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THEORETICAL REVIEW

Association between long sleep duration and increased risk of obesity and type 2 diabetes: A review of possible mechanisms

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SUMMARY

For the last two decades research has revealed an alarming association between short sleep duration and metabolic disorders. In tandem, the hormonal, behavioral, and genetic mechanisms underlying this relationship have been extensively investigated and reviewed. However, emerging evidence is revealing that excessive sleep duration has remarkably similar deleterious effects. Unfortunately, to date there has been little attention to what drives this connection. This narrative review therefore aims to summarize existing epidemiological findings, experimental work, and most importantly putative molecular and behavioral mechanisms connecting excessive sleep duration with both obesity and type 2 diabetes mellitus. It will also address recent findings suggesting a worrisome bidirectional effect such that metabolic disorders create a positive feedback loop which further perpetuates excessive sleep.

Introduction

Nearly half of all adults sleep either too little (commonly defined as ≤6 h sleep per day; up to 33% in the general population) or too much (commonly defined as ≥9 h sleep per day; up to 18% in the general population) [1–5]. This is alarming, as both too little and too long sleep have been associated with an increased risk of obesity and type 2 diabetes mellitus (T2DM) [6,7]. For example, in a Swedish cohort study involving ~5000 women (aged ≥20 y) followed over 10 y, both questionnaire-based habitual short sleep (in this study defined as <6 h) and habitual long sleep (defined as ≥9 h) correlated with a higher prevalence of obesity (31.3% and 38.1%, respectively), as compared with reports of habitual normal sleep duration (defined as 6–9 h, 8.9%) [6]. Moreover, by utilizing self-reported sleep duration data from nearly half a million adult participants (of ages covering the entire adult lifespan) with follow-up periods ranging from 2.5 to 16 y, a recent meta-analysis of prospective studies found the relative risk for T2DM to be increased by about 9% for each 1-h decrement of average sleep duration among individuals who slept less than 7 h per day, and 14% for each 1-h increment of sleep duration among individuals with long sleep duration (defined as >8 h) [7]. Collectively, these studies appear to indicate a U-shaped association between sleep duration and weight gain and T2DM.

Mounting experimental evidence points to a causative role of short sleep duration in obesity and T2DM. A recent study collecting fat tissue biopsies from seven healthy young adults following 4 d of sleep restriction (i.e., 4.5 h in bed) has for instance found an insulin-resistant state in human adipocytes [8]. Moreover, it has been demonstrated that both acute total sleep loss and short-term sleep restriction (i.e., 4 vs. 9 h in bed for six nights) increase brain activation to food stimuli in young adults, including brain areas involved in the regulation of the drive to eat (*e.g.*, prefrontal cortex and anterior cingulate cortex) [9–11]. While behavioral, hormonal and molecular mechanisms underlying the association between short sleep and the risk of obesity and T2DM have been extensively reviewed elsewhere [12–17], there is no comprehensive review of what is driving the association between long sleep duration and the risk of obesity and T2DM in humans. With this in mind, the objective of the present review is to frame recent epidemiological and experimental findings into a comprehensive overview of candidate mechanisms through which long sleep duration drives obesity and T2DM development, and *vice versa*.

Abbreviations: BMI, body mass index; GLP-1, glucagon-like peptide 1; IL-6, interleukin-6; NHANES, US National health and nutrition examination survey; OSA, obstructive sleep apnea; PSQI, Pittsburgh sleep quality index; REM, rapid-eye movement; SWS, slow-wave sleep; T2DM, type 2 diabetes mellitus; TNFα, tumor necrosis factor alpha.

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State of the epidemiological evidence

Long sleep duration and risk of obesity

Cross-sectional studies have reported a higher body mass index (BMI) and prevalence of obesity (BMI ≥30 kg/m^2) among adults reporting habitually excessive sleep duration (typically defined as ≥9 h) [14,18,19]. These observations based on self-reported sleep duration have been confirmed by further studies that objectively measured sleep duration and body weight. For instance, in a Dutch study involving about 1000 community-dwelling elderly people (age range: 57–97 y), long sleep duration (defined as ≥8 h) measured by actigraphy over multiple consecutive nights increased the relative risk of obesity by about 193%, compared with participants who slept 7–8 h [20]. These cross-sectional data comport with results from longitudinal studies. For example, in a sample of 226 adults aged 21–64 y from the Canadian *Quebec Family Study* in which sleep duration was estimated by a questionnaire, long-duration sleepers (defined as 9–10 h per day) gained 1.58 kg body fat more than did average-duration sleepers (defined as 7–8 h per day) over a 6 y stretch [21]. While this may not seem extraordinarily much, reports of long sleep duration in this study were linked with a 21% increased risk of developing obesity (compared to the risk of normal-duration sleepers). Similar findings in which sleep duration derived from questionnaires have been reported for Swedish women who were followed over 10 y [6].

