, Park S, Mason TB, et al: Shortened sleep duration does not predict obesity in adolescents. J Sleep Res 19:559-566, 2010
46. Sun Y, Sekine M, Kagamimori S: Lifestyle and overweight among Japanese adolescents: The Toyama Birth Cohort Study. J Epidemiol 19:303-310, 2009
47. Cespedes EM, Rifas-Shiman SL, Redline S, et al: Longitudinal associations of sleep curtailment with metabolic risk in mid-childhood. Obesity (Silver Spring) 22:2586-2592, 2014
48. Bayer O, Rosario AS, Wabitsch M, et al: Sleep duration and obesity in children: Is the association dependent on age and choice of the outcome parameter? Sleep 32:1183-1189, 2009
49. Iglayreger HB, Peterson MD, Liu D, et al: Sleep duration predicts cardiometabolic risk in obese adolescents. J Pediatr 164:1085-1090, 2014
50. Meininger JC, Gallagher MR, Eissa MA, et al: Sleep duration and its association with ambulatory blood pressure in a school-based, diverse sample of adolescents. Am J Hypertens 27:948-955, 2014
51. Marshall NS, Glozier N, Grunstein RR: Reply to Taheri and Thomas: Is sleep duration associated with obesity—U cannot be serious. Sleep Med Rev 12:303-305, 2008
52. Nixon GM, Thompson JM, Han DY, et al: Short sleep duration in middle childhood: Risk factors and consequences. Sleep 31:71-78, 2008
53. Cappuccio FP, Taggart FM, Kandala NB, et al: Meta-analysis of short sleep duration and obesity in children and adults. Sleep 31:619-626, 2008
54. Gupta NK, Mueller WH, Chan W, et al: Is obesity associated with poor sleep quality in adolescents? Am J Hum Biol 14:762-768, 2002
55. Patel SR, Hu FB: Short sleep duration and weight gain: A systematic review. Obesity (Silver Spring) 16:643-653, 2008
56. Spruyt K, Molfese DL, Gozal D: Sleep duration, sleep regularity, body weight, and metabolic homeostasis in school-aged children. Pediatrics 127:e345-e352, 2011
57. Flynn MA, McNeil DA, Maloff B, et al: Reducing obesity and related chronic disease risk in children and youth: A synthesis of evidence with 'best practice' recommendations. Obes Rev 7:7-66, 2006
58. Sekine M, Yamagami T, Handa K, et al: A dose-response relationship between short sleeping hours and childhood obesity: Results of the Toyama Birth Cohort Study. Child Care Health Dev 28:163-170, 2002
59. Padez C, Mourao I, Moreira P, et al: Long sleep duration and childhood overweight/obesity and body fat. Am J Hum Biol 21: 371-376, 2009
60. Taveras EM, Rifas-Shiman SL, Oken E, et al: Short sleep duration in infancy and risk of childhood overweight. Arch Pediatr Adolesc Med 162:305-311, 2008
61. Touchette E, Petit D, Tremblay RE, et al: Associations between sleep duration patterns and overweight/obesity at age 6. Sleep 31: 1507-1514, 2008
62. Bhattacharjee R, Hakim F, Gozal D: Sleep, sleep-disordered breathing and lipid homeostasis: Translational evidence from murine models and children. Clin Lipidol 7:203-214, 2012
63. Bonuck K, Chervin RD, Howe LD: Sleep-disordered breathing, sleep duration, and childhood overweight: A longitudinal cohort study. J Pediatr 166:632-639, 2015
64. Corbo GM, Fuciarelli F, Foresi A, et al: Snoring in children: Association with respiratory symptoms and passive smoking. Br Med J 299:1491-1494, 1989
65. Gislason T, Benediktsdottir B: Snoring, apneic episodes, and nocturnal hypoxemia among children 6 months to 6 years old. An epidemiologic study of lower limit of prevalence. Chest 107: 963-966, 1995
66. Capdevila OS, Kheirandish-Gozal L, Dayyat E, et al: Pediatric obstructive sleep apnea: Complications, management, and long-term outcomes. Proc Am Thorac Soc 5:274-282, 2008
67. Gozal D, Kheirandish-Gozal L: The multiple challenges of obstructive sleep apnea in children: Morbidity and treatment. Curr Opin Pediatr 20:654-658, 2008
68. Kheirandish-Gozal L, Bhattacharjee R, Gozal D: Autonomic alterations and endothelial dysfunction in pediatric obstructive sleep apnea. Sleep Med 11:714-720, 2010
69. Kheirandish-Gozal L, Kim J, Goldbart AD, et al: Novel pharmacological approaches for treatment of obstructive sleep apnea in children. Expert Opin Investig Drugs 22:71-85, 2013
