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Determinants of Shortened, Disrupted, and Mistimed Sleep and Associated Metabolic Health Consequences in Healthy Humans

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Recent increases in the prevalence of obesity and type 2 diabetes mellitus (T2DM) in modern societies have been paralleled by reductions in the time their denizens spend asleep. Epidemiological studies have shown that disturbed sleep—comprising short, low-quality, and mistimed sleep—increases the risk of metabolic diseases, especially obesity and T2DM. Supporting a causal role of disturbed sleep, experimental animal and human studies have found that sleep loss can impair metabolic control and body weight regulation. Possible mechanisms for the observed changes comprise sleep loss–induced changes in appetite-signaling hormones (e.g., higher levels of the hunger-promoting hormone ghrelin) or hedonic brain responses, altered responses of peripheral tissues to metabolic signals, and changes in energy intake and expenditure. Even though the overall consensus is that sleep loss leads to metabolic perturbations promoting the development of obesity and T2DM, experimental evidence supporting the validity of this view has been inconsistent. This Perspective aims at discussing molecular to behavioral factors through which short, low-quality, and mistimed sleep may threaten metabolic public health. In this context, possible factors that may determine the extent to which poor sleep patterns increase the risk of metabolic pathologies within and across generations will be discussed (e.g., timing and genetics).

Today, more than 30% of the U.S. workforce report getting 6 h or less of sleep per night (1), and the corresponding percentage for the total adult U.S. population has increased among all age-groups during 1985–2004 from an average of 20–25% (2,3). These numbers are alarming as epidemiological studies have found that both reduced sleep quantity and quality increase the risk of weight gain and type 2 diabetes mellitus (T2DM) (4–6). This suggests that a regular good night's sleep (i.e., 7–8 hours per night, as recommended for adults by the U.S. Centers for Disease Control and Prevention) may help people to maintain metabolic health.

Experimental studies on the metabolic effects of experimental sleep loss in healthy humans have lent further support to associations provided by epidemiological studies. Yet, as highlighted in our Supplementary Table 1 and in recent reviews (e.g., 7), there are numerous discrepancies regarding the experimental findings often highlighted as potentially explanatory mechanisms for why poor sleep habits may increase the risk of developing metabolic pathologies, including T2DM and obesity.

In the 1990s, researchers demonstrated that prolonged wakefulness could impair insulin sensitivity in humans without diabetes (8,9). When subjects' nocturnal time in bed was shortened to 4 h for six consecutive nights their systemic glucose disposal rate declined by 40%, compared with the rate observed following six additional nights of 12-h recovery sleep (8). Later studies have indicated that just a single night of restricted sleep (4.5 h instead of 8.5 h) is able to impair glucose metabolism (10), although another study found no such effect after 4 days of gradually increasing sleep restriction (11).

Experimental studies have also investigated whether sleep loss affects parameters that could contribute to weight gain. In one study, healthy men were studied

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following both 10 and 4 h of sleep per night for two nights (12). Sleep restriction was found to increase hunger ratings, coupled with higher plasma levels of the hunger-promoting hormone ghrelin and lower serum levels of the satiety-promoting hormone leptin. Underlining the potential relevance of those findings, studies from other groups have demonstrated that recurrent short sleep increases both 24-h food intake and snack consumption (13–15). However, there are studies that have found no alterations (13,16) or even relative increases in leptin levels or decreases in ghrelin levels following experimental sleep restriction (17,18). Moreover, others have not observed increased food intake following recurrent partial sleep deprivation (16).

To examine why sleep restriction increases food intake in humans, brain responses to food images have been studied after total or partial sleep deprivation by using functional magnetic resonance imaging (19–21). In one study, one night of wakefulness increased activation of a brain region that is involved in reward anticipation in healthy young men (anterior cingulate cortex) (21). In contrast to this first study, another functional magnetic resonance imaging experiment, conducted in both men and women, found that total sleep deprivation decreased activation of this brain region while increasing the activation of the amygdala. Finally, recurrent sleep restriction (4 vs. 9 h/night in bed for 6 nights) was found to increase overall brain activation to food stimuli in men and women, comprising brain areas involved in hedonic control (e.g., prefrontal cortex) (19).

