A randomized crossover study investigating the effect of sleep manipulation on insulin sensitivity and cognitive functions in adolescents at risk of type 2 diabetes: the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes (SMART2D) study.

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Abstract

Background: Sleep duration is a critical determinant of metabolic and cognitive health, yet the effects of modifying sleep in a population of adolescents with severe obesity and at high-risk for type 2 diabetes (T2D) remain poorly understood. Foundational work I conducted—including two published systematic reviews and a cross-sectional study that piloted a motor-preparation task within the context of sleep duration—identified key gaps in youth sleep, health, and brain function. These findings directly informed the design of the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes (SMART2D) randomized crossover study.

Methods: SMART2D used a free-living sleep manipulation protocol with continuous monitoring (Actiwatch2®) in adolescents aged 13–18y with risk factors for T2D. After a baseline week (average sleep duration=7h31min/night), participants completed two one-week sleep conditions in which time-in-bed was manipulated by ±1.5h/night: sleep extension (average sleep increase of +1h02min/night) and sleep restriction (average sleep decrease of -1h19min/night). Conditions were delivered in randomized, sex-stratified, counterbalanced order, separated by a washout week (average sleep duration=7h33min/night). Outcome measures included insulin sensitivity (Matsuda index; 2-hour oral glucose tolerance test), glucose response curve (30-minute intervals), serum brain-derived neurotrophic factor (BDNF; fasted sample), food-cue behavioural inhibition (go/no-go task), motor preparation, and postural stability (dual-task paradigm).

Results: Of 43 participants, 36 (84%) completed all phases (53% female; mean age = 15.1y; BMI >99.9th percentile; >55% with dyslipidemia). Adherence exceeded 80%, confirming feasibility (2h21min/night difference between sleep weeks). Compared to both baseline and restricted sleep, only sleep extension significantly improved insulin sensitivity (~20%) and increased biphasic glucose responses (~30%), suggesting enhanced insulin secretion. BDNF levels decreased (~14%) during sleep extension, coinciding with peak insulin sensitivity, supporting a modulatory relationship between sleep and metabolic regulation. Sleep restriction impaired response inhibition in food-cue tasks, while sleep extension enhanced control and eliminated food-related biases. Motor preparation was unaffected, but voluntary reaction time and postural stability were impaired following sleep restriction, suggesting reduced neuromotor responsiveness under cognitive load.

Conclusion: Sleep extension offers a simple, non-invasive, scalable intervention to improve insulin sensitivity, inhibitory control, and neuromotor function—supporting its inclusion in preventive health strategies for youth at metabolic risk.

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Co-Authorship

This dissertation includes four published and three un-published manuscripts. The authorship for each manuscript it as follows:

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List of Abbreviations

A1C: Hemoglobin A1C

ANOVA: Analysis of Variance

AP: Anterior-Posterior

AST: Affective Shifting Task

BDNF: Brain-Derived Neurotrophic Factor

BMI: Body Mass Index

CAD: Canadian Dollar

CDC: Centers for Disease Control and Prevention

C_EC: Control Tone with Eyes-Closed

C_EO: Control Tone with Eyes-Open

CHAL: Center for Healthy Active Living

CHEO: Children's Hospital of Eastern Ontario

CI: Confidence Interval

CoP: Centre of Pressure

COVID-19: *Coronavirus Disease of 2019*

CRP: C-reactive Protein

DE: Decreased Sleep Week

df: Degrees of Freedom

DKA: Diabetic Ketoacidosis

ELISA: Enzyme-Linked Immunosorbent Assay

EMG: Electromyography

Fi: Food Image

FiNb: Food Image in New Block

FiRb: Food Image in Repeated Block

fMRI: Functional Magnetic Resonance Imaging

GLP-1: Glucagon-Like Peptide-1

HALO: Healthy Active Living and Obesity Research Group

HB: Habitual Sleep Week

HDL-C: High-Density Lipoprotein Cholesterol

HHS: Hyperglycemic Hyperosmolar Syndrome

HIC: High-Income Country

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance

HPA: Hypothalamic-Pituitary-Adrenal

IL-6: Interleukin-6

IOTF: International Obesity Task Force

IN: Increased Sleep Week

LDL-C: Low-Density Lipoprotein Cholesterol

mBDNF: Mature Brain-Derived Neurotrophic Factor

ML: Medial-Lateral

MRI: Magnetic Resonance Imaging

NAFLD: Non-Alcoholic Fatty Liver Disease

Nb: New Block

NGF: Nerve Growth Factor

NREM: Non-Rapid Eye Movement

NT-3: Neurotrophin-3

OGTT: Oral Glucose Tolerance Test

Oi: Object Image

OiNb: Object Image in New Block

OiRb: Object Image in Repeated Block

OOc: Orbicularis Oculi

OR: Odds Ratio

OSA: Obstructive Sleep Apnea

p75NTR: Neurotrophin Receptor p75

PCOS: Polycystic Ovary Syndrome

pro-BDNF: Precursor Brain-Derived Neurotrophic Factor

Rb: Repeated Block

REM: Rapid Eye Movement

RMS: Root Mean Square

RR: Relative Risk

RT: Reaction Time

SAS: Startling Acoustic Stimulus

SAS_EC: Startling Acoustic Stimulus Tone with Eyes-Closed

SAS_EO: Startling Acoustic Stimulus Tone with Eyes-Open

SD: Standard Deviation

SMART2D: Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes

SNS: Sympathetic Nervous System

SWA: Slow-Wave Activity

SWS: Slow-Wave Sleep

T2D: Type 2 Diabetes

TG: Triglycerides

TNF-α: Tumor Necrosis Factor-alpha

TrkB: Tropomyosin Receptor Kinase B

TrkB.FL: Full-Length Tropomyosin Receptor Kinase B

TrkB.T1: Truncated Tropomyosin Receptor Kinase B

TST: Total Sleep Time

UK: United Kingdom

US: United States

WHO: World Health Organization

Chapter 1

General Introduction

1.1 Thesis Overview

The journey into my Ph.D. research program began years ago, sparked by the groundbreaking post-doctoral work of Dr. Jean-Philippe Chaput, an expert in sleep and health research. In late 2016, we embarked on a literature search to unravel the intricate association between sleep patterns and the risk for type 2 diabetes (T2D) in children and adolescents [1]. What we uncovered was not only enlightening but also profoundly impactful. Beyond the well-established factors of obesity and genetic predisposition, inadequate sleep emerged as a potential key player, intricately linked to markers of poor glucose homeostasis in the pediatric population [1].

Our findings and other research led us to discuss that inadequate sleep disrupts the body's glucose metabolism through several possible mechanisms. One possible pathway involves the dysregulation of the hypothalamic-pituitary-adrenal axis system, resulting in an increase in cortisol levels and sympathetic nervous system activity [1,2]. Over time, this could lead to impaired glucose and insulin resistance [1]. Another pathway to explain these finding is the association between inadequate sleep and changes in appetite-regulating hormones, such as leptin and ghrelin, which can increase food intake and weight gain, further increasing the risk for T2D [1,3–5]. Finally, insufficient sleep has been reported to disrupt circadian rhythms, disrupting the timing of glucose metabolism and insulin sensitivity—both crucial for maintain glucose homeostasis [1,2,6]. These pathways underscored the complex interplay between sleep, metabolism, and T2D risk in the pediatric population.

Investigating the connection between sleep and insulin sensitivity in adolescents became an imperative due to the high prevalence of insufficient sleep among this

population. Studies have shown a significantly high proportion of adolescents fail to meet the recommended sleep duration [7–9]. This chronic sleep deficit, coupled with the increasing rates of obesity and T2D diagnoses in youth, underscores the urgent need to better understand the sleep's duration role in glucose metabolism [10,11]. However, despite the growing evidence, most studies were cross-sectional and conducted in healthy adolescents, leaving a significant gap in understanding how sleep impacts insulin sensitivity in those at high risk for T2D. This gap in knowledge sparked my determination to delve deeper into this crucial area of research, laying the foundational work for new insights that could revolutionize the prevention and management of T2D in young individuals.

My quest of understanding did not stop there. I sought to broaden our research to include outcomes that are often underreported and understudied in youth with T2D or those at risk. One such area is the link between T2D and brain functions, a topic that has garnered increasing attention in adults but remains understudied in youth. Adults with T2D, compared with healthy adults, are known to experience cognitive impairments, including deficits in motor function, executive functions, processing speed, memory, and attention and concentration [12,13]. These impairments are likely driven by a combination of factors, including chronic hyperglycemia, insulin resistance, inflammation, and oxidative stress. Yet, very little is known about the existence of cognitive challenges for youth-onset T2D or those who are at high risk for the disease.

Sleep duration is known to affect cognitive functions. In 2017, we conducted a systematic review that investigated the influence of sleep on brain functions and structures in children and adolescents who are apparently healthy [14]. The findings

suggested that inadequate sleep was associated with poor brain functions and reduced brain structures in this population [14]. This understanding of poor sleep's impact on cognitive functions and structures in apparently healthy children and adolescents laid the foundation for the next aim of my research: to explore the effect of sleep duration manipulations on cognitive function in a high-risk population of adolescents. Recognizing the complexity of this research, we enlisted the expertise of Dr. Anthony Carlsen, an expert in neuromotor control, to contribute to our work.

Together, our collaborative efforts culminated in the development of the SMART2D study, a randomized crossover trial designed to investigate the effects of sleep manipulations on insulin sensitivity and cognitive functions in adolescents at high risk for T2D. This innovative research aimed to unravel the intricate relationships between sleep duration, insulin sensitivity, and cognitive performance in a high-risk population of adolescents, with the potential to improve our understanding, prevention and treatment approaches for T2D in youth.

However, like many research journeys, ours was not without challenges. When the COVID-19 pandemic struck, we found ourselves in the midst of our data collection in a high-risk population. Despite the obstacles, we persevered, determined not to compromise the integrity of our study and my own future. This decision, while necessary, came at a cost of significant additional time, as we navigated the complexities and uncertainties brought about by the pandemic. An already ambitious and complex research project became even more complicated to accomplish. Our participant recruitment time more than tripled during the pandemic, from an average of six hours to 19 hours of work to recruit a participant. Safety protocols, already extensive, became

even more stringent. During this difficult and demanding time, our testing team bubble was sustained by the resilience of the adolescent participants, who not only felt they needed to participate but also wanted to be in our laboratory.

Behind most intervention study in humans lies a story often left untold—a journey of human connection, perseverance, and a commitment to something far greater than data or findings. The SMART2D study was born out of challenges, but its success was a direct result of the bonds that we forged as a team. Together, we created an environment built on openness, understanding, and the unwavering belief that every participant's well-being came first. For everyone involved, study staff, volunteers, and participants alike, this was more than just a study. It was a shared experience of growth, support, and compassion, free from judgement. The connections, vulnerability, and trust we fostered will forever be the true backbone of this work, an unquantifiable yet invaluable contribution to the knowledge within my thesis.

Looking ahead, the implications of the SMART2D study go beyond academic discovery. Our findings suggest that healthcare providers should consider sleep duration as a key behaviour in preventing and curbing the risk of T2D in adolescents, particularly those at high risk. Adequate sleep may not only play a crucial role in maintaining proper insulin sensitivity but also in mitigating cognitive function impairments in this vulnerable population. Future interventions targeting sleep behaviours, not just sleep duration, in youth could prove to be an essential component of a comprehensive strategy for diabetes prevention. Additionally, this research opens doors for further exploration into how sleep interventions can be incorporated into clinical practice and public health guidelines for high-risk adolescents. As the prevalence of T2D in youth continues to rise,

integrating sleep-focused recommendations could be a low-cost, widely accessible measure to help manage this growing epidemic. My hope is that this work will inspire new studies and contribute to changes in preventive care and clinical approaches, ultimately improving health and cognitive outcomes for adolescents at high risk for T2D.

As you read the SMART2D main research findings and insights, I hope that you will appreciate not only the data but also the journey that made these discoveries possible.

1.2 Thesis Organization

Following this introductory chapter, **Chapter 2** provides a literature review comprising three original articles that helped frame the study's context. **Chapters 3 through 6** present findings from the SMART2D study, with each chapter focusing on a specific aspect. Finally, **Chapter 7** provides a global discussion that synthesizes the SMART2D findings, addresses study limitations, and offers directions for future research.

Chapter 2

Literature Review

2.1 Sleep

2.1.1 Sleep and its impact on health: from childhood to adulthood

Sleep is a fundamental physiological process that is essential for overall health and well-being across all ages. It plays a critical role in cognitive function, emotional regulation, physical health, and disease prevention. Inadequate sleep refers to sleep that is insufficient in duration, poor in quality, mistimed, or misaligned with an individual's circadian rhythm [1,15–17]. It includes sleep that fails to meet age-specific duration recommendations, is fragmented or non-restorative, occurs at biologically inappropriate times, or is inconsistent with internal circadian cues [1,15–17]. Inadequate sleep, especially during crucial developmental periods such as adolescence, has been linked to a wide range of negative health outcomes, highlighting the importance of sufficient and restorative sleep at every stage of life [1,15–17].

To inform the Canadian 24-Hour Movement Guidelines across all ages, several studies were conducted [18–20]. A total of four systematic reviews were published on the topic of sleep, discussing sleep and health outcomes to provide the first evidence-based sleep recommendations in Canada, fully integrated with other daily movement behaviours [15,17,21,22]. The evidence is presented from the most recent to the oldest.

In adults aged 18 years and older, one of these studies was an overview of systematic reviews that aimed to identify the associations between sleep duration and health outcomes [15]. The study included a total of 36 reviews, of which 11 were selected based on predetermined criteria, such as population, exposure to different sleep durations, and specific health outcomes [15]. These reviews involved data from over 4.4 million participants across 30 countries, with the majority of studies (96%) using

subjective measures to assess sleep duration [15]. The results revealed that both short and long sleep durations, compared to 7–8 hours per night, were linked to increased health risks [15].

Specifically, adults who slept either less or more than 7–8 hours experienced a 6% to 39% higher risk of all-cause mortality, a 7% to 11% increased risk of cardiovascular disease, a 9% to 14% higher risk of T2D, and an 8% to 38% increased risk of obesity [15]. Furthermore, the lowest incidences of cognitive disorders, optimal cognitive functions, and reduced risk of falls were observed in those sleeping 7–8 hours per night [15]. Short sleep durations (less than 6 or 7 hours) were also associated with a higher risk of work-related accidents and injuries, and hypertension, while long sleep durations (> 8 hours) were linked to an elevated risk of osteoporosis in middle-aged and elderly women [15]. Interestingly, sleep duration was not significantly associated with the incidence of depression in adults [15]. The quality of evidence ranged from low to high across different health outcomes, but the overall conclusion was that, for adults, sleeping 7–8 hours per day is most consistently associated with favourable health outcomes, with no significant variations in effect by age [15].

In adults, another systematic review was conducted, focusing on the relationship between sleep timing, sleep consistency/regularity, and health outcomes, rather than sleep duration [17]. This systematic review analyzed 14 health outcomes across 41 studies, which included 92,340 participants, with sleep being assessed objectively in 37% of the studies [17]. The findings revealed that later sleep timing and greater variability in sleep patterns were generally linked to adverse health outcomes, while social jetlag was associated with negative health effects. Weekend catch-up sleep,

however, was shown to have positive health benefits [17]. Sleep timing or consistency was associated with mental health (4/6 studies), brain health (2/2 studies), cognitive function (5/7 studies), biomarkers of cardiometabolic risk (9/14 studies), bone health (2/2 studies), and physical activity and sedentary behaviour (3/4 studies) [17]. However, due to the linear nature of most studies, specific thresholds for what constitutes "late sleep timing" or "large sleep variability" could not be determined [17]. Additionally, no associations, mixed findings, or lack of assessment were found for mortality, cardiovascular disease, falls, accidents and injuries, adiposity, health-related quality of life, and work productivity [17]. Overall, the review emphasized that earlier sleep timing and maintaining consistent sleep patterns, including regular bedtimes and wake-up times, were associated with better health outcomes in adults [17].

Next, in preschool children aged 0 to 4 years, another systematic review was conducted to explore the relationship between sleep duration and various health outcomes [21]. The review included data from 69 studies, the majority (94%) of which were observational in design, covering a total of 148,524 children across 23 countries [21]. Sleep duration was primarily assessed through parental reports (in 70% of the studies), which may have introduced some bias and inaccuracies [21]. The review found that shorter sleep duration was consistently linked to higher levels of adiposity (20/31 studies), poorer emotional regulation (13/25 studies), impaired growth (2/2 studies), increased screen time (5/5 studies), and a greater risk of injuries (2/3 studies) [21]. However, the evidence on cognitive and motor development, physical activity, and quality of life was less clear, with no strong or consistent associations identified [21]. Additionally, no studies examined the relationship between sleep duration and cardiometabolic biomarkers in this age group [21]. Overall, while the quality of evidence

varied significantly, ranging from very low to high depending on the specific health outcome and study design, the findings still underscored the importance of obtaining adequate sleep for preschool children [21].

Finally, in children and adolescents aged 5–17 years, a systematic review was conducted to explore the associations between sleep duration and various key health outcomes [22]. The review analyzed 141 studies, 96% of which were observational, involving 592,215 participants from 40 countries, with sleep duration primarily assessed through self-report or parental questionnaires and only 21% of studies using objective measurements [22]. The review revealed that longer sleep duration was consistently linked to lower adiposity (58/71 studies), improved emotional regulation (49/62 studies), better academic achievement (14/21 studies), and enhanced quality of life and well-being (3/3 studies) [22]. However, evidence regarding sleep duration's impact on cognition (6 studies), harms and injuries (4 studies), and cardiometabolic biomarkers (19 studies) was more mixed or limited [22]. Overall, while the quality of evidence varied across the different health outcomes and study designs, ranging from very low to high, the reliance on cross-sectional studies using self-reported sleep data highlighted a significant need for more intervention-based research with objective sleep measurements to establish clearer dose-response relationships [22]. Despite the limitations, sleep duration was consistently associated with important health outcomes, indicating its crucial role in the overall health and well-being in children and adolescents [22].

Together, these studies provided the evidence for the development of the sleep recommendations within the Canadian 24-Hour Movement Guidelines [18–20]. The

comprehensive research on sleep duration, timing, consistency, and their associations with various health outcomes across all age groups served as a crucial foundation for creating evidence-based sleep recommendations [18–20]. These guidelines now fully integrate sleep with other movement behaviours such as physical activity and sedentary behaviour, highlighting the importance of sleep in promoting overall health and well-being for Canadians of all ages [18–20].

Later sections in this literature review will explore in more depth some of the key health outcomes briefly touched upon in this section, including the associations between sleep and obesity in the pediatric population, sleep and insulin resistance, as well as sleep's impact on brain functions and structures in children and adolescents. These discussions will provide further insight into the role of sleep in various health dimensions and the mechanisms through which sleep influences long-term well-being.

2.1.2 Sleep timing and health indicators in children and adolescents: a systematic review

Title:

Sleep timing and health indicators in children and adolescents: a systematic review

Authors:

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Evidence synthesis

Sleep timing and health indicators in children and adolescents: a systematic review

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Abstract

Introduction: To continue to inform sleep health guidelines and the development of evidence-based healthy sleep interventions for children and adolescents, it is important to better understand the associations between sleep timing (bedtime, wake-up time, midpoint of sleep) and various health indicators. The objective of this systematic review was to examine the associations between sleep timing and 9 health indicators in apparently healthy children and adolescents 5 to 18 years old.

Methods: Studies published in the 10 years preceding January 2021 were identified from searches in four electronic databases. This systematic review followed the guidelines prescribed in PRISMA 2020, the methodological quality and risk of bias were scored, and the summary of results used a best-evidence approach for accurate and reliable reporting.

Results: Forty-six observational studies from 21 countries with 208 992 unique participants were included. Sleep timing was assessed objectively using actigraphy in 24 studies and subjectively in 22 studies. The lack of studies in some of the health outcomes and heterogeneity in others necessitated using a narrative synthesis rather than a meta-analysis. Findings suggest that later sleep timing is associated with poorer emotional regulation, lower cognitive function/academic achievement, shorter sleep duration/poorer sleep quality, poorer eating behaviours, lower physical activity levels and more sedentary behaviours, but few studies demonstrated associations between sleep timing and adiposity, quality of life/well-being, accidents/injuries, and biomarkers of cardiometabolic risk. The quality of evidence was rated as "very low" across health outcomes using GRADE.

Conclusion: The available evidence, which relies on cross-sectional findings, suggests that earlier sleep timing is beneficial for the health of school-aged children and adolescents. Longitudinal studies and randomized controlled trials are needed to better advance this field of research. (PROSPERO registration no.: CRD42020173585)

Keywords: *bedtime, wake-up time, midpoint of sleep, youth, public health, guideline*

Highlights

- Later sleep timing is generally associated with poorer health outcomes in children and adolescents.
- Findings in this research area are based on observational studies.
- Longitudinal studies and randomized trials are needed to investigate the health effects of sleep timing and determine whether these effects are independent of sleep duration.

Introduction

To many people, getting a good night's sleep is synonymous with sleeping a sufficient number of hours. There is no denying that sleep duration is an important component of physical and mental health[1]. Lack of sleep, often fuelled by a mismatch between the social and the internal clocks, has been associated with numerous adverse health outcomes in all ages[2-4].

Sleep experts agree that many characteristics of sleep, in addition to duration, are relevant for optimal health. The *Canadian 24-Hour Movement Guidelines for Children and Youth* were published in 2016 to provide clear public health guidelines for

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physical activity, recreational screen time and sleep for 5- to 17-year-olds[5]. Since then, in an effort to better inform the general population, many countries and organizations worldwide have adopted this holistic, streamlined approach and all-encompassing messaging for the movement behaviours across the full 24-hour period[6]. The sleep recommendations in the *Canadian 24-Hour Movement Guidelines for Children and Youth* include sleep duration targets and consistent bedtimes and wake-up times across the week to minimize sleep variability[2]. While the guidelines emphasize more than one important sleep characteristic (i.e. duration, quality and consistency), they do not mention sleep timing.

Sleep timing refers to the time of day that sleep occurs; it is often measured using bedtime, wake-up time or midpoint of sleep. Much like sleep needs, sleep timing varies among people, and it can be affected by intrinsic and extrinsic factors such as genetics, age, health status, school/work schedule, lifestyle, travel across time zones and light exposure, resulting in bedtimes and wake-up times that differ from individual preferences[7]. A recent systematic review reported that later sleep timing in healthy adults was associated with overall poorer health outcomes[8]. Whether sleep timing is also associated with health in the pediatric population has, to date, not been systematically examined, especially with the inclusion of multiple health indicators. The purpose of this systematic review was to examine the associations between sleep timing and various health indicators in apparently healthy children and adolescents to help inform public health sleep guidelines and the development of future evidence-based healthy sleep interventions in this population.

Methods

Protocol and registration

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to reduce risk of bias, improve transparency and ensure a more complete reporting of the findings[9]. This systematic review was also registered with the International Prospective Register of Systematic Reviews (PROSPERO Registration No.: CRD42020173585).

Eligibility criteria

To identify the research question and facilitate the search strategy, we adopted the Participants, Interventions, Comparisons, Outcomes and Study design (PICOS) framework[10].

Population

Apparently healthy children and adolescents between 5 and 18 years old, including those with overweight/obesity, but excluding those with other diagnosed medical diseases/conditions. Studies with children younger than 5 years or older than 17.99 years were considered as long as the mean age of the sample was between 5 and 18 years.

To capture more generalizable findings, we excluded studies specifically targeting clinical populations with a diagnosed sleep disorder or other diagnosed medical disease/condition. Also excluded were studies that focussed exclusively on a subset of the general population of school-aged children and adolescents, such as orphans, teen pregnancy, inpatient or institutionalized settings, athletes or individuals with a cognitive or a physical disability. Studies with mixed populations, that is, with individuals who met and did not meet the eligibility criteria, were included if the results pertaining to the population of interest were reported separately.

Intervention/exposure

The intervention or exposure of interest was sleep timing, which refers to the time of day that sleep occurs. For experimental studies, the intervention needed to target sleep timing exclusively and not multiple health behaviours simultaneously. Sleep timing is generally reported as sleep onset/sleep offset, bedtime/wake-up time or midpoint of sleep. Studies using objective (e.g. polysomnography, actigraphy/accelerometry) or subjective (e.g. self-report) measures of sleep timing (or both) were eligible. Only studies that quantified sleep timing were included. For example, we excluded studies examining diurnal preference (e.g. morningness/eveningness), chronotype (e.g. morning lark vs. night owl) or sleep consistency (e.g. sleep variability, social jetlag, catch-up sleep). These studies on other sleep characteristics are outside the scope of the present systematic review.

