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Genetics of Sleep and Insights into Its Relationship with Obesity

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Abstract

Considerable recent advancements in elucidating the genetic architecture of sleep traits and sleep disorders may provide insight into the relationship between sleep and obesity. Despite the involvement of the circadian clock in sleep and metabolism, few shared genes, including *FTO*, were implicated in genome-wide association studies (GWASs) of sleep and obesity. Polygenic scores composed of signals from GWASs of sleep traits show largely null associations with obesity, suggesting lead variants are unique to sleep. Modest genome-wide genetic correlations are observed between many sleep traits and obesity and are largest for snoring. Notably, U-shaped positive genetic correlations with body mass index (BMI) exist for both short and long sleep durations. Findings from Mendelian randomization suggest robust causal effects of insomnia on higher BMI and, conversely, of higher BMI on snoring and daytime sleepiness. In addition, bidirectional effects between sleep duration and daytime napping with obesity may also exist. Limited gene-sleep interaction studies suggest that achieving favorable sleep, as part of a healthy lifestyle, may attenuate genetic predisposition to obesity,

but whether these improvements produce clinically meaningful reductions in obesity risk remains unclear. Investigations of the genetic link between sleep and obesity for sleep disorders other than insomnia and in populations of non-European ancestry are currently limited.

Contents

OVERVIEW OF SLEEP

Sleep Is a Fundamental Pillar of Health

Sleep is a critical component of healthy development and overall well-being in humans (11, 55). Healthy sleep is multidimensional and includes adequate duration, good quality, appropriate

timing, and the absence of sleep disorders (19). Despite its large societal burden in terms of morbidity and mortality (138), sleep remains an underrecognized determinant of health. Chronic sleep insufficiency is a global concern in industrialized societies and affects 1 in 3 adult Americans (74). Habitual short sleep duration has been associated with adverse health outcomes, including obesity (14, 94, 101, 136), type 2 diabetes (13), cardiovascular disease (18), and all-cause mortality (138). Sleep deprivation is also associated with daytime sleepiness, fatigue, depressed mood, and overall poor daytime functioning (128). Common sleep disorders such as insomnia and obstructive sleep apnea (OSA) are also associated with reduced quality of life and increased morbidity and mortality (67, 81). Their prevalence, currently estimated between 10% and 20% in the United States, is increasing owing to societal changes and, in the case of OSA, in parallel with the increasing prevalence of obesity levels (59, 84, 98). The American Academy of Sleep Medicine and the Sleep Research Society have summarized the evidence linking favorable sleep and overall health to highlight sleep's role as a fundamental pillar of health (5, 79).

What Is Sleep?

Sleep occupies almost one-third of our lives, yet its precise definition and role remain somewhat ambiguous. Sleep has been defined (27, 90, 97) as (*a*) a reversible behavioral state of perceptual disengagement and unresponsiveness to the environment; (*b*) the naturally recurring state of rest during which consciousness of the world is suspended; (*c*) a reversible behavioral state of decreased responsiveness and interaction with the environment; and (*d*) a readily reversible suspension of sensorimotor interactions with the environment, usually associated with recumbence and immobility. Definitions have been further expanded to include the main electrophysiological hallmarks of human sleep, such as slow-wave sleep and paradoxical or rapid eye movement sleep, highlighting that sleep is not simply a state of rest but also a period of heightened brain activity (106). Indeed, there are times during sleep when the brain is more active than it is during wakefulness.

From an evolutionary perspective, all animal species exhibit sleep or sleep-like states, suggesting its importance for survival (11, 55). The importance of sleep is evidenced by the following: (*a*) It occurs in all multicellular animals, suggesting universal functionality; (*b*) during the sleep state, an organism is unable to respond to external threats, suggesting a critical benefit to be gained from sleeping; (*c*) there exists a homeostatic drive that regulates sleep in a manner similar to that for other critical behaviors such as thirst; and (*d*) complete sleep deprivation leads to death. The exact functions of sleep remain unknown (66). In humans, sleep has been implicated in the maintenance of normal bodily functions, including central nervous system repair and clearance of neural waste products through the glymphatic system; recovery from physical activities and growth and repair of body tissues; learning and processing of memory; maintenance of attention and concentration; and optimal immune performance.

Sleep Architecture Across the Life Span

Sleep architecture changes with age (95). Changes include a decrease in sleep efficiency, earlier sleep timing, and decreased percentage of rapid eye movement and slow-wave sleep and a related increase in the remaining nonrapid eye movement stages of sleep (95). There is no evidence of significant changes to these measurements after the age of 60 (95). General sleep guidelines exist and serve as key tools for education, surveillance, and guidance for intervention strategies. Sleep recommendations in the United States were last issued in 2015 by the National Sleep Foundation (47). Sleep duration recommendations included 12 to 15 h for infants, 9 to 11 h for school-aged children, and 7 to 9 h for adults. However, the precise optimal amount of sleep may vary from person to person.

GENETICS OF SLEEP AND OBESITY

Between 2015 and 2020, major advances in large-scale biorepositories and genetic analyses, such as genome-wide association studies (GWASs), have enabled the discovery of common genetic variants that contribute to complex heritable traits and diseases related to sleep (summarized in **Table 1**) and obesity.

Sleep Duration

Duration is the most commonly investigated sleep dimension among genetic studies of sleep. The heritability of sleep duration ranges between 31% and 55% in twin- and family-based studies (28, 37, 99). Prior to GWASs, candidate gene association studies focused on core clock genes because of the central role of the circadian machinery in sleep regulation (111). Clock genes, including *CLOCK* and *ARNTL*, are required for the coordinated regulation of circadian rhythms (9). Candidate gene studies of adults, and a few of children, have identified some associations between core clock genes, particularly *CLOCK*, *RORA*, and *DEC2*, and sleep duration, as well as timing and quality, in diverse populations (3, 45, 87, 91, 105, 112).

Since 2007, successive waves of GWASs have been conducted for sleep duration, highlighting its polygenic nature. The first GWAS was of 749 adults from the Sleep Heart Health Study (40). Although the study did not identify signals for sleep duration, it implicated circadian-related genes, including *CSNK2A2* and *PROK2*, for sleep timing and daytime sleepiness (40). A GWAS including over 4,000 adults from seven European cohorts identified a genetic variant for sleep duration near *ABCC9* encoding an adenosine triphosphate (ATP)-sensitive potassium channel (1). A larger GWAS meta-analysis composed of 18 population-based cohorts totaling 47,180 adults identified two loci for sleep duration, including *PAX8*, in which each copy of the minor allele was associated with 3.1-min-longer sleep duration (39). *PAX8* was further implicated in sleep duration by another GWAS from the UK Biobank (**https://www.ukbiobank.ac.uk/**) that included ~150,000 adults (57). *PAX8* is a widely expressed transcription factor that plays an essential role in thyroid development (57). The largest GWAS of sleep duration to date is from the UK Biobank and encompasses 446,118 adults of European ancestry (23). In total, 78 genetic variants were identified for self-reported sleep duration, accounting for 0.69% of the variance. Findings were partially validated with accelerometer-derived objective measures of sleep duration and replicated in an independent study from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (23). The largest effect size remained at the *PAX8* locus, with an estimate of 2.44 min per effect allele. Considering the nonlinear U-shaped relationship between sleep duration and health outcomes, GWASs of short and long sleep durations have also been conducted (23, 57), identifying 27 and 8 loci, respectively (23). The variants partly overlapped with continuous sleep duration, suggesting some shared and distinct biological mechanisms (23, 30). Only one GWAS of sleep duration in children has been conducted so far ($n = 10{,}554$), identifying one variant located in an intronic region of *ARAP1* (82).

Other Sleep Traits

Diurnal preference, or chronotype, is the behavioral manifestation of the circadian clock and is another heritable sleep trait, with heritability estimates of 12% to 42% based on twin and family studies (69). Two studies leveraged interim data releases from the UK Biobank (up to $n = 128{,}266$ participants of European ancestry) and responses to a question on morning or evening preference and identified 16 (57) and 12 (69) loci. As expected, the GWASs implicated known components of the circadian clock machinery, including *PER2*. Separately, in a cohort from

Table 1 Summary of large-scale (n > 50,000) GWASs for sleep traits and sleep disorders