Several studies have also investigated how lost or mistimed sleep affects energy expenditure, with similarly discrepant results. In the first such study (13), no effect on 24-h total energy expenditure or its components was found after a 2-week sleep restriction (5.5- vs. 8.5-h sleep/night). Two later studies with restricted food intake also found no effect of sleep restriction on measures of energy expenditure (15,22). In contrast to these findings, Jung et al. (23) found total sleep deprivation to increase energy expenditure. Three studies have found sleep restriction to decrease energy expenditure under conditions of total sleep deprivation (one night of wakefulness) (24), in mistimed sleep (3-week desynchrony paradigm) (25), and in a crossover two-condition study comparing the effects of a 2-week targeted weight-loss intervention under conditions of normal (8.5 h/night) versus restricted sleep (5.5 h/night) (26).

Altogether, functional and behavioral studies on the effects of restricted sleep have provided evidence supporting a role for sleep in the regulation of normal appetitive behavior, specifically related to hedonic processing of food items. Under stressful conditions with overabundant and easily accessible high-energy supplies—a situation that is increasingly prevalent in today's 24-7 society—the role any such disruptions may have on the long-term weight trajectory could likely become clinically significant and promote obesity, overriding even small potentially counteracting changes in energy expenditure.

As summarily detailed and exemplified here, there are numerous inconsistencies with regard to how sleep loss affects metabolic parameters. In light of this, this Perspective aims at comprehensively discussing various factors that may determine the extent to which shortened, disturbed, or mistimed sleep impact metabolic health in healthy humans (e.g., genetics). It will also discuss important future research directions concerning the impact of sleep loss on metabolic integrity in humans.

FACTORS INFLUENCING METABOLIC OUTCOMES OF STUDIES OF SLEEP DISRUPTION

Timing

Several studies have found that subjects reporting short sleep or late sleeping habits—encompassing so-called evening types or late chronotypes (27,28)—have different meal patterns than subjects who sleep longer or go to bed earlier in the evening. Greater differences in sleep occurrence between weekdays and weekends have been associated with increased obesity risk (29). A recent study investigated self-reported sleep duration and its relation to the eating patterns of ~15,000 adult Americans (30). In comparison with average sleepers (habitual sleep duration between 7 and 8 h), short sleepers (i.e., those reporting $\leq$6 h of sleep per night) were found to consume breakfast earlier and have fewer main meals but instead consume a higher number of snacks after dinner and have a higher energy intake after 2000 h. Later sleep timing has also been associated with a higher BMI, with late sleepers (defined as having a sleep midpoint $\geq$0530 h) having shorter sleep duration and consuming more calories both at dinner and after 2000 h (31). This is also supported by a study that restricted the sleep of 44 healthy adults from a 10- or 12-h 2-day baseline period to 4 h per night for five nights. After three nights, this sleep restriction led to ~533 more calories being consumed during the additional waking hours (i.e., 2200–0359 h) (14). Among already obese individuals, a cohort study of 119 individuals reporting <6.5 h of sleep per night found that moving toward eveningness from morningness type (as assessed by the Horne and Östberg Morningness-Eveningness questionnaire) was associated with fewer eating occasions and higher BMI. Furthermore, eveningness types ate later, had higher levels of stress hormones, and had more sleep apnea (32), without any differences in sleep efficiency noted between morningness and eveningness types. Nighttime eating syndrome is also a recognized disorder that can include sleep disturbances and that some studies have linked to increased rates of obesity (33,34). Even in healthy individuals, nighttime eating without a diagnosis of nighttime eating syndrome has been reported to be associated with higher 24-h energy intake and significantly greater weight gain (35). After adjustment for follow-up time—averaging 3.4 years—the mean weight gain was 6.2 kg in the night eaters versus