Comparison/control

Different levels of sleep timing were used as the comparator. However, a comparator or control group was not required for inclusion.

Outcomes

We agreed on a total of 9 health outcomes that targeted a comprehensive range. Of these, we deemed that 5 were critical (primary outcomes) and 4 were important (secondary outcomes). The 5 critical health outcomes were adiposity; emotional regulation (e.g. anxiety, depressive symptoms, stress, mood, hyperactivity/impulsivity); cognitive function and academic achievement (e.g. learning, memory, attention, concentration, grades); quality of life and well-being; and accidents/injuries. The 4 important health outcomes were biomarkers of cardiometabolic risk (e.g. insulin sensitivity/resistance, glucose tolerance, blood pressure, triglycerides); sleep duration and quality; eating behaviour; and physical activity and sedentary behaviour.

Study designs

All published or in-press peer-reviewed, observational or experimental studies were eligible for inclusion. Longitudinal studies with any follow-up length were eligible, but sleep timing had to be measured at least once in children or adolescents aged between 5 and 18 years old. There were no sample size restrictions.

Information sources and search strategy

To ensure a balance of sensitivity and specificity, the search strategy was developed by a research librarian (ARW) with expertise in systematic review searching; the search strategy was reviewed by a second research librarian (MS). The following electronic bibliographic databases were searched for relevant sources: Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO and EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL). The search terms included these keywords for the subject headings and for sleep measurement: (1) headings: "Sleep" AND "Sleep Timing OR Midpoint of Sleep OR Sleep Consistency OR Regular Sleep OR Sleep Variability OR Sleep Schedule OR Catch-up Sleep OR Sleep Routine" OR "Bedtime OR Waketime"; and (2) sleep measurement: "Polysomnography" AND "Accelerometer OR Accelerometry" AND "Actigraphy" AND "Sleep Report OR Sleep

Questionnaire OR Sleep Diary OR Sleep Eval OR Sleep Log OR Sleep Journal."

The results were limited to full-text articles published in the previous 10 years. The initial search, conducted in March 2020, was for studies published from 1 March 2010 to 4 March 2020, in humans (children and adolescents), in English or French. Excluded were case studies and grey literature (e.g. conference abstracts, book chapters and dissertations). We decided on this limited date range to better manage the scope and to focus on the most recent and relevant body of evidence. The publication language was limited to English and French for reasons of feasibility; a recent meta-epidemiological study reported that excluding non-English publications does not impact conclusions[11]. An updated search was performed in January 2021 for studies published between 4 March 2020 and 13 January 2021. Finally, the reference lists of the included studies were reviewed to verify that no articles may have been missed during the search. The full search strategy is available online (https://osf.io/nzt23/?view_only=abcbea551fe545e6b73f44e60600da35).

Selection process

To remove duplicates, bibliographic records were imported into Reference Manager software (Thompson Reuters, San Francisco, CA, US). The individual bibliographical records were then imported into Covidence (Veritas Health Innovation, Melbourne, AU) for level 1 and level 2 screening. During level 1 screening, two reviewers (CD, CMS or BGC), working independently, screened the titles and abstracts of all the potentially relevant articles. Two reviewers (CD, CMS or J-PC), working independently, then reviewed all the full-text articles that passed the level 1 screening. Any discrepancies were resolved via discussion until the reviewers reached consensus. Agreement among the reviewers during the selection process was evaluated using Cohen's κ[12].

Microsoft Excel and Word (2007; Microsoft Corp., Redmond, WA, US) were used for data extraction. Data extraction was completed, in an unblinded manner, by one reviewer, and verified by another (CD, IP). Important features were extracted for each included article: authors' names; publication year; country of study; study design; sample size; participants' age range, mean age and school grade; exposure; comparator; outcome measurement; results; and covariates. When multiple models were reported on the same outcome measurement, results from the most fully adjusted model were extracted. We also reported on whether studies reported differences in effect by age, sex, race/ethnicity, socioeconomic status, weight status or sleep duration (when sleep duration was not the outcome of interest). See Figure 1 for the PRISMA 2020 flow diagram[9] for the identification and selection of studies.

Risk of bias and study quality assessment

The quality of primary research contributing to each health outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework[13]. In accordance with the Cochrane Handbook, the risk of bias assessment was completed for all included studies individually and by outcome[14]. GRADE groups the quality of evidence into four categories ("high," "moderate," "low" and "very low"); the rating begins at "high" for randomized studies and at "low" for all other studies, including non-randomized experiments and all types of observational studies. The quality of evidence can be upgraded one level if there are no serious limitations and if there is a large magnitude of effect or evidence of a dose–response relationship. Conversely, the quality of evidence can be downgraded if there are serious limitations across studies (e.g. serious risk of bias, inconsistency of relative treatment effects, indirectness, imprecision, lack of evidence or other factors)[13]. The quality of evidence assessment was conducted by two authors (CD and IP) and verified by the remainder of the review team, including a systematic review methodology expert (ARW). Disagreements were resolved by discussion among the team members.

Results

Description of studies

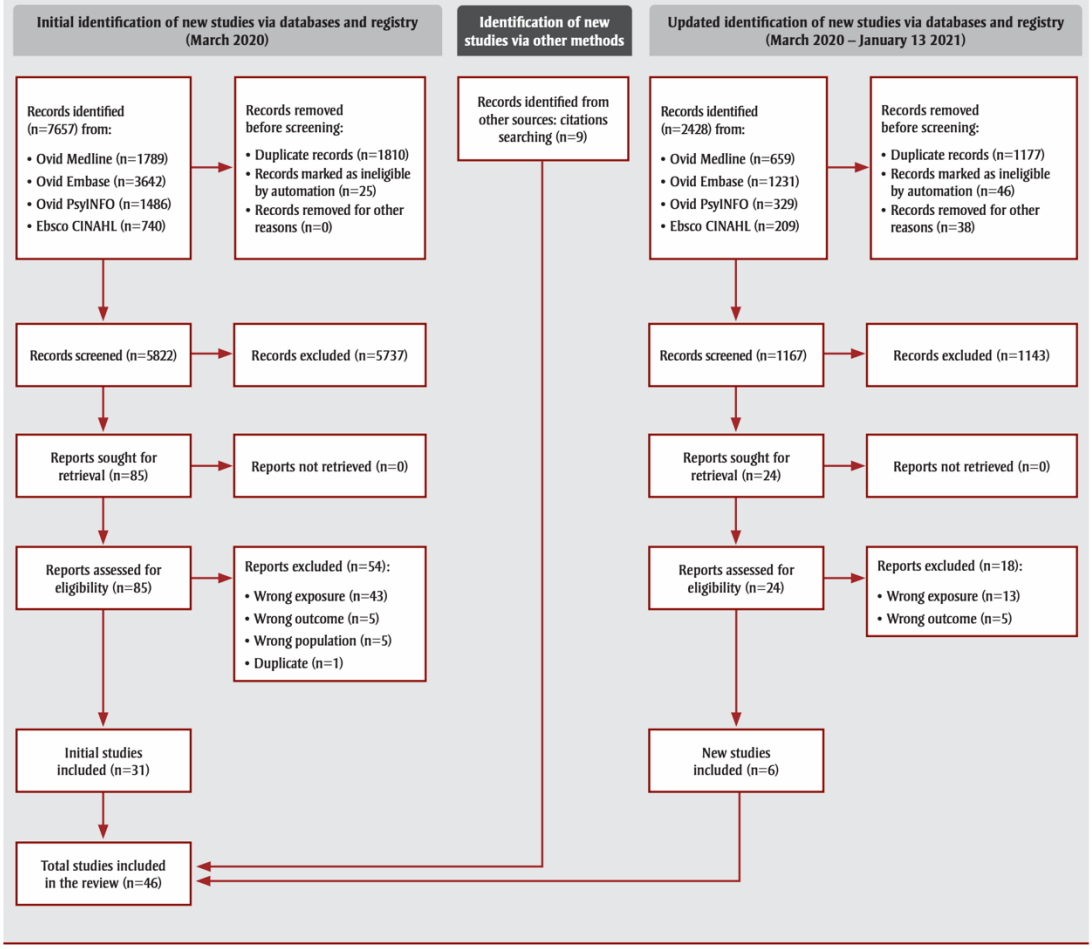
A total of 10 085 records were identified via the original and updated searches of the relevant electronic bibliographic databases (see Methods and Figure 1). After the removal of duplicates, a total of 6989 unique records remained for the level 1 title and abstract screening. The interrater reliability for the level 1 screening process was assessed for substantial agreement ($\kappa > 0.70$)[12].

Following level 1 screening, a total of 109 reports were sought for retrieval and assessed for eligibility. The level 2 eligibility review of the full-text articles excluded 72 articles, with 37 articles meeting the inclusion criteria. Out of the 72 articles excluded, 56 were excluded for having the wrong exposure, 10 for having the wrong outcome, 5 for having the wrong population and 1 for being a duplicate. The interrater reliability for the level 2 eligibility review of the full-text articles was assessed at near-perfect agreement ($\kappa > 0.85$)[12]. See Supplementary Table 1 (https://osf.io/nzt23/?view_only=abcbea551fe545e6b73f44e60600da35) for the complete list of full-text articles excluded. Reviewing the reference lists of included studies generated an additional 9 studies.

Of the 46 observational studies included, 5 were longitudinal and 41 were cross-sectional. Data were collected in 21 countries and included 208 992 unique participants. Twenty studies were included for a single outcome, and 26 were included for two or more outcomes. Sleep timing was assessed objectively, using an actigraphy device, in 24 studies, and subjectively, using questionnaires, sleep diaries or interviews (by proxy or self-report), in 22 studies. Sleep timing was assessed as midpoint of sleep in 14 studies, bedtime in 20 studies and a combination of bedtime/wake-up time or sleep onset/offset in 4 studies. Multiple measurements of sleep timing were independently analyzed in 8 studies. Variation of the effect between sleep timing and health outcomes caused by factors such as age, sex, race/ethnicity, socioeconomic status, weight status and sleep duration (when sleep duration was not the outcome) was only reported in 3 studies, partially addressed (mainly age and/or sex) in 13 studies and not reported in 30 studies.

Because of the small number of studies reporting some outcomes and the heterogeneity across studies in other outcomes, meta-analyses were not possible and we structured narrative syntheses around each health indicator to convey the findings. Population subgroups were defined as children (5–12 years) and adolescents (13–18 years), when possible.

FIGURE 1
PRISMA statement 2020 flow diagram[9] of the identification, screening, eligibility and inclusion of studies in this systematic review



Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data synthesis

The full data extraction and findings of the individual studies, sorted by outcome and study design, are reported in Supplementary Tables 2 and 3 (available from: https://osf.io/nzt23/?view_only=abcbea551fe545e6b73f44e60600da35) for the critical and important health outcomes, respectively. The summarized findings for the individual studies, sorted by outcome and study design, are in Tables 1 and 2 for the critical and important outcomes, respectively. Quality of evidence assessment, sorted by outcome and study design, are in Table 3 for all outcomes. Finally, a high-level summary of findings is presented in Table 4 for all outcomes, sorted by outcome and study design. In Table 4, studies are classified as having mixed findings if (1) the association between sleep timing and the outcome was not consistent across measurements; (2) the measurements of sleep timing did not show consistent associations with the outcome; and (3) the association between sleep timing and the outcome showed variation based on sex, age or other factors.

Adiposity

A total of 20 observational studies—3 longitudinal and 17 cross-sectional studies—examined the association between sleep timing and adiposity in children and adolescents 4 to 18 years old. Two of the 3 longitudinal studies reported that later sleep timing was associated with higher adiposity[15,16], while the third reported null findings[17]. Of the 17 cross-sectional studies investigating the association between sleep timing and adiposity, 10 reported null findings; of these, 2 studies only investigated BMI[28,31], 1 study only investigated

TABLE 1
Summary of findings for the association between sleep timing and critical health outcomes, in apparently healthy children and adolescents

Study design and no. / No. of participants / age range	Measurement of sleep timing (no. of studies)	Findings
Adiposity		
Longitudinal (n = 3) 7756 participants 4–18 years	Objectively, using an actigraphy device (n=1) Subjectively, by self-report (n = 1) and proxy-report (n = 1)	Hierarchical linear models revealed a significant longitudinal association between self-reported later bedtime and increased BMI z-score from adolescence to adulthood ($\beta = 0.035$, $p < 0.05$)[15]. In children, adjusted linear regression analyses revealed that a higher total number of times that children were in proxy-reported late bedtime groups at data collection timepoints was significantly associated with higher BMI z-score ($p < 0.001$) and waist circumference ($p = 0.03$) at 8–9 y[16]. No significant longitudinal associations were found between objectively measured sleep onset or midpoint of sleep and BMI z-score[17].
Cross-sectional (n = 17) 38 798 participants 5–18 years	Objectively, using an actigraphy device (n = 10) Subjectively, by self-report (n = 5) and proxy-report (n = 2)	In a sample of children and adolescents, multivariable linear regression revealed that those in the late-sleep timing groups, established via self-report, had higher BMI z-score relative to those in the early-bed/early-rise group (late-bed/early-rise: $\beta = 0.17$, 95% CI: 0.00–0.35, $p = 0.05$; late-bed/late-rise: $\beta = 0.20$, 95% CI: 0.06–0.34, $p = 0.007$)[18]. In a sample of adolescents, general linear modelling showed that objectively measured later corrected midpoint of sleep was significantly associated with greater waist-to-height ratio ($\beta = 0.015$, 95% CI: 0.003–0.028, $p < 0.05$); however, no significant association was found between corrected midpoint of sleep and BMI[19]. In a sample who self-reported their sleep timing, multivariable logistic regressions revealed that the odds of overweight or obesity were 1.55 for the late-bed/early-rise group of children and 1.47 for the late-bed/late-rise group of adolescents, and the odds of obesity were 1.89 for the late-bed/early-rise group of children and 2.16 for the late-bed/late-rise group of adolescents, compared to participants in the early-bed/early-rise group[20]. In 5-year-old children, analysis of covariance revealed that proxy-reported earlier bedtime (before or at 20:00), was significantly associated with lower BMI z-score ($p < 0.01$), but no significant association was found between wake-up time and BMI z-score[21]. In a sample of adolescents, multivariable logistic regression revealed that self-reported later weekend midpoint of sleep was significantly associated with higher BMI z-score in females only (<3:30: reference; 4:00 to 4:29: OR = 1.81; 95% CI: 0.90–3.63; 4:30 to 5:04: OR = 1.82; 95% CI: 0.96–3.47; ≥5:05: OR = 1.68; 95% CI: 0.85–3.33, $p = 0.04$). Weekday midpoint of sleep was not associated with BMI z-score[22]. In children, proxy-reported late compared to normal midpoint of sleep over the whole week was significantly associated with higher fat mass percentage and waist circumference, but was not associated with BMI z-score or the sum of the skinfolds[23]. In a sample of children with obesity, multivariate linear regression analyses revealed that objectively measured later bedtime on weekdays was associated with greater percent overweight ($\beta = 6.17$, 95% CI: 1.42–10.92, $p < 0.05$), percent over 95th BMI percentile ($\beta = 4.60$, 95% CI: 1.07–8.13, $p < 0.05$), BMI ($\beta = 1.03$, 95% CI: 0.22–1.85, $p < 0.05$) and waist circumference ($\beta = 2.06$, 95% CI: 0.23–3.88, $p < 0.05$). Objectively measured later weekday wake-up time was also significantly associated with higher BMI ($\beta = 0.85$, 95% CI: 0.00061–1.70, $p < 0.05$) and waist circumference ($\beta = 2.03$, 95% CI: 0.13–3.93, $p < 0.05$). Neither objectively measured weekend bedtime nor weekend wake-up time was significantly associated with any of the adiposity outcomes. Of the proxy-reported sleep-timing measures, only later weekday bedtime was significantly associated with higher percent over 95th BMI percentile ($\beta = 4.33$, 95% CI: 0.038–8.63, $p < 0.05$) and BMI ($\beta = 1.01$, 95% CI: 0.021–2.00, $p < 0.05$)[24]. 10 studies reported no significant associations between objectively[25-32] and subjectively[33,34] measured sleep timing and adiposity.
Emotional regulation		
Longitudinal (n = 2) 6331 participants 4–18 years	Subjectively, by self-report (n = 1) and proxy-report (n = 1)	In adolescents, self-reported later school-year bedtime at timepoint 1 (T1; Grades 7–12) and later summertime bedtime at timepoint 2 (T2; Grades 8–12) were associated with higher odds of emotional distress at timepoint 3, 6–8 y later in young adulthood (T1 school-year bedtime: OR = 1.35, 95% CI: 1.0–1.8, $p < 0.05$; T2 summertime bedtime: OR = 1.35, 95% CI: 1.1–1.8, $p < 0.05$)[35]. In children, adjusted linear regression analyses revealed that a higher total number of times children were in proxy-reported late bedtime groups at data collection timepoints (from never to 3 times) was significantly associated with more parent-reported ($p = 0.03$) and teacher-reported ($p = 0.05$) behavioural problems at 8–9 y[16].

Continued on the following page

TABLE 1 (continued)
Summary of findings for the association between sleep timing and critical health outcomes, in apparently healthy children and adolescents

Study design and no. / No. of participants / age range	Measurement of sleep timing (no. of studies)	Findings
Cross-sectional (n = 7) 106 225 participants 7–20 years	Objectively, using an actigraphy device (n = 2) Subjectively, by self-report (n = 5)	In children, logistic regression revealed that self-reported bedtime after 22:00, compared to bedtime before or at 21:00, was associated with an increased odds of self-reported depressive symptoms (≤21:00: reference; 22:00–23:00: OR = 1.89, 95% CI: 1.0–3.6, $p < 0.05$; >23:00: OR = 4.66, 95% CI: 2.1–10.2, $p < 0.01$)[36]. In adolescents and young adults, adjusted Poisson regression modelling revealed that, compared to those with a self-reported bedtime at ~22:00 or earlier, those with bedtime at ~22:30 had better depression scores (β = −0.1, 95% CI: −0.2 to −0.1, $p < 0.0001$), while those with a bedtime at ~23:30 or later had worse depression scores (β = 0.5, 95% CI: 0.5–0.6, $p < 0.0001$). In addition, going to bed at ~23:30 or later, compared to ~22:00 or earlier, was associated with increased odds of having anxiety or nervousness during the last 6 months. Going to bed at ~22:30 or later, compared to ~22:00 or earlier, was associated with increased odds of being irritated and having tantrums during the last 6 months[37]. In 17-year-olds, Tobit regression modelling revealed that objectively measured later midpoint of sleep was significantly associated with 2 out of 10 youth self-report scales: more thought problems (β = 0.9, 95% CI: 0.01–1.8, $p < 0.05$) and more rule-breaking behaviour (β = 1.5, 95% CI: 0.6–2.4, $p < 0.001$). Later midpoint of sleep was also significantly associated with 2 out of 6 Diagnostic and Statistical Manual of Mental Disorders-oriented scales: more affective problems (β = 1.2, 95% CI: 0.05–2.3, $p < 0.05$) and more conduct problems (β = 1.2, 95% CI: 0.2–2.1, $p < 0.05$)[38]. In a sample of adolescents, self-reported later bedtime was significantly correlated with higher anxiety ($r(256) = 0.16$, $p < 0.05$) and depressed mood ($r(383) = 0.20$, $p < 0.01$)[39]. In a sample of adolescents with overweight or obesity, objectively measured later bedtime on weekdays, but not weekends, was associated with increased self-report of behavioural problem symptoms (β = 0.52, $p = 0.01$)[40]. In a sample of children and adolescents, self-reported later weekday and weekend bedtimes, but not wake-up times, were each correlated with higher subjective depression scores ($r(499) = 0.130$, $p = 0.003$ and $r(499) = 0.088$, $p = 0.049$, respectively)[41]. In adolescents, self-reported earlier wake-up time was significantly correlated with low subjective academic stress ($r(479) = 0.12$, $p < 0.01$)[42].
Cognitive function and academic achievement		
Longitudinal (n = 2) 6331 participants 4–18 years	Subjectively, by self-report (n = 1) and proxy-report (n = 1)	Longitudinal associations revealed that self-reported later school-year bedtime at T1 (mean age 15.4 y) and T2 (mean age 16.4 y) was associated with lower high-school cumulative GPA (β = −0.27, 95% CI: −0.37 to 0.17, $p < 0.001$, and β = −0.13, 95% CI: −0.24 to 0.023, $p < 0.01$, respectively). Summertime bedtime was not associated with cumulative GPA[35]. In children, no significant longitudinal associations were found between proxy-reported sleep-timing group and verbal cognition, non-verbal cognition, language literacy and mathematical thinking[16].
Cross-sectional (n = 5) 123 372 participants 7–20 years	Subjectively, by self-report (n = 4) and proxy-report (n = 1)	In a sample of adolescents, there was an increased odds of poor GPA in those who self-reported typical weekday bedtime before 22:00 (OR = 1.74, 95% CI: 1.31–2.33) and after 00:00 (00:00–00:59: OR = 1.6, 95% CI: 1.37–1.91; 01:00–01:59: OR = 2.19, 95% CI: 1.71–2.81; 2:00 or later: OR = 2.76, 95% CI: 1.93–3.94), relative to bedtime between 22:00 and 22:59[43]. In a sample of adolescents and young adults, self-reported bedtime at approximately 22:30 or later, relative to 22:00 or earlier, was associated with increased odds of self-reported trouble with following class education, completing homework assignments, preparing for examinations, writing tasks and reading tasks. In addition, bedtime at approximately 23:00 or later, relative to 22:00 or earlier, was associated with increased odds of having trouble with reading tasks[37]. In adolescents, hierarchical multiple regression analyses revealed that self-reported later bedtime (not waketime) was significantly associated with lower college entrance exam scores (β = 0.133, $p < 0.01$). No associations were found between bedtime or wake-up time and subjective academic performance[42]. 2 studies reported no significant associations between subjectively measured sleep timing and cognitive performance and academic achievement outcomes[41,44].

Continued on the following page

TABLE 1 (continued)
Summary of findings for the association between sleep timing and critical health outcomes, in apparently healthy children and adolescents

Study design and no. / No. of participants / age range	Measurement of sleep timing (no. of studies)	Findings
Quality of life and well-being		
Longitudinal (n = 1) 3631 participants 4–9 years	Subjectively, by proxy-report (n = 1)	In children, adjusted linear regression analyses revealed that a higher total number of times children were placed in proxy-reported late bedtime groups at data collection timepoints (from never to 3 times) was significantly associated with poorer proxy-reported psychosocial (p = 0.001) and physical health (p = 0.002) functioning at 8–9 y[16].
Cross-sectional (n = 1) 6266 participants 9–11 years	Objectively, using an actigraphy device (n = 1)	In an international sample of children, no overall associations were found between objectively measured weekday or weekend midpoint of sleep and health-related quality of life score[45].
Accidents/injuries		
Cross-sectional (n = 1) 103 859 participants 14–20 years	Subjectively, by self-report (n = 1)	In adolescents and young adults, logistic regressions revealed that, relative to those with self-reported bedtime at ~22:00 or earlier, the odds of reporting accidents requiring medical attention during recess and in other classes were lower among those with bedtime at ~23:00. A greater decrease in odds of having accidents on the way to school was observed in those with bedtime at ~23:00, than in those with bedtime at ~22:30, relative to those with bedtime at ~22:00 or earlier. There was no association found between bedtime and accidents requiring medical attention during gym class[37].

Abbreviations: BMI, body mass index; CI, confidence interval; GPA, grade point average; no., number; y, years.

TABLE 2
Summary of findings for the association between sleep timing and important health outcomes, in apparently healthy children and adolescents

Study design and no. / No. of participants / age range	Measurement of sleep timing (no. of studies)	Findings
Biomarkers of cardiometabolic risk		
Cross-sectional (n = 7) 3089 participants 8–19 years	Objectively, using an actigraphy device (n = 6) Subjectively, by self-report (n = 1)	In children and adolescents, adjusted linear regression analyses indicated that objectively measured later midpoint of sleep on weekends (β = 0.049, 95% CI: 0.004–0.093, p = 0.03), but not on weekdays (β = 0.041, 95% CI: 0.005–0.087, p = 0.08), was associated with higher insulin resistance, estimated using the Homeostatic Model Assessment of Insulin Resistance. In girls, each hour increase in weekday and weekend midpoint of sleep represented a significant increase in insulin resistance (β = 0.091, 95% CI: 0.027–0.16, p = 0.006, and β = 0.08, 95% CI: 0.017–0.14, p = 0.01, respectively)[46]. In children, after adjusting for covariates, analyses of covariance revealed that, on average, participants with objectively measured bedtime before 22:30 had significantly better triglyceride/high-density lipoprotein cholesterol ratio (p = 0.026) than participants with bedtime later than 23:15. There was no significant association between bedtime category and blood insulin level or mean arterial pressure[27]. In children, simple linear regression revealed that later midpoint of sleep was significantly associated with lower diastolic blood pressure (β = −0.002, p = 0.04); no significant associations were found between midpoint of sleep and systolic blood pressure, apolipoprotein B/A1 or glycoprotein acetyls[28]. In children and adolescents, adjusted multiple linear regression analyses revealed that objectively measured later bedtimes (total, during the week and on the weekend) were significantly associated with higher systolic blood pressure z-score (total: β = 0.22, p = 0.02; weekday: β = 0.21, p = 0.02; weekend: β = 0.23, p = 0.02). No associations were found between bedtime and insulin resistance, triglycerides z-score, high-density lipoprotein-C z-score, low-density lipoprotein-C or diastolic blood pressure z-score[29]. In a sample of adolescents with overweight or obesity, simple linear regression analyses showed that objectively measured earlier weekday bedtime was significantly associated with better fasting insulin resistance (p = 0.04) but was not associated with the Matsuda Index (p = 0.23)[47]. 2 studies reported no significant associations between objectively[30] and subjectively[33] measured sleep timing and cardiometabolic risk factors including blood pressure, fasting serum levels of glucose and insulin, and dyslipidemia.

