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Sleep Variability and Regularity as Contributors to Obesity and Cardiometabolic Health in Adolescence

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Abstract

Content: Adolescence is a developmental stage of critical changes in sleep and its circadian timing when the contribution of abnormal sleep variability (amount) and sleep regularity (timing) to obesity and its associated adverse cardiometabolic health outcomes appears to increase.

Purpose of review: To summarize findings from studies conducted in adolescents examining both sleep variability and regularity in relation to obesity and cardiometabolic health. We highlight gaps in research and potential causal pathways that future studies should examine.

Findings: Nightly deviations in sleep duration and sleep midpoint appear to contribute to the development of obesity and associated adverse cardiometabolic outcomes in youth. Studies show that increased sleep variability and irregularity are associated with obesity, decreased physical activity, dysregulated eating and inadequate diet, metabolic dysfunction, impaired cardiac autonomic balance and elevated blood pressure in adolescents.

Summary: A stable circadian timing of sleep is essential to the overall physical well-being of youth. Emerging evidence supports that sleep variability and circadian misalignment, including sleep irregularity, contributes to adverse obesity-related health outcomes early on in adolescence. Future studies should focus on the underlying behavioral and biological mechanisms in the causal pathway between day-to-day deviations in the amount and timing of sleep and obesity.

Keywords

Adolescents; Cardiovascular Risk; Obesity; Sleep Disorders

INTRODUCTION

1. Adolescence: A Critical Developmental Stage

1.1. Structural and Functional Changes—Adolescence is a developmental period between childhood and adulthood, from ages 10 to 19, that involves rapid physical, cognitive and psychosocial growth,[1] and is typically demarcated biologically by the onset

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Disclosure

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of puberty. However, both adolescence and puberty are not synonymous, as puberty refers to the attainment of sexual maturation and the timing of puberty may vary greatly among individuals.[1] Hormonal fluctuations associated with puberty contribute to body changes such as increases in weight, height, and development of secondary sex characteristics to name a few.[2] Additionally, this period is characterized by rapid changes in the central nervous system. There is a significant decrease in gray matter between ages 10 and 18,[3] which is driven by synaptic pruning; a natural process that consists of the elimination of overproduced synapses to maximize neuronal efficiency.[4] Conversely, there is an increase in white matter, thanks to an increase in axonal myelination, particularly in the frontal lobe and hippocampus.[5] This gain in myelination strengthens the remaining neural connections, memory and language skills in youth,[6] while the prefrontal cortex will continue to mature into young adulthood.[7] Psychosocial development occurs during adolescence as teenagers strive for more independence while developing a sense of self and social identity.[8] The transition from middle school to high school requires psychological, academic, and social adjustments to be made, such as earlier school start times yet increased after-school activities and social gatherings. Adolescence is, thus, a time of critical neurodevelopment, and the gradual anatomical and physiological changes reflect themselves through behavior, emotion, and cognition[7] as well as sleep.[9] In fact, the increasing events to partake in, whether academic or social, may have a timing that is out of synchrony with the also maturing biological clock, resulting in a potential dysregulation of adolescents' sleep-wake cycle.

1.2. Circadian and Sleep Changes—The central biological pacemaker controls sleeping and waking times as it aligns organisms to the dark-light cycle in 24-hour rhythms known as circadian rhythms.[10] This master clock that establishes endogenous circadian rhythms is entrained by environmental contexts, such as daylight cues, as well as synchronization between the central and peripheral clocks of the body.[11] If they are functioning in harmony, the circadian timing of sleep is aligned to the biological night; however, there are several factors that can cause it to become misaligned (i.e., circadian misalignment).

In the transition from childhood to adolescence, there are naturally occurring changes in sleep that involve modifications to timing, amount, continuity and depth. A substantial number of studies have consistently found that there is a natural sleep phase delay as adolescents' transition from middle school into their high school years.[12–15] During childhood, there is greater consistency in sleep schedules during school days and weekends, resulting in a stable circadian timing of sleep.[9,13] However, there is a natural shift in the circadian biological clock during adolescence, as a youth's sleep-wake cycle, and other circadian-regulated biological processes, become more delayed with the onset of puberty.[9] As adolescents age, they favor an evening-chronotype, which is a phenotype characterized by preference for and feeling your peak-best for activities performed in the evening and later in the day. The more evening-type an adolescent is, the higher their Tanner stage(a measure of pubertal development) is.[16] Therefore, biological processes underlie the adolescent circadian phase preference towards later sleep onset and wake-up times as compared to their childhood years.

Because the transition into adolescence is also marked by changes in social and academic responsibilities, the timing of the sleep period during school days is based on both the school schedule and any social or work tasks, like extracurricular activities or holding part-time jobs.[17] Adolescents working and engaging in afterschool activities during the school week are going to bed and falling asleep later but wake up at the same time as their peers, resulting in insufficient sleep,[14,18,19] which they attempt to make-up for by sleeping-in during the weekends, leading to high variability in sleep duration.[14,20] It is important to factor-in that high schools, particularly in the US, have an early start time similar to middle-school or even earlier,[18,21] which further contributes to a potential mismatch between the maturational changes in sleep timing brought forth by puberty and the social/academic responsibilities of these adolescents, causing them to experience different forms of circadian misalignment, such as a delayed sleep phase, social jetlag, or sleep irregularity.[9,20]

Delayed sleep phase refers to a main of period of sleep that occurs at a later time than culturally or socially expected for age and social/academic responsibilities;[21] typically, a sleep period, measured by the sleep midpoint (see subsection 2.2 below), occurring later than 2:00 or 3:00 AM is considered delayed for a typical adolescent.[22] Social jetlag refers to the discrepancy in sleep midpoint between school/weekdays and free days/weekends;[20] typically, a difference of 2 hours or more (e.g., a midpoint at 1:00 AM on weekdays and of 3:30 AM on weekends) is considered indicative of social jetlag for a typical adolescent in the US.[23,24] Sleep irregularity refers to high day-to-day variability in sleep timing, such as measured by the sleep midpoint or other indices of rest-activity circadian patterns;[25,26] typically, 1 hour of irregularity in the timing of the sleep midpoint is considered abnormal for a typical adolescent.[27] All these forms of circadian misalignment may have a direct impact on adolescent's health and, in addition, may lead to insufficient sleep, which will further impact their ability to perform during the day.[28] Research has also shown that the impact of a misaligned circadian timing of sleep and of insufficient sleep extends beyond academic outcomes, having been linked to mood disorders,[29] substance abuse,[30] behavioral problems,[31] and adverse cardiometabolic health outcomes, as reviewed below.[32,33] In fact, evidence for the cardiometabolic health impact of various forms of circadian misalignment in adults has come from both naturally-occurring models (e.g., shiftwork)[34] as well as experimental studies.[34]

Readers will find in this review focused on adolescence, as a stage of critical sleep and circadian changes, a summary on the contribution of high sleep variability and sleep irregularity to obesity and its associated cardiovascular and metabolic morbidity. Our aim is to examine how day-to-day deviations in the duration and circadian timing of sleep are novel risk factors for adverse cardiometabolic health outcomes. Our evidence encompasses 26 rigorous cross-sectional studies and longitudinal studies, all conducted before August 2022 on adolescents, that support how detrimental adolescent dysregulation of the sleep-wake cycle can be on cardiometabolic health. Our review aims to shed light on the lack of studies examining sleep variability and irregularity both during the developmental period of adolescence and longitudinally across the lifespan, highlighting the need to examine circadian misalignment as a contributor to poor cardiometabolic health, beyond insufficient sleep (i.e., average sleep duration). These findings have important clinical implications as

they can inform preventive strategies in order to improve public health outcomes early in the life cycle.