70. Hakim F, Gozal D, Kheirandish-Gozal L: Sympathetic and catecholaminergic alterations in sleep apnea with particular emphasis on children. Front Neurol 3:7, 2012
71. Kheirandish-Gozal L, Peris E, Gozal D: Vitamin D levels and obstructive sleep apnoea in children. Sleep Med 15:459-463, 2014
72. Dayyat E, Kheirandish-Gozal L, Gozal D: Childhood obstructive sleep apnea: One or two distinct disease entities? Sleep Med Clin 2: 433-444, 2007
73. Ferreira AM, Clemente V, Gozal D, et al: Snoring in Portuguese primary school children. Pediatrics 106:E64, 2000
74. Jeans WD, Fernando DC, Maw AR, et al: A longitudinal study of the growth of the nasopharynx and its contents in normal children. Br J Radiol 54:117-121, 1981
75. O'Brien LM, Holbrook CR, Mervis CB, et al: Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. Pediatrics 111:554-563, 2003
76. Owen GO, Canter RJ, Robinson A: Snoring, apnoea and ENT symptoms in the paediatric community. Clin Otolaryngol Allied Sci 21:130-134, 1996
77. Katz ES, D'Ambrosio CM: Pathophysiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 5:253-262, 2008
78. Arens R, Sin S, Willen S, et al: Rhino-sinus involvement in children with obstructive sleep apnea syndrome. Pediatr Pulmonol 45: 993-998, 2010
79. Mitchell EA, Thompson JM: Snoring in the first year of life. Acta Paediatr 92:425-429, 2003
80. Redline S, Tishler PV, Hans MG, et al: Racial differences in sleep-disordered breathing in African-Americans and Caucasians. Am J Respir Crit Care Med 155:186-192, 1997
81. Rosen CL, Larkin EK, Kirchner HL, et al: Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: Association with race and prematurity. J Pediatr 142:383-389, 2003
82. Urschitz MS, Guenther A, Eitner S, et al: Risk factors and natural history of habitual snoring. Chest 126:790-800, 2004
83. Arens R, Muzumdar H: Childhood obesity and obstructive sleep apnea syndrome. J Appl Physiol 108:436-444, 2010
84. Redline S, Tishler PV, Schluchter M, et al: Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. Am J Respir Crit Care Med 159:1527-1532, 1999
85. Spilsbury JC, Storfer-Isser A, Rosen CL, et al: Remission and incidence of obstructive sleep apnea from middle childhood to late adolescence. Sleep 38:23-29, 2015
86. Bixler EO, Vgontzas AN, Lin HM, et al: Sleep disordered breathing in children in a general population sample: Prevalence and risk factors. Sleep 32:731-736, 2009
87. Dayyat E, Kheirandish-Gozal L, Sans Capdevila O, et al: Obstructive sleep apnea in children: Relative contributions of body mass index and adenotonsillar hypertrophy. Chest 136:137-144, 2009

88. Kahn A, Mozin MJ, Rebuffat E, et al: Sleep pattern alterations and brief airway obstructions in overweight infants. Sleep 12:430-438, 1989
89. Kalra M, Inge T, Garcia V, et al: Obstructive sleep apnea in extremely overweight adolescents undergoing bariatric surgery. Obes Res 13: 1175-1179, 2005
90. Kohler MJ, Thormaehlen S, Kennedy JD, et al: Differences in the association between obesity and obstructive sleep apnea among children and adolescents. J Clin Sleep Med 5:506-511, 2009
91. Mitchell RB, Boss EF: Pediatric obstructive sleep apnea in obese and normal-weight children: Impact of adenotonsillectomy on quality-of-life and behavior. Dev Neuropsychol 34:650-661, 2009
92. Shine NP, Coates HL, Lannigan FJ: Obstructive sleep apnea, morbid obesity, and adenotonsillar surgery: A review of the literature. Int J Pediatr Otorhinolaryngol 69:1475-1482, 2005
93. Verhulst SL, Franckx H, Van Gaal L, et al: The effect of weight loss on sleep-disordered breathing in obese teenagers. Obesity (Silver Spring) 17:1178-1183, 2009
94. Wing YK, Hui SH, Pak WM, et al: A controlled study of sleep related disordered breathing in obese children. Arch Dis Child 88:1043-1047, 2003
95. Horner RL, Mohiaddin RH, Lowell DG, et al: Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnoea and weight matched controls. Eur Respir J 2:613-622, 1989
96. White DP, Lombard RM, Cadieux RJ, et al: Pharyngeal resistance in normal humans: Influence of gender, age, and obesity. J Appl Physiol 58:365-371, 1985