Trait	Phenotype definition	Cohort (n)	Number of loci	SNP-based heritability (%)	Notable genes	Reference
Self-reported sleep traits						
Sleep duration	Continuous hours of 24-h sleep duration	UK Biobank (446,118)	78	9.8	*PAX8*, *FTO*, *FADS1*, *FADS2*, *FOXP2*, *KSR2*	23
Short sleep duration	Sleep duration <7 h versus sleep duration between 7 and 8 h	UK Biobank (106,192 cases; 305,742 controls)	27	7.9	*PAX8*, *SLC39A8*, *FOXP2*	23
Long sleep duration	Sleep duration ≥9 h versus sleep duration between 7 and 8 h	UK Biobank (34,184 cases; 305,742 controls)	8	4.7	*PAX8*, *FTO*	23
Sleep duration (children)	Hours of sleep per day, including naps	EAGLE Consortium (10,554)	1	14.0	*ARAP1*	82
Diurnal preference (chronotype)	Morning or night person	UK Biobank + 23andMe (697,828)	351	13.7	*ARNTL*, *HCRTR2*, *PER1*, *PER2*, *PER3*, *MADD*	56
Daytime napping	Frequency of naps during the day	UK Biobank (452,633)	123	11.9	*KSR2*, *HCRTR2*, *PATJ*, *BTBD9*, *MTNR1B*	19
Daytime sleepiness	Frequency of unintentional dozing off or falling asleep during the day	UK Biobank (452,071)	42	6.9	*KSR2*, *PATJ*, *HCRTR2*, *SLC39A8*, *BTBD9*	128
Ease of getting up	Ease of getting up in the morning	UK Biobank (385,949)	62	7.1	*HCRTR2*, *RGS16*, *PER3*, *FTO*	53
Snoring	Complaints about snoring	UK Biobank (408,000)	42	9.9	*DLEU7*, *MSRB3*, *POC5*, *FTO*	12
Objectively derived sleep measures						
Sleep duration	Nocturnal sleep duration	UK Biobank (85,502)	12	19	*PAX8*, *MEIS1*, *KCNH5*, *DBYD*	58
Sleep duration variability	Interdaily variability in sleep duration	UK Biobank (85,068)	0	2.8	NA	58
Number of sleep episodes	Number of sleep bouts during the night sleep period	UK Biobank (85,502)	21	22.3	*APOE*, *GPR139*, *BANK1*	58
Daytime inactivity duration	Total daily duration outside the sleep period	UK Biobank (85,502)	2	14.8	*KCNH5*, *MPDZ/NFIB*	58
Sleep midpoint	Midpoint between the start and the end of the sleep period	UK Biobank (85,502)	1	10.1	*CAB39*	58

(*Continued*)

Table 1 (*Continued*)

Trait	Phenotype definition	Cohort (*n*)	Number of loci	SNP-based heritability (%)	Notable genes	Reference
M10 timing	Timing of the most active 10 h; measure of sleep midpoint	UK Biobank (85,723)	1	8.7	*CPNE8*, *ALG10B*	58
L5 timing	Timing of the least active 5 h; measure of sleep midpoint	UK Biobank (85,830)	6	11.7	*MEIS1*, *BTBD9*, *RGS16*, *ALG10B*	58
Sleep efficiency	Sleep duration divided by the time between the start and the end of the first and last nocturnal inactivity period, respectively	UK Biobank (85,502)	5	13	*PAX8*, *MEIS1*, *PDE11A*	58
Sleep disorders						
Insomnia	Trouble falling asleep at night or waking up in the middle of the night	UK Biobank + 23andMe (1,331,010)	202	7.0	*PAX8*, *MEIS1*, *BTBD9*	53
Restless legs syndrome	Diagnosis of restless legs syndrome	EU-RLS GENE, INTERVAL, 23andMe (15,126 cases; 95,725 controls)	19	19.6	*MEIS1*, *C1D*, *BTBD9*	109

For traits and disorders for which multiple GWASs were conducted, only the largest study to date is listed. Full GWAS summary statistics can be downloaded from the Sleep Disorder Knowledge Portal (**https://sleep.hugeamp.org/**).
Abbreviations: GWAS, genome-wide association study; NA, not applicable; SNP, single nucleotide polymorphism.

23andMe (a personal genomic testing company) ($n = 489{,}283$), up to 15 variants, including 7 near genes with well-established roles in circadian rhythms (49), were identified. Building on these findings is the largest GWAS of morning preference to date, encompassing 697,828 UK Biobank and 23andMe participants and identifying 351 genetic variants (56). Identified loci were enriched for circadian clock regulatory genes, including *PER1*, *CRY1*, and *ARNTL*. The specificity of these loci was validated by robust associations of the variants with accelerometer-derived measures of sleep timing but not sleep duration or quality.

Daytime napping, another common and heritable behavior (~65% from twin studies), is characterized by short sleep episodes during the day (20). A GWAS including 452,633 UK Biobank participants identified 123 loci, explaining 1.1% of the trait variance (20). The loci were consistent in an independent data set from a 23andMe cohort and showed specific associations with accelerometer-derived measures of daytime inactivity duration. Excessive daytime sleepiness is a common symptom affecting 10–20% of the population primarily due to chronic insufficient sleep and is associated with motor vehicle accidents and impaired social functioning (128). The estimated heritability for daytime sleepiness ranges between 0.38% and 0.48%, and a GWAS of 452,071 UK Biobank participants identified 42 loci (128). A polygenic score for daytime sleepiness—a score that aggregates multiple genetic variants predictive of daytime sleepiness and

thus provides a quantitative measure of genetic susceptibility—was associated with sleep disorders, including restless legs syndrome (RLS) and insomnia, and other sleep traits, including sleep duration, sleep timing, sleep efficiency, and daytime napping. Among 385,949 European adults from the UK Biobank, a GWAS of ease of getting up in the morning identified 62 genomic loci (53). There exist several shared loci, including *HCRTR2*, for daytime napping, daytime sleepiness, and ease of getting up (20, 53, 128). Snoring is the vibration of the upper airway structures that creates noise during sleep, and is more prevalent in males (~35–45%) than in females (15–28%) (12). Approximately 18–28% of the variance in snoring may be accounted for by genetic factors based on twin and family studies, and a GWAS has implicated 42 loci (12).

Subjective sleep quality, latency, efficiency, and disturbance, other dimensions of sleep, are also heritable (28, 37, 99). Using the Pittsburgh Sleep Quality Index in a multi-ethnic discovery cohort ($n = 2{,}868$), Khoury et al. (62) estimated the heritability of sleep quality to be 14.37% (34–37% in twin studies) and identified two novel loci on chromosomes 2 and 7.

Objective Measures of Sleep

Although most large-scale genetic studies have relied on self-reported data, objectively estimated sleep measures from accelerometers, actigraphy, and polysomnography have been analyzed. Objective methods for sleep assessment can robustly phenotype sleep dimensions that are more difficult to derive from surveys. The first GWAS of sleep to use wearable technology investigated 11 parameters derived from actigraphy in 956 adults from the LIFE Adult Study (116). This study identified several novel variants near candidate genes, including *UFL1* and *CSNK2A1*. Another GWAS showed that *ARNTL* was associated with polysomnography-estimated sleep duration (64). In the UK Biobank, ~103,000 participants were fitted with wrist-worn accelerometers for up to 7 days and two parallel studies assessed the genetics of objectively derived estimates of sleep (30, 58). In the first study, 47 signals were identified for 8 sleep parameters, including measures of quality, timing, duration, and the number of nocturnal sleep episodes. Of the 47 signals, 36 variants were not detected in previous GWASs of self-reported sleep traits (58). The second study identified 14 loci, of which 7, including *MAPKAP1* and *AUTS2I*, were novel for sleep duration (30).

Sleep Disorders

Insomnia occurs in 10–20% of the population and is characterized by persistent difficulty initiating or maintaining sleep and consequent daytime dysfunction (67). Family studies have estimated that insomnia heritability ranges between 22% and 25% (67). An initial genetic analysis of insomnia complaints in the UK Biobank ($n = 113{,}006$) identified 3 loci, including *MEIS1*, a locus previously implicated in RLS (43). The largest UK Biobank GWAS of insomnia includes 453,379 participants and identified 57 loci for self-reported insomnia symptoms, which were validated using physician-diagnosed insomnia in independent cohorts (67). Polygenic scores of the 57 loci were associated with accelerometer-derived measures of lower sleep quality and shorter sleep duration and greater day-to-day variability in sleep duration (67). The largest GWAS of insomnia complaints so far includes 1,331,010 adults and identified 202 risk loci, explaining 2.6% of the phenotypic variance (53). The lead signal was for *BTBD9*, another locus implicated in RLS. Despite crude phenotyping based on self-report, 163 risk loci were specific to insomnia and only 39 risk loci were associated with other sleep traits (53). In addition, a multitrait GWAS of sleep disturbance that encompassed insomnia symptoms, sleep duration, and daytime sleepiness from the UK Biobank ($n = 112{,}586$) identified 9 loci, including *PAX8*, *MEIS1*, *HCRTR2*, and *INADL* (68).

The genetic basis of other primary sleep disorders, including OSA, RLS, and narcolepsy, is less studied. OSA is a heritable and common sleep disorder affecting up to 34% of men and

17% of women and is characterized by recurrent upper airway obstruction during sleep (10, 104). OSA often leads to fragmented sleep and recurrent episodes of chronic intermittent hypoxia. A GWAS including 12,558 Hispanic American adults investigated OSA-associated traits, including the apnea–hypopnea index, a biomarker of OSA that estimates the number of episodes of breathing obstruction per hour of sleep, and identified two loci, *GPR83* and *C6ORF183/CCDC162P* (10). Notably, a correlation of up to 0.78 between the genetics of OSA and snoring is observed, providing further insight into the genetic architecture of OSA (12). Larger genetic studies of OSA are ongoing (89). RLS is a neurological disorder involving involuntary and regularly occurring limb movements that disrupt sleep and delay onset of sleep (109). Prevalence of RLS varies widely across populations, and heritability estimates range from 50% to 60% based on family and twin studies. A large GWAS included 15,126 cases and 95,725 controls of European ancestry and identified 19 loci, including *MEIS1*, with odds ratio estimates of 1.82 to 2.16 (109). *MEIS1* has also been implicated in insomnia and in objective estimates of sleep quality. Other RLS loci, such as *C1D* and *BTBD9*, have also been implicated in sleep timing. Narcolepsy is characterized by excessive daytime sleepiness and cataplexy with onset as early as adolescence. GWASs of patients with narcolepsy have implicated *TCR* (42), a T cell receptor α locus, and *CPT1B* (88), an enzyme involved in long-chain fatty acid β-oxidation in muscle mitochondria.

