Curr Sleep Medicine Rep (2015) 1:185–194
DOI 10.1007/s40675-015-0025-9

SLEEP EPIDEMIOLOGY (J NIETO, SECTION EDITOR)

The Association Between Sleep Duration and Leptin, Ghrelin, and Adiponectin Among Children and Adolescents

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Published online: 16 October 2015

Abstract Several studies suggest that habitually shorter-sleep duration is associated with higher risk for overweight and obesity among children. Multiple plausible mechanisms may link chronic short sleep to weight gain among humans, including pathologic alterations in energy-regulating and appetite-influencing hormones. In this manuscript, we review the literature that examines associations between three such hormones—leptin, ghrelin, and adiponectin—and sleep duration, in studies of children and adolescents. The results of this review suggest that there is not currently sufficient evidence to definitively implicate each of these hormones in the sleep duration-obesity pathway in children. However, there are several studies with significant findings, such that a role for sleep curtailment-induced hormonal changes is plausible. Further work is required to elucidate the specific role these hormones play in metabolic dysregulation associated with chronic short sleep.

This article is part of the Topical Collection on *Sleep Epidemiology*

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Keywords Sleep · Sleep duration · Sleep curtailment · Short sleep · Sleep deprivation · Sleep loss · Hormones · Leptin · Ghrelin · Adiponectin · Appetite · Body weight · Obesity · Child · Children · Adolescents

Background

Understanding the etiology of childhood and adolescent obesity is crucial for improving global health. Over the past three decades, rates of childhood obesity have increased in almost every developed country [1]. As a significant contributor to later morbidity and premature mortality, childhood obesity puts individuals at a greater risk for the development of diseases such as diabetes, heart disease, stroke, and hypertension in adulthood [2, 3]. Therefore, it is necessary to identify the important risk factors and mechanisms that contribute to the development of obesity in children and adolescents in order to cultivate effective methods for its prevention.

Perhaps not coincidentally, the increased prevalence of obesity in recent decades parallels a decrease in sleep time in children and adolescents [4]. It is believed that the increased use of technology in the home ("screen time") [5], increased caffeine consumption [6], as well as early school start times [7] potentially contribute to the later bedtimes and shorter-sleep durations observed in school-age children and adolescents. For the past 15 years, studies have sought to determine if there is a relationship between poor sleep and obesity in both adults and children. The cross-sectional data from these studies indicate a significant association in children [8, 9]. As an important step in establishing causality, a temporal sequence in the relationship was also demonstrated in a recent review and meta-analysis performed by Fatima et al. [10], which focused specifically on longitudinal studies in children and adolescent populations. Not only did the review suggest

an association between short-sleep duration and higher subsequent BMI, but a meta-analysis of nearly a dozen longitudinal studies indicated that children and adolescents with regularly short-sleep durations were two times more likely to become overweight and obese than their longer-sleeping counterparts [10].

While there is evidence of temporality in the relationship between short/poor sleep and subsequent obesity, there is still a need for elucidating mechanisms that mediate this association. A particularly promising hypothesis points to the altered release of hormones important for the regulation of energy in the body. Within humans, energy homeostasis is maintained by scheduled releases of key hormones according to the circadian cycle. Abnormal sleep patterns characterized by short duration or poor quality can negatively affect this cycle leading to changes in hormone release including the secretion of important metabolic regulators [11]. Among these hormones are the key appetite-controlling hormones, leptin, and ghrelin, which function antagonistically to promote satiety and hunger, respectively.

Experimental [12] and observational studies [13] carried out in adult populations have shown that both acute and chronic sleep curtailment lead to lower levels of leptin and higher levels of ghrelin. Increased appetite associated with altered levels of leptin and ghrelin identifies these hormones as potential neuroendocrine mediators in the pathway between poor sleep and obesity.

This review will examine studies of similar design as those in adults—experimental and observational—but in school-age and adolescent populations to determine the level of evidence supporting a link between sleep duration and these hormones in children. We will focus specifically on studies of children and adolescents with sleep duration as the "exposure" and hormone levels as outcomes. In addition to leptin and ghrelin, this study will also look at levels of adiponectin. A peptide hormone produced and secreted by adipose tissue, adiponectin, is also affected by poor sleep—especially in cases of sleep apnea [14]. While there is less consensus about the function of adiponectin, it may protect against weight gain and prevent insulin resistance [15].