2. Beyond Average Changes

This review is focused on two complex sleep- and circadian-related constructs that pertain to an individual's day-to-day deviations in the duration and timing of sleep and for which standardized language has not yet been agreed upon. To address the lack of standardized language, we provide in Table 1 the parameters and definitions of each sleep construct used in this review. Specifically, we use the term "sleep variability" to refer to day-to-day deviations in the amount of sleep (duration), while we use the term "sleep regularity" to refer to day-to-day deviations in the timing of sleep (circadian). In addition, we visually depict in Figure 1 how high sleep variability and sleep irregularity are sleep health metrics that go beyond normative average values (e.g., 7 hours of sleep with a sleep midpoint at 2:00 AM) and can present in isolation or combined. These graphic depictions aim to further clarify the use of each of these two constructs, as defined in detail below.

2.1. Sleep Variability—Substantial research has focused on understanding the impact of insufficient sleep across the lifespan,[35] as it is associated with adverse mental and physical health outcomes.[36,37] However, as shown in Table 2, studies have also shown that the day-to-day variability in total sleep time across nights for a given adolescent, known as sleep variability, is highly common and may have health implications, potentially greater than average amount of insufficient sleep alone.[38] Sleep variability is commonly defined as the intraindividual standard deviation of total sleep time (i.e., sleep duration) across a period of measurement (Table 1).[39] Actigraphy, standardized questionnaires, and sleep diaries may be used to calculate sleep variability over a period of time (i.e., 7 or 14 nights), yet actigraphy remains the objective method of choice.[40] Actigraphy, coupled with sleep diaries, minimizes retrospective reporting errors and allows for a more accurate estimation of variability in sleep duration[41] than single-time surveys.[42] Typically developing adolescents show an intra-individual sleep variability of about 90 minutes,[41] a degree of variability that decreases with age reaching just under 25 minutes in adults.[43] In adults, greater sleep variability has been associated with a wide diversity of adverse health outcomes.[44,45] Similar adverse findings have been found in adolescents, and may in fact be more pertinent as sleep variability peaks during this developmental period.[13] Studies have found that adolescence who had greater sleep variability have greater adverse behavioral,[42] brain,[41] energy balance,[46,47] metabolic,[48] and cardiovascular health outcomes,[49] for which the latter two a thorough review is provided below. It is important to note that there may be sex disparities in regards to sleep variability, as some studies have found that females have greater sleep variability than males both as adults[45] and as adolescents.[42] This review will focus below on the association of sleep variability, independent of average sleep duration, with obesity and adverse cardiometabolic health in adolescents.

2.2. Sleep Regularity—Not only has sleep variability been associated with adverse health outcomes, but deviations in the timing of the sleep-wake cycle have emerged as novel risk factors as well. As mentioned above, the circadian timing of sleep is optimal when there is a consistency in sleep onset times and wake up times throughout the

week as well as between weekdays and weekends, as it keeps the organism entrained to the biological night. A common measure of circadian timing of sleep via actigraphy is the sleep midpoint,[26] which is defined as the middle clock-time (midpoint) between sleep onset and offset,[50] where sleep midpoint = sleep onset time + (sleep onset time – wakeup time)/2 (Table 1);[51] for example, if an individual's ad-libitum sleep onset occurs at 22:00 and spontaneous wake-up time at 6:00, the sleep midpoint would fall at 2:00. Alternatively, in scenarios where rising time (out-of-bed) data, but not wakeup time (final awakening) data, is available, the formula sleep midpoint = sleep onset time + (total sleep time)/2, may be used (Table 1).[52] As with sleep duration, the sleep midpoint also shows nightly deviations and, this irregularity in the circadian timing of sleep appears to peak in adolescence.[26,53] There are several different metrics used to quantify sleep regularity (Table 1), which include the intraindividual standard deviation (StDev) in sleep midpoint as calculated through actigraphy and/or sleep logs, inter-daily stability, which is more reflective of rest-activity rhythms as compared to sleep-wake patterns,[26] social jetlag to measure average sleep patterns between weekdays and weekends, composite phase deviation, the sleep regularity index, and sleep onset time as well as wakeup time, to name a few.[26] One hour of irregularity in the timing of the sleep midpoint is considered abnormal for a typical adolescent.[27] As sleep variability, sleep irregularity decreases with age, particularly from young to middle adulthood.[53] As shown in Table 2, Kramer, Kerkhof & Hofman (1999) also found that younger males showed greater day-to-day StDev in their sleep midpoint (i.e., greater sleep irregularity) as compared to older males, suggesting that research should examine maturational periods and developmental changes across the lifespan in relation to irregularity in the circadian timing of sleep.[54] Sleep irregularity has also recently emerged as an important factor for overall health,[55] with several studies observing that irregular sleep is associated with adverse outcomes in adults, ranging from increased inflammation,[56] dysfunctional metabolism,[57] mental health issues,[58] to dysregulated cardiac autonomic modulation.[59] Sleep irregularity also has shown adverse effects on health outcomes earlier in life, as it has been associated with behavioral health[60,61] as well as obesity,[62] decreased cardiorespiratory fitness[63] or increased blood pressure levels in adolescents.[64] This review will focus below on the association of sleep irregularity, independent of average sleep midpoint, with obesity and adverse cardiometabolic health in adolescents.

3. Sleep Variability, Obesity and Cardiometabolic Health in Adolescence

3.1. Sleep Variability and Obesity in Adolescence—

The adverse health effects of adolescent obesity have been well documented[65] as studies also support the existence of an association between insufficient sleep as a risk factor for obesity in youth,[66] an effect that has been replicated longitudinally.[67] In search of a mechanism explaining how sleep factors drive weight gain, researchers found that not only is insufficient sleep associated with body mass index (BMI) in youth,[37,68] but greater sleep variability is associated with BMI and other indices of adiposity as well.[69] More recent studies have also started focusing on how greater sleep variability may predict increased levels of obesity, particularly visceral adipose tissue (VAT), independent of insufficient sleep, and proposed mechanisms for this association include chronic, repeated bouts of sleep debt in addition to sleep-related changes in nutrition and diet, physical activity and sedentary behavior.

As shown in Table 3, research has found that high sleep variability contributes to dysregulated eating, particularly concerning caloric intake, macronutrients, sugar-sweetened beverages (SSBs), caffeine, and snacking.[70] A study conducted on pre-adolescent children showed that for every 10-minute increase in sleep variability per night, there was a 0.20 percentage point increase in added sugar from SSBs in their total diet, independent of sleep duration.[71] This finding was replicated in another study in adolescents, where sleep variability was also associated with poorer dietary quality and greater caloric and fat intake.[72] A recent study by Mathew and colleagues has shown that adolescents with greater sleep variability had 25% lower odds of consuming breakfast, indicating that circadian rhythms pertaining to meal times may be affected as well by deviations in sleep duration.[73] He and colleagues (2015) found that greater sleep variability was associated with increased caloric intake and increased VAT, as every hour increase in sleep variability resulted in a 6.86 cm^2 increase in VAT.[46] Furthermore, 20% of the association between greater sleep variability and VAT was explained by the increased caloric intake, specifically carbohydrates in the evening.[47] Accumulations of fat in the visceral depot are more detrimental to health outcomes, especially earlier in life, as VAT is hormonally active and promotes inflammation and metabolic dysregulation,[74] even in youth.[75]