Obesity

Obesity and body weight are heritable traits partly determined by a highly polygenic genetic architecture and partly influenced by lifestyle and environment (7). Approximately 40–70% of variation in body mass index (BMI) is attributed to genetic differences (32). Various genes have been associated with monogenic, syndromic, and polygenic forms of obesity (6). Genes identified in early candidate gene association studies included *LEPR*, which encodes a receptor for the hormone leptin that regulates energy balance and body weight, and *PPARG*. The first identified obesity-susceptibility locus from GWASs was in the first intron of the fat-mass- and obesity-associated *FTO* gene (33). This locus has the largest effect on BMI and is associated with a higher BMI of ~0.39 kg/m^2 and an approximate 1.20-fold-higher risk of obesity per effect allele (78). The cluster of correlated variants in this locus regulates the expression of two upstream genes, *IRX3* and *IRX5*, both of which influence adipocyte browning and food intake (86). Larger GWASs have implicated additional common variants in genes including *MC4R* that also have established roles in fat mass, weight, and obesity risk (77, 121, 133). In 2015, a large GWAS by the Genetic Investigation of Anthropometric Traits (GIANT) consortium using data from 339,224 adults identified 97 BMI-associated variants, accounting for 2.7% of BMI variation (75). These variants are involved in diverse biological pathways, including fatty acid storage, glucose metabolism, and satiety (75). A genome-wide polygenic score integrating all 2.1 million common variants from the GWAS by GIANT was associated with an over-fourfold-higher risk of obesity and a higher risk of cardiometabolic disease and mortality (60). Larger GWASs of BMI and other adiposity traits by the GIANT consortium remain ongoing and have thus far identified over 900 BMI-related genetic variants (137).

THE RELATIONSHIP BETWEEN SLEEP AND OBESITY

Epidemiological Evidence of the Link Between Sleep and Obesity

Many cross-sectional and longitudinal epidemiologic studies, both of children and adults (14, 94, 101, 136) and across different ancestries and geographical environments (29, 108),

suggest that short and long sleep durations are risk factors for obesity and consequently many other cardiometabolic diseases. The epidemiological evidence indicates that the association between sleep duration and obesity is more robust in children than in adults and that the effect size decreases with age. Other studies have shown no significant associations between sleep and anthropometric measures (118). In addition, few studies have investigated sleep dimensions other than duration and examined the impact of obesity on sleep (rather than sleep on obesity).

Leveraging data on the genetic architecture of sleep and obesity from recent GWASs may delineate the relationship between sleep traits and sleep disorders and adiposity while limiting both bias and confounding from traditional epidemiological studies. The application of novel post-GWAS approaches may also provide insight into distinct gene overlaps, overall genetic correlations, and, through Mendelian randomization, bidirectional causal effects.

Tissue Enrichment of Sleep- and Obesity-Implicated Genes

The coexpression of genes for both sleep and obesity in the same brain regions suggests their potential genetic overlap. Tissue enrichment analyses of gene expression from various GWASs of sleep have implicated the cerebellum, frontal cortex, and hypothalamus (20, 23, 58, 67). These regions are also of emerging importance in adiposity. Indeed, processes related to appetite, homeostasis, reward, and motivation are key to BMI regulation and are controlled by the central nervous system (75, 117).

Genomic Loci Implicated in Both Sleep Traits and Obesity

Considering the dual role of the biological clock in regulating sleep and body weight, as well as metabolic mediators such as leptin and ghrelin (110), it is expected that there exist some shared genetic links between sleep and obesity. These genetic overlaps were previously investigated in candidate gene association studies. Transcription factors encoded by *CLOCK* and other circadian genes play key roles in regulating sleep and various metabolic pathways across multiple tissues (122). Animal studies have shown that *clock* mutant mice have increased body weight, strengthening the potential direct connection between sleep and weight (122). In candidate gene studies of humans, several common *CLOCK* variants, most commonly rs1801260, have shown some associations with BMI, ghrelin, weight loss success, and other adiposity-related traits (3, 35, 115, 125). The association of the circadian clock with various pathologies, including obesity, may involve its effect on sleep duration. In addition, *NR1D1* was also associated with both sleep duration and BMI in adolescent boys (91). Candidate gene association studies of OSA in a Chinese Han cohort also implicated variants in *LEPR* (71).

Building on findings from candidate gene studies, results from GWASs further implicated distinct genomic loci in both sleep and obesity. Among the GWAS signals for obesity, *FTO* most consistently shows associations with sleep traits such as sleep duration, morning preference, ease of getting up, and snoring (see **Figure 1**). Several other obesity loci were also identified in GWASs of sleep, as indicated in **Figure 2**, and include *SLC39A8*, *HCRTR2*, and *PAT1*. *ARAP1*, which encodes a protein associated with the Golgi apparatus and apoptosis, was implicated in both sleep and obesity in a GWAS of children (85). Other sleep variants implicated in key obesity-related metabolic pathways include *FADS1* and *FADS2*, which play a role in unsaturated fatty acid metabolism (23); *PNOC*, which is implicated in feeding behavior (44) and lipid metabolism (20); and the metabolic gene *GCKR* (128). However, most lead GWAS signals for sleep traits are not obesity related (see **Figure 3**).

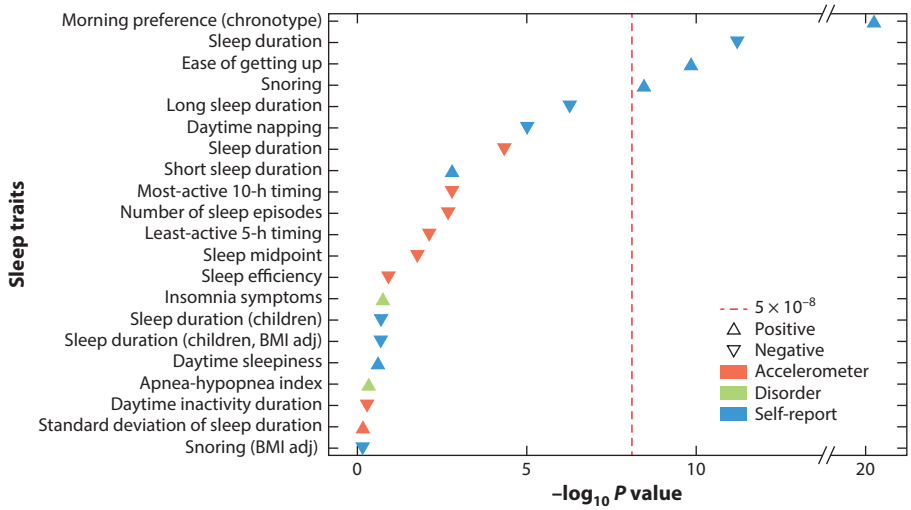

Figure 1

Obesity-associated *FTO* genetic variant associations with sleep traits from GWASs. Effect estimates for *FTO*-rs9939609 on sleep outcomes were retrieved from summary statistics published in the primary manuscript or from the Sleep Disorder Knowledge Portal (**https://sleep.hugeamp.org/**). Vertical dashed red line denotes genome-wide significance ($P = 5 \times 10^{-8}$). Abbreviations: adj, adjusted; BMI, body mass index; GWAS, genome-wide association study.

Lead GWAS Signals for Sleep and Obesity

Studies have investigated associations between polygenic scores composed of GWAS signals for sleep traits and adiposity outcomes, and vice versa, to determine overall pleiotropy in GWAS signals for sleep and obesity. In an analysis of 119,859 adults of European ancestry from the UK Biobank, an obesity polygenic score composed of 97 BMI variants was not associated with sleep duration, daytime napping, or diurnal preference (16). In agreement, other investigations found no associations between a polygenic score for obesity and diurnal preference (69) or associations between a polygenic score for diurnal preference and waist circumference (126) and BMI (49, 69). In another study including 112,586 adults from the UK Biobank, a polygenic score for obesity composed of 95 BMI single nucleotide polymorphisms (SNPs) was associated with higher daytime sleepiness but not with insomnia symptoms (68). In children, no associations were evident between a polygenic score for BMI composed of six leptin-related loci and other common SNPs in obesity genes, including *FTO*, *TMEM18*, and *NRXN3*, and sleep duration (34, 102). Null associations in most studies of healthy children and adults suggest that sleep and obesity GWAS variants are largely distinct.

On the contrary, studies of patient cohorts indicate that polygenic scores for sleep traits may be associated with clinically determined obesity. In a disease-enriched electronic health record clinical biobank, polygenic scores for sleep duration and daytime napping were associated with obesity. Specifically, a polygenic score for sleep duration was associated with 9.7% lower odds for obesity (24), and a polygenic score for daytime napping was associated with higher odds for obesity, whereby the top decile of the score was associated with 38% higher odds of obesity compared with the lowest decile (20).