Methods

Search Strategy

We searched PubMed, Medline, and Web of Science with the following sets of search terms: adiponectin+child*+sleep, adiponectin+adolescen*+sleep, leptin+child*+sleep, leptin+adolescen*+sleep, ghrelin+child*+sleep, and ghrelin+adolescen*+sleep. We included all observational and experimental studies in which one or more of the hormones—leptin, ghrelin, or adiponectin—was the dependent/outcome variable and some measure of sleep duration or sleep quality was the predictor/independent variable. The reference lists of all thusly identified manuscripts were searched for additional relevant studies. We excluded studies that investigated associations only among subjects with a specific disease or condition (e.g., Prader-Willi syndrome).

Results

Below, we describe studies examining associations between sleep duration and leptin (summarized in Table 1, observational studies, and Table 2, experimental studies), then ghrelin (summarized in Table 3, observational studies, and Table 4, experimental studies), and finally adiponectin (Table 5, only observational studies), when relevant results are grouped by study design (observational or experimental).

Leptin

Observational Studies (Table 1)

Many studies have investigated the association between sleep duration and leptin levels in children. Results from these studies are inconsistent, with some studies finding a significant positive association between sleep duration and leptin levels [20, 21•], some studies finding a significant negative association [17, 22•, 24•, 25], and some studies reporting null results [16•, 18, 19, 23].

Two studies with samples that included both boys and girls found no significant association between sleep duration and leptin levels [16•, 18]. In one of these studies [18], adolescents (13–17 years) self-reported their usual sleep durations on typical weeknights and weekend nights. The authors used multiple linear regression models to investigate the association between sleep duration and leptin, adjusting for a variety of potentially confounding variables, and found no significant association. In the other study, researchers compared leptin levels among children who slept less than the recommended time to those who slept at least the recommended amount, according to the U.S. National Sleep Foundation, which for children ages 7–13 is <9 h and for children ages 14–16 is <8 h. Subjects with short sleep did not have significantly different leptin levels compared to subjects with recommended sleep durations. The researchers used linear regression models that adjusted for gender age, BMI, physical activity, and an index that evaluated adherence to a Mediterranean diet [16•]. Another study included only adolescent girls (14–18 years) [19]. Sleep duration, defined as the number of sleep hours in 1 day, was categorized as <5 h, 5–7 h, or >7 h. The girls also reported on whether their sleep pattern was consistent (uninterrupted) or intermittent (interrupted). No significant association was found between sleep duration group and leptin levels. However, two other studies stratified their results by sex and reported null findings for boys but a significant

Table 1 Summary of observational studies assessing the association between sleep duration/quality and leptin