Physical activity is a well-known protective factor against obesity, however, sleep variability may lead to increased sedentary behavior, such as excessive screen times. Screen time has been extensively researched as adolescents with greater sleep variability between weekdays and weekends spent significantly more time in front of the computer or similar electronics,[76] contributing to physical inactivity and promoting obesity. A study by Hrafnkelsdottir and colleagues[62] examined the association between sleep variability, screen time, and physical activity in 315 adolescents. Their findings showed that adolescents, particularly boys, with greater screen times had higher sleep variability, contributing to sedentary behavior. In fact, Hrafnkelsdottir and colleagues found that for every additional hour of screen time, adolescent boys' sleep variability increased by 7.4 minutes.[62] Furthermore, boys in the 90th percentile of screen time had 43 min higher sleep variability.[62] An inverse relationship can be seen in regards to physical activity levels, as participants who were in the 90th percentile of physical activity had around 30 minutes less sleep variability than those in the 10th percentile, suggesting that more physical activity and less screen time help adolescents achieve greater sleep stability across nights.[62] These findings were supported by Rognvaldsdottir and colleagues, who showed that adolescents with a sleep variability greater than 30 minutes had a 1.1 percentage point increase in abdominal fat in addition to a 0.9 percentage point increase in total body fat; an association that became stronger in the 90th percentile of day-to-day sleep variability as adolescents with approximately 89.4 minutes of sleep variability over the school week had a 2.4 percentage point increase in total body fat.[77] Furthermore, those adolescents in the 90th percentile of physical activity (2800 counts/min of wear time per day) had 5.4 mU/L lower fasting insulin and 3.8 percentage point lower abdominal fat than those in the 10th percentile (categorized as those with 1600 counts/min of wear per day), suggesting that greater sleep variability and less physical activity are associated with adverse obesity-related metabolic effects in adolescents.[77]

3.2. Sleep Variability and Cardiometabolic Health in Adolescence—Since sleep contributes to overall health, variability in sleep patterns can disrupt circadian cycles of physiological processes, resulting in metabolic dysfunction and increasing cardiovascular risk.[78] Although morbidities such as cardiovascular disease (CVD) and type 2 diabetes (T2D) most often emerge clinically in adulthood, recent evidence suggests that early cardiometabolic changes may peak during adolescence and increase the risk of chronic CVD and other diseases later on in life,[79] especially those for which obesity is a key risk factor.[80] Although insufficient sleep is associated with adverse CVD outcomes[81] and readers will find in this special issue more in-depth reviews on the topic of insufficient sleep and cardiometabolic health, sleep variability and irregularity have emerged as potential independent risk factors for cardiometabolic health, particularly in adolescents with obesity.

Greater sleep variability not only is associated with increased obesity, but also with adverse cardiovascular and metabolic outcomes.[82] Studies on adults, like the PREDIMED-Plus trial conducted on 1986 elders with obesity, have shown that greater sleep variability was associated with a 14% higher risk for T2D.[83] Furthermore, when considering the combined effects of insufficient sleep and increased sleep variability, participants categorized as “bad sleepers” were positively associated with higher BMI, fasting plasma glucose, and HbA1c, and additionally had a higher prevalence of obesity (12%) and T2D (62%),[83] suggesting that increased day-to-day sleep variability may exacerbate diabetes in adults. As shown in Table 3, studies in adolescents have indicated that high sleep variability influences energy balance and contributes to obesity,[46,47] an important issue given that cardiometabolic risk can be more detrimental long-term in adolescents with obesity[84] as the may suffer from a less favorable metabolic profile.[62,77] Studies in pre-adolescents have found that greater sleep variability is associated with altered insulin levels, and increased C-reactive protein levels.[48] Evidence also suggests that sleep variability directly affects the vascular system, as Hoopes and colleagues examined the association between sleep variability on peripheral vascular function in 51 healthy young adults.[85] Their research showed that sleep variability was associated with poorer microvascular function, even after adjusting for sex, BMI, blood pressure, physical activity, average sleep duration, and alcohol and caffeine use.[85] More specifically, those individuals that were categorized as having high sleep variability (after researchers conducted a median split) experienced 45% less robust passive leg movement (which is a marker of resistance artery microvascular function) compared to those with low sleep variability.[85] Additionally, Rodriguez-Colon and colleagues found that each hour increase in sleep variability was associated with a −0.14, −0.12, and −0.16 ms^2 decrease in power in the total, daytime, and nighttime high-frequency range, respectively, an indication of impaired heart rate variability (HRV) in adolescents;[49] decreased HRV is a marker of cardiac autonomic balance and a risk factor for CVD that is suggestive of a dysregulation in the balance between the sympathetic and parasympathetic nervous system.[86]

In summary, there is emerging support for the role of sleep variability in the risk of developing cardiometabolic conditions, however, there is a clear need for greater emphasis on earlier life periods that are vulnerable for the onset of adverse outcomes at pre-clinical stages. Furthermore, there is a lack of adolescent studies that examined sex and race/ethnicity disparities in sleep variability and irregularity. The existing evidence indicates

that young black females show greater sleep variability when compared to males and non-Hispanic whites.[39,49] He and colleagues additionally found racial/ethnic disparities in sleep variability, as adolescents who identified as, primarily, Black/African American and Hispanic/Latinx experienced greater day-to-day sleep variability as compared to non-Hispanic whites, and this disparity was more pronounced among adolescents with high caloric intake.[87] There is a need for greater research addressing sex/gender and racial/ethnic differences in the association of sleep variability with cardiometabolic health.

4. Sleep Regularity, Obesity and Cardiometabolic Health in Adolescence

4.1. Sleep Regularity and Obesity in Adolescence—

While the previously discussed evidence does highlight a strong association between sleep variability and obesity-related cardiometabolic outcomes, the timing of the sleep-wake cycle is also a contributor to health morbidity early in life. In addition to increased obesity rates, delays in the sleep-wake cycle have been found to contribute to dysregulation in the timing of meals and inadequate diets in adolescents.[73,88] Indeed, late eating appears to promote metabolic dysregulation both in adults and children.[89] However, dysregulations in the circadian timing of sleep, particularly during adolescence, may have an even greater impact in regards to the development of obesity and associated adverse sequelae. Since there is a mismatch between the pubertal-related shift in the sleep-wake cycle and the social/academic responsibilities in adolescence, there is increased irregularity in the timing of sleep in the transition from weekdays to weekends, contributing to social jetlag. As shown in Table 3, studies have found that this misalignment marked by irregularity in the midpoint of sleep is associated with increased adiposity variables, such as greater body fat in adolescence.[90] Furthermore, adolescents with obesity who show greater sleep irregularity across nights have higher BMI percentiles, whereas consistent bedtimes and waketimes are associated with decreased levels of adiposity.[91] For example, Project Viva conducted on 804 subjects found that adolescents, particularly females, with greater sleep irregularity were more metabolically unhealthy, even after adjusting for average sleep duration and lifestyle factors.[92] Specifically, each additional hour in social jetlag was associated with a 1.19 cm wider waist circumference and 0.45 kg/m^2 higher fat mass index.[92] The mechanism behind this association posits that a delayed sleep phase and increased sleep irregularity may cause impaired energy metabolism, contributing to accumulations in distinct adipose depots, particularly VAT.[93]

Studies have also shown that later and more irregular bed and wake-up times are associated with poorer diet quality, lower consumption of fruits and vegetables, and higher consumption of extra food.[94] Furthermore, greater sleep irregularity has been associated with greater preoccupation with food,[72] suggesting that an irregular circadian timing of sleep may also be related to cognitive-emotional processes underlying eating behaviors. Additionally, Mathew and colleagues investigated the association between sleep irregularity and breakfast consumption in 590 adolescents.[73] They found that each hour increase in sleep irregularity was associated with 32% higher odds of skipping breakfast, further supporting how circadian rhythms pertaining to meal times may be impacted.[73]