Furthermore, sensitivity analyses of GWASs of sleep accounting for BMI suggest that sleep variants are largely independent of adiposity. With a few exceptions, including *FTO*, GWASs of

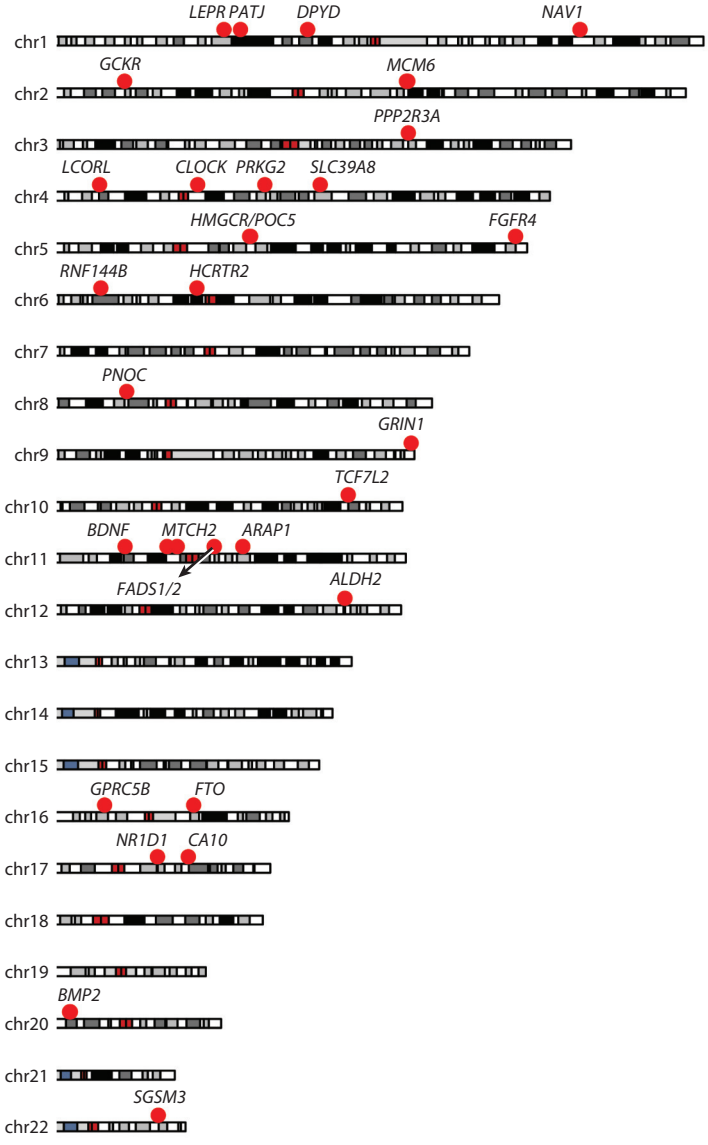

Figure 2

Genes from GWASs of sleep traits that are also implicated in BMI, highlighting genomic loci shared between sleep and obesity. Genomic loci were retrieved from published GWASs of sleep traits and sleep disorders (as listed in **Table 1**) and BMI (from the GIANT consortium meta-analysis of GWASs of BMI in ~700,000 individuals of European ancestry). Abbreviations: BMI, body mass index; GIANT, Genetic Investigation of Anthropometric Traits; GWAS, genome-wide association study.

self-reported variables, including sleep duration, diurnal preference, daytime napping, daytime sleepiness, snoring, insomnia, and accelerometer-based sleep measures, have found largely consistent effect estimates for sleep variants after adjusting for BMI (12, 20, 23, 49, 67, 82, 128) (see **Figure 4**). Statistical models further accounting for BMI × BMI or whole-body fat mass resulted in similar findings (12, 20). In addition, although obesity is a significant risk factor for snoring,

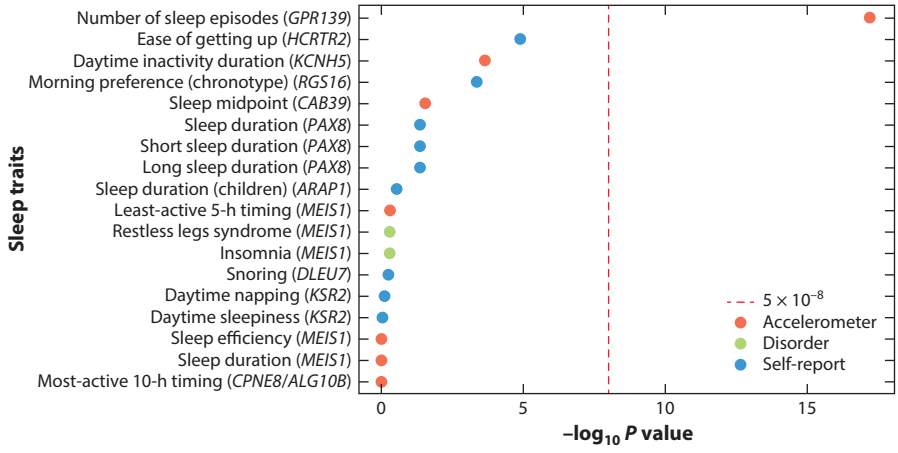

Figure 3

Association of lead sleep signals across several sleep traits with BMI, suggesting largely null associations between lead sleep signals and BMI. Lead sleep signals were determined from published GWASs of sleep traits and sleep disorders (as listed in **Table 1**). BMI effect estimates were retrieved from published summary statistics by the GIANT consortium in a meta-analysis of GWASs of BMI in ~700,000 individuals of European ancestry. Vertical dashed red line denotes genome-wide significance ($P = 5 \times 10^{-8}$). Abbreviations: BMI, body mass index; GIANT, Genetic Investigation of Anthropometric Traits; GWAS, genome-wide association study.

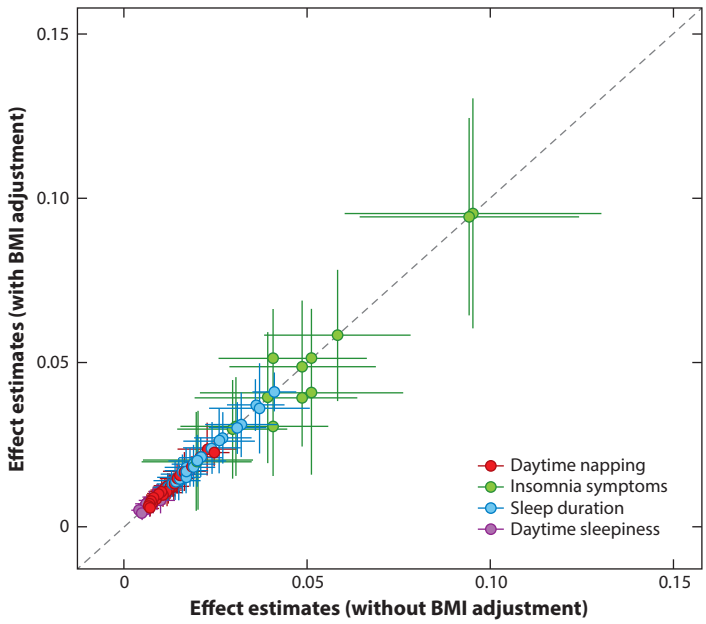

Figure 4

Genetic effect estimates of lead sleep signals associations with sleep traits without and with BMI adjustment, suggesting that most GWAS sleep signals are largely independent of BMI. Presented variants were identified in GWASs of four sleep traits (daytime napping, insomnia symptoms, sleep duration, and daytime sleepiness). Sleep traits were selected on the basis of published data and effect estimates were retrieved from published GWASs of sleep traits (as listed in **Table 1**). Abbreviations: BMI, body mass index; GWAS, genome-wide association study.

large genetic correlations ($r_g > 0.90$) were evident in GWAS models with and without BMI adjustments, supporting the notion that the genetic architecture of snoring is not explained by BMI (12). Accounting for BMI in GWASs may unravel additional obesity-independent sleep-related loci, as has been demonstrated for daytime sleepiness, for which five additional loci were identified only after accounting for BMI (128). Overall, findings from sensitivity analyses of GWASs of sleep suggest minimal influence of BMI on GWAS signals identified for sleep traits.

Sleep-Obesity Cross-Trait Genome-Wide Genetic Correlations

Genetic overlaps between traits can also be inferred from genome-wide genetic correlation analyses (140). Genetic correlations provide the advantage of systematically examining cross-trait relationships that may be underexamined or not well defined in epidemiological studies and within individual cohorts (58). Findings from genetic correlations are often similar to results from phenotypic correlations (114).

All sleep traits and sleep disorders, except for sleep timing variables (e.g., diurnal preference), show some evidence of genome-wide correlations with BMI (e.g., $P < 0.05$) (see **Figure 5**). The largest correlations with BMI were observed for snoring ($r_g = 0.35$) and daytime sleepiness ($r_g = 0.17$). Negative correlations were observed for accelerometer-derived sleep efficiency ($r_g = -0.16$) and accelerometer-derived sleep duration ($r_g = -0.09$). Notably, U-shaped positive correlations with BMI, as well as with waist circumference and waist-to-hip ratio (23), were observed for both short ($r_g = 0.12$) and long ($r_g = 0.08$) sleep durations. No correlations were observed between BMI and self-reported diurnal preference or accelerometer-derived measures of sleep timing, including sleep midpoint, M10 timing, and L5 timing (56). In addition, correlations between daytime napping and daytime sleepiness and BMI were no longer significant after adjusting for BMI in GWAS models (20, 128). Whereas sleep-BMI correlations in adults were largely modest, no correlations were evident in children (20, 67, 82, 85). In addition, earlier findings from smaller GWASs from the UK Biobank were consistent with findings from larger studies (57, 68), with the exception of previously detected positive correlations between morning preference and higher BMI (57, 69) that are no longer supported in larger analyses (56).