Citation	Country	Study/sample description	Sleep variable description	Analysis	Results
Navarro-Solera [16•]	Spain	90 obese children, ages 7–16 years	Children who slept less than recommended time (by National Sleep Foundation) versus children who slept recommended time	Cross-sectional. Linear regression models that were adjusted for gender, age, BMI, and level of adherence to a Mediterranean diet	Subjects with short sleep did not have different leptin levels compared to subjects with recommended sleep 53(24) versus 48(21)ng/mL (p=0.3)
Hitze [17]	Germany	207 boys and 207 girls, ages 6–20 years	Questionnaire-assessed sleep duration dichotomized as not short versus short sleep (<10 h/day for children <10 years and <9 h/day for children >10 years)	Cross-sectional. Partial correlations adjusted for age	In girls, longer-sleep duration was significantly associated with lower leptin levels (partial correlation, adjusted for age, =−0.20 (p<0.05)). No significant association was seen in boys
Martinez-Gomez [18]	Spain	183 adolescents, ages 13–17 years, from a sample in the region of Madrid	Self-reported (by adolescent) usual sleep duration on typical weeknights and weekends	Cross-sectional. Three linear regression models, adjusted for (1) age, sex, and pubertal status; (2) …+physical activity; and (3) …+BMI	Leptin was not significantly associated with sleep duration
Al-Disi [19]	Saudi Arabia	126 Saudi girls ages 14–18 years (62 lean and 64 obese)	Three categories (<5 h, 5–7 h, and >7 h) of self-reported sleep time	Cross-sectional. Unadjusted correlation coefficients	Leptin was not significantly associated with sleep duration
Kjeldsen [20]	Denmark	third- and fourth-grade students, ages 8–11 years, from Danish municipal schools enrolled in the OPUS study	Waist-worn actigraph measured sleep duration for eight nights; weekly average sleep duration was calculated	Cross-sectional. Series of models that sequentially adjusted for (1) age, sex, and pubertal status; (2) …+height and weight; (3)…+screen time and physical activity; and (4) …+parental education and ethnicity	Leptin levels were 27 % (p=0.02) higher for each 1-h increment of sleep duration when adjusted for total body fat. When adjusted for additional variables, the association was no longer significant
Boeke [21•]	USA	(two cohorts)	Project Viva: parent-reported sleep duration during infancy, at age 3 and age 7. Sleep duration score based on short versus adequate sleep at each time point	Project Viva: cross-sectional and longitudinal	Project Viva: univariate associations were not significant. In multivariable adjusted models, low cumulative sleep duration scores, indicative of chronic sleep curtailment throughout infancy and childhood, were associated with lower leptin at age 7 years in females but not males. Cross-sectional associations between sleep duration and leptin at ages 3 and 7 years were not significant
		Project Viva: 655 boys and girls in a prospective cohort of children, recruited when mothers were pregnant; evaluated during infancy, ages 3 and 7 years	Cleveland cohort: self-reported weekday and weekend sleep duration	Cleveland cohort: cross-sectional	
		Cleveland cohort: 502 adolescents ages 16–19 years from the Cleveland Children's Sleep and Health Study		Models for each cohort evaluated for boys and girls separately. Unadjusted and adjusted associations were evaluated. Covariates for both studies included age, race/ethnicity, income, parental education, and preterm status (Cleveland cohort only)	Cleveland cohort: among males, shorter weekday and weekend sleep were associated with lower leptin; each 1-h decrement in weekend sleep duration was associated with a 0.06 decrease in log leptin (95 % CI:0.00, 0.11). A (non-significant) association was found for weekday sleep. There was no association between sleep duration and leptin among females
Fu [22•]	China	114 obese children and 49 non-obese controls, ages 10–15 years	7-day sleep diary used to determine average daily sleep duration	Partial regression coefficients, β(SE)	Each hour increment of greater sleep duration was associated with leptin levels that were mean(SE) 7.9 (1.1) lower, p<0.0001

Table 2 Summary of experimental studies assessing the association between sleep duration/quality and leptin

Citation	Country	Study/sample description	Sleep variable description	Analysis	Results
Klingenberg [23]	Denmark	21 boys, ages 15–19 years, recruited from advertisements and word of mouth	Subjects randomly assigned order to undergo short sleep (sleep between 03:00 and 07:00) and long sleep (sleep between 22:00 and 07:00). The two sleep conditions were separated by 3–4 weeks	Incremental area under the curve compared between conditions (short sleep and long sleep)	Leptin did not differ between long- and short-sleeping conditions (2.25 vs 2.4 μg/L/min)
Hart [24•]	USA	37 children ages 8–11 years recruited from mailings, newspaper advertisements, and flyers posted in community and hospital/study websites	Experimental increasing and decreasing of sleep time. Usual time in bed (TIB) was ~9.5 h for all kids recruited. Randomized to increase or decrease TIB by 1.5 h/night for 1 week. Alternate schedule completed the subsequent week. Subjects achieved a mean 141 min (2 h and 21 min) difference in actigraph-defined sleep period time between increase and decrease periods	Paired sample *t* tests	Fasting morning leptin sig lower during increase sleep period than decrease sleep period (5.67 vs 6.97 ng/mL) ($P<0.05$)
Guilleminault [25]	USA	eight subjects, ages 18–25 years, recruited from a university	Experimental sleep restriction. Normal sleep for three nights, sleep restriction to 4 h/night for seven nights, one recovery night, and return to baseline schedule for 48 h	Paired *t* tests were used to compare leptin levels across the day at 08:00, 12:00, 18:00, 22:00, 02:15, and 8:00 at baseline and on day 7 of sleep restriction	Leptin changed significantly between subjects from baseline to sleep restriction ($p=0.0001$). After sleep restriction, leptin levels were significantly lower at all time points across the day (1.98, 2.46, 3.11, 3.55, 3.84, and 2.08 ng/ml across time points at baseline; 1.23, 1.886, 2.19, 2.19, 2.28, and 1.83 ng/ml across time points after 7 days of sleep restriction)

association among girls [17, 21•]. Still, another study reported no association among girls but a significant association among boys [21•].