Continued on the following page

TABLE 2 (continued)
Summary of findings for the association between sleep timing and important health outcomes, in apparently healthy children and adolescents

Study design and no. / No. of participants / age range	Measurement of sleep timing (no. of studies)	Findings
Sleep duration and quality		
Longitudinal (n = 1) 783 participants 6–10 years	Objectively, using an actigraphy device (n = 1)	In children, no significant longitudinal associations were found between objectively measured sleep onset or midpoint of sleep and sleep duration[17].
Cross-sectional (n = 10) 112 043 participants 5–20 years	Objectively, using an actigraphy device (n = 3) Subjectively, by self-report (n = 6) and proxy-report (n = 1)	In a sample of children and adolescents, self-reported earlier midpoint of sleep on both school and weekend nights was correlated with better self-reported sleep quality ($r = 0.16$, $p = 0.03$ and $r = 0.26$, $p = 0.002$, respectively). No significant association was found between midpoint of sleep on both school and weekend nights and subjectively measured sleep duration[48]. In children, objectively measured later sleep onset and earlier sleep offset were significantly correlated with decreased total sleep time ($r(1229) = -0.60$ and $r(1229) = 0.16$, respectively)[25]. In adolescents and young adults, adjusted Poisson regression modelling revealed that bedtime at ~22:30 or later, compared to ~22:00 or earlier, was associated with more sleep quality problems (~22:30: β = 0.04, 95% CI: 0.02–0.05, $p < 0.0001$; ~23:00: β = 0.08, 95% CI: 0.07–0.09, $p < 0.0001$; ≥23:30: β = 0.2, 95% CI: 0.2–0.2, $p < 0.0001$) and with an increased odds of having trouble falling asleep during the last 6 months[37]. In children and adolescents, self-reported later bedtime was associated with decreased self-reported sleep duration[20]. In a sample of adolescents, self-reported later bedtime was found to be significantly correlated with lower self-reported total sleep time and with greater report of unrefreshing sleep, $r(306) = -0.50$, $p < 0.001$ and $r(306) = 0.22$, $p < 0.001$, respectively[49]. In children, a significant correlation was found between objectively measured later bedtime and shorter total sleep time ($r = -0.61$, $p < 0.001$)[31]. Children in the proxy-reported late midpoint-of-sleep group had significantly less total sleep duration, by approximately 15 min during weekdays and during the whole week, compared to children in the normal midpoint-of-sleep group ($p < 0.01$)[23]. In a sample of children, fractional multinomial logit models revealed significant associations between objectively measured later bedtime (30 min above the mean compared to 30 min below the mean) and less total sleep time by 35.6 min/night at age 5 and by 39.0 min/night at age 7 ($p < 0.05$)[50]. 2 studies reported no significant associations between subjectively measured sleep timing and sleep duration[15,51].
Eating behaviours		
Cross-sectional (n = 13) 42 138 participants 5–18 years	Objectively, using an actigraphy device (n = 7) Subjectively, by self-report (n = 5) and proxy-report (n = 1)	In a sample of children and adolescents, self-reported later weeknight bedtime was associated with an increased odds of reporting missing breakfast (9–11 years: OR = 4.5, 95% CI: 3.3–6.0; 12–14 years: OR = 4.7, 95% CI: 4.1–5.4; 15–17 years: OR = 4.1, 95% CI: 2.3–7.5) and consuming junk food ≥5 times in a week (9–11 years: OR = 2.7, 95% CI: 2.0–3.5; 12–14 years: OR = 2.9, 95% CI: 2.6–3.3; 15–17 years: OR = 2.1, 95% CI: 1.4–3.3)[52]. In a sample of children, objectively measured later bedtime and sleep onset time were both significantly associated with higher self-reported restrained eating score (β = 0.40, $p < 0.05$ and β = 0.41, $p < 0.05$, respectively). No significant associations were found between sleep timing and emotional or external eating behaviours[53]. In an international sample of children, objectively measured later bedtime was associated with less healthy diet pattern (β = −0.07, 95% CI: −0.11 to −0.02, $p < 0.01$) and more unhealthy diet pattern (β = 0.08, 95% CI: 0.04–0.13, $p < 0.001$)[54]. In an international sample of children, objectively measured later bedtime was associated with greater frequency of cola and soft drink consumption per week ($p < 0.01$), while earlier bedtime was associated with higher frequency of energy drink and sports drink consumption (for both, $p < 0.01$)[55].

Continued on the following page

TABLE 2 (continued)
Summary of findings for the association between sleep timing and important health outcomes, in apparently healthy children and adolescents

Study design and no. / No. of participants / age range	Measurement of sleep timing (no. of studies)	Findings
		In a sample of children and adolescents, multivariable linear regression revealed that, compared to those in the early-bed/early-rise self-reported sleep-timing group, those in the two late-bed groups had significantly lower total Dietary Guideline Index for Children and Adolescents scores (late-bed/early-rise: β = −3.09, 95% CI: −5.32 to −0.86, $p = 0.007$; late-bed/late-rise: β = −3.99, 95% CI: −5.66 to −2.32, $p < 0.001$). No significant association was found between sleep-timing group and energy intake[18]. In a sample of children, those in late-sleep groups had significantly lower fruits and vegetables dietary pattern scores (late-sleep/early-wake: mean = −0.1; late-sleep/late-wake: mean = −0.06; $p < 0.05$) than those in the early-sleep/early-wake group (mean = 0.19). Children in the late-sleep/late-wake group, compared to the early-sleep/early-wake group, also reported significantly lower weekly frequency of consumption of fruits and vegetables (mean = 16 vs. mean = 19, mean difference [95% CI]: −2.9 [−4.9 to −0.9], $p < 0.05$) and higher weekly frequency of consumption of sugar-sweetened beverages (mean = 7 vs. mean = 5, mean difference [95% CI]: 1.8 [0.2 to 3.3], $p < 0.05$), after adjusting for covariates. No significant associations were found between sleep-timing group and snack patterns or extra consumption[26]. In children, adjusted linear regression models revealed that objectively measured later bedtime was associated with greater fat (β = 0.02, $p < 0.02$) and lower carbohydrate (β = −0.02, $p < 0.05$) intake daily. No association was found between bedtime and daily caloric intake or daily protein intake. Later bedtime was associated with greater after-dinner caloric intake (β = 0.81, $p < 0.01$) in the form of protein (β = 0.08, $p < 0.04$) and fat (β = 0.37, $p < 0.02$), but not carbohydrate. Later bedtime was also associated with later timing of the last (β = 0.57, $p < 0.001$) and first (β = 0.76, $p < 0.001$) meals of the day[31]. Among children and adolescents who self-reported their midpoint of sleep, those in the late (vs. early) midpoint-of-sleep group had a significantly higher probability of consuming sweet and caffeinated beverages and sugary, salty and fatty foods, starting in the afternoon and for the rest of the day. No association was found between sleep-timing group and the probability of consumption of vegetables, proteins, fruits and carbohydrates. Those in the early (vs. late) midpoint-of-sleep group were more likely to report not skipping breakfast (96% vs. 30%, respectively, X^2 [2, N = 55] = 26.7, $p < 0.01$). No other associations were found between sleep-timing group and the two other meals[51]. In children, analyses of variance revealed that being in the proxy-reported late midpoint-of-sleep group on weekdays ($p < 0.05$) and weekend days ($p < 0.01$) was associated with an increased cumulative number of self-reported eating risk factors[23]. 4 studies reported no significant associations between objectively[24,29] and subjectively[15,56] measured sleep timing and eating behaviours.
Physical activity and sedentary behaviours		
Longitudinal (n = 1) 1059 participants 7–12 years	Objectively, using an actigraphy device (n=1)	In children, fixed effect models revealed that an incremental increase by 30 min in objectively measured sleep onset was significantly associated with less time spent in LPA, moderate physical activity, MVPA and VPA (by 12, 3.5, 6.2 and 0.4 min, respectively) and more sedentary time (by 31 min) (all $p < 0.001$)[57].
Cross-sectional (n = 15) 14 642 participants 5–18 years	Objectively, using an actigraphy device (n=10) Subjectively, by self-report (n=4) and proxy-report (n=1)	In a sample of children and adolescents with obesity, after adjusting for covariates, linear regression revealed a significant association between later midpoint of sleep and daily amount of screen time (β = 105.7, 95% CI: 36.4–175.1, $p < 0.01$). However, no significant associations were found between sleep timing and time spent in MVPA or sedentary time[56]. In children and adolescents, self-reported later midpoint of sleep on school days was significantly associated with higher total time spent watching TV, using a tablet, using a smartphone and watching TV at night (all $p < 0.04$) as well as lower smartphone use during the day ($p = 0.001$). No association was found between midpoint of sleep on school days and 4 of the screen-time use outcomes. In addition, later weekend midpoint of sleep was significantly associated with higher total time spent watching TV, using a smartphone, watching TV at night, using a cell phone at night (all $p < 0.02$) and lower tablet and smartphone use during the day (both $p < 0.05$). Weekend midpoint of sleep was not associated with 3 of the screen-time use outcomes[48]. In an international sample of children, adjusted analyses revealed that objectively measured later bedtime was associated with less time spent in MVPA (β = −1.08, 95% CI: −1.13 to −1.03, $p < 0.0001$), more time spent in sedentary behaviour (β = 0.36, 95% CI: 0.31–0.41, $p < 0.0001$) and higher screen-time score (β = 1.19, 95% CI: 1.14–1.25, $p < 0.0001$)[54].

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TABLE 2 (continued)
Summary of findings for the association between sleep timing and important health outcomes, in apparently healthy children and adolescents

Study design and no. / No. of participants / age range	Measurement of sleep timing (no. of studies)	Findings
		In a sample of children, those in both objectively measured late-wake sleep-timing groups were significantly less active (early-sleep/late-wake: mean = 72 min/day; late-sleep/late-wake: mean = 70 min/day) than those in the early-sleep/early-wake group (mean = 81 min/day). In addition, children in the late-sleep/late-wake group were significantly less active than those in the late-sleep/early-wake group (late-sleep/late-wake: mean = 70 min/day; late-sleep/early-wake: mean = 79 min/day). No significant association was found between objectively measured sleep timing and meeting screen-time guidelines[26]. In children, fixed interindividual analysis revealed that objectively measured later sleep onset was associated with less objectively measured time spent in MVPA per hour ($\beta = -0.012$, $p = 0.001$), independent of total sleep time[58]. In children, adjusted linear regression models revealed significant associations between objectively measured later midpoint of sleep ($\beta = -0.11$, $p < 0.05$), earlier bedtime ($\beta = 0.10$, $p < 0.05$) and later wake-up time ($\beta = -0.13$, $p < 0.05$) and less time spent in LPA. Also, later midpoint of sleep ($\beta = 0.08$, $p < 0.05$) and later wake-up time ($\beta = 0.10$, $p < 0.05$), but not bedtime, were significantly associated with more time spent being sedentary. No significant associations were found between sleep-timing variables and VPA, MVPA and moderate PA[32]. In children at timepoint 1 (mean age 12.3 y), objectively measured later midpoint of sleep was significantly associated with lower PA ($r(165) = -0.10$, $p = 0.03$), LPA ($r(165) = -0.10$, $p = 0.04$), MVPA ($r(165) = -0.10$, $p = 0.04$) and higher sedentary behaviour ($r(165) = 0.12$, $p = 0.02$). At timepoint 2 (mean age 16.9 y), no significant associations were found between sleep timing and PA or sedentary behaviour[59]. In children and adolescents who self-reported their sleep timing, the late-bed groups (vs. the early-bed/early-rise group) had the highest odds of lower PA and higher sedentary behaviour. No significant differences in odds of outcome were found between the two early-bed groups on each outcome studied. Compared to participants in the early-bed/early-rise group, the odds of low MVPA were 1.77 for the late-bed/late-rise group and 1.58 for the late-bed/early-rise group; the odds of high amounts of screen time were 2.92 for the late-bed/late-rise group and 1.94 for the late-bed/early-rise group; and the odds of both high amounts of screen time and low MVPA were 2.87 for the late-bed/late-rise group and 2.10 for the late-bed/early-rise group. In addition, on average, the early-rise groups engaged in significantly more minutes of MVPA, VPA, play and active transport per day and had higher daily pedometer step counts than the late-rise groups. The late-bed groups engaged in significantly more minutes of total sedentary time, screen time, watching television, playing videogames and computer time[20]. In children, fractional multinomial logit models at age 5 y revealed significant associations between later bedtime (30 min above the mean vs. 30 min below the mean) and more sedentary time and LPA time (10.1 and 21.6 min/day, respectively), but not with MVPA. At age 7 y, there were significant associations between later bedtime (30 min above the mean vs. 30 min below the mean) and more sedentary, LPA and MVPA time (14.7, 23.2 and 5.3 min/day, respectively)[50]. In children, objectively measured later weekday bedtime was associated with self-reported screen time that was longer by an average of 3.19 (1.42) h/week ($p < 0.05$). No significant associations were found between objectively or subjectively measured bedtime or wake-up time and time spent in MVPA[24]. 5 studies reported no significant associations between objectively[25,31,60] and subjectively[15,23] measured sleep timing.

Abbreviations: LPA, light physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; no., number; VPA, vigorous physical activity; y, years.

TABLE 3
Quality assessment and quality of evidence rating for the association between sleep timing and health outcomes in apparently healthy children and adolescents, by health outcome and study design

Health outcome	Study design	No. of studies	No. of participants	Quality assessment indicator					Quality (GRADE)[b]
				Risk of bias	Inconsistency	Indirectness	Imprecision	Other[a]	
Critical health outcomes									
Adiposity	Longitudinal	3	7756	Serious risk[c]	No serious risk	No serious risk	No serious risk	None	Very low
	Cross-sectional	17	38 798	No serious risk	Serious risk[d]	No serious risk	No serious risk	None	Very low
Emotional regulation	Longitudinal	2	6331	Serious risk[c]	No serious risk	No serious risk	No serious risk	None	Very low
	Cross-sectional	7	106 225	Serious risk[c]	No serious risk	No serious risk	No serious risk	None	Very low
Cognitive function and academic performance	Longitudinal	2	6331	Serious risk[c]	Serious risk[c]	No serious risk	No serious risk	None	Very low
	Cross-sectional	5	123 372	Serious risk[c]	No serious risk	No serious risk	No serious risk	None	Very low
Quality of life and well-being	Longitudinal	1	3631	No serious risk	Only one study	No serious risk	Serious risk[e]	None	Very low
	Cross-sectional	1	6266	No serious risk	Only one study	No serious risk	Serious risk[e]	None	Very low
Accidents/injuries	Cross-sectional	1	103 859	Serious risk[c]	Only one study	No serious risk	Serious risk[e]	None	Very low
Important health outcomes									
Biomarkers of cardiometabolic risk	Cross-sectional	7	3089	No serious risk	Serious risk[c]	No serious risk	No serious risk	None	Very low
Sleep duration and quality	Longitudinal	1	783	No serious risk	Only one study	No serious risk	Serious risk[e]	None	Very low
	Cross-sectional	10	112 043	Serious risk[c]	No serious risk	No serious risk	No serious risk	None	Very low
Eating behaviour	Cross-sectional	13	42 138	Serious risk[c]	No serious risk	No serious risk	No serious risk	None	Very low
Physical activity and sedentary behaviour	Longitudinal	1	1059	No serious risk	Only one study	No serious risk	Serious risk[e]	None	Very low
	Cross-sectional	15	14 642	Serious risk[c]	No serious risk	No serious risk	No serious risk	None	Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; no., number.

[a] Large magnitude of effect, dose response, and accounting for all plausible confounding.

[b] Quality was assessed using the GRADE framework as per the GRADE Working Group, which grades the quality of evidence as follows[13]: "high" means that further research is very unlikely to change our confidence in the estimate of effect; "moderate" means that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; "low" means that further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate; and "very low" means that we are very uncertain about the estimate.

[c] One or more studies was published and both the exposure and outcome were measured via questionnaire with unknown psychometric properties.

[d] Mixed findings reported in an outcome, which resulted in the quality of the outcome to be downgraded.

[e] Serious imprecision due to the lack of evidence in the outcome, which resulted in the quality of the findings for the outcome to be downgraded.

waist circumference[27] and 7 studies used BMI and at least one additional measure of adiposity[25,26,29,30,32-34]. Five studies reported mixed findings in the associations between sleep timing and adiposity[19,21-24]. Two studies that assigned participants to one of four sleep-timing groups by dichotomizing bedtimes and wake-up times reported a significant association between sleep-timing groups and an adiposity outcome. Relative to the early-bed/early-rise group, those in the late-to-bed sleep-timing groups had higher BMI z-score[18] and greater odds of having overweight and obesity[20].

The quality of evidence for the 3 longitudinal studies investigating the association between sleep timing and adiposity was downgraded from low to very low due to a serious risk of bias. The quality of the evidence for the 17 cross-sectional studies investigating this association was downgraded from low to very low due to inconsistency in the findings.

Emotional regulation

A total of 9 observational studies—2 longitudinal and 7 cross-sectional—reported on the association between sleep timing and emotional regulation in children and adolescents 4 to 20 years old. In children, being categorized as having a late bedtime over multiple timepoints was significantly associated with more behavioural problems[16]. The other longitudinal study reported mixed findings between sleep timing at different time points and emotional distress[35]. Eight cross-sectional studies were initially extracted, but to avoid inflating the results in the emotional regulation outcome, one of the studies by Short and colleagues[49] was removed as the authors published twice on the same outcome measurement, using the same sample and the same statistical analysis. The study by Short et al.[39] had the highest number of outcome measurements within the emotional regulation health outcome and was therefore retained (see Supplementary Table 2). Of the remaining 7 cross-sectional studies, 2 reported mixed findings[38,41]. Three studies reported that later bedtime was associated with more behavioural problems[40], depressive symptoms[36,39] and anxiety[39]. Compared to a bedtime at approximately 22:00 or earlier, bedtime between 22:30 and 23:00 was associated with lower depression symptoms among adolescents, while bedtime at 23:00 or later was associated with higher depression symptoms, anxiety or nervousness, feeling irritated and having tantrums[37]. Wang and colleagues[42] reported that in Grade 12 adolescents, an earlier wake-up time was associated with less academic stress.

TABLE 4
High-level summary of findings and effect for the association between sleep timing and health outcomes in apparently healthy children and adolescents, by health outcome and study design

Health outcome	No. and type of studies / No. of participants / age range	Summary of findings
Critical health outcome		
Adiposity	3 longitudinal 7756 4–18 years	1 study reported a longitudinal association between later bedtime during adolescence and higher BMI z-score later in adolescence and adulthood 1 study reported a longitudinal association between reoccurring late bedtime over multiple timepoints and higher BMI z-score and waist circumference in children 1 longitudinal study reported null findings
	17 cross-sectional 38 798 5–18 years	1 study reported that children and adolescents in the late-to-bed groups had higher BMI z-score than those in the early-bed/early-rise group 1 study found that children and adolescents in the late-to-bed groups had greater odds of overweight and obesity than those in the early-to-bed/early-to-rise group 1 study with mixed findings reported an association between later midpoint of sleep and greater waist-to-height ratio, but not BMI, in adolescents 1 study with mixed findings reported an association between later bedtime, but not wake-up time, and higher BMI z-scores in 5-year-old children 1 study with mixed findings reported an association between later weekend midpoint of sleep, but not weekday midpoint of sleep, and increased odds of higher BMI z-score in female (but not male) children and adolescents 1 study with mixed findings reported that children in the late-sleep group had higher fat mass percentage and waist circumference but not higher BMI z-scores or the sum of the skinfolds 1 study with mixed findings reported an association between later weekday, not weekend, bedtime and greater adiposity in children with obesity 10 studies reported null findings
Emotional regulation	2 longitudinal 6331 4–18 years	1 study reported a longitudinal association between reoccurring late bedtime over multiple timepoints and higher behavioural problems in children 1 study with mixed findings reported a longitudinal association, between both late school-year and summertime bedtime, but not at all time points, and higher odds of emotional distress 6–8 years later in late adolescence or early adulthood
	7 cross-sectional 106 225 7–20 years	1 study in children reported an association between bedtime after 22:00 and increased odds of higher depressive symptoms 1 study in adolescents reported that, compared to a bedtime at ~22:00 or earlier, bedtime between ~22:30 and before 23:00 is associated with better depression score, while bedtime at ~23:00 or later is associated with worse depression scores, greater odds of having anxiety or nervousness, and greater odds of being irritated and having tantrums 1 study in adolescents reported an association between later bedtime and higher depressed mood and anxiety scores 1 study in adolescents with obesity reported an association between later bedtime and higher behavioural problems score 1 study in adolescents reported an association between later wake-up time and greater academic stress 1 study with mixed findings reported an association between later bedtime, but not wake-up time, and increased depression score in children and adolescents 1 study with mixed findings reported an association between later midpoint of sleep and psychiatric problems, including more thought problems, more rule-breaking behaviour, more affective problems and more conduct problems, but not with a majority of the scales, in adolescents

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TABLE 4 (continued)
High-level summary of findings and effect for the association between sleep timing and health outcomes in apparently healthy children and adolescents, by health outcome and study design

Health outcome	No. and type of studies / No. of participants / age range	Summary of findings
Cognitive function and academic performance	2 longitudinal 6331 4–18 years	1 study with mixed findings reported a longitudinal association between later school-year bedtime, but not summertime bedtime, and lower grades in adolescents 1 longitudinal study reported null findings
	5 cross-sectional 123 372 7–20 years	1 study in adolescents reported an association between bedtimes before 22:00 or after 00:00 with increased odds of lower grades relative to bedtime between 22:00 and 22:59 1 study in adolescents reported an association between bedtime at ~22:30 or later and increased odds of trouble with following class education, completing homework assignments, preparing for examinations, and writing tasks, while bedtime at ~23:00 or later is also associated with increased odds of having trouble with reading tasks 1 study with mixed findings reported a significant association between later bedtime, but not waketime, and lower college entrance exam scores, in adolescents 2 studies reported null findings
Quality of life and well-being	1 longitudinal 3631 4–9 years	1 study reported a longitudinal association between reoccurring late bedtime over multiple timepoints and poorer psychosocial and physical health functioning in children
	1 cross-sectional 6266 9–11 years	1 study reported null findings
Accidents / injuries	1 cross-sectional 103 859 14–20 years	1 study with mixed findings reported associations between bedtime at ~23:00 (relative to bedtime at ~22:00 or earlier) and lower odds of having an accident at recess, in the classroom, and on the way to school in adolescents. No association was found between bedtime and accidents during gym class
Important health outcome		
Biomarkers of cardiometabolic risk	7 cross-sectional 3089 8–19 years	1 study with mixed findings reported that, in children and adolescent boys and girls, later midpoint of sleep on weekends, but not on weekdays, is associated with higher insulin resistance. In girls, each hour increase in weekday and weekend midpoint of sleep represented a significant increase in insulin resistance 1 study with mixed findings reported that, in children, a bedtime before 22:30 is associated with better triglyceride/high-density lipoprotein cholesterol ratio compared to a bedtime later than 23:15. No significant association was found between bedtime category and blood insulin level nor mean arterial pressure 1 study with mixed findings reported that, in children, later midpoint of sleep is associated with lower diastolic blood pressure, but no significant associations were found between midpoint of sleep and systolic blood pressure, apolipoprotein B/A1 or glycoprotein acetyls 1 study with mixed findings reported that, in children and adolescents, later bedtime is associated with higher systolic blood pressure z-score, but that there were no associations between bedtime and insulin resistance, triglycerides z-score, high-density lipoprotein-C z-score, low-density lipoprotein-C or diastolic blood pressure z-score 1 study with mixed findings reported a significant association between an earlier bedtime and better fasting insulin resistance but not with the Matsuda Index in adolescents with overweight or obesity 2 studies reported null findings