Genetic correlations of sleep with other adiposity traits, including body fat, waist-to-hip ratio, and obesity class, were consistent with correlations with BMI. Of all the sleep traits, snoring had the largest positive correlations with other adiposity traits, including class 2 obesity ($r_g = 0.38$), class 1 obesity ($r_g = 0.36$), and overweight ($r_g = 0.35$). Accelerometer-derived sleep efficiency had the largest negative correlations with other adiposity traits, including body fat ($r_g = -0.21$), class 3 obesity ($r_g = -0.20$), and class 1 obesity ($r_g = -0.18$).

Overall, the genetic correlations between sleep and adiposity traits suggest that common genetic vulnerabilities may influence both phenotypes. As polygenic scores do not implicate lead GWAS signals for both sleep and obesity, genetic correlations may instead be attributed to extensive pleiotropy in SNPs weakly associated with both traits (31). Consistent with these observations are earlier bivariate genetic analyses of twin pairs indicating little evidence of shared genetics between sleep duration and BMI (130). Therefore, the moderate genetic correlations detected between sleep and obesity may be mediated by shared environmental factors rather than by genetic effects (85).

Causal Links Between Sleep and Obesity Through Mendelian Randomization

Mendelian randomization (MR) analysis provides a robust and cost-efficient approach to demonstrate temporal relationships and causal pathways between sleep and obesity through genetics (26).

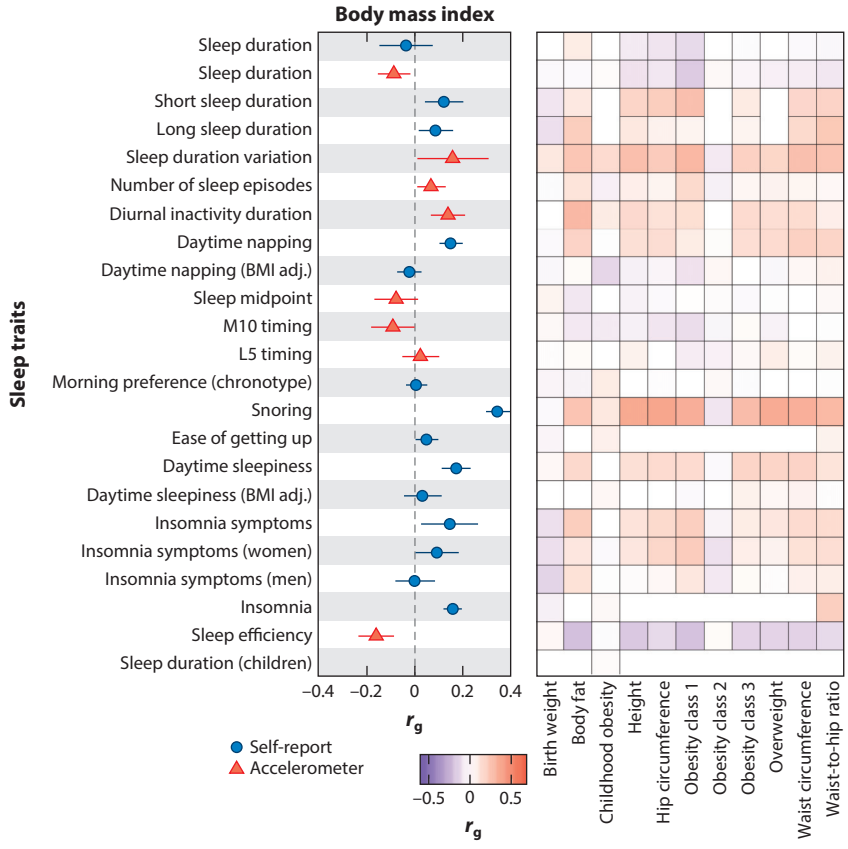

Figure 5

Cross-trait genetic correlations (r_g) between sleep traits and adiposity traits based on genome-wide genetic data. Most sleep traits (self-report and accelerometer) and sleep disorders, except for sleep timing variables (e.g., morning preference), show modest evidence of genome-wide correlations with BMI and other adiposity traits. Correlations with BMI are shown in the forest map; remaining correlations with other adiposity traits are shown in the heatmap. Red indicates positive genetic correlation and blue indicates negative genetic correlation in the heatmap. Genetic correlations are limited to data presented in published genome-wide association studies of sleep traits and sleep disorders (as listed in **Table 1**). Entries for which data are missing are left blank. Abbreviation: BMI, body mass index.

MR exploits the fact that genes are randomly assigned from parents to offspring, which are unlikely to be affected by confounding factors, and that genotypes are fixed at zygote formation and cannot be changed (26).

Overall, there is some evidence from MR of causal effects of sleep traits and sleep disorders on BMI and other adiposity outcomes (**Figure 6**; **Table 2**). There exists a causal link between genetic liability for insomnia and higher BMI and waist-to-hip ratio and between genetic liability for more frequent daytime napping and higher waist circumference (20). There is some evidence based on accelerometer data (30, 58), but not self-report (23), that longer sleep duration may cause higher BMI in adults. In children, MR results suggest potential effects of longer sleep duration on lower childhood BMI (129). For snoring, two-sample, generalized summary-data-based MR supports a potential bidirectional causal relationship with BMI, whereby genetic liability for snoring exerts a causal effect on increased BMI and genetic liability for higher BMI, as well as higher whole-body

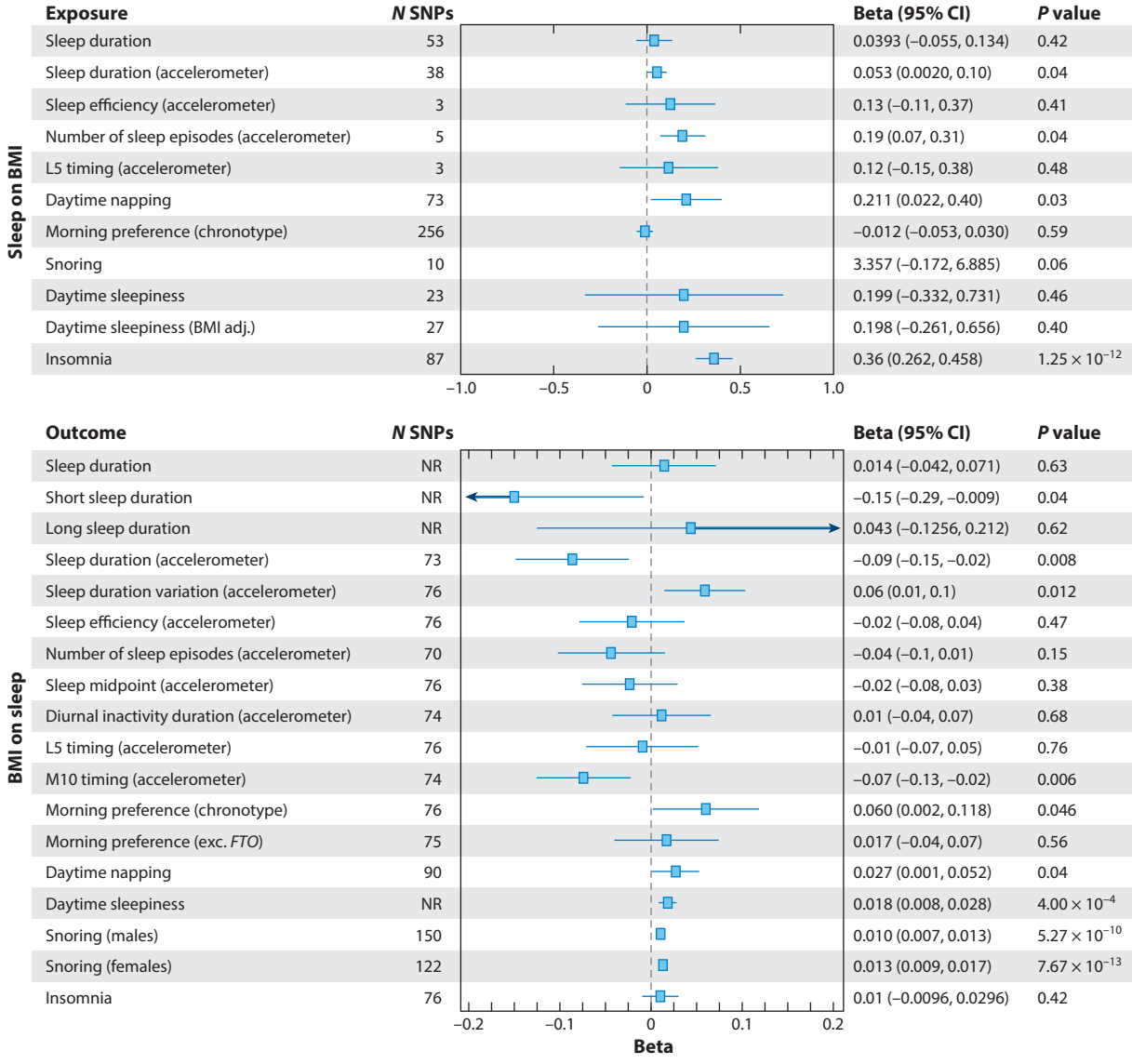

Figure 6

Bidirectional causal relationships between sleep traits and sleep disorders and BMI using Mendelian randomization. Mendelian randomization effect estimates are from inverse-variance-weighted models, estimates for insomnia and snoring are from generalized summary-statistics-based Mendelian randomization analysis, and estimates for accelerometer-derived sleep duration are from the maximum-likelihood method. Beta is the estimated directional effect of the exposure trait on the outcome trait per unit of exposure (if continuous) or log odds ratio for case/control traits. Positive beta indicates positive causal effects. *N* SNPs is the number of single nucleotide polymorphisms used as an instrumental variable. BMI effect estimates are derived from the meta-analysis by the GIANT consortium. Data presented are from published genome-wide association studies of sleep traits and sleep disorders (as listed in **Table 1**). Abbreviations: BMI, body mass index; CI, confidence interval; GIANT, Genetic Investigation of Anthropometric Traits; NR, not reported.