1.7 kg in the non-night eaters. Similar follow-up studies based on energy input/output changes under conditions of sleep restriction would be of value to determine how sleep restriction–induced changes in these parameters relate to the risk of gaining body weight. Finally, a study has shown that testosterone and prolactin are differentially affected when sleep is restricted during the first or second night half, adding further support to the importance of sleep timing when assessing metabolic outcomes following experimental sleep restriction (36).

Experimental studies in animals also support meal timing as being important for body weight regulation. In comparison with normal 16:8 h lights-on/-off conditions, mice gained more weight via shifted meal intake patterns when light was also switched on at night, both when nighttime light was at a dim level (dim light at night [DLN] (~5 lux) or equal to the daytime light level (~150 lux) (37). The DLN-exposed mice consumed significantly more food during their normal sleep hours, as compared with the mice with the standard light-dark cycle. When food intake was prevented during this period of the day, this averted the gain in body weight in the DLN group, further suggesting that meal timing as well as abnormal light exposure can determine energy homeostasis. Another similar study with a shorter duration (2 vs. up to 8 weeks of observation) found similar results, also demonstrating that DLN altered the circadian rhythm of the core body temperature (38). These findings likely mimic the scenario of shift workers, who are often exposed to light during the biological night, alongside the opportunity to concomitantly consume food. Altogether, such aforementioned metabolic signals may conflict with circadian rhythms and may be factors that produce the observed greater susceptibility for shift workers to develop obesity and T2DM (39). At the other side of the spectrum, a study aiming for weight loss in 420 participants has indicated that the timing at which food intake occurs is linked to the success of weight loss: Late lunch eaters lost significantly less weight than early lunch eaters (the cut-off time being lunch after or before 1500 h) during the 20-week intervention (40). As meal timing is also an important factor in many obesity and T2DM treatment paradigms, this underlines the complex relationship that meal timing has in and outside the laboratory environment.

Age

With age, metabolism and resting metabolic rate decline (41). Coincidentally, sleep architecture also changes. A meta-analysis found that both slow-wave and rapid eye movement sleep—as percentages of sleep—decline continuously with age, in addition to total sleep time and time awake after sleep onset (42). Age-dependent differences in slow-wave sleep could constitute a determining factor for how various sleep restriction interventions impact metabolic outcomes. Supporting this view, glucose metabolism has been found to be negatively affected when slow-wave sleep is selectively disrupted without altering total sleep duration (43,44). This emphasizes how age-dependent sleep architecture may regulate effects on glucose metabolism—but also possibly hunger (45)—when sleep is restricted.

Sex

Under conditions of sleep restriction, some metabolic responses to sleep loss have also been found to be sex dependent, with recent findings highlighting the important role that the menstrual cycle can have, such as cortisol changes in response to sleep restriction (46). Moreover, it has been demonstrated that sleep restriction from a baseline of 10 or 12 h to 4 h/night led to a greater increase in food intake in men than in women (14). With largely unrestricted food access, food intake rose by almost 22% during sleep restriction compared with baseline values, with men showing a significantly greater increase than women (28.5 vs. 16.9%). Supporting a metabolic outcome of such sex differences, in the largest sleep restriction study to date (4-h vs. 10-h nightly sleep periods for five consecutive nights, n = 225), men were found to gain more weight than women under experimental sleep restriction (47). Hormonal responses have also been found to differ under conditions of sleep loss, such as findings of greater leptin increases following sleep restriction in women than in men (48). Another study found that sleep restriction (4- vs. 9-h time in bed) led to increased morning levels of ghrelin only in men, whereas an afternoon decrease in GLP-1 was seen only in women (49).