Interestingly, there are also population-based cross-sectional and longitudinal studies in which no association was found between long sleep duration and the risk of weight gain or obesity [22–25]. For instance, in a cohort of 83,377 US men and women aged 51–72 y at baseline, followed up with an average of 7.5 y, no association was observed between reporting ≥9 h sleep/night and obesity [25]. However, there are essential methodological differences between these studies that may contribute to some of the controversial findings in the field. One explanation could relate to whether sleep duration was estimated based on a retrospective recall method (*e.g.*, by questionnaires) [18,19,21,23–25] or multiple-night recordings (*e.g.*, by sleep diary) [14]. Inclusion of subjective and objective measures of sleep duration may also explain why some researchers consider current evidence base to be not strong enough to conclude that sleep duration is a risk factor for obesity [26]. Some of the inconsistency of results in the literature could also be explained by the fact that in some studies, sleep duration was related to all days, *i.e.*, sleep on weekend and workdays was not discriminated [19,21,23–25], whereas in other studies duration was only based on workdays [18,22]. This is consequential as sleep behavior tends to show dramatic differences between workdays and weekends [27]. It must also be noted that in many studies nocturnal sleep duration was considered a primary variable of interest [14,18,23,24], whereas other studies also included daytime naps in the estimation of 24-h sleep duration [19,21,25]. Another source of inconsistency between studies emerges from which cut offs were used to define long sleep duration (*e.g.*, ≥8 h sleep in *e.g.*, [20] vs. ≥9 h sleep in *e.g.*, [25]). Finally, variation in confounding factors considered for the analyses, such as age, education level, physical activity, and smoking may limit the generalizability of results from epidemiological studies investigating the association between sleep duration and metabolic traits.

Long sleep duration and risk of T2DM

Strong evidence points to an association between excessive sleep and the risk of developing T2DM. A cross-sectional study involving 740 adults aged 21–64 y showed that in comparison with adults who reported 7–8 h of sleep, those who reported sleeping 9–10 h had an odds ratio of 1.58 for having impaired glucose tolerance or T2DM, after adjusting for various confounders such as age, physical activity level, and waist circumference [28]. Through longitudinal studies, the association between reports of habitual long sleep duration and future incidence of T2DM was first reported among women and men in 2003 and 2006, respectively [29,30]. Since then, increasing prospective studies have found consistent results across a variety of populations. Two meta-analyses (including 482,502 and 107,756 adults, respectively) covering the entire adult lifespan demonstrated a clear longitudinal relationship between reports of long sleep duration at baseline (defined as >8 h) and future incidence of T2DM [7,31]. Extending these findings, in an observational study involving 59,031 women aged 55–83 y at baseline, a habitual increase of average daily self-reported sleep duration by ≥2 h has been shown to increase incidence of T2DM by about 15% over a period of ~14 y [32].

Possible mechanisms linking long sleep duration with obesity and T2DM

As described in the subsequent sections, multiple pathways could mediate the association between long sleep duration and the risk of obesity and T2DM, and *vice versa*. A schematic representation of some of these candidate mechanisms is provided in Fig. 1.

Prolonged sleep duration due to impaired nocturnal sleep quality

Epidemiological data show that poor quality sleep, assessed by the Pittsburgh sleep quality index (PSQI), is associated with an increased risk of obesity and T2DM [33,34]. However, it does not speak to specific mechanisms, which requires some analysis and speculation. One possibility involves disrupted sleep patterns. Insomnia and obstructive sleep apnea (OSA) – constituting major sleep disorder categories – are manifested with impaired nocturnal sleep quality, including single or recurrent long-lasting wake episodes after sleep onset, frequent awakenings after sleep onset, light sleep, extended sleep onset, low sleep efficiency (typically defined as time asleep divided by time in bed), and excessive daytime sleepiness. Given that especially deep sleep (also known as slow-wave sleep, SWS or sleep stage N3) has been proposed to be restorative and also to reduce sleep pressure [35], light and fragmented sleep may not sufficiently reduce sleep pressure generated during daytime wakefulness, and could therefore result in prolonged habitual sleep duration.

Noteworthy, compared to sleepers who report normal sleep duration (i.e., between 7 and 8 h), long-duration sleepers more frequently use pharmaceutical sleep aids [3] – indicating problems to fall and stay asleep –, more often snore [36], have a higher risk to be diagnosed with moderate to severe OSA (apnea hypopnea index >15 events/h; [37]), and more frequently suffer from insomnia symptoms, such as increased sleep fragmentation, wake after sleep onset and sleep latency [38,39]. Finally, time in bed has been positively correlated with the abundance of light sleep (stages other than SWS) in insomnia patients [40]. Hence, it could be hypothesized that prolonged time in bed is an attempt of long-duration sleepers to cope with and compensate for poor sleep quality. In this context it must, however, be noted that there is no available evidence to suggest that traditional treatment for insomnia and OSA, such as cognitive behavioral therapy and continuous positive airway pressure, normalize sleep duration in long-duration sleepers. Moreover, a considerable portion of people with insomnia and OSA report habitual short sleep duration rather than long sleep duration, which would also argue against this hypothesis. There are, however, possible explanations for why most short-duration sleepers with insomnia and OSA might not show a compensatory increased time in bed. For instance, they may have early morning obligations such as school or work. By this theory long sleep duration patients who suffer

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