Table 2 Bidirectional causal relationship of sleep traits and sleep disorders with adiposity traits using Mendelian randomization[a]

Exposure	Outcome	*N* SNPs	Beta (95% CI)	*P* value	Reference
Sleep on adiposity					
Daytime napping	Waist circumference	73	0.282 (0.11, 0.453)	0.001	19
Daytime napping	Waist-to-hip ratio (adjusted for BMI)	75	0.185 (0.038, 0.331)	0.01	19
Insomnia	Waist-to-hip ratio	94	0.29 (0.1724, 0.4076)	1.58×10^{-7}	53
L5 timing, accelerometer	Body fat %	3	−0.24 (−0.59, 0.12)	0.32	58
L5 timing, accelerometer	Waist-to-hip ratio (adjusted for BMI)	3	−0.07 (−0.25, 0.11)	0.53	58
Number of sleep episodes, accelerometer	Body fat %	5	0.2 (−0.02, 0.42)	0.15	58
Number of sleep episodes, accelerometer	Waist-to-hip ratio (adjusted for BMI)	5	0.1 (−0.03, 0.24)	0.21	58
Sleep duration	Obesity (clinically determined)	NR	0.995 (0.987, 1.003)	0.242	24
Sleep duration, accelerometer	Body fat %	38	0.071 (−0.003, 0.145)	0.058	30
Sleep duration, accelerometer	Waist-to-hip ratio	38	−0.007 (−0.0776, 0.0636)	0.836	30
Sleep efficiency, accelerometer	Body fat %	3	0.1 (−0.26, 0.46)	0.64	58
Snoring (females)	Whole-body fat %	10	3.395841 (−2.637, 9.42)	0.27	12
Adiposity on sleep					
Waist circumference	Daytime napping	46	0.03 (−0.007, 0.067)	0.11	19
Waist-to-hip ratio	Insomnia	34	−0.03 (−0.0496, −0.0104)	7.16×10^{-3}	53
Waist-to-hip ratio (adjusted for BMI)	Daytime napping	46	0.03 (0.007, 0.052)	0.01	19
Waist-to-hip ratio (adjusted for BMI)	L5 timing	53	−0.02 (−0.07, 0.04)	0.55	58
Waist-to-hip ratio (adjusted for BMI)	M10 timing	53	−0.04 (−0.09, 0.01)	0.17	58
Waist-to-hip ratio (adjusted for BMI)	Sleep duration	53	−0.14 (-0.19, −0.08)	5.03×10^{-6}	58
Waist-to-hip ratio (adjusted for BMI)	Sleep duration variation	53	0.07 (0.02, 0.12)	0.01	58
Waist-to-hip ratio (adjusted for BMI)	Sleep midpoint	53	0.01 (−0.04, 0.06)	0.80	58
Waist-to-hip ratio (adjusted for BMI)	Sleep efficiency	50	−0.12 (−0.18, −0.06)	2.73×10^{-4}	58
Waist-to-hip ratio (adjusted for BMI)	Number of sleep episodes	52	0.02 (−0.04, 0.07)	0.60	58
Waist-to-hip ratio (adjusted for BMI)	Diurnal inactivity	53	−0.01 (−0.07, 0.06)	0.83	58
Whole-body fat (females)	Snoring (males)	140	0.0054 (0.0039, 0.007)	1.28×10^{-11}	12
Whole-body fat (males)	Snoring (females)	109	0.0054 (0.0035, 0.0074)	2.90×10^{-8}	12

[a]Mendelian randomization effect estimates are from inverse-variance-weighted models, estimates for insomnia and snoring are from generalized summary-statistics-based Mendelian randomization analysis, and estimates for accelerometer-derived sleep duration are from the maximum-likelihood method. Data included are from published genome-wide association studies of sleep (as listed in Table 1). Adiposity trait effect estimates are derived from the meta-analysis by the GIANT consortium. Beta is the estimated directional effect of the exposure trait on the outcome trait per unit of exposure (if continuous) or log odds ratio for case/control traits. Positive beta indicates positive causal effects. *N* SNPs is the number of SNPs used as an instrumental variable.

Abbreviations: BMI, body mass index; CI, confidence interval; GIANT, Genetic Investigation of Anthropometric Traits; GSMR, generalized summary Mendelian randomization; NR, not reported; SNP, single nucleotide polymorphism.

fat mass, exerts a causal effect on snoring (12). However, only the relationships between BMI and whole-body fat mass causing snoring retained significance after accounting for multiple testing. Last, there is no evidence from MR on causal effects of diurnal preference (56, 57, 69) and daytime sleepiness (128) on BMI.

Conversely, there is also some evidence from MR of potential causal effects of adiposity traits on sleep architecture. In addition to snoring (12), genetic liability for higher BMI was causally associated with increased daytime sleepiness (128), and genetic liability for higher waist-to-hip ratio (adjusted for BMI) was nominally associated with increased frequency of daytime napping (20). In addition, genetic liability for higher waist-to-hip ratio (adjusted for BMI) was causally associated with shorter sleep duration and lower sleep efficiency estimated from accelerometer data (58).

As findings from genetic correlations are often used to prioritize subsequent MR analyses, not all combinations of causal links between sleep traits and obesity have been tested so far. Findings from MR should be interpreted cautiously, as instruments for sleep traits often explain only <1% of variance in sleep phenotypes. Also, despite sensitivity analyses, there is always the possibility of various MR violations, including horizontal pleiotropy (26).

Sleep Disorders and Obesity

Except for insomnia, genetic evidence for the link between sleep disorders and obesity is limited because there are few large-scale genetic studies of sleep disorders. As described above, there is evidence of positive genetic correlations and causal effects of insomnia on adiposity. Family- and twin-based studies provide some insight into the genetic link between OSA and insomnia and obesity. Obesity is a well-recognized risk factor for OSA (59). For every 10 kg of weight gain, OSA incidence is estimated to increase sixfold (59). In support of this relationship are findings from linkage analyses of European Americans adults from the Cleveland Family Study implicating loci at 6q23-25 and 10q24-25 in both apnea–hypopnea index and BMI (70). The two loci identified for OSA-related traits in GWASs retained significance after BMI adjustment, suggesting that their influence on OSA risk is independent of obesity (10). Other genes are also expected to be shared between OSA and obesity. Indeed, all BMI-increasing alleles are partly considered potential risk factors for OSA (100). So far, no genetic evidence supports the link between RLS or narcolepsy and obesity.

GENE-SLEEP INTERACTION STUDIES OF OBESITY

The Role of Gene–Environment Interactions in Precision Medicine

Susceptibility to chronic diseases, including obesity, is often determined by the interplay between genetic and environmental risk factors (41). Emerging evidence from gene–environment interactions suggests that genetic predispositions to heritable chronic diseases are not entirely deterministic of disease onset and instead may be modified, either attenuated or accentuated, by environmental exposure (41). For example, adhering to a favorable lifestyle may attenuate genetic risk conferred by variants robustly associated with heart disease (61). Gene–environment interactions also contribute to varying biological responses to environmental exposures based on genetics (8).

Strong indication of the presence of gene–environment interactions for obesity comes from the observation that the magnitude of the association between genetic risk for obesity and obesity is stronger in more recent years, in the presence of a more obesogenic environment, than in earlier years (127). Considering metabolic alterations driven by sleep restriction (15), it is possible that unfavorable sleep may increase genetic influences on obesity, and conversely, it is also possible

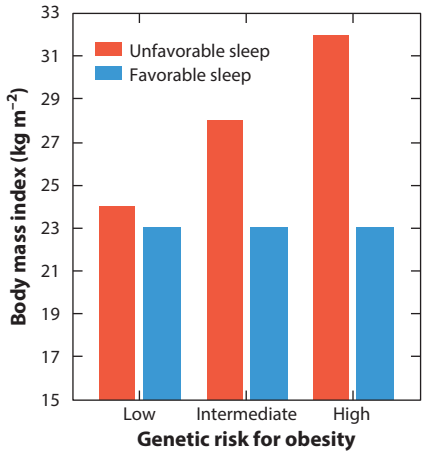

Figure 7

Simulated associations between genetic risk for obesity and BMI outcome in individuals with unfavorable sleep (*red bars*) and individuals with favorable sleep (*blue bars*) in the presence of gene–environment interactions (e.g., obesity genetics × sleep behavior). The interaction indicates that favorable sleep may suppress genetic influences of obesity on BMI, whereas unfavorable sleep may exacerbate genetic influences of obesity on BMI. Favorable sleep may encompass measures of sleep quantity, quality, and timing. Abbreviation: BMI, body mass index.

that favorable sleep may suppress genetic influences on obesity (see **Figure 7**). Disentangling the precise interplay between genetic risk for obesity and sleep parameters may then be leveraged to emphasize the critical role of sleep, particularly among the most genetically vulnerable (41).