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TABLE 4 (continued)
High-level summary of findings and effect for the association between sleep timing and health outcomes in apparently healthy children and adolescents, by health outcome and study design

Health outcome	No. and type of studies / No. of participants / age range	Summary of findings
Sleep duration and quality	1 longitudinal 783 6–10 years	1 longitudinal study reported null findings
	10 cross-sectional 112 043 5–20 years	1 study in children reported an association between earlier sleep onset and later offset with longer total sleep time 1 study in adolescents reported an association between a bedtime at ~22:30 or later and lower sleep quality, relative to a bedtime at ~22:00 or earlier 1 study in children and adolescents reported an association between later bedtime and lower sleep duration 2 studies in children reported a significant association between later bedtime and less total sleep time 1 study in adolescents reported significant associations between later bedtime and less total sleep time and more reports of unrefreshing sleep 1 study in children reported an association between later midpoint of sleep and less total sleep duration 1 study with mixed findings reported associations between earlier midpoint of sleep during both school and weekend nights and better sleep quality, but not sleep duration, in children and adolescents 2 studies reported null findings
Eating behaviour	13 cross-sectional 42 138 5–18 years	1 study in children and adolescents reported an association between later weeknight bedtime with increased odds of missing breakfast and of frequent junk food consumption 1 study in children reported associations between later bedtime and less healthy and more unhealthy diet patterns 1 study in children reported associations between later midpoint of sleep on weekdays and weekend and an increased cumulative number of self-reported eating risk factors 1 study with mixed findings reported associations between later bedtime and sleep onset and higher restrained eating score, but no other significant associations between sleep timing and all other eating behaviours, in children 1 study with mixed findings reported associations between later bedtime and greater frequency of cola and soft drinks consumption, and between earlier bedtime and greater frequency of energy and sports drink consumption, in children 1 study with mixed findings reported associations between children in the late-sleep/late-wake group, compared to children in the early-sleep/early-wake group, and lower fruits and vegetables dietary score, lower weekly frequency of consumption of fruits and vegetables and higher weekly frequency of consumption of sugar-sweetened beverages, but the sleep-timing groups were not associated with snacking patterns or extra consumption 1 study with mixed findings reported associations between the 2 late-to-bed groups, compared to the early-to-bed/early-to-wake group, and lower total dietary score but not energy intake, in children and adolescents 1 study with mixed findings reported associations between later bedtime and higher daily fat intake, lower daily carbohydrate intake, greater caloric intake after dinner and later timing of breakfast and dinner, but no associations with daily total caloric intake or protein intake, in children 1 study with mixed findings reported associations between later midpoint of sleep and higher sustained probability of consuming sweet and caffeinated beverages and sugary, salty and fatty foods, from the afternoon onwards, but no associations with the probability of consuming vegetables, proteins, fruits or carbohydrates, in children and adolescents 4 studies reported null findings

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TABLE 4 (continued)
High-level summary of findings and effect for the association between sleep timing and health outcomes in apparently healthy children and adolescents, by health outcome and study design

Health outcome	No. and type of studies / No. of participants / age range	Summary of findings
PA and sedentary behaviour	1 longitudinal 1059 7–12 years	1 study in children reported a longitudinal association between an incremental increase in sleep onset and less time spent in PA at all intensities and more time spent in sedentary behaviour the following day
	15 cross-sectional 14 642 5–18 years	1 study in children reported that later bedtime is associated with less time spent in MVPA and more time spent being sedentary and having more screen time 1 study in children reported that, at 5 years old, later bedtime is associated with more sedentary time and more LPA, but at 7 years old, it is also associated with more MVPA 1 study in children and adolescents reported numerous associations between later midpoint of sleep and more screen time across most devices on both week and weekend days 1 study in children reported an association between later sleep onset and less MVPA 1 study in children and adolescents reported associations between the late-to-bed sleep groups, compared to the early-to-bed/early-to-wake group, and lower odds of PA and higher odds of sedentary behaviours 1 study with mixed findings reported an association between later midpoint of sleep and more screen time, but not with time spent in MVPA or sedentary time, in children and adolescents with obesity 1 study with mixed findings reported associations between children in the late-to-wake sleep groups, compared to children in the early-to-bed/early-to-wake group, and less time spent being active but not with meeting the screen-time guidelines 1 study with mixed findings reported associations between later midpoint of sleep at 12 years old and lower amounts of PA overall, of LPA and of MVPA and more sedentary behaviour, but no associations were found at 17 years old 1 study with mixed findings reported associations between children's later midpoint of sleep, earlier bedtime and later wake-up time and less time spent in LPA, but not with higher intensities of PA. Later midpoint of sleep and later wake-up time, but not bedtime, are also associated with more time spent being sedentary 1 study with mixed findings reported an association between later weekday bedtime, but not wake-up time, with more screen time, but not with MVPA, in children 5 studies reported null findings

Abbreviations: BMI, body mass index; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity.

The quality of evidence for the 2 longitudinal studies and the remaining 7 cross-sectional studies investigating the association between sleep timing and emotional regulation was downgraded from low to very low due to serious risk of bias.

Cognitive function and academic achievement

Of the 7 studies reporting on cognitive function/academic performance in children and adolescents 4 to 20 years old, 2 were longitudinal and 5 were cross-sectional. One longitudinal study reported null findings between sleep timing and cognitive performance[16], while the other reported mixed findings, with only school-year bedtime across the timepoints associated with academic performance[35]. Of the 5 cross-sectional studies, 2 studies reported null findings[41,44], 1 study reported mixed findings[42] and 2 studies reported significant associations[37,43]. In a large sample of older adolescents aged 14 to 20 years, compared to a bedtime between 22:00 and 22:59, bedtimes before 22:00 or after 00:00 were associated with increased odds of poor academic performance[37]. Among adolescents aged 16 to 19 years, compared to a bedtime at 22:00 or earlier, later bedtimes were associated with difficulties following in class, completing homework assignments, preparing for exams and with writing and reading tasks[43].

The quality of evidence was downgraded from low to very low due to serious risk of bias and inconsistency in the findings for the 2 longitudinal studies and due to serious risk of bias for the 5 cross-sectional studies.

Quality of life and well-being

Two studies, one longitudinal and the other cross-sectional, reported on the association between sleep timing and quality of life and well-being. Longitudinal findings revealed that reoccurring late bedtime over multiple timepoints was associated with lower psychosocial and physical health functioning in children aged 4 to 9 years[16]. The cross-sectional study, in children aged 9 to 11 years, reported null findings for the overall association between midpoint of sleep and health-related quality of life[45].

The quality of evidence for both studies was downgraded from low to very low, due to serious risk of imprecision for the longitudinal study and for the cross-sectional study.

Accidents/injuries

A single cross-sectional study reported on the association between sleep timing and accidents/injuries. A bedtime at approximately 23:00 for adolescents was associated with the lowest odds of having an

accident at recess, in the classroom and on the way to school, relative to a bedtime at 22:00 or earlier; however, no association was reported between sleep timing and accidents during gym class[37].

The quality of evidence was downgraded from low to very low due to serious risk of bias and imprecision.

Biomarkers of cardiometabolic risk

Seven cross-sectional studies examined the association between sleep timing and biomarkers of cardiometabolic risk (e.g. insulin, lipid profile, blood pressure) in children and adolescents between 8 and 19 years old. Out of these 7 studies, 2 reported null findings[30,33] and 5 reported mixed findings[27-29,46,47].

The quality of the evidence for the 7 cross-sectional studies was downgraded from low to very low due to inconsistency in the findings.

Sleep duration and quality

Initially, 12 studies were extracted for the sleep duration and quality health outcome; however, to avoid inflating the results in this outcome, one of the studies by Short and colleagues[39] was removed because the authors published twice on the same outcome measurement and using the same sample and statistical analysis. The study by Short et al.[49] had the highest number of measurements within the sleep duration and quality health outcome and was therefore retained (see Supplementary Table 3 https://osf.io/nzt23/?view_only=abcbea551fe545e6b73f44e60600da35).

A total of 11 observational studies, 1 longitudinal and 10 cross-sectional, examined the association between sleep timing and sleep duration and quality. The longitudinal study reported null findings between sleep timing and sleep duration in children[17]. Of the 10 cross-sectional studies in children and adolescents 5 to 20 years old, 5 studies reported that later bedtime, wake-up time or midpoint of sleep were associated with significantly shorter total sleep time[20,23,25,31,50]; 1 reported that later bedtime was associated with shorter total sleep time as well as lower quality of sleep[49]; 1 reported that later bedtime was associated with more sleep quality problems[37]; 1 reported mixed findings with a significant association between later midpoint of sleep and lower sleep quality, but no association between midpoint of sleep and sleep duration[48]; and 2 reported null findings between sleep timing and sleep duration[15,51].

The quality of evidence for the longitudinal study was downgraded from low to very low due to imprecision in the findings. The quality of the evidence for the cross-sectional studies was downgraded from low to very low due to serious risk of bias.

Eating behaviours

A total of 13 cross-sectional studies examined the association between sleep timing and eating behaviours in children and adolescents between 5 and 18 years old. Of these 13 studies, 4 reported null findings[15,24,29,56]; 6 reported mixed findings[18,26,31,51,53,55]; and 3 reported significant associations[23,52,54]. In children and adolescents aged 9 to 17 years, later bedtime was associated with greater consumption of junk food and missing breakfast more often[52]. Later bedtime was also associated with a higher amount of unhealthy food consumption and a lower amount of healthy food consumption in children aged 9 to 11 years[54]. In children aged 6 to 10 years, a later midpoint of sleep was associated with a higher eating risk factor score[23].

The quality of evidence for the studies with the eating behaviour health outcome was downgraded from low to very low due to serious risk of bias.

Physical activity and sedentary behaviour

A total of 16 observational studies, including 1 longitudinal and 15 cross-sectional studies, examined the association between sleep timing and physical activity and sedentary behaviour. Antczak and colleagues'[57] longitudinal findings showed that later bedtime in children was associated with significantly higher sedentary time and lower amount of physical activity at all intensities. Of the 15 cross-sectional studies, 5 reported null findings[15,23,25,31,60]; 5 reported mixed findings[24,26,32,56,59]; and 5 reported significant associations between sleep timing and physical activity and sedentary behaviour[20,48,50,54,58]. Two studies in children and adolescents reported that later bedtime was significantly associated with less moderate-to-vigorous physical activity and more sedentary behaviours including screen time[20,54]. A study that measured bedtime and physical activity and sedentary behaviour at two different time points reported that later bedtime was associated with more sedentary time and more light physical activity at age 5 years; at age 7 years, later bedtime was also associated with more sedentary time and more light physical activity but also with more moderate-to-vigorous physical activity[50]. One study showed that later weekday and weekend midpoint of sleep was associated with more screen time across multiple devices in children and adolescents[48]. In children, 2 studies reported that later bedtime and sleep onset, independent of sleep duration or wake-up time, were associated with less physical activity[58].

The quality of evidence was downgraded from low to very low due to imprecision for the longitudinal study and due to serious risk of bias for the cross-sectional studies.

Discussion

Many characteristics of sleep are important for good health. We conducted the present systematic review to improve understanding of the association between sleep timing and health in a population of children and adolescents. Our objectives were to update the knowledge for the sleep recommendations in the *Canadian 24-Hour Movement Guidelines for Children and Youth*[5] and to provide evidence that can be used to better inform the development of future evidence-based healthy sleep interventions.

This systematic review synthesized peer-reviewed scientific evidence from 46 observational studies, including 5 longitudinal and 41 cross-sectional studies, across 21 countries. Overall, the findings suggest that later sleep timing may be associated with poorer emotional regulation, cognitive function/academic performance, eating behaviours, lower sleep duration and quality, and lower physical activity and higher sedentary behaviours. The findings were sparse or less consistent for the associations between sleep timing and adiposity, quality of life/well-being, accidents/injuries and cardiometabolic risk. The quality of the evidence was rated as very low according to GRADE for all outcomes.

The majority of studies that examined the critical outcomes reported on adiposity (n = 20), while studies on accidents/injuries (n = 1) and quality of life/well-being (n = 2) were underrepresented. Studies reporting on the important health outcomes were more evenly spread with 16 studies reporting on the physical activity and sedentary behaviour outcome, 13 on eating behaviour, 11 on sleep duration/quality and 7 on cardiometabolic risk (Table 3).

The evidence presented for the association between sleep timing and adiposity is inconsistent, as more than half of the studies reported null findings (n = 11), which mirrors findings from a recently published systematic review by Chaput et al. in adults[61]. Another finding in both this review and Chaput et al.'s[61] systematic review was that later sleep timing was associated with lower physical activity and higher sedentary behaviour. In addition, both these systematic reviews identified a lack of studies investigating the association between sleep timing and accidents/injuries or quality of life/well-being in their respective populations.

The findings between the two systematic reviews differed for some outcomes. Our current findings indicate that later sleep timing was generally associated with poorer emotional regulation and cognitive function/academic performance in children and adolescents, whereas in adults the associations for mental health and cognitive function were inconsistent[61]. In children and adolescents, more studies are needed to confirm these associations (especially longitudinal studies and randomized trials), including the mechanisms behind them.

Some of the health outcomes we considered in this systematic review differed from those chosen for the adult population[61]. For example, we reviewed the association between sleep timing and eating behaviour in this paper. In children and adolescents, later sleep timing was associated with poorer eating behaviours; this is of concern given that eating behaviours are also independently associated with health outcomes[62]. In addition, as children and adolescents do not always have full control over their eating behaviours, investigating the moderating effect of socioeconomic status, parental figure influence and family structure in the association between sleep timing and eating behaviours of children and adolescents is essential.

In the articles included in this present review, sleep timing was mainly assessed using bedtime, wake-up time, midpoint of sleep or a combination of dichotomized bedtime and wake-up times divided into four different sleep-timing groups. None of these measurements of sleep timing account for sleep duration; in fact, very few studies adequately controlled for sleep duration in their analyses. Controlling for sleep duration is important given the well-established associations between short sleep duration and higher adiposity, lower emotional regulation, lower academic achievement, lower quality of life/well-being[2], lower cognitive performance[63] and altered brain functions and structures[64].

Not surprisingly, one of the most consistent findings in the present systematic review is the association between later sleep timing and shorter sleep duration (given that school start times are fixed). In addition to controlling for sleep duration in observational studies, this research area requires intervention studies that modify sleep timing. Our systematic review did not identify even a single intervention study that focussed on sleep timing. Future intervention studies should try to manipulate sleep timing while maintaining a constant sleep duration (e.g. sleep duration of 8 hours in adolescents, with one group sleeping from 22:00 to 6:00 and the other from 00:00 to 8:00) to understand the effects of sleep timing, independent of sleep duration, on health outcomes.

Strengths and limitations

Our findings should be interpreted in light of the following limitations. The low number of studies and their heterogeneity made comparisons problematic and meta-analyses ill-advised for all health outcomes. Opting for a narrative synthesis prevents adequate weighting of the included studies. In addition, we could not assess publication bias, which is a pervasive problem in the reporting of scientific findings. However, choosing to only include studies published in the last 10 years could have somewhat mitigated that risk, as many more journals have published null findings more frequently in recent years.

A strength of this review is our comprehensive search strategy. However, the studies selected for this review were not without limitations; the quality of evidence included was rated as very low according to GRADE, even considering that GRADE defaults all study designs other than randomized trials to "low quality." The contributing factors for the quality of evidence included study design (mainly cross-sectional studies), serious risk of bias, imprecision and inconsistency. In addition, only a few of the included studies adequately controlled for sleep duration, which makes it difficult to interpret the findings. A large proportion of the included studies relied on a small sample size or used statistical analyses (e.g. correlations) that prevented controlling for important covariates. Almost half of the studies (n = 22) used a subjective assessment for sleep timing, with many using a single question or a questionnaire with unknown psychometric properties. Although this means that more than half of the studies (n = 24) used an objective measure of sleep timing, the number of nights recorded differed greatly across studies.

Conclusion

The evidence suggests that later sleep timing may be associated with poorer health outcomes in children and adolescents, namely emotional regulation, cognitive function/academic performance, sleep duration/quality, eating behaviours and physical activity and sedentary behaviours. However, the findings have predominantly been generated from cross-sectional evidence and studies with stronger designs are needed to investigate the association between sleep timing and health outcomes independent of sleep duration in the pediatric population.

No bedtime recommendation can be proposed based on the available evidence as the evidence presented was modest and the findings reported mostly linear associations. Nevertheless, having an early enough bedtime that allows children and adolescents to meet sleep duration recommendations would be a sensible public health recommendation based on the current findings and the body of evidence that links short sleep duration to adverse health outcomes.

Registration of the protocol

PROSPERO registration no. CRD42020173585; available from www.crd.york.ac.uk/PROSPERO/). No amendment was made

to the protocol or information that was provided at registration.

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Conflicts of interests

No competing interests are declared by the authors.

Authors' contributions and statement

CD, CMS, BGC and JPC screened the papers.

CD and IP extracted the data and performed the quality assessment.

CD drafted the final version of the manuscript under the guidance of JPC.

All authors were involved in the study conception and reviewed and approved the final version of this article for publication.

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2.1.3 Adolescent sleep: guidelines, prevalence, and patterns in Canada and globally

As part of the 24-Hour Movement Guidelines, the recommendations for sleep in adolescents are as follows: for those aged 13 years, it is recommended they obtain 9 to 11 hours of uninterrupted sleep per night [18]. For older adolescents (14-17 years), this range is reduced to 8 to 10 hours of uninterrupted sleep per night [18]. Additionally, maintaining a consistent sleep schedule is emphasized [18]. While sleep consistency is highlighted, sleep timing is not explicitly mentioned here due to the limited research available at the time. However, this important aspect was addressed a few years later in another systematic review, which was shown in the previous section *2.1.2 Sleep timing and health indicators in children and adolescents: a systematic review* [23].

Not that guidelines are meant to be broken, but how many adolescents actually meet the sleep duration recommendations in Canada and around the world? Several studies have attempted to answer this challenging question. Research indicates that a significant proportion of adolescents fall short of achieving the recommended sleep duration, both in Canada and globally, with large variations in the estimates. Various factors, such as increased screen time, decreased physical activity, academic pressures, social demands, income of the country, socioeconomic status, family factors, abundance of light and electrical pollution, poor nutrition, air quality, and the natural chronotype shift towards ‘eveningness’ during adolescence, all contribute to this widespread issue. This highlights the need for ongoing efforts to promote healthy sleep habits among adolescents. This section will report on estimates of the prevalence of lack of sleep, average sleep duration, sleep timing, consistency, and social jetlag.

Research has provided valuable insights into the sleep habits of adolescents, both in Canada and globally. Chaput and Janssen's [24] study, which included 24,896 participants aged 10–17 years from the 2013-2014 Canadian Health Behaviour in School-aged Children study, a nationally representative cross-sectional study, collected subjective sleep data through self-reported questionnaires. The study found that approximately 31% of school-aged children and 26% of adolescents in Canada are considered short sleepers, obtaining less sleep than recommended [24]. In contrast, long sleepers were rare in this age group, with less than 2% sleeping more than the recommended duration [24]. This low prevalence of long sleepers makes it particularly challenging to investigate the potential health risks associated with longer sleep in children and adolescents. In contrast, in adults, a U-shaped relationship between sleep duration and poor health outcomes is well-established, indicating that both short and long sleep are associated with increased risks of poor health [15]. However, in younger populations, while short sleep has consistently been linked to negative health outcomes, the small proportion of long sleepers limits the ability to assess whether excessive sleep poses similar risks in school-aged children and youth.

In 2018, we published a narrative review that examined sleep duration across the lifespan titled: “Sleeping hours: what is the ideal number and how does age impact this?” [25]. Many of the included studies relied on subjective sleep measurements, such as sleep diaries or questionnaires, which is unsurprising given the challenges of objective assessment especially in large-scale studies [25]. However, one of the studies covered in our review was the study by Galland et al. [26]. They conducted a systematic review and meta-analysis of 79 articles from 17 countries, using objectively assessed sleep measurements in children and adolescents aged 3 to 18 years [26]. Their analysis

showed a gradual decline in sleep duration with age: from an average of 9.68 hours per night in children aged 3–5 years (14 studies), to 8.98 hours for children aged 6–8 (14 studies), 8.85 hours for those aged 9–11 (21 studies), 8.05 hours for 12–14-year-olds (15 studies), and 7.4 hours for adolescents aged 15–18 years (15 studies) [26]. While these objectively measured sleep durations offered valuable insights on sleep duration during childhood through adolescence, the sample sizes in the 79 studies were relatively small, ranging from 20 to 515 participants, limiting the representativeness of these findings for the age groups. Additionally, other studies have shown that sleep duration varies by country, further complicating efforts to generalize these results.

A recent study by Garcia-Roman et al. [27] examined cross-national differences in adolescents' sleep and activity patterns across nine countries, including Finland, France, Hungary, Italy, Netherlands, South Africa, South Korea, Spain, and the United Kingdom (UK). Using a 24-hour time-diary approach, the study found that sleep duration ranged from 7:21 hours (South Korea) to 8:46 hours (South Africa and UK) on school days, and from 9:13 hours (South Korea) to 10:33 hours (Netherlands) on non-school days [27]. The prevalence of insufficient sleep (less than 8 hours) on school days was particularly high, ranging from 19.4% in South Africa to 68.9% in South Korea [27]. Several countries, such as France (30.2%), Finland (30.1%), Netherlands (26.1%), and the UK (22.4%), showed similar short sleeper rates to Canada [27]. The study also highlighted differences in sleep timing, with South Africa having the earliest, and Spain the latest, sleep onsets and wake times [27].

The study by Gariepy et al. [28], part of the World Health Organization's (WHO) Health Behaviour in School-aged Children study, examined sleep patterns in over 165,000

children and adolescents aged 11, 13, and 15 years from 24 European and North American countries during school months. Results indicated that weeknights (Sunday to Thursday nights) sleep duration varied widely, ranging from 7:47 hours in Poland to 9:07 hours in Flemish Belgium, while weekend nights (Friday and Saturday nights), sleep duration extended from 9:31 hours in Greece to 10:22 hours in Flemish Belgium [28]. Across countries, more children and adolescents did not meet sleep duration recommendations on weeknights (14%–68%) compared to weekend nights (8%–21%) [28]. In Canada, the average sleep duration was 8:41 hours on weeknights and 9:49 hours on weekend nights, with 34.4% not meeting sleep duration recommendations on weeknights compared to 14.8% on weekend [28]. The percentage of children and adolescents not meeting weeknight sleep duration recommendations in Canada was similar to rates observed in French Belgium (31.1%), Denmark (33.2%), UK (35%), and Sweden (36.1%) [28].

They also reported on average bedtimes which on weeknights ranged from 21:42 in Flemish Belgium to 23:18 in Greece, with wake times spanning from 06:18 in Hungary to 07:23 in Spain [28]. On weekends, bedtimes extended from 23:14 in Flemish Belgium to as late as 00:54 in Spain, while wake times shifted later, from 09:11 in Hungary to 10:36 in Spain [28]. Social jetlag, defined as the difference between weekend and weekday midpoint sleep, was prevalent, ranging from 1:11 hours in Moldova to 2:12 hours in Sweden [28]. In Canada, social jetlag averaged 1:24 hours, with no significant difference between boys and girls, but it worsened with age: 1:15 hours for 11-year-olds, 1:27 hours for 13-year-olds, and 1:30 hours for 15-year-olds [28]. In two-thirds of the countries, older adolescents experienced greater social jetlag than their younger peers [28].

Additionally, the study found that, in 62.5% of the countries (15 out of 24), boys reported slightly longer sleep durations on weeknights than girls, with differences around 10 minutes [28]. In Canada, boys averaged 6 minutes more sleep than girls on weeknights, while girls averaged 8 minutes more on weekend nights [28]. Not surprisingly, findings revealed that older adolescents consistently reported shorter sleep durations across all countries [28]. In Canada, average sleep duration on weeknights was 9:18 hours for 11-year-olds, 8:38 hours for 13-year-olds, and 8:04 hours for 15-year-olds [28]. On weekend nights, sleep duration increased across all ages but still declined with age, with averages of 10:03 hours for 11-year-olds, 9:49 hours for 13-year-olds, and 9:33 hours for 15-year-olds [28]. This equated to an approximate annual reduction of 18.5 minutes of sleep per night as age increased [28].