Several studies had significant findings, but these results were inconsistent (i.e., some studies find that short sleep is associated with higher leptin levels, and some find that short sleep is associated with lower leptin levels). In one study of children and adolescents, ages 6–20 years, the authors reported partial correlations, adjusted for age, between self- or parent-reported sleep durations and leptin. Among girls, longer-sleep duration was associated with lower leptin levels ($r=-0.20$ ($p<0.05$)). No significant association was found for boys [17].

Chronic sleep curtailment during early childhood was associated with lower leptin at age 7 in females but not males in the only longitudinal study conducted among children [21•]. Project Viva is a Boston area prospective cohort of 655 boys and girls, recruited when mothers were pregnant. Parents reported sleep duration during infancy and at ages 3 and 7 years. A sleep duration score was created to quantify adequate sleep duration over time based on short versus adequate sleep at each time point. At each of the time points (infancy, age 3, and age 7), cross-sectional associations were not statistically significant. However, in multivariable-adjusted regression models, low cumulative sleep duration scores, indicative of chronic sleep curtailment in infancy and childhood, were significantly associated with lower leptin at age 7 years in females but not males.

Another study found an association between shorter sleep and lower leptin levels among adolescent males (age 16–19 years) and no association among adolescent females [21•]. Shorter weekday and weekend sleep were associated with lower leptin: each 1-h decrement in weekend sleep duration was significantly associated with a 0.06 decrement in the logarithm of serum leptin levels.

In a study that included both boys and girls, Fu et al. [22•] found a significant inverse association between leptin levels

Table 3 Summary of observational studies assessing the association between sleep duration/quality and ghrelin

Citation	Country	Study/sample description	Sleep variable description	Analysis	Results
Navarro-Solera [16•]	Spain	90 obese children, ages 7–19 years (obese defined as ≥95th percentile for gender and age by WHO standards)	Children who slept less than recommended compared to children who slept recommended hours (by National Sleep Foundation)	Cross-sectional. Linear regression models that were adjusted for gender, age, BMI, and level of adherence to a Mediterranean diet	Subjects with short sleep did not have different ghrelin levels compared to subjects with recommended sleep 691(341) versus 697(352) pg/mL (p=0.5)
Al-Disi [19]	Saudi Arabia	126 Saudi girls, ages 14–18 years (62 lean and 64 obese)	Self-reported total sleep time, divided into three categories: <5 h, 5–7 h, and >7 h. Self-reported sleep pattern (intermittent or consistent)	Cross-sectional. Unadjusted correlation coefficients	Overall (i.e., combining obese and non-obese groups), ghrelin significant inverse association with hours of sleep (r=−0.18, p=0.04). The association was stronger among lean girls. Continuous sleep was significantly associated with ghrelin (r=0.20, p=0.02)
Fu [22•]	China	114 obese children ages 10–15 years (referred to endocrinology department because of obesity) and 49 controls (non-obese children undergoing annual health exam)	7-day sleep diary used to determine average daily sleep duration.	Partial regression coefficients, β(SE)	Each hour increment of greater sleep duration was associated with ghrelin levels that were 21.7 (1.7) ng/mL lower, p<0.0001
Kjeldsen [20]	Denmark	third- and fourth-grade students, ages 8–11 years, from Danish municipal schools enrolled in the OPUS study	Waist-worn actigraph measured sleep duration for eight nights; weekly average sleep duration was calculated	Cross-sectional. Series of models that added variables for adjustment. Model 1 adjusted for age, sex, and pubertal status; model 2 added height and weight; model 3 added screen time and physical activity; and model 4 added parental education and ethnicity	Ghrelin was positively associated with sleep duration when adjusting for age, sex, and pubertal status [85(15–154)%, p=0.02]. When models adjusted for additional variables, association was no longer significant

and sleep duration. This study included a sample of obese children, ages 10–15 years, recruited from an obesity clinic, and age-matched group of normal weight students undergoing annual health examinations. In the combined sample of normal and obese children, each hour of longer sleep was associated with leptin levels that were mean(standard error (SE)) 7.9 (1.1)ng/ml lower (p<0.001).