Studies of Gene-Sleep Interaction in Adults

Initial investigations of gene-sleep interactions focused primarily on individual core clock genes and other circadian-related loci implicated in both sleep and obesity (119). For example, in a large meta-analysis by the CHARGE consortium, nominal evidence of gene-sleep interaction between *MTNR1B*-rs1387153 and sleep duration was observed for BMI (22). The interaction suggested that, only in the presence of the diabetes-associated T allele, short (<7 h) and long (≥9 h) sleep durations were associated with a higher BMI of 0.25 kg/m^2 and 0.60 kg/m^2, respectively, compared with normal sleep duration. In a study of obese adults, a significant interaction between *CLOCK*-rs1801260 and chronotype was identified for body weight, indicating that, among carriers of the C allele (an allele associated with less robust circadian rhythms), having an evening preference was associated with higher body weight compared with having a morning preference (107).

Gene–environment interaction studies have also considered interactions of sleep with polygenic scores for obesity. In an analysis of 119,859 adults of European ancestry from the UK Biobank, self-reported sleep traits, including short sleep duration (<7 h), long sleep duration (>9 h), daytime napping, and evening chronotype, accentuated the effect of the polygenic score for obesity [composed of 93 SNPs identified from GWASs of BMI (75)] on BMI and waist circumference (16). Specifically, among individuals in the highest quartile for the polygenic score for obesity, being a short sleeper was associated with a higher BMI of 0.6 kg/m^2 and being a long sleeper was associated with a higher BMI of 1.1 kg/m^2 compared with BMI values of those with normal sleep duration. In contrast, in the lowest genetic quartile, short and long sleep durations were associated with a higher BMI of only ~0.2 kg/m^2 compared with normal sleep duration.

Building on these investigations is a systematic, hypothesis-free gene–environment interaction study examining a polygenic score for obesity composed of 94 BMI-associated variants and 131 lifestyle factors, examined separately, in 362,496 adults of European ancestry from the UK Biobank (103). In total, 15 lifestyle traits interacted with the polygenic score for BMI. Of the examined sleep traits, only daytime napping, but not sleep duration, getting up in the morning, chronotype, or daytime dozing, was implicated. For daytime napping, stronger genetic effects of BMI were evident in the group that reported taking a nap during the day compared with the group that did not take a nap. Furthermore, among the 94 BMI-associated variants that were examined separately, *FLJ30838*-rs1016287 interacted with daytime napping. Reproducibility of these effects of gene-sleep interactions on BMI from the UK Biobank in independent cohorts and validation using objective assessments of sleep are necessary to confirm these findings.

Lifestyle factors, including sleep traits themselves, are highly correlated, and it is possible that interactions with one factor might not be specific to the tested trait but rather to a marker of an overall obesogenic lifestyle (123). In recognizing that environmental risk factors are highly correlated, Young et al. (139) used joint modeling to examine simultaneously the interactions between the obesity-associated *FTO* variant and lifestyle factors (e.g., sleep duration, alcohol consumption, smoking status). The observed interaction with sleep duration suggested a 0.13% greater effect of the obesity variant with each standard deviation from the mean sleep duration per *FTO* risk allele. No interaction was evident with sleep duration modeled continuously. The enhanced effect of *FTO* on BMI as a result of deviating from mean sleep duration is likely not confounded by other correlated lifestyle traits, such as smoking or TV watching, because of the joint modeling approach.

Gene–environment interaction studies examining sleep parameters besides duration, such as chronotype and insomnia, and cardiometabolic outcomes other than obesity, such as glucose levels, remain few and largely null (21, 25, 48, 96, 120).

Studies of Gene-Sleep Interaction in Children

The effects of gene-sleep interaction on obesity in children have been examined to devise strategies to target obesity in early life. In a cohort of Chinese children, a polygenic score composed of six leptin-related loci showed interaction with sleep duration, whereby the score was associated with a higher BMI of 0.72 kg/m^2 in participants reporting $\leq$7 h of sleep per night compared with other durations (34). Similarly, a polygenic score composed of common obesity variants in *FTO*, *TMEM18*, and *NRXN3* had a greater negative association with body weight among short sleepers (102). Specifically, in genetically susceptible children, a self-reported 2-h-shorter sleep per night was associated with a BMI higher than 1 standard deviation and an 8-cm-higher waist circumference. In another cohort of children in New Zealand, among 30 tested circadian-related genes, nominal interactions with actigraphic sleep duration were evident between *CLOCK*-rs4864548, *PEMT*-rs936108, and *GHRELIN*-rs696217 and BMI (65). In adolescents, no interactions between self-reported sleep duration and *FTO*-rs9939609 for obesity were observed (54).

Uncovering Missing Heritability of Obesity with Gene-Sleep Interaction Studies

Studying gene–environment interactions can also unravel missing heritability of obesity that is not currently explained by common variants from GWASs (80). The influence of sleep on BMI heritability is suggested in a classical study of twins in the United States. In a cohort of 1,088 adult twin pairs, the heritability of BMI was more than twice as large when sleep duration was <7 h (h^2 = 70%) compared with when sleep duration was $\geq$9 h (h^2 = 32%) (131). This observation

suggests that the proportion of variance in BMI explained by genetics may be modified by sleep duration and that accounting for sleep duration may reveal novel genetic contributors to BMI. Genome-wide interaction analysis accounting for the effect of sleep on obesity has not yet been conducted; however, a comparable study of blood lipid outcomes (93) suggests promising results. The genome-wide gene–sleep duration interaction study by the CHARGE consortium tested whether short and long sleep durations modify the effects of genetic loci associations on blood lipids (93). By systematically accounting for potential gene-sleep interactions, researchers identified 49 loci previously unreported in relation to lipid traits, including 3 BMI loci, *FHIT*, *MAGI2*, and *KLH3*, and 3 sleep-related loci, *MAGI2*, *TMEM132B*, and *EPHB1*.

Current Limitations of and Future Considerations for Gene-Sleep Interaction Studies

There are some important limitations regarding published gene-sleep interaction studies. Genetic interactions with sleep have focused primarily on obesity- and circadian-related genes, but interactions for other variants and at the epigenetic level may also exist (15). In addition, whereas polygenic scores for obesity explain large variance in BMI compared with individual genetic variants, aggregating variants into a score assumes that the interaction effect of the BMI-increasing alleles is consistently in the same direction, which may not be the case (103). Thus, it is prudent to also test variants separately in sensitivity analyses. Sleep duration remains the most commonly tested sleep parameter in gene-sleep interaction studies, but findings for duration must be cautiously interpreted, as they may be related to another correlated sleep trait or to a proxy of an overall obesogenic environment (123). In addition to inadequate sleep, an obesogenic environment is further characterized by poor nutrition, sedentary behavior, and smoking. Examining these behaviors in aggregate is possible with a composite environmental score, as has been previously conducted (61). Large biobanks, such as the UK Biobank, provide access to individual-level data, which enables multiple environmental exposures to be considered (139). The joint and standardized assessment of lifestyle and genetics in hundreds of thousands of participants from these biobanks also limits heterogeneity that may occur when aggregating data from smaller heterogeneous studies. Due to the cross-sectional nature of most gene–environment interaction studies, causality cannot be inferred and change in obesity in response to modified sleep behavior cannot be implied (76). Replicable evidence for gene–environment interactions, as has been shown for physical activity and sugar-sweetened beverages, remains missing for sleep (46). Thus, continued evaluation of population-based biobanks and other data sources, including electronic health records as well as randomized clinical trials, is necessary.

Nonetheless, the importance of studying gene–environment interactions is well recognized (46). Gene–environment interactions exist for obesity, and identifying them can potentially improve risk assessment for obesity and opportunities for personalized health interventions. There exists ample evidence from studies of children and adults that suggests the particular importance of achieving favorable sleep in individuals genetically predisposed to obesity. Whether targeting sleep alone in personalized medicine will yield a sizeable and clinically meaningful improvement in weight remains unknown. More importantly, sleep should instead be considered in assessments of obesogenic behaviors in gene–environment interactions. Moreover, because genetics have a lifelong cumulative effect, public health strategies that promote a healthy lifestyle, including favorable sleep, should be pursued irrespective of age and presence of comorbidity (17). Assessment of interactions in children and adolescents is also pertinent to determine whether inadequate sleep in early life may have a long-term adverse impact on genetically susceptible individuals (34). In addition, continued evaluation of gene–environment interactions may further define mechanistic pathways linking sleep to obesity (50).

FUTURE DIRECTIONS

A series of important methodological and conceptual considerations, some of which are also relevant for nongenetic sleep studies (36), should be taken into account to further our knowledge of the precise link between sleep and obesity through genetics.