Ethnicity

Previous studies have shown that both metabolic and behavioral differences exist in response to sleep loss between people of different ethnicities, in addition to differences in habitual sleep. For instance, it has been demonstrated that African Americans gained more body weight than Caucasians when participants' sleep was restricted from 10 or 12 h per night during a 2-day baseline period to 4 h/night for five nights (47). In a National Health Interview Survey of 29,818 Americans aged 18–85, African Americans reporting shorter (≤5 h) or longer (≥9 h) sleep than average (6–8 h) were found to be more likely than their white counterparts to have T2DM, effects that were independent of between-group differences in sociodemographic factors (50). However, in a separate larger study also finding an increased risk of T2DM in blacks versus whites with habitual short sleep duration, these effects were instead attenuated when adjusting for socioeconomic factors (6). This highlights both a metabolic and disease-outcome vulnerability of African Americans with respect to sleep loss that warrants further investigations to determine whether ethnicity-based differences primarily depend on lifestyle, genetics, or both.

Genetics and Transgenerational Effects

Previous research has indicated that those harboring a mutation in the gene *BHLHE41*, also known as *DEC2*, had shorter sleep duration, with a total sleep time of 6.25 h in carriers versus 8.06 h in noncarriers (51). A recent study of 100 twin pairs found that *Y362H*, a novel variant of *BHLHE41* that occurs in the same previously described exon 5, also affected sleep and consequences of sleep deprivation. The variant was associated with reduced sleep duration (299 vs. 365 min), fewer performance lapses throughout 38 h of sleep deprivation, and shorter recovery sleep following this sleep restriction (482 vs. 573 min) (52). Genetic association studies have also linked variations in clock genes (e.g., *CLOCK* and *PER2*) to measures of glucose metabolism (53) and susceptibility to obesity and T2DM (54,55). Importantly, in the study by Garaulet et al. (54), the protective effects of investigated *CLOCK* gene variants on insulin sensitivity were found to be modulated by dietary intake of different types of fatty acids. Given that variants of clock genes can influence sleep parameters, metabolic functions, and sleep-related phenotypes, it would be of interest to investigate whether clock genes are able to modulate how sleep restriction affects both short- and long-term metabolic outcomes and to what extent lifestyle can impact on any such associations, as has been observed for genetic variants linked to T2DM (56).

Studies of how the transcriptome is affected by sleep restriction, with or without concurrent circadian misalignment, have provided further evidence that sleep loss also affects metabolism at the transcriptional level (57). At the peripheral level, even though the adipose tissue is important for metabolic and glucose regulation, only one study has been conducted on the molecular effects that short-term sleep restriction has on such insulin-dependent tissues (58). Interestingly, the metabolic disturbances imposed by sleep restriction may arise through alterations in pancreatic insulin secretion (25,44,59) or via effects on peripheral tissues. For instance, a study published in 2012 found that when sleep was restricted to 4.5 h per night for four days in a row—compared with the control condition of an 8.5-h sleep opportunity per night—there was a 30% reduction in the ability of adipocytes from subcutaneous adipose tissue to be stimulated by insulin (58). How such metabolic perturbations are reflected at the transcriptional level is currently unknown. Equally unknown currently is whether such perturbations occur following less extensive sleep deprivation and how circadian misalignment can influence the response of the adipose tissue or that of other metabolically active tissues, such as skeletal muscle (60).