Apart from unhealthy diet, research has shown that a delayed sleep phase (e.g., later chronotype) in youth is associated lack of physical activity, as supported by Amigo and

colleagues who administered questionnaires on sleep (duration and timing) and sedentary and active leisure time to 291 adolescents from Asturias, Spain.[95] Commensurate, greater sleep irregularity has been associated with increased sedentary behavior (i.e., greater screen time) in Rognvaldsdottir and colleagues,[77] who examined the association between sleep irregularity, physical activity, and metabolism in 252 adolescents across six schools in Reykjavik, Iceland.[77] Their findings showed that increased sleep irregularity was positively associated with BMI, waist circumference, total body and abdominal fat percentage, even after controlling for physical activity, sex, parental education, and day length.[77] In fact, adolescents in the 90th percentile who showed a sleep irregularity of 83.4 minutes over the school week had 3.4% increased body fat as compared to those in the 10th percentile (sleep irregularity of 16.2 minutes), an association that was stronger in females.[77] Hence, high sleep irregularity may affect appetite control and, therefore, contribute to greater adiposity, leading to adverse metabolic health. These findings were supported by Hrafnkelsdottir and colleagues, who showed that total screen time was significantly associated with day-to-day sleep irregularity, as indexed by bed and rising times instead of sleep midpoint or similar metrics, even after adjusting for body fat percentage, parental education, and physical activity in 315 adolescents.[62] More specifically, for each additional hour of screen time, sleep irregularity in bed and rising times increased by 7.8 minutes and 5.6 minutes, respectively;[62] an effect was particularly stronger in males in the 90th percentile of screen time, as they had a sleep irregularity in bed and rising times 46 and 31 minutes higher, respectively, compared to those in the 10th percentile.[62] Overall, these reviewed studies provide some insight mechanistically into how an irregular timing of sleep may contribute to weight gain by influencing energy balance.

4.2. Sleep Regularity and Cardiometabolic Health in Adolescence—Since many metabolic and endocrine functions have oscillatory patterns, a misaligned sleep-wake cycle expressed in the form of high sleep irregularity or social jetlag may contribute to dysregulation of these systems, and result in poor cardiometabolic health.[20,96] In adults, studies have shown that greater sleep irregularity, particularly between work and non-work days, was associated with reduced insulin sensitivity and increased BMI.[97] As shown in Table 3, this metabolic dysregulation has also been shown in various studies in adolescents. A study by Simon and colleagues[32] examined the relationship between insulin resistance and circadian health in 31 adolescents who had either overweight or obesity. After undergoing one week of actigraphy as well as a glucose tolerance test in-lab, they found that having a more regular weekday-to-weekend schedule was associated with better insulin sensitivity (HOMA), as having a delayed and irregular circadian timing of sleep across the week was strongly associated with insulin resistance.[32] Other studies in adolescence have found that greater sleep irregularity is associated with decreased cardiorespiratory fitness in adolescents, as observed in a study by Higgins and colleagues[63] on 276 adolescents from the OSSLS2 cohort in New Zealand. This study measured cardiorespiratory function (VO_{2max}) after a fitness test, in addition to collecting self-reports on sleep habits.[63] Higgins and colleagues found strong associations between greater sleep irregularity and decreased cardiorespiratory fitness, particularly in males, who had 25.1 more minutes of social jetlag as compared to females.[63] Specifically, each hour increase in social jetlag, independent of other sleep variables, was associated with a 0.72 ml/kg/min decrease in VO2max.[63]

Additionally, adolescents with a shifted sleep phase delay and irregular habitual bedtimes and wake-up times have been shown to be at higher risk of elevated blood pressure.[64] This association has been found to be particularly strong in females, as observed through the longitudinal study by Jansen and colleagues[64] conducted in 2033 adolescents from Mexico, where adolescents with a later and more irregular bedtime had 1.87 times higher risk of developing elevated blood pressure over the follow-up period.[64]

In summary, the studies reviewed above suggests that impaired metabolism may have a mechanistic role in the relationship between a dysregulated sleep-wake cycle and adverse cardiovascular health; however, there is a lack of studies investigating sleep irregularity during adolescence as compared to other factors such as insufficient sleep or sleep quality.[81] While it appears that females with more advanced pubertal development (later Tanner stages) have a later sleep midpoint on weekends as compared to males,[12] more research is needed that addresses sex/gender differences and other health disparities, such as racial/ethnic inequalities, when it comes to physiological responses to circadian misalignment.[96]

DISCUSSION

While the emerging evidence collected in this review shows an association between intra-individual day-to-day deviations in the duration (variability) and timing (irregularity) of sleep and obesity and adverse cardiometabolic health, there are numerous gaps in research that need to be highlighted. It is clear that future research needs to focus on early developmental periods where the onset of adverse health outcomes may be incipient. A wealth of the literature has focused on adults who have already developed cardiovascular or metabolic diseases, while the causes of increased sleep variability and irregularity could differ by age, which can only be determined with increased research targeting youth. The evidence collected in this paper was supported by 25 cross-sectional studies but only one longitudinal study, which despite its large sample size followed-up adolescents only 14 months after their baseline visit.[64] This emphasizes a need for more longitudinal studies to examine the association of sleep variability and irregularity across the lifespan, from childhood through adulthood, in order to better ascertain temporal and causal associations with obesity and cardiometabolic morbidity. Randomized clinical trials are also necessary to help establish causality and help create a conceptual model where it is possible to examine how sleep-wake patterns impact adiposity and cardiometabolic factors such as glycemic regulation[96] or immune/stress system activation. Studying younger populations will, thus, inform preventive measures and interventions to improve public health outcomes. Furthermore, future studies should focus on including more diverse populations to account for sex and racial/ethnic disparities and target those with greater risk of cardiometabolic diseases and circadian misalignment, since research examined within this paper found that females, particularly Black/African Americans, experience greater sleep variability[39,49] and sleep irregularity[12] as compared to males. Therefore, there are significant inequalities and health disparities in sleep-wake patterns at play that warrant further investigation. Finally, the role of genetics/epigenetics is a critical scientific gap that needs to be addressed, as preliminary studies suggest that sleep irregularity may be associated with altered DNA methylation in genes previously associated with cardiovascular disorders.[98] Despite all these

research needs, current evidence suggest that a stable sleep-wake cycle is essential for preventing adverse health outcomes and managing optimal health in adolescence.