In summary, the Canadian 24-Hour Movement Guidelines recommend 9 to 11 hours of uninterrupted sleep per night for 13-year-olds and 8 to 10 hours for older adolescents, along with maintaining a consistent sleep schedule [18]. However, research shows a gap between these recommendations and actual sleep habits, with many adolescents failing to meet the guidelines, particularly on school nights. Factors such as early school start times, increased screen time, academic pressures, social demands, socioeconomic status, and biological shifts toward eveningness during adolescence all contribute to this shortfall in adequate sleep.

According to studies, a significant portion of Canadian children and adolescents, between 26% and 34%, do not meet the recommended sleep duration guidelines, while long sleep is very rare in this age group and remains largely unassessed due to its low

prevalence globally [24,28]. Similar proportions of youth failing to meet sleep duration recommendations are observed in other high-income countries, including France, Finland, the Netherlands, the UK, French Belgium, Denmark, and Sweden [24,27,28]. Canadian youth, like their peers internationally, also face challenges in maintaining a consistent sleep schedule, as demonstrated by widespread social jetlag, with later bedtimes and longer sleep durations on weekends compared to school nights [27,28]. These insights underline the need for targeted interventions to improve sleep among adolescents.

2.1.4 Summary

Sleep is a fundamental component of overall health and is crucial across all ages, influencing cognitive, emotional, and physical well-being [14,15,17,21,23,29]. Research highlights that inadequate sleep can lead to numerous health issues, especially during adolescence, a critical period of development. A series of studies informed the Canadian 24-Hour Movement Guidelines, which offer age-based sleep recommendations, integrating sleep with other daily movement behaviours to optimize health outcomes for Canadians [18–20].

In adults, systematic reviews emphasize a U-shaped relationship between sleep duration and health risks, where both short and long sleep durations are linked to increased risks of mortality, cardiovascular disease, and T2D [15]. These studies support a recommended 7–9 hours of sleep for adults and further note the health risks associated with inconsistent sleep timing and social jetlag [15,17].

In preschool children aged 0 to 4 years, shorter sleep duration has been linked to adverse health outcomes, such as increased adiposity and poorer emotional regulation, underscoring the need for adequate sleep to support growth and development [21]. For children and adolescents aged 5–17 years, longer sleep duration has been associated with lower adiposity, better emotional regulation, enhanced academic performance, and improved quality of life, although further intervention-based research is needed to clarify these associations [22].

Our systematic review, shown in *section 2.1.2*, extends this understanding by focusing on sleep timing's impact on health in children and adolescents (ages 5 to 18), providing evidence to further guide sleep health recommendations [23]. The systematic review included 46 studies observational studies, from 21 countries involving 208,992 unique participants and sleep was assessed subjectively via actigraphy in 52% of the studies. Findings revealed that later sleep timing was generally associated with a higher risk of obesity, unhealthy dietary habits, reduced physical activity, and poorer mental health, such as increased anxiety and depression [23]. It also noted that later bedtimes often result in shorter sleep durations, negatively impacting cognitive and metabolic health [23]. The findings underscore the importance of interventions to encourage earlier sleep onset, such as adjusting school start times and promoting better sleep hygiene [23].

For adolescents, the guidelines recommend 9 to 11 hours of sleep for 13-year-olds and 8 to 10 hours for older teenagers, with an emphasis on keeping a consistent sleep schedule for all, regardless of age [18]. Despite these recommendations, evidence reveals that 26–34% of Canadian adolescents fall short of the guidelines, with similar trends observed globally [24,28]. Factors such as early school start times, screen time,

academic and social pressures, and shifts toward eveningness in adolescence contribute to inadequate sleep. Social jetlag is prevalent, with adolescents going to bed later and sleeping longer on weekends compared to school nights, indicating inconsistency in sleep schedules that can negatively impact health [28].

Comparably, high-income countries including Canada, France, Finland, the Netherlands, the UK, French Belgium, Denmark, and Sweden face similar sleep challenges in youth populations [24,27,28]. The scarcity of long sleep durations further complicates assessments of associated health risks, with most research focused on the adverse effects of short sleep [24]. Canadian adolescents, like their peers globally, experience more pronounced social jetlag and reduced sleep duration with age, underscoring the need for initiatives promoting adequate and consistent sleep [28].

Given the widespread prevalence and health risks of insufficient and inconsistent sleep among adolescents, immediate action is warranted to implement targeted sleep interventions for youth. This is particularly critical for high-risk groups, such as those with obesity or at elevated risk for T2D, where establishing healthy sleep habits may play a vital role in mitigating further health complications. To aid clinicians and health practitioners, we previously published six concise questions assessing key sleep attributes: duration, timing, and consistency [30]. In another publication, we have outlined strategies to improve sleep, which include encouraging regular physical activity, maintaining a balanced diet and avoiding late-night eating, exposure to brighter light during the day and dimmer light at night, avoiding caffeine late in the day, considering short naps, limiting alcohol and avoiding smoking, and seeking treatment for specific sleep issues [16].

2.2 Associations Between Sleep and Obesity in the Pediatric Population

2.2.1 Introduction

The WHO defines obesity as the excessive accumulation of body fat that poses significant health risks [31]. While the definition is widely accepted, the classification of obesity as a chronic disease is not universally recognized. However, many health organizations around the world do consider obesity a chronic disease, influenced by genetic, metabolic, and behavioural factors, which requires targeted prevention and intervention strategies for both adults and children [31–36]. Individuals with obesity often encounter weight bias, stigma, discrimination, and difficulties in accessing compassionate, evidence-based healthcare [37].

According to recent data, it was estimated that in 2022 over 1 billion people globally are living with obesity [38]. The global prevalence of childhood obesity is approximately 5.6% in girls and 7.8% in boys [38]. In Canada, obesity prevalence among children increased from around 5% in girls and 4% in boys in 1990 to approximately 9% and 14%, respectively, by 2020, with a plateau in rates observed around 2010 [38]. Obesity rates have plateaued in many high-income countries and they continue to increase in low- and middle-income countries, especially in parts of Asia [38]. Although obesity rates have plateaued in many high-income countries, the incidence of severe obesity has grown considerably, now accounting for one-quarter to one-third of all obesity cases [38].

A recent study revealed that obesity imposes a significant economic burden on Canada, with an estimated annual cost of CAD $23 billion in 2021 [38]. This includes CAD $9.4 billion in lost revenue from reduced employment activity and CAD $7.9 billion in

healthcare expenses, alongside CAD $3.69 billion in disability-related costs [38]. On a per capita basis, the fiscal impact amounts to CAD $752 per taxpayer annually [38]. The study also highlights that a 1% reduction in obesity prevalence could result in annual net fiscal gains of CAD $229.7 million [38]. However, a key limitation of the study is its focus on the current fiscal burden of obesity in adults, without considering the long-term economic impacts related to childhood and adolescent obesity. Although obesity rates in children and adolescents have plateaued in Canada, the persistence of high prevalence rates could still contribute to significant future healthcare costs.

Pediatric obesity is typically measured using body mass index (BMI), adjusted for age and sex to account for natural variations during growth. Three critical guidelines are widely used in both research and clinical practice to assess weight status: the 2007 WHO Growth Reference, the 2000 CDC Growth Charts, and the Extended International (International Obesity Task Force [IOTF]) BMI cut-offs for overweight, obesity, and thinness [39–43]. Each systems rely on age- and sex-specific BMI percentiles or thresholds, reflecting differences in growth patterns between boys and girls at various ages [39–43].

The 2007 WHO Growth Reference applies to children and adolescents aged 5–19 years [42]. It assesses weight status by calculating BMI and comparing it to reference curves specific to age and sex [42]. This globally recognized standard helps monitor growth and identify risks of malnutrition or obesity [42]. According to this reference, obesity is defined as a BMI greater than 2 standard deviations above the median, which corresponds to a BMI at or above the 97th percentile [42]. Both BMI z-scores and BMI percentiles can be calculated using this system [42].

The 2000 CDC Growth Charts, used for children and adolescents aged 2–20 years, provide similar age- and sex-specific curves for assessing weight status based on BMI-for-age percentiles [43]. The CDC Growth Charts define obesity as a BMI at or greater than the 95th percentile, with severe obesity categorized as a BMI at or above 120% of the 95th percentile or at or above the 99th percentile [43]. The 2000 CDC Growth Charts are widely employed in the United States for both pediatric clinical and public health purposes.

The IOTF BMI cut-offs, developed by Cole and colleagues [39–41], provide an alternative framework for assessing overweight, obesity, and thinness in children and adolescents aged 2–18 years. These cut-offs are derived from an international reference population, linking BMI percentiles to adult BMI categories (e.g., BMI ≥25 for overweight and BMI ≥30 for obesity) through age- and sex-specific centiles [39–41]. The IOTF system is particularly useful for international comparisons, as it standardizes weight status thresholds across diverse populations [39–41]. Additionally, this system includes cut-offs for thinness grades I, II, and III, which are based on adult BMI equivalents of 18.5, 17, and 16, respectively, facilitating the identification of undernutrition risks [39–41].

Adolescent obesity is driven by various environmental and behavioural factors. Obesogenic environments, which include limited opportunities for active transportation, widespread marketing of unhealthy foods to children, and the increased availability of energy-dense, nutrient-poor foods, play a significant role [44–46]. Additionally, behavioural factors such as increased screen time, sedentary lifestyles, poor dietary habits, and inadequate sleep are closely linked to the rates of obesity in the pediatric

population. This section will explore the relationship between sleep and obesity in children and adolescents, focusing on how sleep duration, quality, and regularity contribute to the obesity epidemic in this age group.

2.2.2 Key findings on the relationship between sleep and obesity in pediatrics

Numerous systematic reviews and meta-analyses have shown that inadequate sleep plays a critical role in determining obesity risk during childhood and adolescence. For example, a systematic review and meta-analysis of longitudinal studies by Fatima et al. [47] found that short sleep duration is strongly linked to obesity, with children and adolescents who sleep less than recommended having twice the risk of having overweight or obesity compared to those who meet sleep guidelines (OR: 2.15; 95% CI: 1.64–2.81). Another meta-analysis, which included 25 studies with a total of 56,584 children and adolescents, found that those with shorter sleep duration (~10 hours per night) were 76% more likely to develop overweight or obesity compared to peers who slept longer (~12.2 hours per night) (OR: 1.76; 95% CI: 1.39–2.23) [48]. Shorter sleepers also experienced a more rapid BMI increase over time, with an annual gain of 0.13 kg/m² (pooled β coefficient: 0.13; 95% CI: 0.01–0.25 kg/m²) [48]. Increasing sleep duration by just one hour per day was associated with a 21% reduction in the risk of overweight or obesity (OR: 0.79; 95% CI: 0.70–0.89), reinforcing the critical role of sleep duration in mitigating obesity risk [48]. These findings suggest that inadequate sleep is a significant risk factor for obesity during childhood and adolescence, with shorter sleep duration being strongly linked to higher risks of overweight and obesity [48]. Longer sleep durations, even by just one additional hour per day, are associated with a notable reduction in obesity risk, emphasizing the protective role of adequate sleep in managing weight gain [48]. These associations hold true across various regions, age groups, and

follow-up periods, underscoring the importance of promoting healthy sleep habits to mitigate obesity risk in young populations [48].

A large systematic review of 42 studies analyzed the relationship between sleep duration and obesity in various age groups, revealing age-specific differences in this association [49]. In infants (0–2 years old), shorter sleep duration was linked to a 40% higher risk of developing overweight or obesity (RR: 1.40; 95% CI: 1.19–1.65) [49]. The risk was even greater in early childhood (3–8 years old), where shorter sleep increased the risk of obesity by 57% (RR: 1.57; 95% CI: 1.40–1.76), and in middle childhood (9–11 years old), where the risk increased by 123% (RR: 2.23; 95% CI: 2.18–2.27) [49]. Among adolescents (12–18 years old), short sleep was associated with a 30% higher risk of overweight or obesity (RR: 1.30; 95% CI: 1.11–1.53) [49]. Additionally, every additional hour of sleep duration was associated with lower BMI and BMI z-scores, suggesting a protective effect of adequate sleep on weight gain [49]. These findings suggest that shorter sleep has a greater impact on obesity risk in younger children, especially in middle childhood [49]. Increased sleep duration shows a protective effect, with each additional hour linked to lower BMI and BMI z-scores, highlighting the importance of adequate sleep in preventing obesity [49].

Another systematic review and meta-analysis, which included 33 studies with a total sample of 57,848 children and adolescents, found significant associations between both short and long sleep durations and obesity risk [50]. Short sleep duration increased the risk of obesity (RR: 1.57; 95% CI: 1.36–1.81), while long sleep duration was found to be protective (RR: 0.83; 95% CI: 0.75–0.93) [50]. Dose-response analyses showed that short sleep duration increased the risk of obesity by 82% in children aged 6-13 years

(RR: 1.82; 95% CI: 1.51–2.21; P < 0.001), by 20% in children aged 1-2 years (RR: 1.20; 95% CI: 1.07–1.34; P = 0.001), and by 18% in adolescents aged 14-17 years (RR: 1.18; 95% CI: 1.00–1.38; P = 0.050) [50]. These findings show that the impact of sleep duration on obesity risk varies by age, with children in middle childhood being the most vulnerable [50]. They also indicate that increased sleep has a protective effect against obesity, highlighting the importance of adequate sleep in preventing obesity across age groups [50].

Beyond sleep duration, the quality of sleep has also been identified as an important factor. A systematic review by Fatima et al. [51] highlighted the role of poor sleep quality in increasing the risk of overweight and obesity. In a pooled analysis of a total sample of 26,553 in children, adolescents, and young adults, inadequate sleep, encompassing both short duration and poor quality, was associated with 27% higher odds of having overweight or obesity (OR: 1.27; 95% CI: 1.05–1.53) [51]. Subgroup analyses revealed that poor sleep quality alone, even independent of sleep duration, was significantly linked to a 46% higher risk of overweight or obesity (OR: 1.46; 95% CI: 1.24–1.72), suggesting that more than one characteristic of sleep is important in the association between sleep and obesity, both how long children sleep and how well they sleep are critical components in preventing obesity [51].

In addition to sleep duration and quality, social jetlag has emerged as another factor contributing to obesity risk in children and adolescents. Social jetlag refers to the misalignment between an individual's biological clock and social schedule, often resulting from differences in sleep patterns between weekdays and weekends [17]. A systematic review and meta-analysis that included 43 studies (17 studies in children and

adolescents) with a total sample size of 231,648 participants of all ages (average age ranged from 9.6 to 63.6 years) examined the relationship between social jetlag and various adiposity-related measures [52]. The findings demonstrated a positive association between social jetlag and BMI, with a correlation coefficient of 0.12 (95% CI: 0.07–0.17, $P < 0.001$) [52]. Additionally, social jetlag was linked to increases in fat mass (r: 0.10; 95% CI: 0.05–0.15, $P < 0.001$) and fat mass index (β: 0.14 kg/m²; 95% CI: 0.05–0.23, $P < 0.001$), as well as higher percent body fat (r: 0.37; 95% CI: 0.33–0.41, $P < 0.001$) and waist circumference (r: 0.15; 95% CI: 0.06–0.24, $P = 0.001$) [52]. Moreover, individuals experiencing social jetlag had a 20% increased likelihood of having overweight or obesity (OR: 1.20; 95% CI: 1.02–1.40, $P = 0.039$) [52]. These findings suggest that the misalignment between biological and social time plays a significant role in adiposity, highlighting the need for addressing sleep regularity, alongside sleep duration and quality, as part of comprehensive obesity prevention strategies.

2.2.3 Summary

The childhood obesity epidemic has been linked to various behavioural and environmental factors, with sleep duration, quality, and regularity emerging as key contributors to the risk of overweight and obesity. Systematic reviews and meta-analyses consistently demonstrate that shorter sleep durations are strongly associated with an increased risk of obesity, while longer sleep or sleep that meets recommended guidelines offers protective benefits. Shorter sleep durations, particularly those below the recommended guidelines, are linked to an increased risk of overweight and obesity, with estimates showing a 27% to 123% higher risk for overweight and obesity combined, and a 57% to 123% increased risk for obesity alone [47,48]. In contrast, children and

adolescents who achieve longer sleep durations or meet the guidelines generally have 17% to 21% lower odds of developing overweight or obesity compared to those with shorter sleep durations [48].

The effect of short sleep duration on obesity varies by age group. The lowest increased risk of obesity is found in adolescents (18-30%), followed by infants (20-40%), then early childhood (57%), with the highest risk observed in middle childhood (82-123%) [49,50]. Furthermore, irregular sleep patterns, such as social jetlag, have been shown to increase the odds of overweight and obesity by 20%, emphasizing the importance of consistent sleep schedules [52]. Additionally, poor sleep quality independently raises the odds of overweight and obesity by 46%, indicating that sleep quality should also be considered in the prevention of obesity [51].

The importance of sleep is especially pronounced in adolescents who are already experiencing obesity, as inadequate sleep can exacerbate weight gain and hinder weight management efforts. Research shows that shorter sleep durations not only increase the risk of developing obesity but also worsen metabolic health, contributing to further complications such as insulin resistance, increased fat accumulation, and impaired cognitive function. For adolescents already struggling with obesity, improving sleep duration, quality, and regularity becomes a crucial component in mitigating these risks and supporting healthier outcomes. Addressing sleep-related issues in this population is essential for breaking the cycle of weight gain and improving both physical and mental health during this critical developmental stage.

2.3 Sleep and Insulin Resistance

2.3.1 Effect of sleep manipulation on insulin resistance

Given the widespread prevalence of insufficient sleep and the high rates of obesity in the pediatric population, examining insulin resistance in this context becomes particularly relevant. Emerging evidence suggests that inadequate sleep is associated with poor glucose homeostasis, even when controlling for obesity. This section addresses the evidence primarily linking inadequate sleep with alterations in insulin resistance and sensitivity, based on both fasting measures and glucose challenge protocols, and briefly explores the possible pathways that may regulate this association.

As briefly mentioned in *Chapter 1: General Introduction*, in 2017, we published a narrative review examining the association between inadequate sleep and T2D risk in children and adolescents [1]. This review included 21 observational and 2 experimental studies, with 65% of them using objective measures of sleep, such as actigraphy or polysomnography. The studies collectively represented a sample of 16,106 children and adolescents aged 0.5 to 19 years [1]. Despite some inconsistency in the findings, 48% (11 out of 23 studies) reported a significant association between sleep parameters (duration, quality, or architecture) and T2D biomarkers, while two additional studies observed similar associations that were attenuated when adjusted for adiposity [1]. Longitudinal data (2/2 studies) provided a more consistent picture, linking short sleep duration to elevated insulin resistance, independent of age and sex [1]. Cross-sectional evidence, though less consistent, generally supports that short sleep duration and poor sleep quality are associated with insulin resistance in children and adolescents [1]. Additionally, data from both experimental studies suggest that specific sleep architecture elements, such as slow-wave sleep (SWS) and rapid eye movement (REM) sleep, may

be crucial for maintaining glucose homeostasis in this population [1]. We concluded that study by stating that although evidence in this demographic is somewhat limited, all sleep characteristics appear to offer valuable insights and warrant measurement to better understand their relationship with glucose homeostasis [1]. Additionally, that there was a need for future research to focus on more high-risk populations rather than predominantly healthy samples, to gain a deeper understanding of sleep's role in T2D risk [1].

One of the earliest and most frequently cited studies on the subject, with over 4,500 citations, is by Spiegel et al. [53]. This 16-day inpatient sleep manipulation study involved 11 healthy male adults (ages 18-27 years) [53]. Participants initially spent 8 hours in bed for 3 nights, followed by 4 hours in bed for the next 6 nights, and then 12 hours in bed for the final 7 nights [53]. This was the first study to show in humans that sleep restriction over 6 consecutive nights in healthy males led to disruptions in metabolic and endocrine function, linking sleep deprivation to risk factors for insulin resistance and T2D [53]. More studies followed, including an inpatient study in non-obese adult males (average age 26.8 years) that investigated the effects of sleep manipulation on insulin sensitivity [54]. Participants initially spent 10 hours in bed per night for 8 nights, with the last three nights conducted in an inpatient setting, this was followed by a sleep restriction phase of 5 hours in bed per night for 7 consecutive nights, concluding with a recovery night of 10 hours in bed [54]. Results indicated that one week of restricted sleep (5 hours per night) significantly reduced insulin sensitivity, raising concerns about how prolonged insufficient sleep might influence disease processes associated with insulin resistance [54]. While sleep extension studies are more rare than sleep restriction or deprivation, Leproult et al. [55] conducted a study involving 16 non-

obese female adults (average age 25 years) who were sleep-restricted (average 6.3 hours). Increasing time-in-bed by one hour per night over six weeks resulted in an average gain of 44 minutes per night during weeknights, leading to significant improvements in fasting glucose, insulin, and insulin sensitivity [55]. Again, highlighting the need for improving sleep duration in adults with and without additional risk factors for T2D, and that targeted sleep interventions in high-risk populations are needed since it might help curb the incidence of T2D [55].

Recently, a study by Souza et al. [56] examined sleep deprivation versus sleep restriction in non-obese, healthy, male adults. Twenty-eight participants (average age: 26.2 years) were randomly assigned to either a 24-hour sleep deprivation group or a sleep restriction group (4 hours per night for four nights) [56]. Findings showed that the sleep restriction group experienced a significant increase in insulin resistance compared to the sleep deprivation group, highlighting the more substantial metabolic impact of extended sleep restriction [56].

Few studies have focused on individuals with overweight or obesity. One such study by Hart and colleagues [57], found no significant association between sleep duration manipulation (2 nights of 5 hours and 2 nights of 9 hours) and fasting glucose, insulin, or insulin resistance in a sample of twelve adult females with overweight or obesity (average age 41.7 years, BMI 31.0 kg/m^2). Despite its strengths, such as using polysomnography to measure sleep and a focus on female participants, several limitations may have contributed to the null findings [57]. These limitations included a small sample size, absence of a washout period, lack of baseline assessments for insulin resistance, and a wide age range (SD = 10.3 years), which may have included

women experiencing menopause, potentially influencing insulin resistance outcomes. In contrast, two other studies on adults with overweight, conducted by Nedeltcheva and colleagues [58,59], found a significant decrease in insulin sensitivity following 14 nights of sleep restriction (5.5 hours per night in bed) compared to 14 nights of sufficient sleep (8.5 hours in bed), with a 3-month washout period between interventions. These findings highlight the potential negative impact of prolonged sleep restriction on insulin sensitivity in adults with overweight. However, another study by Zielinski et al. [60] using a parallel design rather than a crossover approach reported null findings. This study compared 8 weeks of regular sleep to a 1.5-hour reduction in time in bed per night over 8 weeks in adults with overweight, finding no effect on insulin resistance [60]. Methodological flaws, including a lack of randomization and minimal changes in actual sleep duration between groups, likely contributed to these null results, as such a failed intervention make it unrealistic to expect significant changes in outcome measurements.

In 2022, Sondrup and colleagues [61] published a systematic review and meta-analysis investigating the effects of sleep manipulation on insulin sensitivity. This review incorporated several of the previously mentioned studies, except for the more recent study by Souza et al. [56] and the study by Leproult et al. [55], as Leproult's intervention focused only on extending sleep rather than restricting it further. This systematic review included 35 experimental studies with parallel and crossover designs, covering an age range of 16.8 to 59.9 years [61]. Of these studies, 88% were conducted in populations with a normal BMI, and 58% involved exclusively or predominantly male samples [61]. Interventions analyzed included sleep restriction, disturbances to SWS and REM sleep, sleep fragmentation, and circadian misalignment, with the meta-analysis focusing mainly on 21 sleep restriction studies [62]. The findings demonstrated that sleep restriction

significantly decreased insulin sensitivity, with circadian misalignment and SWS suppression also impairing insulin sensitivity, whereas REM sleep disturbance and sleep fragmentation had no significant impact [61]. Overall, the review highlights that sleep duration, quality, and timing are essential for metabolic health and may influence the risk of developing T2D.