97. Naimark A, Cherniack RM: Compliance of the respiratory system and its components in health and obesity. J Appl Physiol 15:377-382, 1960
98. Beebe DW, Lewin D, Zeller M, et al: Sleep in overweight adolescents: Shorter sleep, poorer sleep quality, sleepiness, and sleep-disordered breathing. J Pediatr Psychol 32:69-79, 2007
99. Chervin RD, Weatherly RA, Ruzicka DL, et al: Subjective sleepiness and polysomnographic correlates in children scheduled for adenotonsillectomy vs other surgical care. Sleep 29:495-503, 2006
100. Gozal D, Wang M, Pope DW Jr.: Objective sleepiness measures in pediatric obstructive sleep apnea. Pediatrics 108:693-697, 2001
101. Melendres MC, Lutz JM, Rubin ED, et al: Daytime sleepiness and hyperactivity in children with suspected sleep-disordered breathing. Pediatrics 114:768-775, 2004
102. Tauman R, O'Brien LM, Holbrook CR, et al: Sleep pressure score: A new index of sleep disruption in snoring children. Sleep 27:274-278, 2004
103. Spruyt K, Sans Capdevila O, Serpero LD, et al: Dietary and physical activity patterns in children with obstructive sleep apnea. J Pediatr 156:724-730, 2010
104. Gozal D, Kheirandish-Gozal L: Obesity and excessive daytime sleepiness in prepubertal children with obstructive sleep apnea. Pediatrics 123:13-18, 2009
105. Gozal D: Sleep, sleep disorders and inflammation in children. Sleep Med 10:S12-S16, 2009
106. Kim J, Gozal D, Bhattacharjee R, et al: TREM-1 and pentraxin-3 plasma levels and their association with obstructive sleep apnea, obesity, and endothelial function in children. Sleep 36:923-931, 2013
107. Kim J, Hakim F, Kheirandish-Gozal L, et al: Inflammatory pathways in children with insufficient or disordered sleep. Respir Physiol Neurobiol 178:465-474, 2011
108. Gozal D, Serpero LD, Kheirandish-Gozal L, et al: Sleep measures and morning plasma TNF-alpha levels in children with sleep-disordered breathing. Sleep 33:319-325, 2010
109. Gozal D, Serpero LD, Sans Capdevila O, et al: Systemic inflammation in non-obese children with obstructive sleep apnea. Sleep Med 9: 254-259, 2008
110. Khalyfa A, Capdevila OS, Buazza MO, et al: Genome-wide gene expression profiling in children with non-obese obstructive sleep apnea. Sleep Med 10:75-86, 2009
111. Kim J, Bhattacharjee R, Snow AB, et al: Myeloid-related protein 8/14 levels in children with obstructive sleep apnoea. Eur Respir J 35: 843-850, 2010
112. Tauman R, Ivanenko A, O'Brien LM, et al: Plasma C-reactive protein levels among children with sleep-disordered breathing. Pediatrics 113: e564-e569, 2004
113. Gozal D, Capdevila OS, Kheirandish-Gozal L: Metabolic alterations and systemic inflammation in obstructive sleep apnea among non-obese and obese prepubertal children. Am J Respir Crit Care Med 177:1142-1149, 2008
114. Kheirandish-Gozal L, Sans Capdevila O, Kheirandish E, et al: Elevated serum aminotransferase levels in children at risk for obstructive sleep apnea. Chest 133:92-99, 2008
115. Spruyt K, Gozal D: Mr. Pickwick and his child went on a field trip and returned almost empty handed...What we do not know and imperatively need to learn about obesity and breathing during sleep in children! Sleep Med Rev 12:335-338, 2008
116. Tsaoussoglou M, Bixler EO, Calhoun S, et al: Sleep-disordered breathing in obese children is associated with prevalent excessive daytime sleepiness, inflammation, and metabolic abnormalities. J Clin Endocrinol Metab 95:143-150, 2010
117. Tan HL, Gozal D, Kheirandish-Gozal L: Obstructive sleep apnea in children: A critical update. Nat Sci Sleep 5:109-123, 2013
118. Kheirandish-Gozal L, Gileles-Hillel A, Alonso-Alvarez ML, et al: Effects of adenotonsillectomy on plasma inflammatory biomarkers in obese children with obstructive sleep apnea: A community-based study. Int J Obes (Lond) 2015
119. Gileles-Hillel A, Alonso-Alvarez ML, Kheirandish-Gozal L, et al: Inflammatory markers and obstructive sleep apnea in obese children: The NANOS study. Mediators Inflamm 605280. doi:10.1155, 2014.