Finally, one large study that employed waist-worn accelerometers to objectively assess sleep duration in a sample of 630 boys and girls found a significant positive association between leptin levels and sleep duration [20]. Leptin levels were mean(95 % confidence interval (CI)) 26.7(3.3–55.3)% (p= 0.02) higher for every 1-h greater sleep duration.

Experimental Studies (Table 2)

Three experimental studies have investigated the relationship between short sleep and leptin levels in children. As with findings from observational studies, results from these experiments were inconsistent. One study of thirty-seven 8–11-year-old boys and girls found that lower leptin levels were associated with experimentally elevated sleep duration compared to reduced sleep duration [24•]. A study of late-adolescent males subjected to sleep restriction found that mean leptin levels were significantly lower after 1 week of sleep restriction compared to baseline [25]. And, a study of twenty-one 15–19-year-old boys, assigned to undergo 1 week of shortened sleep duration and a week of longer sleep duration (in random order), found no association between leptin levels and sleep duration [23].

Ghrelin

Observational Studies (Table 3)

Two studies found a significant inverse association between sleep duration and ghrelin levels [19, 22•]. A third study that

Table 4 Summary of experimental studies assessing the association between sleep duration/quality and ghrelin

Citation	Country	Study/sample description	Sleep variable description	Analysis	Results
Hart [24•]	USA	37 children ages 8–11 years. Recruited from mailings, newspaper advertisements, and flyers posted in community and hospital/study websites	Usual time in bed (TIB) was ~9.5 h for all kids recruited. Randomized to increase or decrease TIB by 1.5 h/night for 1 week. Alternate schedule completed the subsequent week. Subjects achieved a mean 141 min (2 h and 21 min) difference in actigraph-defined sleep period time between increase and decrease periods	Paired sample *t* tests	There was no significant difference in ghrelin levels between the increase and decrease sleep duration conditions (909.1 vs 866.8 pg/ml, $p=0.21$)
Klingenberg [23]	Denmark	21 boys, ages 15–19 years, recruited from advertisements and word of mouth	Subjects randomly assigned order to undergo short sleep (sleep between 03:00 and 07:00) and long sleep (sleep between 22:00 and 07:00). The two sleep conditions were separated by 3–4 weeks	Incremental area under the curve compared between conditions (short sleep and long sleep)	No significant differences in ghrelin levels between long-and short-sleeping conditions (410 vs 420 mg/L/min)

investigated this association found no association between a dichotomized sleep duration variable and ghrelin [16•].

Ghrelin was significantly associated with hours of sleep in a sample of adolescent girls (ages 13–17), where self-reported sleep duration was divided into three categories: <5 h, 5–7 h, and >7 h. In the overall sample, ghrelin was significantly inversely associated with hours of sleep ($r=-0.18$, $p=0.04$). However, the association was stronger among lean girls [19].

A study of both boys and girls in China found that longer-sleep duration was associated with lower ghrelin levels; for each hour of additional sleep, ghrelin was a mean (SE) 21.7 (1.7)ng/ml lower ($p<0.0001$) [22•].

A study of 8–11-year-old children that used waist-worn actigraphy to measure nightly sleep duration found that ghrelin levels were positively associated with sleep duration, when adjusting for age, sex, and pubertal status. However, when the models were adjusted for additional variables (height, weight, screen time, physical activity, and other covariates), the association was no longer significant [20].