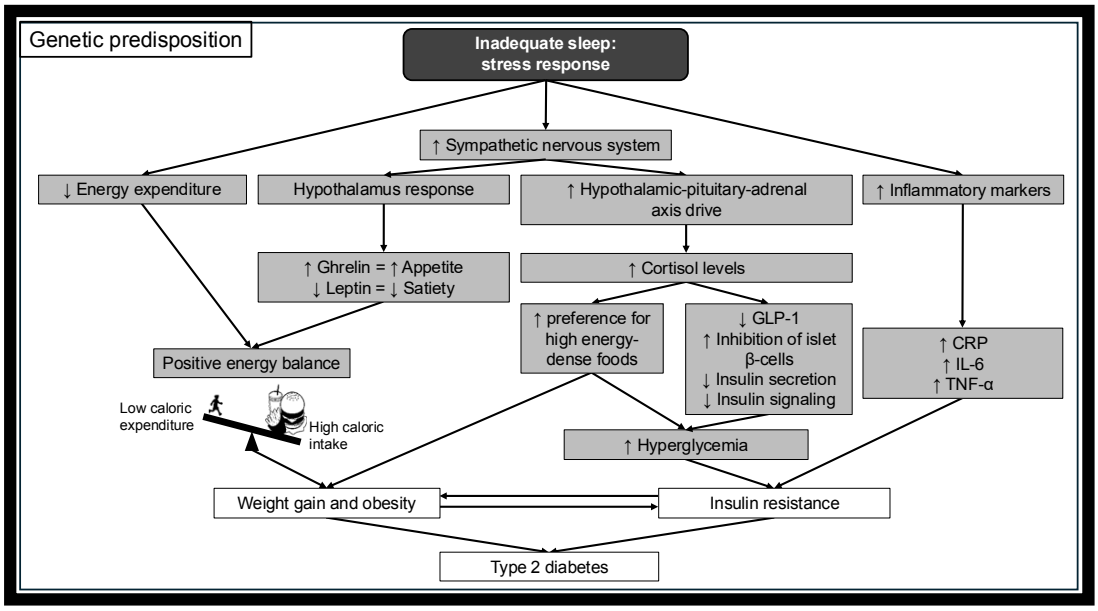
In summary, with the high prevalence of sleep restriction and rising obesity rates in the pediatric population, understanding the connection between sleep and insulin resistance is essential, as inadequate sleep is linked to impaired glucose homeostasis independent of obesity. Pioneering work by Spiegel and colleagues laid the groundwork for numerous studies in this field [53]. Our 2017 review [1] highlighted significant associations between sleep patterns and T2D biomarkers in youth, while research in adults by Leproult et al. [55] demonstrated that extending sleep improved insulin sensitivity, and Souza et al. [56] showed that four nights of sleep restriction worsened insulin resistance more than a single night of deprivation. Studies in adults with overweight or obesity remain limited and show mixed results; while some studies reported significant associations, others found none. A systematic review by Sondrup et al. [61], synthesizing data from 35 studies, found that sleep restriction, circadian misalignment, and SWS suppression impair insulin sensitivity, underscoring the importance of sleep duration, quality, and timing for metabolic health and T2D risk [61]. Additionally, the predominance of male samples in these studies limits generalizability, highlighting a need for greater ecological validity in future research. Overall, these findings reinforce the need for sleep intervention studies targeting high-risk adolescents with insulin resistance and an elevated risk of developing T2D.

2.3.2 Mechanisms linking inadequate sleep to insulin resistance

Understanding the mechanisms linking inadequate sleep to insulin resistance is essential for clarifying how sleep impacts metabolic health and the risk of T2D. This section explores key pathways, including hormonal regulation, inflammation, autonomic nervous system activity, and metabolic alterations, that may drive the association between insufficient sleep and impaired insulin sensitivity. A study by Simon et al. [63] put the mechanism simply stating that insufficient sleep in adolescence acts in a direct manner by increasing the risk for T2D through its impact on insulin sensitivity and indirectly through increased dietary intake, sedentary activity, and weight gain. However, what does it mean? Although there is no definitive consensus on the exact mechanism, numerous theories supported by varying degrees of evidence offer insights. We previously discussed these mechanisms in our 2017 review which Figure 1 further illustrates with an updated graphic representation linking inadequate sleep to insulin resistance, obesity, and T2D [1].

Most mechanistic pathways suggest that inadequate sleep acts as a physiological stressor, activating networks that collectively promote weight gain, insulin resistance, and an increased risk of T2D [1]. Behaviourally, sleep restriction often reduces non-resting energy expenditure on the following day while increasing appetite and calorie intake [64,65]. Fatigue and low motivation from insufficient sleep can decrease physical activity, while elevated sympathetic nervous system (SNS) activity increases levels of ghrelin, a hunger-stimulating hormone, and lowers leptin, which signals satiety [66]. Although controlled laboratory studies have reported increases in ghrelin and decreases in leptin following sleep restriction, recent evidence suggests the opposite pattern may occur in real-world settings [16]. Therefore, the observed positive energy balance

associated with inadequate sleep in free-living conditions is more likely driven by hedonic food intake, which overtime may contribute to weight gain [16].



2.3.2 Figure 1. Proposed pathways linking inadequate sleep as a stressor to weight gain, insulin resistance, and T2D risk.

Hormonal shifts also play a critical role, particularly through activation of the hypothalamic-pituitary-adrenal (HPA) axis, which increases cortisol levels [67]. Cortisol is essential for managing metabolism, immune responses, and the body's adaptation to stress [67]. Elevated cortisol from chronic stress or sleep deprivation promotes gluconeogenesis production in the liver but reduces insulin sensitivity, leading to higher blood glucose levels [67,68]. High cortisol also directly inhibits insulin-producing β-cells in the pancreas, reducing insulin secretion, which can impair glucose regulation and worsen insulin resistance [69]. Cortisol affects other hormones like glucagon-like peptide-1 (GLP-1), a central regulator of glucose and appetite [70,71]. GLP-1, typically released after eating, enhances insulin secretion, suppresses glucagon release, and slows gastric emptying, stabilizing blood sugar and promoting satiety [70]. However,

elevated cortisol can suppress GLP-1 release, weakening these regulatory effects and further disrupting glucose metabolism [72]. Additionally, high cortisol levels promotes abdominal fat storage and increases appetite, often for calorie-dense foods, driving weight gain and insulin resistance over time [73].

In sum, elevated cortisol from chronic stress such as inadequate sleep disrupts HPA axis function and metabolic balance by promoting gluconeogenesis, reducing insulin sensitivity, inhibiting insulin-producing β-cells, and indirectly impairing GLP-1 function [69–73]. The theory is that the combined effect from the HPA axis response can increase the risk of weight gain, insulin resistance, and T2D, emphasizing the importance of adequate sleep for metabolic health.

Inflammatory markers are another possible pathway by which chronic inadequate sleep are associated with obesity, insulin resistance, and T2D. C-reactive protein (CRP), a primary marker produced by the liver in response to cytokines like interleukin-6 (IL-6), often rises with sleep deprivation and is linked to metabolic disorders [74]. Elevated CRP levels are sometimes observed in individuals with sleep deprivation and are associated with an increased risk of metabolic disorders [74,75]. CRP can interfere with insulin receptor activity, reducing the cells' sensitivity to insulin and impairing glucose uptake. Similarly, IL-6, which has been shown to be elevated after sleep loss, promotes insulin resistance by inhibiting insulin signaling at the cellular level [67,74]. IL-6 interferes with the insulin signaling cascade, reducing the efficiency of glucose uptake and contributing to higher blood glucose levels [67]. Another significant inflammatory marker, tumor necrosis factor-alpha (TNF-α), also plays a role in insulin resistance [74,76]. TNF-α is secreted by immune cells such as macrophages and adipocytes, especially under

conditions of stress, like inadequate sleep [67,74]. This cytokine inhibits insulin receptor activity through a process called serine phosphorylation, which prevents insulin from binding effectively to its receptor [67]. This blockage in the insulin signaling pathway reduces the cells' responsiveness to insulin, thereby decreasing glucose uptake and increasing blood sugar levels [67].

In addition to these individual effects, the combined presence of these inflammatory markers contributes to what has been termed as metabolic inflammation or “metaflammation” [76,77]. Unlike the acute inflammation that occurs in response to injury or infection, “metaflammation” is a chronic, low-grade inflammation primarily driven by lifestyle factors like sleep deprivation, poor diet, and inactivity [76,77]. This persistent inflammatory state leads to oxidative stress and mitochondrial dysfunction in cells, further impairing glucose metabolism and insulin sensitivity [76,77]. Over time, these disruptions could lead to sustained insulin resistance and increase the risk of developing T2D [76,77].

In sum, chronic inadequate sleep could induce inflammation that disrupts insulin signaling and glucose metabolism through a cascade of inflammatory markers, including CRP, IL-6, TNF-α, and others. By continuously activating inflammatory pathways, inadequate sleep could foster a cellular environment that is increasingly resistant to insulin [77]. This pathway, once again, emphasizes the importance of adequate sleep as a modifiable factor to reduce inflammation and mitigate the risk of insulin resistance and associated metabolic diseases. But also implies that anti-inflammatory strategies might not only be a possible treatment for T2D but also a prevention strategy [76].

Genetic predisposition plays a significant role in shaping an individual's risk of T2D, obesity, and sleep-related traits, including unique sleep needs and responses to stressors such as inadequate sleep [78–81]. Several genetic variants are associated with a heightened risk of T2D and obesity, independent of behavioural or environmental influences [79–82]. Individual variability in sleep need and vulnerability to sleep loss may also be partially determined by specific polymorphisms that influence both cognitive and metabolic responses to restricted sleep [83]. Variants in genes regulating sleep-wake cycles and sleep efficiency contribute to differences in sleep architecture, thereby affecting the amount and quality of sleep required to maintain optimal metabolic function [84]. Together, these genetic factors suggest that individuals differ in their susceptibility to metabolic consequence of inadequate sleep. For those with a genetic predisposition to T2D, obesity, or increased sleep requirements, optimizing sleep duration and quality may be particularly important for mitigating metabolic risk. This interplay of genetic and lifestyle factors reinforces the need for personalized health strategies to improve sleep, manage weight, and reduce the risk of insulin resistance and related disorders.

In conclusion, understanding the complex relationship between inadequate sleep and insulin resistance is essential for addressing metabolic health and reducing the risk for T2D. This section and Figure 1 have highlighted various pathways, hormonal shifts, inflammation, autonomic nervous system activity, and genetic predisposition, that likely contribute to impaired glucose regulation and metabolic imbalance. Although further research is needed to fully elucidate these mechanisms, particular attention should be given to confirming that these pathways are not limited to highly controlled laboratory settings but are also relevant in free-living conditions. The mechanisms identified thus far provide logical and valuable directions for future exploration.

2.3.3 Summary

The relationship between inadequate sleep and insulin resistance is increasingly recognized as a significant factor in metabolic health, particularly in relation to T2D risk. Section 2.3.1 reviewed studies investigating how sleep manipulation impacts insulin sensitivity. Seminal work by Spiegel et al. [53] and more recent studies demonstrate that sleep restriction and poor sleep patterns can disrupt glucose regulation and increase insulin resistance. Although findings are mixed for populations with overweight or obesity, the systematic review by Sondrup et al. [61] supports that sleep restriction, circadian misalignment, and disturbances in SWS are associated to higher insulin resistance.

Section 2.3.2 explored the potential mechanisms linking insufficient sleep to insulin resistance. Whether these responses represent a cascade of stress responses or an overreaction to restore homeostasis, they involve multiple interconnected pathways. In controlled laboratory settings with regulated food intake, inadequate sleep triggers a series of autonomic responses, including hypothalamic regulation. This results in increased levels of ghrelin (a hunger-stimulating hormone) and decreased levels of leptin (the satiety hormone), collectively promoting greater appetite and caloric intake. However, this model has been debated. In other experimental contexts where insufficient sleep is paired with an ad-libitum diet results in decreased ghrelin levels and increased leptin level, which would typically suggest a reduced appetite, but despite this hormonal reversal energy intake remained excessive [16]. These discrepancies across experimental settings underscore the need for further research to better understand the complexity of appetite regulation under conditions of insufficient sleep.

Under conditions of inadequate sleep, the HPA-axis is thought to be activated, leading to elevated cortisol levels. This hormonal response promotes glucose production, reduces insulin sensitivity, and impairs pancreatic β-cell function. Elevated cortisol levels also interferes with GLP-1, an hormone essential for glucose regulation and satiety, further compromising glucose homeostasis. Additionally, inadequate sleep is associated with increased levels of inflammatory markers like CRP, IL-6, and TNF-α. These makers contribute to chronic low-grade inflammation “metaflammation”, which disrupts insulin signaling pathways. Genetic predisposition further modulates the risk for obesity, T2D, and individual sleep needs, highlighting the need for personalized approaches to address these metabolic pathways disrupted by inadequate sleep.

Together, these sections underscore the potential of sleep as a modifiable factor in reducing inflammation, improving glucose regulation, and lowering the risk of insulin resistance, particularly in high-risk populations. Targeted sleep interventions in these populations offer promising strategy to mitigate the adverse metabolic effects of insufficient sleep, emphasizing the need to prioritize adequate sleep as a key component of metabolic health and T2D prevention.

2.4 Type 2 Diabetes in Children and Adolescents

2.4.1 Introduction

The terms “adult-onset diabetes” and “juvenile diabetes”, once used to differentiate between T2D and type 1 diabetes, have become outdated and misleading. Over the past three decades, mirroring the worldwide epidemic of childhood obesity, T2D diabetes in children and adolescents has risen to a well-established global health concern. While obesity rates have largely stabilized worldwide, the incidence of T2D in the pediatric population continues to rise.

The progression to T2D typically begins with normal glucose tolerance, advancing to prediabetes, which includes impaired fasting glucose and impaired glucose tolerance, eventually leading to both a lack of insulin sensitivity and impaired insulin secretion. Traditionally, in adults, this progression unfolded over several years, with secondary complications emerging much later in life. However, the early onset of T2D in youth indicates a potentially faster and more aggressive disease progression, suggesting that the pathophysiology of T2D in children and adolescents may involve unique factors. Studies aimed at preventing T2D in children at high risk for the disease have had limited effectiveness and fail to demonstrate long-term effects.

This section will synthesize the current understanding of risk factors, pathophysiology, and the prevalence of T2D in children and adolescents, providing insight into the distinct mechanisms driving this condition in younger populations.

2.4.2 Risk factors, pathophysiology, and prevalence of T2D in children and adolescents

The pathophysiology of T2D in children and adolescents involves a complex interplay between insulin resistance and declining β-cell function [85–87]. In youth, particularly those with obesity, insulin resistance is central, often accompanied by fat accumulation in visceral tissues, such as the liver and muscles, which impairs glucose regulation [88,89]. As insulin resistance worsens, β-cells struggle to produce enough insulin to maintain glucose levels [88,89]. This decline in β-cell function, driven by genetic and environmental factors, disrupts insulin secretion during the first and second phases, critical for glucose control [88,89]. Lipotoxicity further exacerbates the issue, leading to β-cell failure and driving the progression from normal glucose tolerance to prediabetes and, eventually, T2D [88–90].

In Canada, a national surveillance study monitoring new cases of non-type 1 diabetes in children was conducted between 2006–2008 and again between 2017–2019, utilizing a network of over 2,800 physicians certified in pediatrics or pediatric subspecialties [91,92]. Data from the first surveillance period showed an incidence rate of 1.54 per 100,000 children per year for T2D, with a median diagnosis age of 14.0 years [91,92]. A decade later, the incidence rate rose to 2.47 per 100,000 children per year, with a median diagnosis age of 14.1 years [91]. This represents a 60% overall increase in T2D among Canadian children and adolescents ($p < 0.001$), with a 37% increase in females ($p = 0.005$) and a 50% increase in males ($p = 0.001$) [91]. However, the overall proportion of female youth affected continues to remain higher compared to males, consistent with other published data and the first surveillance study [91–93]. These Canadian findings are in line with previous research showing that T2D in children and

adolescents most often occurs during the second decade of life, coinciding with the physiological increase in insulin resistance that occurs during puberty [85,86].

Similar trends have been observed globally. In the United States (US), the incidence of T2D increased from 9.0 per 100,000 children per year between 2002–2003 to 12.5 between 2011–2012 [94,95]. In Western Australia, data collected from 2000 to 2019 showed a 5.2% annual increase in childhood T2D incidence, with an overall mean incidence of 2.3 per 100,000 children under 16 years of age per year [96]. In the United Kingdom (UK), the incidence of T2D rose more slowly, from 0.53 per 100,000 children under 17 years of age per year between 2004–2005 to 0.72 between 2015–2016 [97].

Several risk factors contribute to the development of T2D in children and adolescents, with obesity being a well-established risk due to its role in promoting insulin resistance. Additionally, children with impaired glucose tolerance are at greater risk of progressing to T2D. In a model adjusted for sociodemographic factors, the risk of developing T2D increased significantly with higher levels of obesity in both male and female adolescents, with hazard ratios for severe obesity at 25.8 (95% CI 21.0–31.6) for males and 44.7 (95% CI 32.4–61.5) for females[98]. When comparing Canadian children diagnosed with T2D in 2006–2008 to those diagnosed in 2017–2019, the proportion of cases with obesity remained similar (87.9% vs. 86.3%). However, the median BMI z-score was higher in the more recent cohort (2.93 vs. 2.84), suggesting an increase in the severity of obesity over time [91].

A family history of T2D in a first- or second-degree relative is a strong predictor of the disease, as is exposure to diabetes in utero, which significantly raises the risk of T2D

development in children [99]. Gestational diabetes, a common pregnancy complication characterized by elevated blood sugar levels during pregnancy, typically resolves after delivery but increases the long-term risk for both mother and child to develop T2D and other health issues [100,101]. Globally, gestational diabetes may affect up to one in four pregnancies, heightening the risk for T2D in future generations [100,102–105]. A comparison of Canadian children diagnosed with T2D from 2006–2008 to those diagnosed in 2017–2019 revealed a consistent proportion of cases with a family history of T2D (91% vs. 88.6%) [91]. However, the rate of in-utero diabetes exposure increased from 35.7% to 44.3%, an 8.6% increase over ten years, indicating a rise in maternal and gestational diabetes over time [91].

Belonging to certain high-risk ethnic groups, including individuals of African, Arab, Asian, Hispanic, Indigenous, or South Asian descent, significantly elevates the risk of developing T2D in children and adolescents [99]. In Canada, Indigenous children, particularly from First Nations communities, have the highest incidence of childhood-onset T2D, with an incidence rate of 36.6 per 100,000 children per year [91]. Black children follow with an incidence rate of 5.7 per 100,000, Asian children at 4.0 per 100,000, and White children at 0.49 per 100,000 [91]. Similarly, in the UK, Asian children have the highest incidence (2.92 cases per 100,000 annually), while White children have the lowest (0.78 cases per 100,000) [97]. In the US, from 2002 to 2015, the steepest annual increase in childhood-onset T2D occurred in Asians and Pacific Islanders (7.7% per year), followed by Hispanics (6.5%), Blacks (6.0%), and American Indians (3.7%) [95].

Complicating the issue, the degree of obesity at diagnosis varies across ethnic groups. For instance, Canadian First Nations children with T2D tend to have lower BMI z-scores compared to White children and other high-risk groups [91]. Additionally, Canadian White children also had a higher mean BMI z-score compared to Asian children (2.47 vs. 1.85), a pattern also observed in the UK, where Asian children had significantly lower BMI z-scores than White children [91,97]. This suggests that children from certain ethnic and racial minority groups may develop T2D at a lower BMI threshold.

In addition, genetic factors, such as transcription factor variants, have been identified as increasing the risk of T2D in African American and in Indigenous Communities [91,99,106,107]. However, social determinants of health including socioeconomic status, food insecurity, and obesogenic environments, along with in utero exposure to diabetes, play a significant role in the intergenerational transmission of T2D [91,99]. Ethnicity and the intrauterine environment are both crucial risk factors for early-onset T2D, emphasizing the pressing need for targeted prevention efforts in these vulnerable populations [108].

Birth weight is another important factor in the development of childhood-onset T2D. A Mendelian randomization analysis of data from 49 studies examined the link between genetically influenced lower birth weight and T2D risk [109]. The study found that a decrease in birth weight by 1 standard deviation significantly increased the risk of T2D, with odds ratios of 2.10 for all participants, 1.96 for those of European descent, and 1.39 for those of East Asian descent [109]. Additionally, lower birth weight was associated with higher fasting glucose levels, though no significant associations were found with fasting insulin, 2-hour glucose, or hemoglobin A1C levels [109]. A systematic review and

meta-analysis further supported these findings, showing that each kilogram increase in birth weight was linked to a 22% reduction in the risk of developing T2D later in life (OR: 0.78, 95% CI: 0.70–0.87) [110]. Another recent study found that lower birth weight was associated with an increased risk of T2D, independent of adult BMI and genetic risk factors [111].

Certain medical conditions are linked to an elevated risk of T2D in children and adolescents, such as polycystic ovary syndrome (PCOS) and acanthosis nigricans, a skin condition that frequently signals insulin resistance [99]. A systematic review and meta-analysis found that one in five women, including adolescents, with T2D has PCOS, a rate two to four times higher than among women without T2D [112]. In Canada, recent surveillance data show that 14.6% of female children and adolescents with T2D also had PCOS [91]. Likewise, another study found that acanthosis nigricans was present in 17% of children and 21% of adults with T2D, with its prevalence increasing as more T2D risk factors accumulated ($p < .001$) [113]. After adjusting for age, BMI, and the number of T2D risk factors, the prevalence ratio for T2D in individuals with acanthosis nigricans was 1.97 (95% CI, 1.18–3.27; $p = .01$) [113].

Other notable metabolic risk factors include hypertension and dyslipidemia, both commonly seen in children with obesity and significantly contributing to the overall risk profile for T2D [99]. Approximately one in four adolescents with T2D has hypertension [114]. Dyslipidemia in youth with T2D has been reported in over 80% of cases, with the most common abnormalities occurring in this order: high LDL-C, low HDL-C, elevated triglycerides, and high total cholesterol [115]. In Canada, recent data show that 65.6% of children and adolescents with T2D have dyslipidemia, while 47% have hypertension,

reflecting increases of 20.8% and 18.7% over a ten year period, respectively [91]. For children and adolescents with T2D, annual lipid screening is recommended once glycemic control is achieved, with target levels for LDL-C below 2.59 mmol/L, HDL-C above 0.91 mmol/L, and triglycerides under 1.69 mmol/L [116].

Non-alcoholic fatty liver disease (NAFLD) is another metabolic disorder associated with an increased risk of T2D [99]. Research has shown that children and adolescents with NAFLD have a significantly higher prevalence of abnormal glucose tolerance, including prediabetes and diabetes, compared to those without NAFLD (20.6% vs. 11%, $p = .02$) [117]. Specifically, 19.8% of those with NAFLD met the criteria for prediabetes, while 0.8% were diagnosed with diabetes [117]. A recent systematic review and meta-analysis estimated the pooled prevalence of NAFLD in youth with T2D at 33.8%, although this varied significantly depending on the diagnostic method used, ranging from 24.2% when only liver function tests were applied to 54.7% when more sensitive methods like magnetic resonance imaging or spectroscopy were utilized [118]. Regionally, studies from the Middle East reported the highest NAFLD prevalence in youth with T2D at 55.9%, while European studies reported the lowest at 22.5% [118] Recent Canadian surveillance data show that 26.2% of children and adolescents with T2D also had NAFLD, representing an increase of 4% over a decade [91].

Certain medications have also been identified as contributing to the risk of T2D in children and adolescents [99]. Atypical antipsychotic medications, in particular, are associated with substantial weight gain, insulin resistance, and T2D [99,119–121]. Furthermore, neuropsychiatric disorders and the use of neuropsychiatric medications are more prevalent among children with obesity and T2D compared to their peers in the

general pediatric population [99,122]. Thus, medications used to treat other conditions, which are common in children and adolescents with obesity and T2D, can further exacerbate the risk of developing the disease.

Obstructive sleep apnea (OSA) is a sleep disorder characterized by more than five episodes per hour of either partial obstruction (over 30%, causing a reduction in blood oxygenation by at least 3%) or complete obstruction (over 90% for more than 10 seconds) of the upper airway, despite ongoing efforts to breathe [123,124]. In adults with T2D, the prevalence of OSA has been reported to range from 56% to 78% [125,126]. OSA has been associated with a 2.34 times higher risk of impaired fasting glucose (95% CI 1.16–4.72), a 1.58 times higher risk of impaired glucose tolerance (95% CI 1.15–2.15), a 1.65 times higher risk of impaired glucose regulation (95% CI 1.12–2.42), and a 2.15 times higher risk of diabetes (95% CI 1.68–2.75), with a particularly strong association between OSA and diabetes, showing a 3.62 times higher risk (95% CI 2.75–4.75) (C. Wang et al., 2022). In adults, OSA appears to be both a risk factor for and a consequence of T2D. While the prevalence of OSA in youth with T2D is not well established, it is recommended to monitor sleep in these individuals and refer them to a specialist if any signs or symptoms of OSA arise [99]. Notably, sleep disorders were not addressed in the Canadian national surveillance study.

The diagnosis of T2D in children and adolescents is typically based on well-established laboratory criteria, which include a fasting plasma glucose level of 7.0 mmol/L or higher, a 2-hour plasma glucose reading of 11.1 mmol/L or greater during a 75 g oral glucose tolerance test (OGTT), a random plasma glucose level of 11.1 mmol/L or more, or an A1C value of 6.5% or above, as recommended by Diabetes Canada [99,128,129].