Methodological Considerations

From a methodological standpoint, there are several different measures that capture deviations in habitual sleep patterns in the home environment and that are known to predict health-related outcomes.[96] However, there is no single approach to measuring sleep irregularity, given that there are overall and consecutive metrics whose accuracy varies depending on the methodology of the study.[26] Traditional metrics such as intra-individual StDev, inter-daily stability and social jetlag compare daily sleep irregularity to the overall average, whereas consecutive sleep metrics such as composite phase deviation and sleep regularity index measure sleep irregularity between consecutive days/nights.[26] Most of the studies reviewed herein used actigraphy to estimate sleep variability and sleep irregularity, calculating each metric based on the intra-individual StDev in sleep duration[62,73,77,85] or sleep midpoint,[62,73,77] respectively. Qian and colleagues, in contrast, estimated sleep irregularity based on inter-daily stability,[75] which is more reflective of rest-activity rhythms as compared to sleep-wake status.[26] To inform what sleep metric might be the most accurate and generalizable across populations,[96] future studies must take into consideration methodological differences and study parameters, as extensively detailed by Fischer and colleagues.[26] For example, sleep regularity index and composite phase deviation require a large sample size, at least 7 days of actigraphy and no limited data, while StDev and inter-daily stability metrics are relatively accurate with a smaller sample size, with more than 7 days of data, and StDev, specifically, can perform well with limited data.[26] In regards to study length, actigraphy should record a subject for at least 7 days, but 14 days is recommended as it can capture weekday vs. weekend StDev differences, more accurately reflects habitual sleep patterns, and prevents StDev and inter-daily stability metrics from overestimating sleep irregularity.[26] On a positive note, most studies reviewed herein did record actigraphy data for 7[32,33,46–49,62,69,71,73,75,77,84,87,90,] to 14[85] days, as suggested by Fischer and colleagues.[26] Future studies should analyze their parameters and select the most accurate generalizable metric (or metrics) to understand which is most predictive for obesity, cardiovascular and metabolic outcomes. Upcoming studies should also consider the role of entrainment conditions, as a misaligned circadian timing of sleep may express differently if individuals are studied while on work/school months or free-days/breaks/vacation.[64,72,90,92] For example, a delayed sleep midpoint during weekdays may more reliably identify increased cardiometabolic risk when adolescents are studied while on work/school months, whereas sleep irregularity may more reliably identify increased risk when adolescents are studied during breaks/vacation.[99] In addition, future research should take into consideration metrics that go beyond global body habitus when examining the development of cardiometabolic diseases associated with obesity as a function of sleep variability and irregularity. Most studies reviewed above focused on BMI, which is a global metric of obesity that may not entirely capture the extent to which individuals, particularly youth, are at greater risk of morbidity. Future research should examine adipose tissue distribution and composition profiles, particularly VAT, as it may better identify metabolically unhealthy adolescents.[74] In fact, there is prior evidence that greater sleep variability is associated with increased accumulations of adipose tissue in the visceral

depot,[47] but future studies must examine whether this same association holds true for sleep irregularity and its different overall and consecutive metrics as well as how they may interact with VAT in predicting obesity-related cardiovascular and metabolic sequelae.

From a conceptual standpoint, most studies reviewed herein focused on sleep variability and irregularity acting as independent predictors of obesity, cardiovascular and metabolic health outcomes. There is a need to evaluate potential mechanistic roles for these deviations in the amount and timing of sleep in the context of cardiometabolic health. For example, deviations in the circadian timing of sleep may be in the causal pathways between obesity and adverse cardiovascular health, acting as mediators of such association. However, given that changes in circadian timing occur with typical development, it is possible that deviations may occur in conjunction with weigh gain and obesity and may increase its impact on health outcomes, acting as moderators of such association. Recent preliminary evidence points in this latter direction, where the association of VAT with elevated blood pressure appears strong in adolescents with high sleep irregularity, while non-significant in those with optimal sleep regularity.[100] Finally, future studies should examine whether sleep variability and irregularity impact obesity-related outcomes beyond cardiovascular and metabolic health in order to attain a more holistic understanding on the effect of circadian misalignment on overall health during adolescence as it associated with obesity.

Conclusion

In summary, many cross-sectional and a few longitudinal studies from the adolescent literature point towards emerging evidence supporting an association between intra-individual day-to-day deviations in the duration (variability) and timing (irregularity) of sleep with obesity and adverse cardiometabolic health outcomes. Specifically, greater sleep variability and irregularity have been both associated with increased rates of obesity, particularly enlarged metrics of central/visceral adiposity, T2D, cardiac autonomic dysregulation, and elevated blood pressure, among other outcomes in adolescents. There is a need for longitudinal studies covering different developmental stages across the lifespan that can shed light on the developmental trajectories of sleep variability and irregularity as well as their temporal or causal associations with cardiometabolic health in adulthood, a period in which this type of morbidity increases exponentially in terms of prevalence and adverse prognosis (e.g., CVD). The evidence reviewed herein further support the need for school start times and life schedules to best fit with adolescents' maturational changes from a circadian standpoint, in order to prevent different forms of circadian misalignment. These data also support the need for preventive interventions and clinical trials targeting sleep variability and irregularity in youth, testing their downstream effect on weight loss and cardiometabolic outcomes.

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STUDY IMPORTANCE

What is already known about this subject?

Insufficient sleep is a risk factor for obesity, cardiovascular and metabolic morbidity. This risk is particularly high in youth, who are more likely to also follow erratic sleep-wake schedules.

What are the new findings in your manuscript?

Inconsistency in the amount (variability) and timing (regularity) of sleep in adolescents is associated with obesity and dysregulated energy balance as well as altered cardiometabolic outcomes such as impaired cardiac autonomic modulation or elevated blood pressure.

How might your results change the direction of research or the focus of clinical practice?

Our reviewed findings inform preventive measures targeting earlier developmental periods when stability in the duration and circadian timing of sleep may protect youth from developing obesity and cardiometabolic conditions.

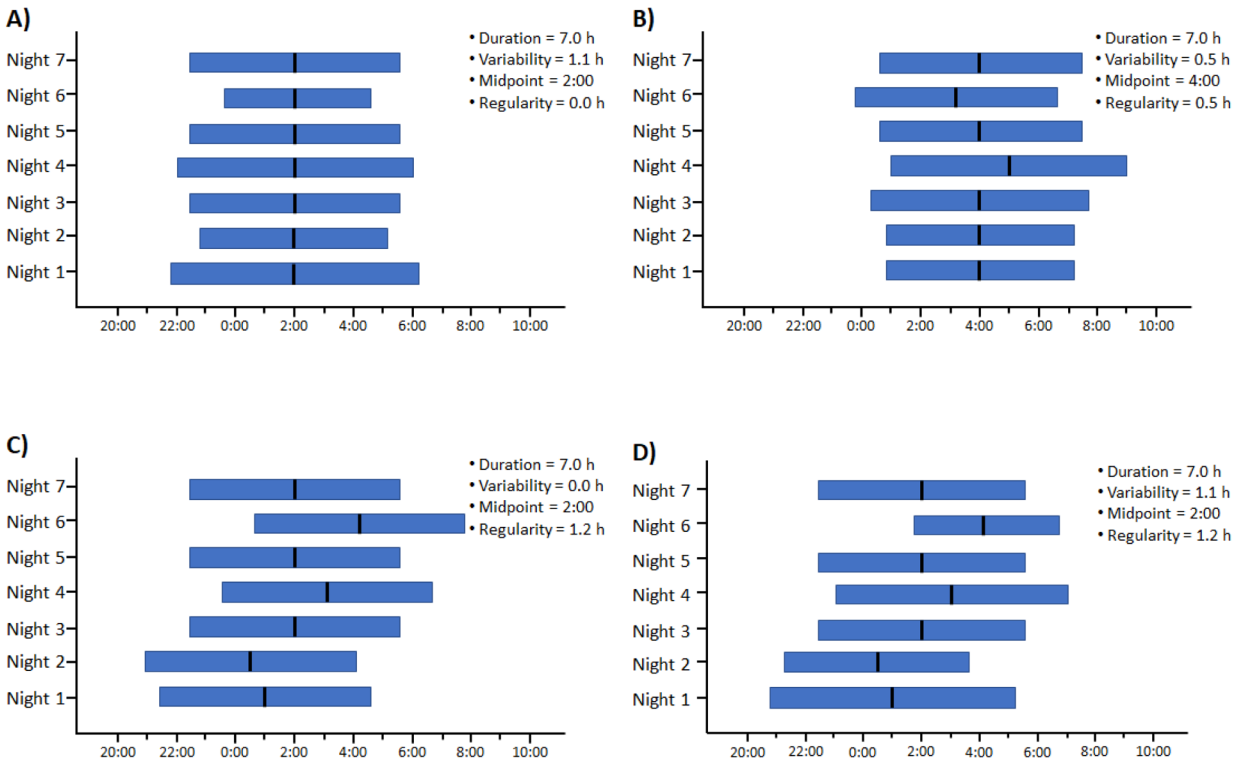

Figure 1. Sleep variability and sleep regularity as sleep health metrics that go beyond normative average values.