Recent evidence suggests that metabolic traits induced by lifestyle interventions (e.g., glucose intolerance following diet-induced obesity) can be transferred from parents to the offspring (61), most likely by epigenetic mechanisms (62). Complementing those results, a recent animal study has demonstrated that fragmentation of maternal sleep during gestation led to long-lasting metabolic consequences in the next generation, comprising increased food intake, body weight, visceral white adipose tissue, and insulin resistance (63). Those effects were accompanied by metabolically unfavorable molecular conditions, such as increased DNA promoter methylation of the insulin-sensitizing adipokine adiponectin, which concomitantly reduced adiponectin mRNA expression (63). An important next step for this unfolding research field is to answer some basic questions. Does the timing of sleep fragmentation matter? Would it be enough to sleep poorly only prior to or during pregnancy or are both required to produce the observed metabolic perturbations in the offspring? Do other poor sleep patterns during gestation, such as short sleep duration and mistimed sleep, cause similar metabolic perturbations in the offspring? Does the magnitude by which sleep fragmentation impairs glucose tolerance in mothers during gestation determine the extent to which their offspring's glucose metabolism is affected? To what extent do lifestyle interventions during gestation supporting metabolic integrity of the offspring, such as exercise (62), attenuate the impact of maternal sleep fragmentation on the offspring's metabolic health? Additionally, a recent study in mice has shown that the female offspring of obese male rats develop metabolic dysfunction, such as an impaired postprandial glucose tolerance (61). With this in mind, do strictly paternal or maternal sleep habits, or both, lead to long-lasting metabolic consequences in the next generation? Finally, as methylation has been shown to be acutely affected by physiological interventions, such as exercise (60), to what extent can even short-term changes in lifestyle habits, via changes in DNA methylation, chromatin modifications, or circulating miRNAs, counteract or exacerbate the effects of poor sleep habits, and how long-lasting can such effects be? While there are many open questions regarding longitudinal efficacy and the mechanisms underlying the effects of poor sleep habits on future metabolic health in an individual and the offspring, interventions improving sleep may help prevent metabolic dysregulation later in life or even in future generations.

Health Status

Sleep is detrimentally affected by many comorbidities (e.g., T2DM [64]), and in a vicious circle, sleep disturbances can also increase the risk of these comorbidities, such as obesity and T2DM (7,39). Most studies to date have only ascertained metabolic outcomes on sleep restriction in healthy subjects, exclusively so for energy expenditure in relation to sleep disruptions. As sleep restriction has been linked to an increased risk of many metabolic diseases, including those of positive energy balance, an important question is whether individuals with such comorbidities or related metabolic diseases have different metabolic responses when subjected to sleep disruption—allowing for an important characterization of how improved sleep may benefit these patient categories and

vice versa. This would be of relevance for obese subjects, as sleep has been implicated in weight-loss outcome (26). Another important question is whether individuals who display greater metabolic adverse effects following short-term sleep restriction also are at a higher risk of suffering from long-term health outcomes under conditions of chronic sleep loss. Evidence supporting such a role exists for patients with T2DM, with an association between HbA_{1c} levels and sleep debt (65). Interestingly for T2DM, there is also evidence for decreased slow-wave sleep (64), which is known to be associated with glucose metabolism (44). While some studies on patients at risk for T2DM exist (66), direct sleep intervention studies on such patient categories are lacking. Contributing to this dearth of sleep studies in such patient categories is perhaps the aforementioned fact that such studies can be confounded by the sleep impairment attributable to the pathologies themselves (e.g., in obstructive sleep apnea syndrome). This highlights both the complexity and the importance of sleep in states of health and disease.

Sleep Architecture

In studies where comparisons have been made between different periods of baseline sleep (for most studies ranging from 8–10-h time in bed/night) with ensuing partial sleep deprivation, the length of the sleep opportunity in each studied condition may impact the metabolic response to sleep loss, as sleep length affects the percentage of different sleep stages in relation to total time asleep. During sleep restriction nights, studies indicate there is a higher proportion of time spent in primarily slow-wave sleep (8,22,45,58)—reflecting the homeostatic sleep drive. Different sleep stages have been associated with differences in brain and whole-body metabolic rates (45,67). As slow-wave sleep and rapid eye movement sleep have been associated with glucose metabolism (44) and hunger (45), respectively, experimentally induced differences in sleep architecture may determine the extent to which experimental sleep restriction causes metabolic perturbations in humans.