However, these diagnostic thresholds are derived from studies in adults and may not be fully validated for pediatric populations, highlighting the need for further research to ensure their accuracy in diagnosing T2D in children and adolescents [99,129].

With the rising prevalence of T2D among youth, there has been a growing number of acute metabolic complications, including hyperglycemic crises such as diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS), observed in both type 1 and T2D cases [99,130]. DKA occurs when insulin deficiency becomes severe, resulting in both hyperglycemia and ketosis due to increased lipolysis [99,130,131]. It is characterized by a blood glucose level exceeding 11 mmol/L, acidosis with a pH below 7.3, bicarbonate levels under 15 mmol/L, and the presence of ketones [130,132]. In contrast, HHS develops when there is sufficient insulin to prevent ketosis but not enough to control hyperglycemia [130,132]. HHS is marked by extreme hyperglycemia with blood glucose levels over 33.3 mmol/L, minimal acidosis with a pH above 7.25, bicarbonate levels greater than 15 mmol/L, minimal to no ketonuria, and hyperosmolality with serum osmolality exceeding 320 mmol/kg [132]. Although historically viewed as distinct conditions, DKA and HHS often overlap, with mixed presentations of DKA, severe hyperglycemia, or hyperosmolality being relatively common in youth and adults experiencing acute hyperglycemic crises [99,130–132].

Although our understanding of the pathophysiology of T2D in children and adolescents has advanced, effective prevention and treatment strategies have not kept pace. Research involving youth at risk for or diagnosed with T2D has shown that metformin, whether used alone or in combination with insulin, a treatment effective in adults, does not slow the rapid decline in β-cell function [133–137]. However, newer treatments, such

as glucagon-like peptide-1 (GLP-1) agonists, have shown promise and are considered safe for pediatric use [138–140]. Additionally, efforts to improve sleep quality, quantity, and consistency, alongside reducing sedentary behaviour (especially screentime) and increasing both light and moderate-to-vigorous physical activity as outlined by the Canadian 24-hour Movement Guidelines, can yield significant metabolic health benefits [18]. Nutrition interventions, such as reducing sugar-sweetened beverage consumption, should also be prioritized, as they are linked to obesity and the development of T2D in children and adolescents [141–143].

2.4.3 Summary

The increasing prevalence of T2D in adolescents highlights the pressing need for targeted intervention studies, particularly for those at high risk of developing the disease. T2D in youth progresses more rapidly than in adults, often due to a combination of obesity, insulin resistance, and declining β-cell function. Obesity is a primary risk factor, but other important contributors include a family history of T2D, in-utero exposure to diabetes, and being part of high-risk ethnic groups, such as Indigenous, Black, and South Asian populations. These groups experience earlier onset and faster disease progression, often at lower BMI thresholds compared to their White counterparts.

In designing interventions, it is crucial to account for other metabolic conditions frequently associated with T2D, such as PCOS, hypertension, dyslipidemia, and NAFLD. Additionally, risk factors like OSA and the use of medications like atypical antipsychotics, which can worsen insulin resistance and weight gain, need to be considered.

A sleep intervention targeting adolescents at high risk for T2D has never been conducted, highlighting a critical gap in research and an important area for exploration. Drawing from the insights in this section, such an intervention could prioritize improving sleep duration, while also addressing other risk factors like obesity, insulin resistance, and metabolic conditions. Moreover, recruiting a diverse ethnic population, particularly those from high-risk groups such as Indigenous, Black, and South Asian communities, would enhance the inclusivity and generalizability of the findings by addressing the unique vulnerabilities of these populations. This comprehensive approach offers a promising new strategy that could help prevent the early onset of T2D and improve long-term health outcomes.

2.5 Sleep on Brain Functions and Structures in Children and Adolescents

2.5.1 Introduction

Several systematic reviews have been published on the association between sleep and cognition in the pediatric population, highlighting the complexity of this relationship across different age groups and study designs. Reynaud and colleagues conducted a systematic review examining the relationship between sleep and cognition or behaviour in preschool-aged children (2 to 6 years old) across 26 studies [144]. All studies were observational, with only 30% being longitudinal (n=8) and a mere 12% (n=3) employing objective sleep measurements [144]. The review found a high degree of heterogeneity in the sleep variables measured, and notably, 38% of the studies did not control for any confounding factors [144]. Additionally, 54% of the included studies posed a serious risk of bias [144]. Despite these challenges, 12 out of the 13 highest-quality studies found significant associations between higher sleep duration or quality and improved behavioural and cognitive outcomes [144]. However, the strength of these associations was relatively small [144]. This review underscores the challenge of studying this young population, which relies heavily on proxy reports, and highlights the need for research of higher quality. Nonetheless, the observation that inadequate sleep can negatively impact cognition as early as the preschool years raises concerns about the long-term developmental consequences.

Short and colleagues [145] conducted a systematic review and meta-analysis focused on the impact of objectively measured sleep duration on cognition in children aged 5 to 13 years. Of the 23 studies included, 19 were suitable for the meta-analysis, and 35% were experimental [145]. The meta-analysis revealed a significant positive association between longer sleep and better overall cognitive functioning ($r = .06$, $p = .01$) [145].

However, it was noted that most children in the included studies did not meet current sleep duration recommendations, which may have obscured the effects, as many children were sleep-restricted [145]. The review had several limitations including the lack of proper assessment of risk of bias and study quality, as well as the absence of publication bias assessment. Despite these limitations, the review indicates a promising direction in the relationship between sleep duration and cognition, warranting further high-quality experimental studies that extends sleep duration to meet recommended levels and more accurately assess cognitive effects.

The systematic review by de Bruin and colleagues [146] examined the effects of experimental sleep manipulation on cognition in adolescents. This review included 16 studies and highlighted several key findings [146]. Notably, sleep extension or improvement was associated with better working memory [146]. In contrast, partial short-term sleep restriction had minimal or no effects on cognitive functioning, while acute sleep deprivation consistently led to declines in psychomotor vigilance task performance [146].

However, several limitations in the review warrant attention. Similar to the review by Short et al. (2018), de Bruin's review lacked a proper assessment of risk of bias and study quality, and it did not evaluate publication bias. The studies included in this review spanned a broad age range (8 to 20 years), encompassing different developmental stages than the targeted adolescent population, making interpretation of the results more challenging. Another notable limitation was the inclusion of a study on napping alongside studies on nighttime sleep. Since napping has its own distinct benefits on learning, which can be independent of nighttime sleep, this inclusion could have confounded the results

[147]. Furthermore, a study involving adolescents with insomnia was included. Since chronic sleep problems such as insomnia have their own impact on the brain, it is challenging to compare these findings with those from studies on healthy populations [148]. More well-defined inclusion criteria would have been necessary to systematically address the research questions related to nighttime sleep and cognition in healthy adolescents.

In addition, while most studies used objective sleep measures such as actigraphy and polysomnography, two studies relied on subjective sleep measures, which may lead to variability in data quality [146]. Another important limitation is that only three studies included sleep extension manipulations, one of which involved adolescents with insomnia, making it difficult to generalize the findings on the effects of increased sleep in healthy populations [146]. Additionally, two studies did not provide baseline sleep duration, eight studies used self- or proxy-reported sleep duration, and seven studies objectively measured sleep duration; of these, more than half reported average sleep durations that did not meet the recommended sleep guidelines [18–20]. These limitations highlight the need for more rigorous studies to clarify the relationship between sleep and cognition in adolescents.

In summary, while the evidence supports an association between sleep and cognition in the pediatric population, the current body of literature is limited by methodological inconsistencies and gaps. More well-designed, high-quality studies are needed to better elucidate the relationship between sleep and cognitive outcomes in children and adolescents. Despite these limitations, finding evidence of association between sleep

and cognitive function, even in very young children, raise concerns about the potential long-term effects of inadequate sleep.

To build on these insights, we conducted our own systematic review to investigate the association between sleep and brain functions and structures in apparently healthy children and adolescents, including those with obesity, aged 1 to 17 years [14]. This review aimed to deepen the understanding of how sleep impacts brain development and cognitive outcomes in this population, contributing to the growing evidence on the importance of adequate sleep for optimal neurodevelopment during childhood and adolescence [14].

2.5.2 Influence of sleep of developing brain function and structures in child and adolescents: a systematic review

Title:

Influence of sleep of developing brain function and structures in child and adolescents: A systematic review.

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CLINICAL REVIEW

Influence of sleep on developing brain functions and structures in children and adolescents: A systematic review

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SUMMARY

This systematic review examined the associations between sleep and brain functions and structures in children and adolescents aged 1–17 ys. Included studies (n = 24) were peer-reviewed and met the *a priori* determined population (apparently healthy children and adolescents aged 1 y to 17 ys), intervention/exposure/comparator (various sleep characteristics including duration, architecture, quality, timing), and outcome criteria (brain functions and/or brain structures, excluding cognitive function outcomes). Collectively, the reviewed studies report some relationships between inadequate sleep and resultant differences in brain functions or structures. Although the research presented supports and offers more insight into the importance of sleep for the developing brain of children and adolescents, no firm conclusions that apply broadly may be drawn from these results, particularly because of the diversity of the sleep variables and outcomes. However, it is clear that sleeping habits in the pediatric population should be prioritized. Health care providers should continue to recommend healthy sleep practices and adequate time for sleep, as they are essential for overall health, including brain health.
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Introduction

Healthy sleep is vital for good health, and can generally be defined as attaining adequate sleep duration, good sleep quality, maintaining appropriate sleep timing, and having no sleep disorders [1]. Inadequate sleep patterns characterized by short sleep duration, poor sleep quality, and late bedtimes have become pervasive in contemporary societies [2–4]. Getting adequate sleep is important at all ages, yet many youth do not get enough sleep [5–7]. Studies conducted in the pediatric population have reported many adverse associations between health indicators and inadequate sleep patterns, such as body composition, emotional regulation, growth, cognition, academic achievement, quality or life, insulin sensitivity, and blood pressure [8–11]. A comprehensive understanding of the health implications of inadequate sleep patterns during childhood is critical to inform public policies, and to develop promising interventions aimed at mitigating these sleep-related adverse effects. Examining the influence of sleep on neurological functions and structures in the pediatric population is an important part of this effort.

A recent systematic review (n = 26) examined the relationship between sleep and cognition in preschool-aged children [12]. The results of this review supported that increased sleep duration or quality

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Abbreviations

BOLD	blood oxygen level-dependent
CBFV	cerebral blood flow velocity
dACC	dorsal anterior cingulate cortex
dlPFC	dorsolateral prefrontal cortex
DMN	default mode network
dmPFC	dorsomedial prefrontal cortex
DTI-MRI	diffusion tensor imaging scan
EEG	electroencephalography
ERP	event-related potentials
fMRI	functional magnetic resonance imaging
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IR-FSPGR	T1-weighted inversion recovery fast spoiled gradient recalled
mcDESPOT	multi-component driven equilibrium single pulse observation of T1 and T2
MEG	magnetoencephalography
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
NREM	non-rapid eye movement
PICOS	participants, interventions, comparisons, outcomes, and study design
PFC	prefrontal cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
REM	rapid eye movement
SWA	slow-wave-activity
SWS	slow-wave sleep
TCD	stable transcranial Doppler

is associated with better cognitive development in preschool years; however, the strength of associations was small. A systematic review (n = 23) and meta-analysis (n = 19) [13] published in 2018 investigated the relationship between objectively-measured sleep and cognitive function in school-aged children (5–13 ys). The review by Short and colleagues [13] found a significant relationship between sleep duration and cognition, suggesting that longer sleep duration is associated with better cognitive functioning. Specifically, full/verbal intelligent quotient was significantly associated with sleep loss, whereas memory, fluid intelligent quotient, processing speed and attention were not [13]. Another systematic review [14], comprising 16 articles, examined the effects of experimental sleep manipulation on cognitive functioning of adolescents. The authors observed that partial short-term sleep restriction has small or no effects on cognitive functioning of adolescents, while acute sleep deprivation studies showed decrements in psychomotor vigilance task performance as the most consistent finding [14]. Moreover, de Bruin and colleagues [14] reported that sleep extension/improvement results in better working memory, and that sleep periods following learning improved memory consolidation. However, the authors noted that definite conclusions could not be drawn about which cognitive domains in particular were influenced by sleep manipulations. Finally, a recent systematic review and meta-analysis comprising 61 studies evaluated the effects of experimentally manipulated sleep restriction on neurocognitive functioning in healthy humans across the lifespan (from preschool years to senior adult years) [15]. The authors observed a significant negative effect of sleep restriction on cognitive processing across cognitive domains [15]. This effect held for executive functioning, sustained attention and long-term memory, while there was insufficient evidence to detect an effect within the domains of attention, multitasking, impulsive decision-making, or intelligence [15].

Although previous reviews have mainly examined the influence of sleep on cognitive function, to our knowledge no study has attempted to systematically and comprehensively examine the literature on sleep and brain functions and structures. The notion that inadequate sleep may have detrimental effects and possibly even protracted recovery effects on brain functions has only recently begun to be substantiated [16–18]. Accordingly, a comprehensive review of the collective evidence examining the influence of sleep on functional and structural aspects of the brain in children and adolescents is warranted. Examining sleep as it relates to neurodevelopment in the pediatric population is especially critical, because the frontal cortex (PFC) is still developing and imaging studies show that the prefrontal cortex is specifically sensitive to inadequate sleep patterns [19,20]. Given these findings and the pervasive decline in child and adolescent sleep trends over the past decades [5–7,21], it is imperative to establish the structural and functional manifestations of sleep on the developing brain of children and adolescents. Thus, the present work aims to provide a global picture on the influence of sleep on brain functions and structures in children and adolescents aged 1–17 ys.

Methods

Protocol and registration

This review was registered *a priori* with the International Prospective Register of Systematic Reviews (PROSPERO; Registration no. CRD42017060386; available from https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017060386), and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses [22].

Eligibility criteria

The participants, interventions, comparisons, outcomes, and study design (PICOS) framework [23] was followed to determine the research question, plan the search strategy, and refine the screening approach and eligibility criteria.

Population

The population included apparently healthy (i.e., general populations, including those with overweight or obesity, but with no diagnosed medical condition) children aged 1 y to 17 y for at least one exposure measurement point. Clinical populations (e.g., patients with sleep apnea or medical disorders) were excluded. However, control groups that included apparently healthy participants in studies conducted with clinical populations were retained. Subgroups were defined as: toddlers (1–2 y), preschoolers (3–4 y), school-aged children (5–13 y), and adolescents (14–17 y).

Intervention (exposure)

The intervention or exposure was sleep duration and/or sleep quality and/or sleep timing (bedtime and wake-up time or midpoint of sleep). Even studies examining the effect of daytime napping were included. There was no restriction imposed on the type of sleep assessment; studies using objective (e.g., polysomnography, actigraphy/accelerometry) or subjective (e.g., self-report, proxy-report) measures (or both) were included.

Experimental studies were included only if the intervention targeted sleep exclusively and not multiple health behaviours (e.g., interventions that targeted sleep together with other lifestyle behaviours were excluded).

Comparison

Various sleep characteristics (e.g., duration, architecture, quality) including the absence of sleep (i.e., during the retention period) were included. However, a comparator or control group was not required for inclusion.

Outcomes

Two neurological health indicators (i.e., brain functions and brain structures) were chosen based on expert input and consensus. Originally, cognitive function (e.g., attention, concentration, executive control, learning, memory, reaction time) was included as a third neurodevelopmental indicator but was excluded given that four systematic reviews have been published in the past year on the relationship between sleep and cognitive function [12–15]. We defined our outcomes of interest as follows: *brain function* studies as those using neuroimaging techniques to indirectly measure functional neurological changes or associations with sleep (e.g., expression of growth factors, neuronal activity), whereas *brain structure* studies as those using similar neuroimaging techniques to indirectly quantify structural neurological changes or associations with sleep (e.g., cerebral blood supply, neuro-receptor occupancy, volume, shape, and thickness) of the brain anatomy [24]. For a more comprehensive list of outcomes see Supplementary table S1.

Study designs

All study designs, except case studies, were eligible for inclusion. In longitudinal studies, any follow-up length was allowed; however, the sleep exposure had to be assessed at least once during the identified age range. There were no sample size restrictions for studies included in this manuscript. Published peer-reviewed original manuscripts and "in press" articles were eligible for inclusion. Reviews, commentaries, expert opinions, protocols, grey literature, book chapters, dissertations and conference abstracts were excluded.

Information sources and search strategy

The electronic search strategies were developed by a research librarian (M. Sampson) with expertise in search strategies for systematic reviews. See Supplementary table S2 for the complete search strategy. The following databases were searched using the Ovid interface: MEDLINE (1946 to October 5, 2017), EMBASE (1980–2017 Week 40), and PsycINFO (1987 to Week one October 2017). Reference lists of relevant reviews were also checked. Studies were included if they were published in English or French.

Study selection

References were extracted as text files and imported into the Reference Manager Software (Thompson Reuters, San Francisco, CA, USA) for removal of duplicate references. Titles and abstracts of potentially relevant articles were imported to DistillerSR (Evidence Partners, Ottawa, ON, Canada), and were screened independently by four reviewers (C. Dutil, J.J. Walsh, R.B. Featherstone and J.-P. Chaput). Exclusion by two reviewers was required for a study to be excluded at the first level screening; all other abstracts were sent to level two. At the level two screening, a full-text copy of each article that met initial screening criteria was obtained, and two reviewers independently (J.J. Walsh and J.-P. Chaput) examined all full-text manuscripts. Any discrepancies were resolved with a discussion and consensus between the reviewers and the first author (C. Dutil, J.J. Walsh and J.-P. Chaput).

Data extraction

Data extraction was completed in Excel (Microsoft) and checked for accuracy by a second reviewer (C. Dutil, J.J. Walsh and J.-P. Chaput). Results from the most fully adjusted models were extracted for studies that reported findings from multiple models. Important study features (i.e., author, publication year, study design, country, sample size, age and sex of participants, measure of sleep and neurodevelopmental outcomes, results, and covariates) were extracted.

Risk of bias and study quality assessment

A risk of bias assessment was completed for all included studies, as described in the Cochrane Handbook [25]. Briefly, the risk of bias assessment identifies methodological features of each study that can impact confidence in the overall estimate of effect for an outcome. However, blinding of participants was not considered for quality assessment, as it would have been impossible to blind participants to their allocated sleep conditions. The quality of evidence for each outcome by type of study design was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [26]. The GRADE framework categorizes the quality of evidence into four groups (high, moderate, low, and very low). The quality of evidence rating starts at "high" for randomized studies and at "low" for all other studies (e.g., non-randomized experiments or observational studies). The quality of evidence can be downgraded if there are serious limitations across studies (e.g., serious risk of bias, inconsistency of relative treatment effects, indirectness, imprecision, or other factors) [26]. The quality of evidence assessment was conducted by three authors (C. Dutil, J.J. Walsh and J.-P. Chaput), and verified by one another. Disagreements were resolved by discussion among the team members.

Synthesis of results

A meta-analysis was planned in the event that findings were found to be sufficiently homogenous in terms of methodological, statistical, and clinical characteristics. If not sufficiently homogeneous, narrative syntheses were planned.

Results

The full details of the search results are presented in the PRISMA flow diagram (Fig. 1). A total of 8192 records were identified through database searches. After removing duplicates, a total of 5978 records remained. Of those, 5769 records were deemed ineligible during the titles and abstracts screening process, 209 full-text articles were obtained for further review, and 24 studies met the inclusion criteria. Reasons for ineligible articles included: not reporting sleep as it relates to brain functions or structures (n = 81), ineligible age (n = 79), participants not apparently healthy (n = 10), not original research (e.g., review paper) (n = 8), intervention not targeting sleep exclusively (n = 6), and not with human participants (n = 1). Some studies were excluded for multiple reasons. Among the 24 studies that met our inclusion criteria, 16 studies involved brain functions and eight studies involved brain structures.

Included studies employed either a randomized intervention (n = 6) [27–32], non-randomized intervention (n = 1) [33], longitudinal design (n = 3) [34–36] or cross-sectional (n = 14) [37–50] design. The 24 studies that met all inclusion criteria represented 2091 participants (1972 participants from unique

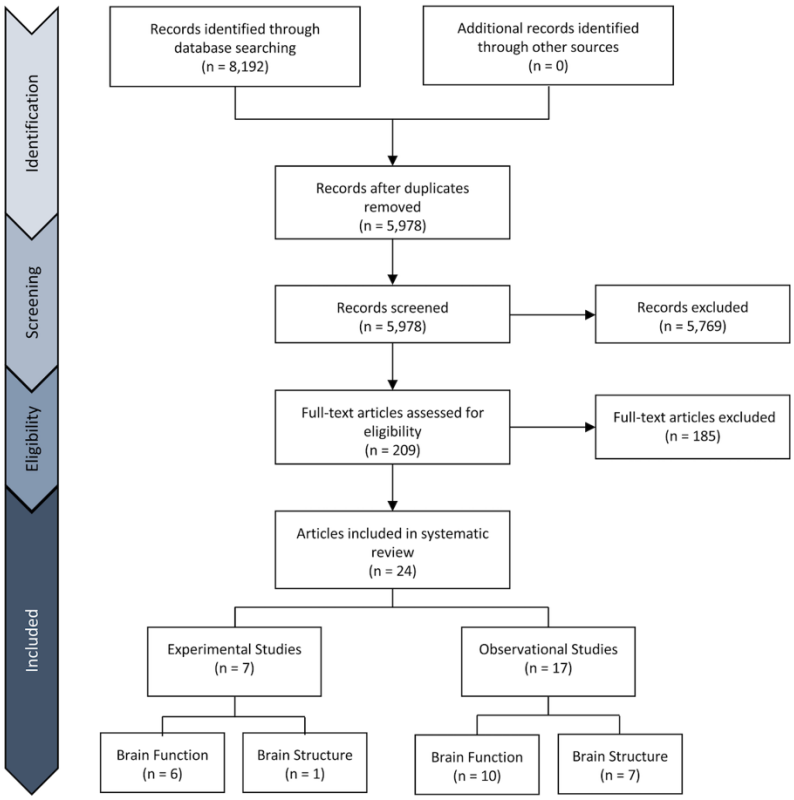


Fig. 1. PRISMA flow diagram for the identification, screening, eligibility, and inclusion of studies.

samples). Study-specific sample sizes ranged from 6 [29,33] to 720 [34] participants, and spanned a mean age of 1.1 [27] to 16.6 [40] ys (see Table 1). Sleep was assessed subjectively (i.e., via proxy- or self-reported questionnaire) in 37.5% of studies (n = 9) and was measured objectively (i.e., using polysomnography or actigraphy) or both objectively and subjectively in 62.5% of studies (n = 15). Individual study findings are summarized in Table 1, and a more detailed summary for included studies can be found in Supplementary tables S3 and S4. The quality of the evidence for this systematic review ranged from moderate to very low. All studies had high and low risk of bias judgements for the different biases, and all studies had at least one bias that was rated as unclear risk of bias due to the lack of information provided. The overview of quality of the evidence is reported for both experimental and observational study designs, and summarised across all the included studies in Figs. 2 and 3.

A high-level summary of findings is reported in Table 2, and the evidence is presented by outcomes (brain functions and brain structures), and also subdivided into specific categories. Studies identified as mainly "brain functions" were classified under four domains: 1) attention processing connectivity (n = 3); 2) memory consolidation connectivity (n = 3); 3) risk, reward and/or impulsivity connectivity (n = 8); and 4) emotion-dependent functional connectivity (n = 2). Three of the eight studies within the risk, reward and/or impulsivity connectivity domain were from the same larger study sample [39,41,47]. The studies examining brain structures were categorised into three structural measurements: 1) myelin water fraction (n = 1); 2) global brain, grey and white matter volumes (n = 6); and 3) cerebral blood supply (n = 1).

Data synthesis

Due to the high levels of heterogeneity across studies, it was determined by the review team that a meta-analysis was not possible. Narrative syntheses of the study results are presented below by outcome, in order of the quality rating of the evidence and followed by the highest number of studies within each category. All studies are given equal weight in a narrative synthesis of the evidence. If not otherwise specified, the presented values in this section are means ± standard deviations.

Brain functions

Memory consolidation connectivity

All three studies (two randomized controlled trials [27,30] and one cross-over trial [31]), appeared to show favorable findings between napping/sleep [27,31] or a full night sleep [30] (compared with a period of remaining awake) during the retention period and memory consolidation in toddlers and school-aged children. In the study by Urbain and colleagues [31], the school-aged children in the nap group slept on average 1.4 ± 0.3 h and spent an average of 37 ± 13% in slow-wave sleep (SWS) during the napping period,

Table 1
Summary of findings and quality of evidence for the studies included (n = 24) in this systematic review on the association between sleep, and brain functions and structures in children and youth.