Experimental Studies (Table 4)

Two experimental studies investigated the relationship between ghrelin levels and sleep duration; both studies reported null results [23, 24•]. In a study of 8–11 year olds, children were instructed to increase time in bed for 1.5 h for 1 week and then decrease time in bed for 1.5 h for 1 week (or vice versa). Subjects achieved a mean 141 min (2 h and 21 min) difference in actigraphically assessed sleep time between the sleep duration increase and decrease conditions. Blood samples were taken on the morning of the last day of each 1-week sleep condition. There were no significant differences in fasting morning ghrelin levels ($p=0.21$) [24•]. Another study of late-adolescent boys, assigned to undergo 1 week of shortened sleep duration and a week of longer sleep duration (in random order), found no association between ghrelin levels and sleep condition [23].

Adiponectin (Table 5)

Four studies have investigated associations between adiponectin and sleep duration [16•, 17, 18, 19]; each study used samples of older children and adolescents; no studies investigated this association in younger children. The results of these studies demonstrated a mix of positive associations [17, 19] (i.e., higher adiponectin levels with longer-sleep duration and higher adiponectin levels with less interrupted sleep) and null findings [16•, 18].

In a sample of adolescent girls [19], researchers found a positive association between self-reported sleep duration and adiponectin levels among lean girls (mean values were 7.6, 8.6, and 10.8 ng/mL for the <5 h, 5–7, and >7 h sleep categories, respectively). No association was found among obese girls; mean levels were 6.3, 6.5, and 6.5 ng/mL for the three sleep categories, respectively. The girls also reported on whether their sleep pattern was consistent (uninterrupted) or intermittent (interrupted). Adiponectin levels were higher among girls who reported continuous sleep than girls whose sleep was intermittent, but this difference was not statistically significant.

Another study included a large sample of both boys and girls, ages 6–20 years [17]. Sleep was categorized as short according to cutoffs that varied by age: <10 h per day for children <10 years and <9 h per day for children ≥10 years.

Table 5 Summary of studies (all observational) assessing the association between sleep duration/quality and adiponectin

Citation	Country	Study/sample description	Sleep variable description	Analysis	Results
Navarro-Solera [16•]	Spain	90 obese children, ages 7–19 years (obese defined as ≥95th percentile for gender and age by WHO standards)	Children who slept less than recommended compared to children who slept recommended hours (by National Sleep Foundation)	Cross-sectional. Linear regression models that were adjusted for gender, age, BMI, and level of adherence to a Mediterranean diet	Subjects with short sleep did not have different adiponectin levels compared to subjects with recommended sleep (1.16 (0.45) vs 1.13 (0.36) μg/mL, p=0.4)
Hitze [17]	Germany	207 boys and 207 girls, ages 6–20 years	Questionnaire-assessed sleep duration dichotomized as not short versus short sleep (<10 h/day for children <10 years and <9 h/day for children >10 years)	Cross-sectional. Partial correlations adjusted for age	Short sleep duration (vs long) associated with lower adiponectin levels in boys (11.7 (9.8–13.5) vs 14.4 (12.6–16.2) μg/mL, p<0.05. No difference in adiponectin levels for girls
Martinez-Gomez [18]	Spain	183 adolescents, ages 13–17 years, from the AFINOS study, a representative sample of adolescents in the Madrid, Spain, region	Self-reported (by adolescent) usual sleep duration on typical weeknight and weekend. Average sleep/day calculated as [(weekday sleep duration×5+ weekend sleep duration×2)/7]	Cross-sectional. Three multiple linear regression models, adjusted for (1) age, sex, and pubertal status; (2) model 1 variables+ physical activity; and (3) model 2 variables +BMI	Adiponectin not significantly associated with sleep duration (β values for adiponectin between −0.03 and −0.05, p>0.5 for all models)
Al-Disi [18]	Saudi Arabia	126 Saudi girls, ages 14–18 years (62 lean and 64 obese)	Self-reported total sleep time, divided into three categories: <5 h, 5–7 h, and >7 h. Self-reported sleep pattern (intermittent or consistent)	Cross-sectional. Unadjusted correlation coefficients	Among lean girls, adiponectin increased with increasing sleep duration (mean serum adiponectin levels were 7.6, 8.6, and 10.8 ng/mL for those who slept <5 h, 5–7 h, and >7 h respectively); among obese girls, adiponectin was not associated with hours of sleep (6.3, 6.4, and 6.5 ng/mL across sleep duration categories)

Short-sleep duration (vs long) was associated with lower mean adiponectin levels in boys (11.7 vs 14.4 μg/mL; p<0.05); there was no significant difference in girls.