Plots depict purported individuals with normative average data but high sleep variability (amount) and/or irregularity (timing). These night-to-night deviations can cannot be equated to each other and can, in fact, interplay, where individuals with greater sleep irregularity experience alternate nights of insufficient and normative/recovery sleep (high sleep variability). These graphic depictions aim to further clarify the use of these constructs as used in this review. **A)** A given individual recorded for 7 consecutive nights with actigraphy showing normative sleep data for average amount (7 hours sleep duration) and timing (2:00 sleep midpoint) and high night-to-night sleep regularity (0.0 hour in their intra-individual standard deviation of sleep midpoint across nights), but presenting with high night-to-night sleep variability (1.1 hours in their intra-individual standard deviation of sleep duration across nights). This individual is anchored to the biological night (e.g., 22:00 to 6:00), is extremely regular in their sleep-wake cycle but experiences alternate nights of insufficient (e.g., 4 hours) and normative/recovery (e.g. 8 hours) sleep. **B)** A given individual showing normative sleep data for average amount (7 hours) and night-to-night deviation in sleep variability (0.5 hours) and regularity (0.5 hours), but presenting with a later average sleep timing (4:00 sleep midpoint). This individual sleeps later in respect to the biological night than individual A above (e.g., 1:00 to 8:00), with high regularity, and obtains a normative average amount of sleep with little variability; some individuals present with a more delayed sleep-wake cycle with an average sleep midpoint at, for example, 7:30 (4:00 sleep onset to 11:00 sleep offset). **C)** A given individual showing normative sleep data for average amount (7 hours sleep duration) and timing (2:00 sleep midpoint) and night-to-night deviation in sleep variability (0.0 hours), but presenting with

high night-to-night sleep irregularity (1.2 hours). This individual is highly irregular in their sleep-wake cycle, if assessed solely based on average metrics of sleep duration or midpoint or of sleep variability, but not sleep regularity, this individuals' unique sleep-wake pattern would have been missed. **D)** A given individual showing normative sleep data for average amount (7 hours sleep duration) and timing (2:00 sleep midpoint), but presenting with high night-to-night sleep variability (1.1 hours) and irregularity (1.2 hours). This individual is highly irregular in their sleep-wake cycle and experiences alternate nights of insufficient and normative/recovery sleep, which keeps them misaligned and exposed to bouts of partial sleep deprivation.

Table 1.

Sleep and circadian constructs used in this review

Construct	Source variable	Formula(s)	Calculation
Sleep Duration	Minutes of total sleep time (TST)	TIB – (SOL + WASO)	Within-subject mean TST across consecutive nights
Sleep Variability	Day-to-day deviations in TST	StDev of TST	Within-subject StDev of TST across consecutive nights
Sleep Midpoint	Clock time of the middle point of the sleep period (SM)	SOT + (SOT – WUT) / 2 SOT + TST/2	Within-subject mean of SM across consecutive nights
Sleep Regularity	Day-to-day deviations in SM	StDev of SM SRI IS CPD	Within-subject StDev of SM across consecutive nights See SRI, IS, and CPD in Fischer et al.[26]

CPD = composite phase deviation; IS = inter-daily stability; SM = sleep midpoint; SOL = sleep onset latency; SOT = sleep onset time; SRI = sleep regularity index; StDev = standard deviation; TIB = time in bed; TST = total sleep time; WASO = wake after sleep onset; WUT = wakeup time

Table 2.

Studies characterizing sleep-wake phase, sleep variability and sleep regularity

First Author, Year	Sample size (age) ♀	Design	Sleep Measures	Other measures	Findings
Lenneis et al. 2021[53]	111 (19y) 71	Cross-sectional, undergraduate students from UK	Actigraphy for 14 nights Sleep midpoint Sleep regularity (intra-individual variability in sleep midpoint across 14 days) Sleep diaries MEQ across 14 days	2nd study on adults ages 18–87 who completed MCTQ twice up to 5 years apart	↑ sleep irregularity in the transition into young adulthood from adolescents, particularly between weekdays and weekends
Hena & Garmy 2020[23]	1518 (13.9y) 770	Cross-sectional, survey for youth in Sweden	SMHQ Bedtime Waketime Social jetlag (>2hΔ bedtime and waketime on schooldays and weekends)	Screen time Night-time texting	Prevalence of social jetlag was 53.9% ↑screen time and texting at night associated with social jetlag and sleep irregularity
Dillon et al. 2015[39]	592 (20–96y) 298	Cross-sectional, randomly selected sample of US adults surveyed for 14 days	Sleep diary for 14 nights Sleep variability (intra-individual variability in total sleep time) # night-time awakenings Sleep onset latency Wake-time after sleep onset		Sleep variability and # of nighttime awakenings ↓with older age Young black females show greatest sleep variability
Lovato et al. 2013[15]	374 (15.6y) 227	Cross-sectional, health survey of youth from 8 schools in Australia	Actigraphy for 7 nights Sleep diary for 7 nights Bedtime and waketimes in school/free days Sleep duration Sleep habits questionnaires	ICSD-2 diagnostic criteria for DSPD	Significantly delayed sleep timing ↑ time in extracurriculars
Kang & Chen 2009[27]	160 (20.3y) 79	Cross-sectional, semi-structured interview and survey	Sleep questionnaires (PSQI, ESS, FSS) Sleep diary for 14 days Bedtime Sleep duration	CHQ-12	↑bedtime irregularity associated with ↓ sleep duration
Gupta et al. 2008[19]	1920 (15.1y), 749	Cross-sectional, questionnaire for 6–9th graders in Delhi	Sleep questionnaires Sleep duration Wake-time after sleep-onset Sleep debt Time in bed		↑ Grade level = ↓sleep duration, ↑ daytime napping, ↑ nocturnal awakenings, ↑ daytime sleepiness Sleep debt of 1 hour, ↑ with higher grades
Iglowstein et al. 2003[35]	493 (1m-16y)	Longitudinal, questionnaires at 1,3,6,9,12,18,24 months and annually until 16 years old	Sleep questionnaires until 16y Sleep duration Time in bed		↓sleep duration at 6m (14.2h) to 16y (8.2h) Later bedtimes but unchanged waketimes
Thorleifsdottir et al. 2002[13]	668 (1–20y)	Cross-sectional and longitudinal (followed-up 5 to 10 years later), survey	Sleep diary for 7 nights Sleep habits questionnaire Bedtime Wake-up time Sleep duration Sleep variability Weekdays vs. weekends Naps	Demographics TV watching	Older = ↑ sleep variability, later bedtimes, ↓ sleep duration, sleep longer on weekends (most significant in adolescents) Shift to earlier wake-up in adolescents, resulting in ↓ sleep duration

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First Author, Year	Sample size (age) ♀	Design	Sleep Measures	Other measures	Findings
Laberge et al. 2001[12]	1146, 10–13y (558)	Longitudinal, yearly parent survey and sleep questionnaire from 6–16y	Standardized questionnaires and annual interviews Bedtime Waketimes	PDS	↓nocturnal sleep times = bedtimes were delayed Δweekend/school day sleep schedules ↑ with age associated with difficulty falling asleep.
Kramer, Kerkhof & Hofman 1999[54]	19 (20.8y) 0 21 (65.1y) 0	Cross-sectional, two groups (youth and elderly)	Actigraphy for 11 days Sleep log for 14 days Sleep midpoint Sleep regularity (day-to-day variability in sleep-wake behavior)		Youth had more irregular sleep-wake pattern as compared to elderly sample
Carskadon, Vieira & Acebo 1993[16]	458 (11–12y), 275	Cross-sectional, survey of youth and parents in US	Parent reported M/E questionnaire Self-reported sleep habits Bedtime/waketime Weekdays/weekends sleep habits	Pubertal Status Birth order Measure of peer group	Pubertal status associated with M/E in females

CHQ-12 = Chinese Health Questionnaire; DSPD = Delayed Sleep Phase Disorder; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; ICSD-2 = 2nd edition International Classification of Sleep Disorders; MCTQ = Munich Chronotype Questionnaire; M/E = morningness-eveningness; MEQ = Morningness-Eveningness Questionnaire; PDS = Pubertal Development Scale; PSQI = Pittsburgh Sleep Quality Index; SMHQ = Sleep and Media Habits Questionnaire.

