ELSEVIER

Seminars in
Pediatric
Neurology

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

Fahed Hakim, MD,* Leila Kheirandish-Gozal, MD, MSc,† and David Gozal, MD†

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.
Semin Pediatr Neurol 22:77-85

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.

From the *Pediatric Pulmonary Institute, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel.
†Department of Pediatrics, Pritzker School of Medicine, University of Chicago, Chicago, Illinois.
D.G. and L.K.G. are supported by National Institutes of Health, USA Grant HL-65270.
Address reprint requests to David Gozal, MD, Department of Pediatrics, The University of Chicago, KCBD, Room 4100, 900 E. 57th St, Mailbox 4, Chicago, IL 60637. E-mail: dgozal@uchicago.edu

1071-9091/15/$-see front matter
http://dx.doi.org/10.1016/j.spen.2015.04.006

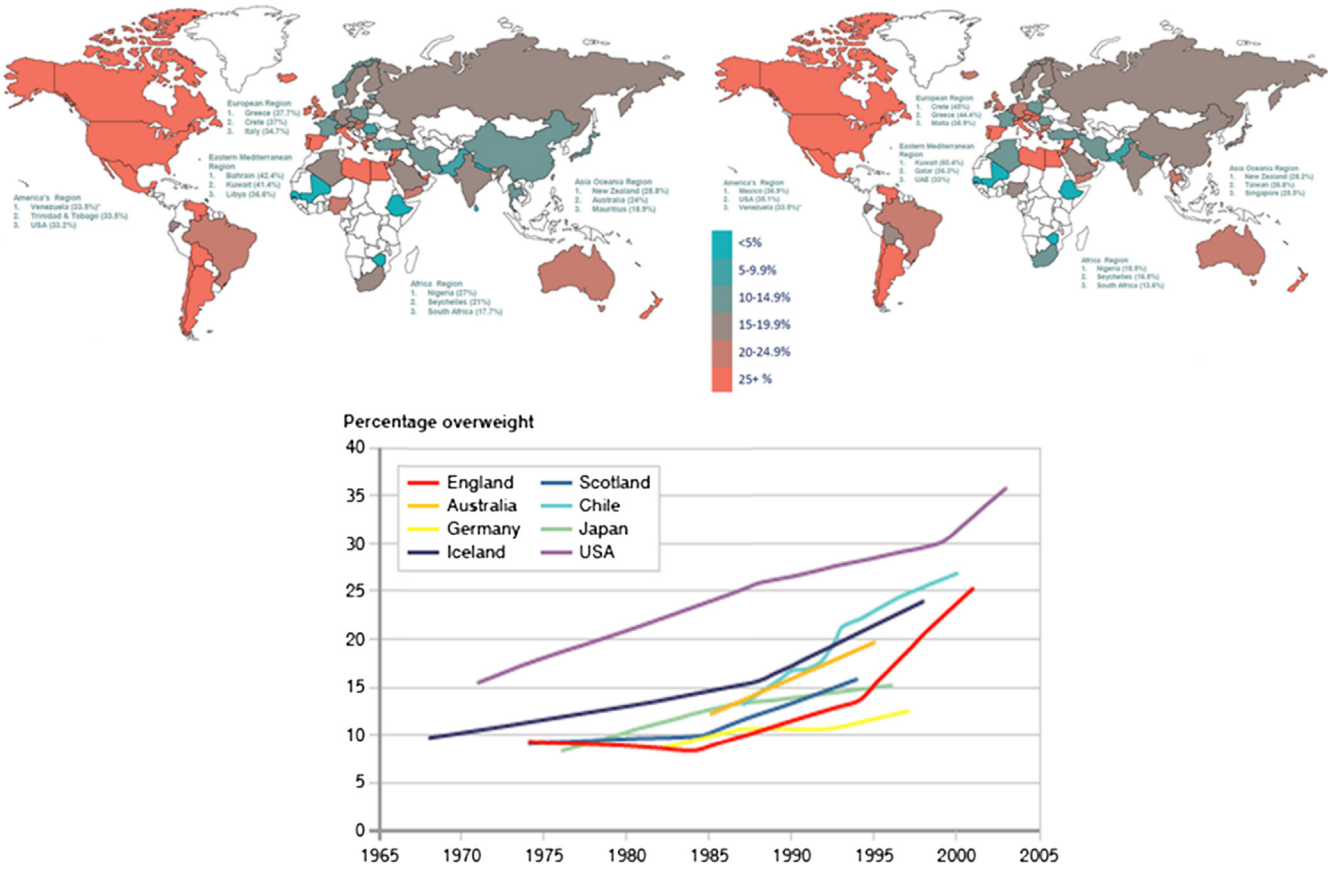

Figure 1 Prevalence trends in pediatric overweight and obesity around the world in girls (left upper panel) and boys (right upper panel), as well as yearly trends from 1965-2005 in different countries. (Modified from: http://www.worldobesity.org/ and https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/295685/07-926A3-obesity-international.p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

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]