The validity and interpretation of findings from sleep studies are highly dependent on the utilized method of sleep measurement, with some methods (e.g., activity monitors, self-reported sleep) providing especially less qualitative information than that obtained from polysomnography recordings, which are required to establish relations to specific sleep stages and sleep intensities (43,45).

Experimental and Environmental Conditions

Several environmental factors are also able to influence the impact of poor sleep patterns on metabolic parameters. These include light at night (37,68), study-associated stress or interindividual differences in basal stress levels or stress tolerability (e.g., via effects on cortisol and sympathetic activity) (18,69), lifestyle factors of the participants, sedentary versus mobile state (9), and ambient temperature (70). As an example, environmental temperature can affect energy expenditure under both sedentary and active conditions (71). Variability in such environmental parameters, indirectly or directly affecting physiological parameters, may thus yield results that are true of the studied environmental setting, without necessarily reflecting real-world changes or isolating the effect of sleep restriction.

As results have varied with regard to investigated possible mediating molecular factors and outcomes, it must be kept in mind that selection or publication bias—where negative results are disregarded—may have occurred. There are also other appetite-regulatory factors, such as the endocannabinoids (72,73), that may play a contributing role to hunger-promoting effects of sleep restriction. Depending on timing, hormonal changes may not be evident in a given experimental setting or may at time of measurement involve a different set of functionally overlapping factors (e.g., CCK-1 and leptin).

FINAL CONCLUSIONS

A summarizing overview of mechanisms by which sleep loss may lead to weight gain and T2DM is illustrated in Fig. 1. The studies conducted so far on how sleep loss affects energy metabolism argue for impaired insulin sensitivity and increased food intake following sleep restriction, with more inconclusive results regarding how sleep loss affects circulating appetite signals and energy expenditure. The mechanisms by which sleep loss affects metabolism not only have yielded conflicting results but also have not been studied under all commonly utilized sleep-loss paradigms (i.e., partial/total sleep deprivation, disrupted or mistimed sleep). For example, studies linking shift work with increased obesity risk (73) and extended wakefulness to increased concurrent snack intake (13) point to altered hedonic processing during nocturnal wakefulness. In spite of this, it is currently not known how hedonic food processing is affected during the normal night or when sleep is mistimed as in shift work. Likewise, at the peripheral level, even though the adipose tissue is important for metabolic and glucose regulation, only one study has been conducted on the molecular effects that short-term sleep restriction has on such insulin-dependent tissues (58).

Importantly, as discussed in our Perspective, a range of factors may affect the directionality or degree of metabolic effects that sleep restriction induces, such as timing of the intervention, extent of sleep restriction in comparison with baseline or control conditions, sex, and genetics. Overall, diverging results suggest that shorter coupled with longer sleep interventions will likely be required to fully determine the role that sleep has for overall regulation of metabolic homeostasis. Similarly, future studies will likely begin to further unfold how sleep extension might benefit metabolic health and counteract conditions such as obesity and T2DM. For instance, optimal sleep length has indirectly already been proven to aid in successful short-term weight loss (26). A recent study also demonstrated that sleep extension can improve measures of insulin sensitivity in habitual short sleepers (75).