A study of adolescent boys and girls (ages 13–18 years) found no significant association between adiponectin and self-reported sleep duration [18]. These adolescents self-reported their typical weekday and weekend sleep duration (a weighted daily average daily sleep time was used for analyses). The researchers used multiple linear regression models to assess the association between sleep duration and adiponectin. Their first model adjusted for age, sex, and pubertal status; the second model added physical activity as a covariate; and the third model additionally included BMI (unadjusted results were not presented). Adiponectin was not significantly associated with sleep duration in any of the models.

Another study from Spain that included only obese children (ages 7–16 years) found no association between short sleep and adiponectin. Short sleep was defined as sleeping less than recommended sleep ranges by age according to the U.S. National Sleep Foundation. Subjects with short sleep did not have significantly different mean adiponectin levels compared to subjects with recommended sleep (1.16 vs 1.13 μg/mL (p=0.4)). The researchers used linear models that adjusted for gender age, BMI, physical activity, and an index that evaluated adherence to a Mediterranean diet [16•].

Discussion

Many investigations of both children and adult populations have identified associations of shorter-sleep durations with excess body weight [8, 26]. However, establishing that the associations represent a causal influence of short sleep on body weight regulation is challenging. Several plausible, but largely hypothetical, mechanisms have been postulated linking chronic inadequate sleep to substantial and sustained

weight gain in human populations [26]. Some potential mechanisms include increased opportunities to eat (i.e., in societies and households in which food is plentiful, more awake time may lead to greater calorie consumption by the simple fact that someone awake will be more likely to consume food than if he or she were asleep), suppression of the quantity of physically active behaviors due to sleepiness and fatigue, and pathologic alterations in energy-regulating and appetite-influencing hormones. In this review, we summarized evidence addressing the latter hypothesized mechanism, focusing on three specific hormones—leptin, ghrelin, and adiponectin—in children. Consistent associations between short sleep and reduced levels of the adipocyte-derived hormones leptin and adiponectin, or elevated levels of the gut-derived hormone ghrelin, would provide evidence consistent with a hormone-mediated mechanistic link between short sleep and weight gain. Unfortunately, the studies reviewed here do not collectively present a strong consensus or clear picture regarding the nature of associations of sleep duration with these hormones. Both experimental (leptin) and observational (leptin, ghrelin, and adiponectin) studies of hormones and sleep duration produced a range of seemingly incompatible results—positively associated, negatively associated, or not significantly associated.

What might explain this wide variation in findings? Likely, it is a combination of influences from the "usual suspects" that include chance variations in effect estimates as well as differences among studies in study populations, measurement techniques of key variables (e.g., sleep duration), robustness of confounder assessment, statistical approaches, and variations in basic study designs (observational vs. experimental and cross-sectional vs. longitudinal). We take for granted that chance variations (e.g., due to sampling variability and measurement error) contribute to varied study results and focus the rest of the discussion on salient challenges in comparing these studies with their varied samples, measurements, statistical methods, confounder control, and study designs.

There were marked differences in gender, age, pubertal status, and ethnic heritage distributions in study samples summarized here; as such, it would have been remarkable if the studies had found substantially similar results. For example, the two observational studies that examined associations of sleep duration and ghrelin levels included a population of obese Spanish boys and girls with mean age of 11 years [16•] and a population of obese and non-obese Saudi Arabian girls with mean age of 16.5 years [19]. Non-significant findings in the former study versus moderately significant findings in the latter would not be surprising if there were modest underlying causal associations between sleep duration with ghrelin levels, moderated, if only subtly, by age, gender, ethnicity, or body mass. Thus, the diversity of demographic characteristics of the samples employed in studies examined in this review would be expected to result in a range of estimated sleep duration-hormone level associations.