Table 3.

Studies on the association between sleep variability and sleep regularity with obesity or cardiovascular (CV) health in youth

First Author, Year	Sample size (age) ♀	Design	Sleep Measures	Obesity/CV Measures	Other measures	Findings
Mathew et al. 2022[73]	590 (15.4y) 313	Cross-sectional subset (Year 15) of the longitudinal FFCWS	Actigraphy and sleep diaries for 7 nights Sleep duration Sleep variability (SD of sleep duration) Sleep midpoint Sleep regularity (SD of sleep midpoint) SRI Social jetlag	Height and weight to calculate BMI	Ate breakfast (yes/no)	Later sleep onset/midpoint associated with lower odds of having breakfast ↑variability and ↑irregularity associated with lower odds of having breakfast.
Overberg et al. 2022[93]	149 (14.7y) 78	Cross-sectional study from pediatric obesity outpatient clinic	Nocturnal melatonin secretion in morning urine MCTQ	Cholesterol, triglycerides, uric acid, insulin, glucose, HDL, and kidney function parameters	Regular physical activity Daily electronic media consumption	Insulin resistance, triglycerides and elevated uric acid levels associated with lower melatonin levels Later chronotype and sleep irregularity associated with impaired energy metabolism
Hoopes et al. 2021[85]	51 (20y) 31	Cross-sectional, undergraduate students without obesity	Actigraphy for 14 nights Sleep diary for 14 nights Sleep duration Sleep variability (SD of sleep duration)	PLM induced hyperemia and FMD - measure microvascular function Fasting glucose and lipid profile	Habitual alcohol consumption Habitual caffeine consumption	High sleep variability is associated with poorer microvascular function (associated with all three measures)
Qian et al. 2021[75]	411 (10y) 209	Cross-sectional, ONTIME-JR cohort from Mediterranean	Actigraphy for 7 nights Sleep duration Sleep variability CFI Sleep midpoint (5 vs. 10h period) Sleep regularity (IS) MCTQ	Obesity related inflammatory markers measured through saliva (CRP), melatonin, cortisol	Food timing and food intake diary Physical activity diary	Blunted rest-activity rhythms = ↑BMI and ↑ pro-inflammatory salivary markers
Skjåkødegård et al. 2021[90]	85 (12y) 50	Cross-sectional, youth with severe obesity and peers with normal weight	Actigraphy for 7 nights, with weekdays/ends data Sleep duration Social jetlag Sleep midpoint (Δsleep midpoint weekdays – ends) Parent reported screen time and sleep problems	BMI through measured height and weight	Physical activity (accelerometer) Self-reported emotional eating Parent reported screen time and eating behavior	Children with severe obesity had significantly later mean mid-sleep time and greater irregularity from school nights to weekends, in addition to more sleep problems.
Higgins et al. 2020[65]	276 (14–18y) 145	Cross-sectional, cohort from OSSLS2	Self-report surveys Sleep duration Sleep disturbances Social jetlag Sleep regularity	VO2max (relative to body mass) measured post-20 m multistage fitness test BMI	Physical activity and screen time and # of screens survey	Social jetlag and increased sleep irregularity are negatively associated with cardiorespiratory fitness in males

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First Author, Year	Sample size (age) ♀	Design	Sleep Measures	Obesity/CV Measures	Other measures	Findings
Hrafnkelsdottir et al. 2020[63]	315 (15.8y) 144	Cross-sectional, six schools in Reykjavik, Icelan	Actigraphy for 7 nights Sleep duration Sleep variability (intra-individual SD of sleep duration) Sleep midpoint Sleep regularity (intra-individual SD of sleep midpoint) Social jetlag (Δ weekdays vs. weekends)	Body weight BMI (calculated using height and weight) Body fat % (DXA)	Daily screen time Physical activity (accelerometer)	↑screen time associated with ↑variability and irregularity, particularly irregularity ↑physical activity associated with ↓variability and irregularity, and ↑ duration (significant in males)
Jansen et al. 2020[64]	2033 (12.5y) 1111	Longitudinal, youth from Mexican schools followed up after 14 months	Questionnaires, lifestyle habits Habitual bedtime weekdays/ weekends ΔBedtime weekday-end	N/A	Seated BP measured 2x at visit 1 and follow-up visit	No hypertension at baseline 14m = 10% ↑ BP Delayed bedtime (>11 p.m.) =↑ BP Earlier bedtime (<9p.m) = ↑BP U-shaped association +2hΔDay-end bedtime =↑ BP Association stronger in females
Rognvaldsdottir et al. 2020[77]	252 (15.8y) 146	Cross-sectional subset of longitudinal study	Actigraphy for 7 nights Sleep duration Sleep variability (night-to-night SD of sleep duration Bedtime (time of sleep onset) Bedtime variability (night-to-night SD of sleep onset)	Body weight, BMI (height and weight), waist circumference, body fat % (DXA), BP, glucose and insulin	Actigraphy to measure physical activity	Significant variability in night-to-night sleep duration, which was associated with higher body fat %, particularly trunk fat
Cespedes Feliciano, 2019[92]	804 (13.2y) 418	Cross-sectional, adolescent cohort from Project Viva	Chronotype (MEQ) Social jet lag (ΔSM weekday-end) – actigraphy (7–10 days) Sleep logs	BMI z-scores, DXA fat mass index	Cardiometabolic risk score	Median SJL = 0.9h Eveningness +↑ social jet lag = ↓SD Eveningness + ↑ social jet lag = ↑ adiposity in females
Simon et al. 2019[32]	31 (16y) 24	Cross-sectional, youth from outpatient clinics	Actigraphy for 7 nights during academic year Bedtime/waketime Time in bed Sleep duration Sleep midpoint DLMO sampling every 30 minutes from 5 p.m. to noon of following day	BMI percentile, 3-hour glucose tolerance test		Later and more irregular circadian timing of sleep onset significantly associated with insulin resistance Earlier bedtimes (on weekdays) = better insulin sensitivity
Jansen et al. 2018[69]	528 (14.4y) 276	Cross-sectional, adolescent follow-up from the ELEMENT cohort study	Actigraphy for 7 nights Sleep duration Sleep variability (intra-individual SD of average sleep duration)	BMI, waist circumference, and % body fat	Tanner staging	↓Duration = ↑adiposity across all measures and higher obesity prevalence ↓Duration/↑ Variability = ↑BMI than stable sleepers
Zhou et al. 2018[91]	188 (10.5y) 108	Cross sectional, cohort from Stanford CHANGES	Actigraphy >3nights Sleep duration Bedtime/waketime (and their intra-individual SDs) Parent self-report on sleep habits	% overweight, height, weight, waist circumference, BP, fasting blood lipids, glucose, insulin, CRP, glycated hemoglobin	TV screen time Total caloric intake (dietary phone calls) Physical activity (accelerometer)	Later bedtimes and greater irregularity associated with greater percentage overweight. Consistent bedtimes necessary to reduce adiposity in high-risk children