120. Cox AJ, West NP, Cripps AW: Obesity, inflammation, and the gut microbiota. Lancet Diabetes Endocrinol 3:207-215, 2015
121. Hansen TH, Gobel RJ, Hansen T, et al: The gut microbiome in cardio-metabolic health. Genome Med 7:33, 2015
122. Maranduba CM, De Castro SB, de Souza GT, et al: Intestinal microbiota as modulators of the immune system and neuroimmune system: Impact on the host health and homeostasis. J Immunol Res 2015:931574, 2015
123. Moreno-Indias I, Torres M, Montserrat JM, et al: Intermittent hypoxia alters gut microbiota diversity in a mouse model of sleep apnoea. Eur Respir J 45:1055-1065, 2015
124. Kheirandish-Gozal L, Peris E, Wang Y, et al: Lipopolysaccharide-binding protein plasma levels in children: Effects of obstructive sleep apnea and obesity. J Clin Endocrinol Metab 99:656-663, 2014
125. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al: Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: A multicenter retrospective study. Am J Respir Crit Care Med 182: 676-683, 2010
126. Tauman R, Gulliver TE, Krishna J, et al: Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr 149:803-808, 2006
127. Cortese S, Vincenzi B: Obesity and ADHD: Clinical and neurobiological implications. Curr Top Behav Neurosci 9:199-218, 2012
128. Kalarchian MA, Marcus MD: Psychiatric comorbidity of childhood obesity. Int Rev Psychiatry 24:241-246, 2012
129. Puder JJ, Munsch S: Psychological correlates of childhood obesity. Int J Obes (Lond) 34:S37-S43, 2010
130. Liang J, Matheson BE, Kaye WH, et al: Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int J Obes (Lond) 38:494-506, 2014
131. Gozal D: Sleep-disordered breathing and school performance in children. Pediatrics 102:616-620, 1998
132. Gozal D, Pope DW Jr.: Snoring during early childhood and academic performance at ages thirteen to fourteen years. Pediatrics 107:1394-1399, 2001
133. Spruyt K, Gozal D: A mediation model linking body weight, cognition, and sleep-disordered breathing. Am J Respir Crit Care Med 185:199-205, 2012
134. Gregory AM, Sadeh A: Sleep, emotional and behavioral difficulties in children and adolescents. Sleep Med Rev 16:129-136, 2012
135. Maski KP, Kothare SV: Sleep deprivation and neurobehavioral functioning in children. Int J Psychophysiol 89:259-264, 2013

136. Spruyt K, Gozal D: Sleep disturbances in children with attention-deficit/hyperactivity disorder. Expert Rev Neurother 11:565-577, 2011
137. Urbain C, Galer S, Van Bogaert P, et al: Pathophysiology of sleep-dependent memory consolidation processes in children. Int J Psychophysiol 89:273-283, 2013
138. Yoon SY, Jain U, Shapiro C: Sleep in attention-deficit/hyperactivity disorder in children and adults: Past present, and future. Sleep Med Rev 16:371-388, 2012
139. Ptacek R, Kuzelova H, Stefano GB, et al: Disruptive patterns of eating behaviors and associated lifestyles in males with ADHD. Med Sci Monit 20:608-613, 2014