Varied approaches to measuring and parameterizing sleep duration would also be expected to contribute to disparate results among studies. There are at least two issues related to sleep duration quantification that could affect the quality and comparability of estimates of associations of sleep duration with hormone levels. First, sleep duration was inevitably measured with error in all studies. Self- and parent-reported sleep durations are (of course) imperfect tools for assessing average sleep duration [27, 28]. Even studies that used objective measures—e.g., waist actigraphy—measured sleep duration with some error and over a time span that likely would not sufficiently capture intra-individual variances in sleep duration germane to the regulation of examined hormones. Second, estimates of measures of association of sleep duration with hormone levels will depend upon statistical assumptions regarding the functional form between sleep duration and hormone levels that investigators make in their analyses; for example, that sleep duration-hormone associations are linear or logarithmic or in the selection of specific "optimal"/normal reference sleep duration categories (which almost certainly varies with age). The studies reviewed here followed no one's standard approach to parameterizing and fitting models, likely contributing to their varied results. Both of these issues (imperfect sleep duration measurement and unknown functional form of sleep duration-hormone associations) would be expected to result in underestimation of the "true" magnitudes of associations of interest.

In addition, studies that employed short-term (e.g., 1-week) experimental manipulation of sleep duration may be addressing fundamentally different questions than cross-sectional and longitudinal observational studies. From the perspective of the question of whether short-sleep duration affects hormone regulation and long-term weight control, relatively brief experimental manipulations of sleep duration could provide proof-of-concept insights but will not directly answer the question because of the potential for long-term adaptations to chronic partial sleep deprivation—a subject about which very little is known in humans. This contrasts, for example, with the relatively larger bodies of knowledge accumulated around adaptations to exposure to other long-term systemic "stressors" such as living in a low-oxygen-pressure environment (high altitude [29]), regular strenuous physical activity [30], or chronic caloric restriction [31, 32]. Acute and short-term responses to these exposures (e.g., elevated blood pressure and oxidative stress immediately resulting from strenuous physical activity) may not provide direct insight into organisms' eventual adaptations and health consequences; thus, results from brief manipulations of sleep durations may not directly speak to long-term health outcomes of chronic sleep curtailment. Long-term sleep curtailment experiments in humans are unlikely to be performed due to ethical and feasibility constraints, especially in children.

Properly designed and executed observational studies, by contrast, could be able to assess longer-term associations of chronic partial sleep deprivation, hormone regulation, and body weight.

However, there are substantial difficulties in performing such studies, a salient challenge being the inevitable effects of confounding by a wide variety of health-affecting factors that are associated with variations in sleep habits within populations (children and adults), including socioeconomic status, health behaviors (e.g., physical activity and diet), and health status [33–35]. In addition, disentangling sleep-related versus circadian effects on hormones is difficult in observational studies, particularly so in adolescents in which school schedules and social activities (among others) may simultaneously impair both accumulation of sufficient sleep and timing of behaviors (including sleep) "in harmony" with intrinsic circadian rhythms [36]. Full control for potential confounding factors requires repeated precision measures of the confounding variables and appropriate statistical adjustments (as well as sufficient knowledge of what to measure and how to appropriately adjust) that are unlikely to be achieved in any near-future study of habitual sleep duration and metabolic outcomes in children.

Finally, we also note that it is possible to "overcontrol" for variables in a way that might result in underestimation of associations between sleep duration and hormone levels. For example, if short-sleep duration truly results in neuroendocrine dysregulation that subsequently causes excess body fat accumulation in children, then conditioning on body weight (e.g., controlling for total body fat as in [20] or stratifying by obese/non-obese status as in [19]) would be expected to bias causal estimates to the null (i.e., by conditioning on a causal descendent of the outcome of interest [37]).

Conclusion

Some bromides are true: more research is needed. Chronic short sleep may be an important endocrine disrupter in children leading to harmful weight gain and obesity. However, available evidence does not provide robust and unified evidence for that assertion. Nevertheless, a sufficient number of studies, observational and experimental, have found associations between short-sleep duration and weight-regulating hormones in children implicating short-sleep duration as an obesity culprit. This is in spite of methodologic limitations that could collectively conspire to suppress the magnitude of estimated associations. Sufficiently powered long-term longitudinal studies of objectively assessed sleep duration, appetite- and energy balance-regulating hormones, excess body weight, and accurately measured confounding factors are required to robustly quantify the contribution of insufficient sleep to metabolic dysregulation and obesity in children.

Compliance with Ethical Standards

Conflict of Interest Erika W. Hagen, Samuel J. Starke, and Paul E. Peppard declare that they do not have any conflicts of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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