First Author, Year	Sample size (age) ♀	Design	Sleep Measures	Obesity/CV Measures	Other measures	Findings
Amigo et al. 2016[95]	291 (10y) 142	Cross-sectional, youth from Asturias, Spain	Questionnaire on sleep Bedtime Sleep duration	BMI (height and weight)	Sedentary and active times questionnaire	Sedentary behavior associated with increased BMI, and those who sleep late and have more screen time have greater BMI as well.
Ievers-Landis et al. 2016[72]	315 (14.5) 202	Cross-sectional, cohort from HKHW	CSHQ Sleep duration Sleep variability (sleep duration shift from weekdays to weekends) Bedtime/waketime shifts	BMI (height and weight)	Dietary intake (REAP) Eating cognitions (chEAT)	Delays in sleep phase on weekends is associated with drinking more SSBs. Sleeping in (and sleeping more) on weekends associated with greater food preoccupation
Kjeldsen et al. 2014[71]	676 (8–11y)	Cross-sectional, cohort from OPUS school meal study	Actigraphy for 8 nights Sleep duration Sleep variability (average and day-to-day sleep variability score based on SD of sleep duration) Parent self-report (CSHQ)	Dietary intake log for 7 days (WebDASC) Leptin and ghrelin from fasting blood samples BMI (height and weight)	Parent reported screen time Tanner staging Physical activity (accelerometer)	↓Duration = ↑ energy density of diet, +sugar, SSB ↑Variability = SSB Short sleep duration, high variability, and sleep problems associated with obesity promoting diet
Paiva et al. 2016[76]	3476 (14.9y) 1870 Portugal	Cross-sectional, HBSC study survey	Health Behavior Questionnaire on sleep duration (Δ between weekdays/weekends) and sleep variability		Screen time Externalizing behaviors Substance use	Sleep deprived adolescents and those with ↑ variability is associated with excessive screen time, substance use, and more externalizing behaviors
Arora & Taheri 2015[33]	511 (11–13y) 299	Cross-sectional, cohort from MASSES study	Cleveland Adolescent Sleepiness Questionnaire Actigraphy for 7 nights (n=236) Sleep duration MEQ	BMI (height and weight) Paternal obesity (yes/no)	School Sleep Habits Survey for depression and anxiety Dietary behaviors survey	Evening chronotype associated with greater BMI, higher consumption of unhealthy snacks, night-time caffeine consumption, and inadequate fruit/vegetable consumption.
He et al. 2015[46]	324 (16.7) 156	Cross-sectional, cohort from PSCC	Actigraphy for 7 nights Habitual sleep duration Habitual sleep variability (intra-individual SD of sleep duration)	BMI (height and weight)	Energy and snack intake (YAQ)	↑sleep variability = ↑energy intake (fat, carb) ↑sleep variability = ↑snack consumption (post-dinner)
He et al. 2015[47]	305 (16.7y) 145	Cross-sectional, cohort from PSCC	Actigraphy for 7 nights Habitual sleep duration Habitual sleep variability (intra-individual SD of sleep duration)	Abdominal obesity (DXA) - TAT, ARG, AWP, GWP, VAT, SAT	Energy and snack intake (YAQ)	↑ sleep variability = ↑ abdominal obesity Partially explained by caloric intake
He et al. 2020[87]	324 (16.7) 156	Cross-sectional, cohort from PSCC	Actigraphy for 7 nights Habitual sleep duration Habitual sleep variability (intra-individual SD of sleep duration)	BMI (height and weight)	Energy and snack intake (YAQ)	Racial./ethnic minorities had shorter sleep duration and greater night-to-night sleep variability as compared to non-Hispanic whites Disparity was more pronounced among adolescents with high caloric intake
Rodríguez-Colón et al. 2015[49]	322 (16.7y) 156	Cross-sectional, cohort from PSCC	Actigraphy for 7 nights Sleep duration Sleep variability (intra-individual SD of sleep duration)	Cardiac Autonomic Modulation (HRV) - ECG BMI percentile		↑obesity = ↓HRV in youth Heart rate (parasympathetic modulation) peaked at 3:00AM, then decreased during the day (in those without obesity)
Iglayreger et al. 2014[84]	37 (14y) 20	Cross-sectional, cohort from Michigan Pediatric Outpatient	Actigraphy for 7 nights Sleep duration	Waist circumference, BP (seated BP and mean arterial pressure)	Physical activity (accelerometer) for 7 nights	Sleep duration inversely predicts cardiometabolic risk in adolescents with obesity

First Author, Year	Sample size (age) ♀	Design	Sleep Measures	Obesity/CV Measures	Other measures	Findings
		Weight Evaluation & Reduction program		HDL, triglycerides, glucose BMI (height and weight)		
Golley et al. 2013[94]	2200 (9–16y)	Cross-sectional, Australian nationally representative survey data	4 days of time data (MARCA), 4 groups based on chronotype Bedtime Waketime Sleep duration Sleep timing	BMI (height and weight)	2 days food intake data (Dietary Guideline Index for Children and Adolescents) Physical activity (MARCA)	Late bed and late rise as well as early bed early rise had higher BMI, lower diet quality, and higher intake of extra food
Boschloo et al. 2012[88]	605 (11–18y) 339	Cross-sectional, youth from Dutch secondary schools	Morningness-Eveningness – quantified by midpoint of sleep on free days Bed and rise times through parental questionnaires		Breakfast consumption survey Attention self-report School performance	Breakfast skippers perform lower in school Evening chronotypes/delayed midpoint associated with skipping breakfast
Spruyt, Molfese & Gozal 2011[48]	308 (4–10y) 157	Cross-sectional, youth from public school system in Kentucky	Actigraphy for 7 nights Sleep duration Sleep variability (% SV relative to the mean TST)	BMI (height and weight) Fasting glucose, insulin, lipids, CRP		↓sleep duration and ↑variability on weekends for youth with obesity Associated with altered insulin, CRP, and lipids

AGR = android/gynoid fat mass ratio; AWP = android/whole body fat mass proportion; BMI = Body Mass Index; BP = blood pressure; CFI = Circadian Function Index; ChEAT = Children's Eating Attitude Test; CRP = C-reactive protein; CSHQ = Children's Sleep Habits Questionnaire; DLMO = Dim light melatonin sampling; DXA = Dual-energy x-ray absorptiometry; ECG = electrocardiogram; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; FFCWS = Fragile Families and Child Wellbeing Study; FMD = flow-mediated dilation; GWP = gynoid/whole body fat mass proportion; HBSC = Health Behavior in School-Aged Children; HDL = high-density lipoprotein; HKHW = Healthy Kids, Healthy Weight; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; HRV = heart rate variability; IS = Inter-day stability; MARCA = Multimedia Activity Recall for Children and Adults; MASSES = Midlands Adolescent Schools Sleep Education Study; MEQ = Morningness-Eveningness Questionnaire; MCTQ = Munich Chronotype Questionnaire; ONTIME-JR = Obesity, Nutrigenomics, Timing, Mediterranean, Junior; OPUS = Optimal well-being, development and health for Danish children through a healthy New Nordic Diet; OSSL2 = Otago School Students Lifestyle Survey Two; PLM = Passive leg movement; PSCC = Penn State Child Cohort; REAP = Rapid Eating Assessment for Patients; SAT = subcutaneous adipose tissue; SD = standard deviation; SJL = Social jetlag; SM = Sleep midpoint; SRI = Sleep Regularity Index; SSB = sugar-sweetened beverages; TAT = total fat area; TST = total sleep time; VAT = visceral adipose tissue; WebDASC = Web-based Dietary Assessment Software for Children; YAQ = Youth/Adolescent Questionnaire.