Multidimensional Sleep Phenotyping

Despite the multidimensional nature of sleep, self-reported habitual sleep duration remains the most commonly surveyed and investigated sleep variable in genetic studies—in both GWASs and gene–environment interaction analyses. Sleep duration can easily be obtained through a single-question survey and is relatively easy to harmonize and standardize across large cohorts. Considering alternative assessments such as bed and wake times allows further investigation of important yet often unexamined sleep variables such as timing and weekly variability (19). As with most self-reported data, responses to questions about sleep are susceptible to reporting and recall biases and prone to imprecision due to rounding (e.g., 8 h instead of 8.2 h) (51, 52). Therefore, consideration of objective measures of sleep such as actigraphy or polysomnography is necessary to limit bias and capture multiple sleep dimensions, including quality.

Wearable technology, including research-grade accelerometers and actigraphy, continues to be a viable option for precise and long-term sleep phenotyping (58). As self-report measures only moderately correlate with objective sleep measures (132), objectively derived sleep measures may exhibit unique links to adiposity (23). Accelerometer data are available from only one-fifth of the UK Biobank likely due to increased participant burden. Accelerometer-derived sleep measures are also subject to various inaccuracies. For example, sleep duration may be overestimated in patients with insomnia with extended sedentary time in bed (19). Although polysomnography continues to be regarded as the gold standard for quantifying sleep, it remains impractical to conduct on a large scale, particularly for robust GWASs.

In addition, sleep phenotyping is often limited to a single assessment. Repeated measures are necessary to determine the duration of exposure and stability of sleep over time, especially in relation to obesity trajectory. Thus, future work using a composite, multidimensional sleep score via self-report or objective measures of sleep may reconcile discrepancies in findings regarding the link between sleep and obesity.

Unraveling Subtypes of Sleep Architecture and Heterogeneity in Sleep Disorders

Novel clustering analyses have indicated mechanistic subtypes and biological heterogeneity contributing to sleep phenotypes. For example, clustering of the 42 loci identified for daytime sleepiness revealed two subtypes for daytime sleepiness: one for sleep propensity and the other for sleep fragmentation (128). It is possible that these subtypes may have distinct clinical phenotypes and vary in their association with obesity. Indeed, for daytime napping, only two of the three identified genetic clusters (disrupted sleep and early sleep timing but not sleep propensity) were associated with higher adiposity (20). Heterogeneity is also detected in common diseases such as type 2 diabetes (124). Thus, examining genetic heterogeneity for sleep disorders such as OSA may indicate subtype-specific associations with obesity.

Acute versus Chronic Effects of Sleep on Obesity

The described genetic link between sleep and obesity from GWASs is largely related to chronic and long-term changes in sleep, such as long-term preference for daytime napping. These chronic

effects may not apply to acute changes in sleep. Indeed, human experimental studies have shown that short-term alterations in sleep, such as 5 nights of sleep restriction and deprivation, incur changes in appetite hormones and food consumption, which may subsequently alter weight regulation (63). Acute changes in sleep also contribute to changes in epigenetics and expression profiles of circadian clock genes (113) and other metabolic pathways (134) across multiple tissues (15). The genetics of metabolite signatures of sleep restriction—small molecules that fluctuate with acute changes in sleep patterns—may be leveraged to provide insight into how acute changes in sleep may affect adiposity in the short term (73).

Advancing Toward Precision Medicine

Precision medicine aims to prevent, treat, and manage diseases, including obesity, through targeted therapies by recognizing fundamental differences among individuals (3). The premise of precision medicine is that there is no one-size-fits-all for sleep needs and that sleep recommendations cannot be applied broadly to the entire population.

With the exception of a handful of recent studies (48, 92), most genetic studies of sleep have been conducted primarily on older adults of European ancestry. Large-scale genome-wide efforts in diverse populations are necessary to advance genetic discoveries and reduce health disparities (135). First, sleep architecture and sleep needs vary across populations, races, and ethnicities, and therefore genetic contribution may vary accordingly (19). For example, the average sleep duration in the Taiwan Biobank, a cohort of Chinese adults, of 6.6 h is almost 0.5 h longer than the average sleep duration in cohorts of European ancestry, such as in the UK Biobank (23, 48). Second, minority populations are disproportionately burdened by sleep disturbance and obesity, and thus a Eurocentric approach to genetics research may exacerbate health inequality (83). Last, effect sizes of sleep- and adiposity-related loci may be ancestry specific due to varying genetic frequencies and differences in linkage. Emphasizing diverse ancestries may contribute to key insights into heterogeneous, ancestry-specific sleep-obesity links.

Sleep patterns, needs, and recommendations change with age and health status; thus, the relationship between sleep and obesity may evolve over the life course. Whereas both *FTO* and a polygenic score for obesity derived from a GWAS of adults conferred higher risk for obesity in childhood (33, 60), most sleep variants from GWASs appear to be age specific. Indeed, data suggest distinct genetic architectures for sleep in children and adults, as evidenced by null correlations in the genetics of sleep duration between children and adults and by the smaller effect estimates of sleep duration variants from an adult GWAS in children and adolescents (23, 82). Most genetic findings for sleep are from analyses of participants from the UK Biobank, a population biased toward participants of higher socioeconomic status and with lower BMI. Alternative data sources, including electronic health record clinical biobanks, should be considered in order to further investigate the role of sleep in adiposity in patient populations (19). Reexamining the relationship between sleep and obesity across the life course may elucidate age- and health-specific variants (72).

Diversifying efforts in terms of ancestry and age, which is crucial to delineate personalized approaches to obesity prevention and treatment, may be possible with the *All of Us* Research Program (**https://allofus.nih.gov/about**) (3). The large and long-term initiative from the National Institutes of Health is a historic effort to collect and study data from one million or more people living in the United States. The program began enrollment in 2018 and is expected to last at least 10 years. Such a study design will allow a more definitive understanding of sleep loci across diverse populations.

The link between sleep and obesity may also be sex specific. Sex effects are likely because of marked sex differences in (*a*) sleep traits and sleep disorders, including snoring and OSA;

(*b*) adipocyte gene expression profiles and fat distribution driven partly by sex hormones; and (*c*) dimorphism in expression of clock genes (38). Some GWASs have systematically investigated the effects of biological sex on sleep and obesity genetics. In summary, 2 loci for both snoring (12) and daytime sleepiness (128), 1 locus for daytime napping (20), and 13 loci for insomnia (67) showed differential associations between men and women. Genetic correlations between men and women for insomnia symptoms ranged from 0.81 to 0.92, further supporting the hypothesis that associations between insomnia symptoms and adiposity differ between sexes. On the contrary, little evidence for sexual dimorphism in sleep duration and BMI was observed (75). Genetic correlation between men and women for sleep duration was 0.99 (30, 53, 67). Also, X-chromosomal analyses have not been systematically considered in GWASs. Continued evaluation of sex-specific genetic predictors of sleep is necessary to determine distinct genetic predictors of sleep for men and women (129).

Other considerations are necessary to advance toward precision medicine. Refining the genetic determinants of sleep and obesity through recent advances in genomics, including whole-genome sequencing, consideration of rare and structural variation, and functional analyses is imperative to clarify causal variants, particularly those from findings mapped to large genomic regions with many genes. Continued evaluation of the genetic interplay governing both sleep and metabolism can also unravel molecular targets that can effectively regulate both sleep and metabolism (4). Thus, the incorporation of multi-omics measures, including metabolomics, will be of great value to further establish the relationship between sleep and obesity.

CONCLUSIONS

Epidemiological studies suggest associations between sleep and obesity; however, they are often limited in scope and may be prone to various biases and confounding. Recent advancements in elucidating the genetic architecture of sleep traits and sleep disorders and obesity further our knowledge regarding their relationships. All sleep traits and sleep disorders are heritable, and their distinct genetic underpinnings have been unraveled in recent large-scale GWASs, primarily from studies of adults of European ancestry from the UK Biobank.

Despite the considerable involvement of the circadian clock in sleep and metabolism, few shared genes, including *FTO*, were implicated in GWASs of sleep and obesity. Furthermore, polygenic scores composed of signals from GWASs of sleep traits show null associations with obesity. Overall, signals for sleep are distinct and independent of BMI. The modest genome-wide genetic correlations between sleep and obesity may be attributed to extensive pleiotropy in SNPs weakly associated with both traits rather than to GWAS signals. Findings from MR suggest robust causal effects of insomnia on higher BMI and conversely of higher BMI on snoring and daytime sleepiness. In addition, bidirectional effects between sleep duration and daytime napping with obesity may also exist. Genetic evidence suggests that the association of sleep with obesity may be stronger in children and in adult clinical populations, and further studies are warranted. Thorough investigations of the genetic link between sleep disorders and obesity are limited by the number of identified loci and public availability of summary statistics for OSA, RLS, and narcolepsy. Gene-sleep interaction studies suggest that achieving favorable sleep, as part of a healthy lifestyle, may attenuate genetic predisposition to obesity. Whether favorable sleep will yield clinically meaningful improvements in BMI among those at high genetic risk for obesity remains to be elucidated in longitudinal studies. Furthermore, interaction analyses suggest that accounting for sleep in future BMI genetic analyses, and vice versa, may unravel novel loci and explain missing heritability. Genetic studies of sleep are disproportionately conducted on adults of European ancestry, and future studies must consider other ancestries, sex-specific analyses, and age groups across the life span. In

addition, future genetic studies should consider objectively derived multidimensional sleep phenotyping, incorporation of sleep quality measures, and genetic estimates of acute alterations in sleep.

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