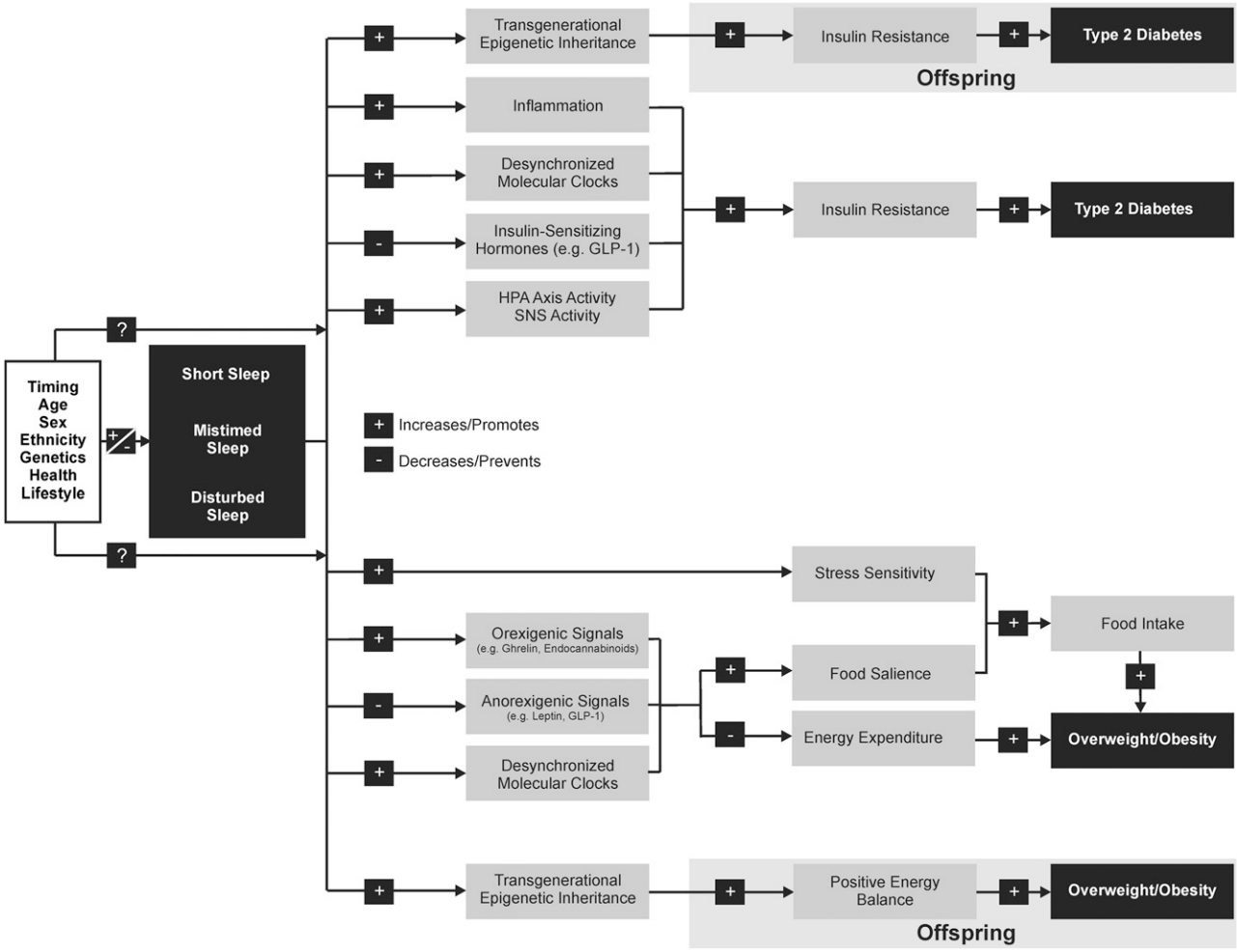

Figure 1—Proposed mechanisms through which habitual poor sleep patterns may increase the risk of weight gain and T2DM both within and across generations. The figure provides an overview of potential mechanisms through which sleep disruption—if chronic—may increase the risk of T2DM and obesity. GLP-1, glucagon-like peptide 1; HPA, hypothalamic–pituitary–adrenal; SNS, sympathetic nervous system.

Taken together, accumulating evidence clearly defines a regular good night's sleep as a crucial factor for normal metabolic functioning, with sleep loss producing perturbations through effects that span from the brain to peripheral metabolic organs. Thus, sleep represents a promising therapeutic target for the prevention and treatment of metabolic pathologies, including obesity and T2DM.

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