Study design	Age subgroups	Authors, y	# of participants	Outcome measurement	Summary of findings (mean age ± standard deviation)	Quality
Randomized trials	Toddlers	Friedrich et al., 2015 [27]	90	EEG	Compared to the no-nap group, infants in the nap group had transferred the newly encoded word meanings into long-term memory as evidenced by the comparison in event-related potentials (ERP), namely N200 −500 and N400. The power of sleep spindle band (10–15 Hz) during non-rapid eye movement (NREM) sleep was correlated with the ERP, namely the parietal N400 component. Slow-wave-activity (SWA) during napping was not correlated with any of the ERP activity, which may be due to a ceiling effect in SWA (mean age = 385 ± 70 d).	MODERATE[a]
	School-aged children	Kurth et al., 2016 [28]	13	mcDESPOT MRI	The SWA restricted to habitual sleep ratio was negatively associated with myelin water fraction in the optic radiation (that relationship occurred bilaterally). Following acute sleep deprivation children displayed increased SWA in the parieto-occipital region (age ranged between 5 and 12 ys).	
		Wilhelm et al., 2013 [30]	31	fMRI	A strong correlation between SWA and explicit knowledge of a motor sequence task was observed. Sleep, compared with no sleep group, was associated with a higher blood oxygen level-dependent (BOLD) response in the left posterior hippocampus. After 1 night of sleep, superior explicit recall was associated with an increase activation in the superior frontal gyrus and in the cuneus. No difference was observed in the prefrontal activation between those who slept and those who did not sleep during consolidation (mean age = 9.7 ± 0.3 ys).	
		Urbain et al., 2016 [31]	21	MEG	Results suggest that sleep post-learning (napping in this case) was associated with increased evoked magnetic response in the prefrontal cortex (PFC) during the delayed retrieval, while in children who stayed awake the delayed retrieval process relied on the right hippocampal regions. The percentage spent in slow-wave sleep (SWS) during the post-learning nap (in the sleep group) was positively correlated with increased recruitment of the right hippocampal regions during immediate recall (mean age = 10.1 ys).	
	Adolescents	Robinson et al., 2018 [32]	18	fMRI	A night of normal sleep, compared to a night of sleep restriction, resulted in greater local and global efficiency in the bilateral amygdala and left	

Table 1 (*continued*)

Study design	Age subgroups	Authors, y	# of participants	Outcome measurement	Summary of findings (mean age ± standard deviation)	Quality
					fusiform gyrus. However, sleep restriction was associated with greater local and global efficiency in the posterior cingulate cortex, and the left superior portion of the lateral occipital cortex. Increased sensory processing networks were positively associated with a night of normal sleep, while greater path lengths were associated with sleep restriction in the left thalamus and fusiform regions. Sleep restriction was associated with hyperactive nodes within the default mode network (DMN) and hypoactive dorsolateral prefrontal cortex (dlPFCs) (14.4 ± 0.2 ys).	
		Beebe et al., 2009 [29]	6	fMRI	While the performance on an attentional and working memory task was preserved after 1 week of sleep restriction (6.5 h in bed per night), compensatory cerebral response was observed via fMRI. This sleep restriction induced compensation was characterised by greater activation of the dorsal PFC and the inferior parietal lobes, and by a greater suppression of peripheral mental processes in the medial frontal gyri and posterior cingulate areas (mean age = 15.3 ± 0.7 ys).	
Non-randomized trial	School-aged children	Molfese et al., 2013 [33]	6[e]	EEG	Minor sleep restriction (1 h per night for a week) was shown to alter the pattern of ERP responsivity, namely reduced P300 amplitude, of the temporal, parietal and occipital electrodes recordings as measured during three cognitive function tasks, compared with a week of ideal sleep (mean age = 7.7 ys).	VERY LOW[a,b]
Longitudinal study	Toddlers to school-aged children	Kocevska et al., 2016 [34]	720	IR-FSPGR	Adverse or persistent sleep disturbances (i.e., one frequent symptoms or two less frequent symptoms measured by questionnaire) in the first 6 ys (assessment at 2 m, 1.5, 2, 3 and 6 ys) of life was associated with smaller global brain volume, and smaller grey matter volumes in the dlPFC (mean age = 7.9 ± 1.0 ys at time of the MRI scan).	VERY LOW[c]
	School-aged children to adolescents	Telzer et al., 2015 [36]	48	DTI-MRI	In adolescents who averaged 8 h of sleep (assessed with 14-d sleep log) per night, greater sleep variability (calculated by the standard deviation in bedtime over the 14 d) in sleep duration one y prior to the DTI-MRI scan was associated with reduced fractional anisotropy (an investigation of the integrity of the white matter tracts) in the parietocortical, frontocortical and frontostriatal tracts (mean age = 16.3 ys at the DTI-MRI scan).	

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Table 1 (*continued*)

Study design	Age subgroups	Authors, y	# of participants	Outcome measurement	Summary of findings (mean age ± standard deviation)	Quality
		Casement et al., 2016 [35]	123[e]	fMRI	Associations were found between persistent (yearly assessments from age 9 to 13 ys and one more time point between 16 and 17 ys of age) insomnia symptoms (increased difficulty falling and staying asleep [sleep efficiency], and feeling poorly rested upon awakening [sleep quality]), and higher BOLD response in the dorsomedial prefrontal cortex (dmPFC) in female adolescents (males were not recruited) during anticipation of monetary rewards. While BOLD in the dmPFC during reward anticipation phase was also positively associated with high scores for poor sleep quality it was not associated with the sleep efficiency measure (between 16 and 17 ys of age during fMRI scan).	
Cross-sectional studies	Toddlers	Hoyniak et al., 2015 [46]	20[d]	EEG	Sleep irregularities (irregular timing and duration assessed with actigraphs worn for a week) were associated with a poorer ability to sustained attention, as observed by longer target P3 ERP latencies. Sleep duration was not significantly associated with P3 latencies or P3 amplitudes (mean age = 2.8 ± 0.3 ys).	VERY LOW[c]
	School-aged children	Peng et al., 2016 [43]	26	TCD-VEEG	During NREM sleep in children with partial sleep deprivation (children were instructed to wake up at 2:00a.m. and remain awake until the TCD-VEEG), two main associations were found: (i) light sleep (stages N1 and N2) was associated with increased cerebral blood flow velocity (CBFV) of the middle and anterior cerebral arteries, and (ii) deep sleep was associated with reduced systolic CBFV in all vascular arteries with sustained increased pulsatility index (7.8 ± 2.3 ys).	
		Reidy et al., 2016 [50]	15[e]	fMRI	Emotion-dependent functional connectivity between bilateral amygdala and PFC, cingulate, fusiform and occipital cortex were negatively associated with sleep duration (mean age = 8.7 ± 1.1 ys).	
		Taki et al., 2012 [45]	290	MRI	Weekdays sleep duration (measured by questionnaire) was positively correlated with regional grey matter volumes in the bilateral hippocampal body, and the right dlPFC (mean age = 11.0 ± 2.9 and 11.6 ± 3.4 ys of boys and girls, respectively).	
		Forbes et al., 2012 [39]	63[d]	fMRI	Sleep midpoint was negatively correlated with activity in the medial prefrontal cortex (mPFC) in response to reward stimuli (mean age = 11.9 ± 0.7 ys).	
		Hasler et al., 2012 [41]	56[d]	fMRI	In the same sample as the previous study [47], the larger	

Table 1 (*continued*)

Study design	Age subgroups	Authors, y	# of participants	Outcome measurement	Summary of findings (mean age ± standard deviation)	Quality
					advances in timing of midpoint sleep from Saturday to Sunday night were associated with less mPFC and striatal activation during the anticipation and receipt of reward (mean age = 12.3 ± 0.9 ys).	
		Holm et al., 2009 [47]	58[d]	fMRI	Using the same sample as the 2 previously mentioned studies [39,41], association between shorter sleep duration, later sleep onset, and lower sleep quality were associated with decreased activation in the caudate during reward anticipation (mean age = 12.3 ± 0.9 ys).	
		Buchmann et al., 2011 [37]	36	MRI	A positive correlation between sleep SWA and grey matter volumes was observed in the posterior cingulate, bilateral parietal, and left dlPFC, as well as sensorimotor, occipital and posterior temporal areas (mean age = 13.5 ± 3.3 ys).	
	Adolescents	Carlisi et al., 2017 [38]	19	fMRI	Sleep duration was negatively correlated with BOLD neural responses to negative faces in the dorsal anterior cingulate cortex (dACC) and in the hippocampus. A psychophysiological interaction analysis between dACC-dmPFC and sleep duration was correlated. However, subjective reports of tiredness did not modulate neural responses to negative faces (mean age = 14.2 ± 2.4 ys).	
		Urrila et al., 2017 [42]	177	MRI	Later bedtime on weekends (measured by questionnaire) correlated with smaller grey matter volumes in three separate clusters located in the right precuneus and paracentral lobule, the right middle/ superior frontal gyrus, and the right frontal superior medial cortex, and left anterior cingulate cortex. Longer time in bed during weekdays correlated with higher grey matter volumes in a frontal cluster comprising the left superior and middle frontal gyrus (mean age = 14.4 ± 0.5 ys).	
		Telzer et al., 2013 [48]	46	fMRI	Poor sleep quality was associated with: (i) decreased activation in dlPFC during cognitive control but an increased insula activation during reward processing. Reduced functional coupling between dlPFC and affective regions (i.e., insula and ventral striatum) were negatively correlated with sleep quality (mean age = 15.2 ys).	
		Goldstone et al., 2018 [44]	132	MRI	Greater grey matter volumes and cortical thickness of the frontal and parietal regions were positively associated with sleep SWA; these brain regions partially mediated the	

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Table 1 (*continued*)

Study design	Age subgroups	Authors, y	# of participants	Outcome measurement	Summary of findings (mean age ± standard deviation)	Quality
					relationship between age and SWA (mean age = 15.6 ys).	
		Tashjian et al., 2017 [45]	55	fMRI	Poor sleep quality (i.e., the number of awakening, and the duration of the awakenings) was positively correlated with functional coupling between the DMN and the PFC, specifically the ventrolateral PFC and dlPFC (mean age boys = 16.2 ± 1.2 ys and mean age girls = 16.3 ± 1.0 ys).	
		Uy & Galván, 2017 [40]	22	fMRI	Longer sleep duration was associated with greater functional coupling between the anterior insula and the dlPFC under high stress evoked by risky decision-making tasks, whereas sleep duration was not associated with this functional coupling during low stress (mean age = 16.6 ± 0.7 ys).	

Population: apparently healthy children with a mean age between 385 d and 16.6 ys.
Setting: any setting, including sleep laboratory or at home.
Intervention and comparator, or independent variable: intervention studies were between no daytime sleep (no napping), 45 min (nap) and three weeks of nighttime sleep manipulations. Longitudinal studies were up to seven years. Sleep was assessed by actigraphy, EEG, proxy- or self-report.
Outcome or dependent variable: brain functions and structures were assessed through various methods (i.e., functional magnetic resonance imaging [fMRI], magnetic resonance imaging [MRI], electroencephalography [EEG], magnetoencephalography [MEG], diffusion tensor imaging scan [DTI-MRI], stable transcranial Doppler through real-time video electroencephalogram [TCD-VEEG] ultrasound, multi-component driven equilibrium single pulse observation of T1 and T2 [mcDESPOT] MRI, and T1-weighted inversion recovery fast spoiled gradient recalled [IR-FSPGR]).
GRADE Working Group grades of evidence [26].
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.
Note. Due to the heterogeneity in the measurement of sleep and outcomes across studies a meta-analysis was not advisable. Studies are sorted by study design (experimental first), followed by age subgroups as per the reported mean age. Age subgroups were defined as: toddlers (1–2 y), preschoolers (3–4 y), school-aged children (5–13 y), and adolescents (14–18 y). The mean age along with the standard deviation (when it was reported by authors) are stated in brackets for each study. The GRADE framework [26] was used to assess the quality of the evidence.
Abbreviations: BOLD, blood oxygen level-dependent; CBFV, cerebral blood flow velocity; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; DTI, diffusion tensor imaging scan; EEG, electroencephalography; ERP, event-related potentials; fMRI, functional magnetic resonance imaging; IR-FSPGR, T1-weighted inversion recovery fast spoiled gradient recalled; mcDESPOT-MRI, multi-component driven equilibrium single pulse observation of T1 and T2; MEG, magnetoencephalography; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; PFC, prefrontal cortex; SWA, slow-wave-activity; SWS, slow-wave sleep; TCD, stable transcranial Doppler.
[a] Downgraded once because of risk of bias.
[b] Downgraded once because of imprecision of results.
[c] Downgraded once because of heterogeneity among included studies.
[d] The following studies [39,41,47] used the same sample from a lager study. A study [46] had a sample of 15 unique toddlers in which five were measured at two different time points but were used as a sample of 20 independent cases. For the cross-sectional studies the sample included 896 unique children.
[e] Two studies [33,50] used a sample that included only male participants and one study [35] had a sample composed of only female participants.

measured by polysomnography. The magnetoencephalography (MEG) results showed that the school-aged children in the napping group, compared to the awake group, showed sleep-dependent changes in the PFC [31]. The average sleep for both groups was approximately 10 h of sleep (proxy-reported by a parent) in the two nights preceding the experiment [31], which is within the recommended amount of sleep for this age group [51]. In the study conducted in toddlers, by Friedrich et al. [27], the average amount of sleep, measured via electroencephalography (EEG), during the retention period for the nap group was 0.75 ± 0.4 h and the majority of the time asleep was spent in SWS (76.3 ± 12.8%). Results showed that in toddlers, sleep spindles (frequency range of 10–15 Hz) was negatively correlated with event-related potential (ERP) N400 priming effect (a negative component), suggesting that in toddlers the sleep spindles had been involved in the learning of the new word meanings [27]. The study by Wilhelm and colleagues' [30] involved school-aged children learning the task in the evening for the sleep group, or in the morning for the awake group that was followed by a 12 h retention period that included sleep or daytime wakefulness for both groups, respectively. During the retention period, the sleep group slept an average of 9.7 h and spent an average of 37.3 ± 13.6% of the night in slow-wave activity (SWA) as measured by polysomnography [30]. The functional magnetic resonance imaging (fMRI) results for the sleep group, compared with the awake group, revealed a positive association between sleep during the consolidation period and increased blood oxygen level-dependent (BOLD) response in the left posterior hippocampus [30].

Together, the results (presented in Tables 1 and 2) for the relationship between sleep and memory consolidation connectivity suggest that sleep, specifically SWS, SWA and sleep spindles, after learning a novel task may positively affect memory reorganization from an early age that persists in school-aged children. The measurement in this section offer diverse advantages; the EEG recordings offers higher temporal resolution, while MEG and fMRI

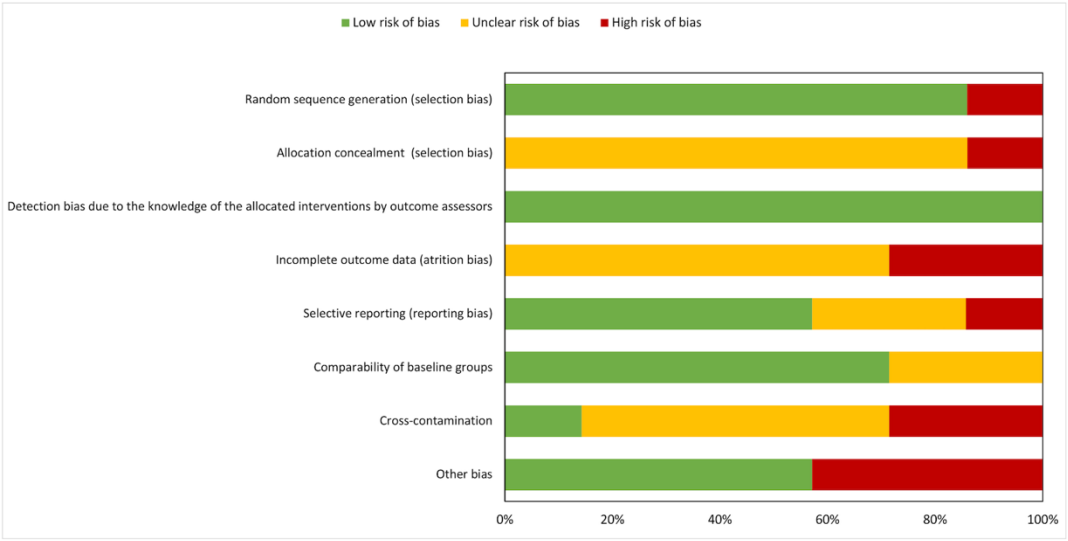


Fig. 2. Overview of experimental study quality and risk of bias [low, high, and unclear] assessment according to the authors' judgement (n = 7).

have higher spatial resolution. The fMRI provides a means to measure brain activation by recording the changes in blood oxygenation in the brain that are assumed to indicate changes in neuronal activation [52,53].

Attention processing connectivity

A total of three studies [29,33,46] with 32 participants overall (27 unique participants) examined the association between objectively measured sleep (via actigraphy) and attentional processing. The study designs included a cross-over design [29], a non-randomized experimental trial [33], and a cross-sectional study [46]. Both experimental trials had very small sample sizes (n = 6 for each study). All three studies found significant effects or associations between inadequate sleep (shorter duration [29,33] and larger day-to-day sleep variability [46]) and poorer attentional processing.

In terms of sleep manipulation in adolescents, the randomized cross-over study of Beebe et al. [29] included a one-week baseline sleep assessment (mean sleep = 7.7 ± 1.1 h), followed in random order by a week of ideal sleep (mean sleep = 8.7 ± 0.4 h), and a week of sleep restriction (mean sleep = 6.3 ± 0.5 h) with no break between conditions. The results by Beebe and colleagues [29] revealed a compensatory effect to maintain task performance after the sleep restriction week, that was characterised by an increased in activation in dorsal PFC and the inferior parietal lobes with a simultaneous decrease in mental processes in the medial

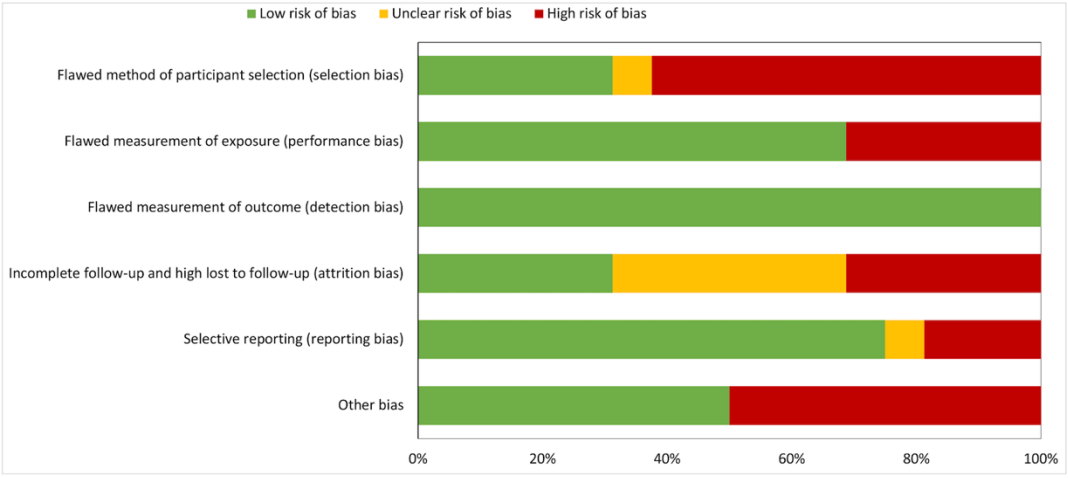


Fig. 3. Overview of observational study quality and risk of bias [low, high, and unclear] assessment according to the authors' judgement (n = 17).

Table 2
High-level summary of findings by brain functions and structures (n = 24).

Outcome	# of participants (# of studies)	Quality of evidence[a]	Absolute effect
Brain function			
Attention processing connectivity	32[b] (3)	Moderate to very low	one study reported on the effect between prolonged sleep restriction in adolescents (compared with ideal sleep and baseline) and the increased task positive activation, and increased task negative suppression during a demanding attentional task. The study showed a compensatory brain activation to maintain performance during sleep restriction [29]. one study reported favorable findings between ideal sleep duration, compared with mild sleep restriction, and increased amplitude in ERP during attention demanding tasks in school-aged children [33]. one study showed that irregular sleep in preschool children was associated with a decrease ability to maintain attention [46].
Memory consolidation connectivity	142 (3)	Moderate	one study reported that daytime sleep spindles over the parietal region was positively correlated with N400 in toddlers [27]. one study reported the favorable relationship between sleep (during the consolidation period), compared to no sleep, in school-aged children and its positive association with higher BOLD response in the left posterior hippocampus [30]. one study reported the positive relationship between daytime napping sleep in school-aged children during the consolidation phase of learning and memory-related activity in the prefrontal areas of the brain [31].
Risk, reward and/or impulsivity connectivity	441[b] (8)	Moderate to very low	one study reported a relationship between a night of normal sleep, compared with a night of restricted sleep, and greater local and global efficiency in the key limbic structures. A single night of sleep restriction was associated with weaker local connectivity of the posterior cingulate cortex, which may be associated with poor flexibility in cognitive processes compared with a night of normal sleep [32]. one study reported a longitudinal association between persistent non-restorative sleep during early adolescence and higher BOLD activation in the dorsomedial PFC during reward anticipation tested during late adolescence [35]. one study reported a correlation between later sleep midpoint in school-aged children and decreased activation in mPFC in response to reward stimulus [39]. one study reported that in school-aged children increased weekend sleep variability between Saturday and Sunday night (measured by midpoint of sleep) was associated with less mPFC and striatal activation during the anticipation and receipt of reward [41]. one study reported that shorter sleep duration, later sleep onset, and lower sleep quality were associated with decreased activation in the caudate during reward anticipation in school-aged children. However, during the reward outcome phase shorter sleep duration was not associated with decreased activation in the caudate, while later sleep onset, earlier sleep offset time, and lower sleep quality were associated [47]. one study reported that poor sleep quality in adolescents was associated with greater risk taking as shown by the reduced activation in the dlPFC during cognitive control, greater insula activation during the reward processing, and decreased connectivity coupling between dlPFC, insula and ventral striatum during reward processing [48]. one study reported mixed findings, as poor sleep quality in adolescents, but not sleep duration, was associated with greater affect-related impulsivity with low strength connectivity coupling between the default mode networks and the PFC [49]. one study reported that longer sleep in adolescents was associated with greater connectivity coupling between the anterior insula and the dlPFC during a high pressure risky decision-making task, but the association did not remain during low pressure [40].
Emotion-dependent functional connectivity	34 (2)	Very low	one study reported the negative association between sleep duration in school-aged children and greater functional

Table 2 (*continued*)

Outcome	# of participants (# of studies)	Quality of evidence[a]	Absolute effect
			connectivity in response to emotional stimuli in regions linked to the emotion generation [50]. one study reported mixed findings; sleep duration deficits, but not sleep quality, in adolescents was associated with higher emotional reactivity in the anterior cingulate cortex and in the hippocampus [38].
Brain structure			
Myelin water fraction	13 (1)	Moderate	one study reported that following acute sleep deprivation a negative relationship was observed between increased SWA and the decreased myelin content in bilateral optic radiation in school-aged children [28].
Global brain, grey and white matter volumes	1403 (6)	Very low	one study reported that sleep disturbances during early years onward was associated with smaller global brain, white, and grey matter volumes [34]. one study reported a favorable positive association between adequate weekday sleep duration in school-aged children and grey matter volumes [45]. one study reported that both shorter sleep duration during the week and later weekend sleeping hours in adolescents correlated with lower grey matter volumes in specific brain regions [42]. one study reported an association between greater sleep variability over time and less white matter integrity in adolescents [36]. one study reported a favorable association between sleep SWA in school-aged children and greater grey matter volume [37]. one study reported a favorable association between sleep SWA in adolescents, greater cortical thicknesses, and grey matter volume [44].
Cerebral blood supply	26 (1)	Very low	one study reported that NREM sleep in sleep deprived children was positively associated with increased CBFV [43].

High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.
Abbreviations: BOLD, Blood oxygen level dependent response; CBFV, cerebral blood flow velocity; dlPFC, dorsolateral prefrontal cortex; ERP, event-related potentials; mPFC, medial prefrontal cortex; NREM, non-rapid eye movement; PFC, prefrontal cortex; and, SWA, slow-wave activity.

[a] The GRADE Working Group grades of evidence [26] was used as follows.

[b] The following studies [39,41,47] in the risk, reward and/or impulsivity section used the same sample from a lager study (n = 327 unique children). A study [46] in the attentional processing connectivity section had a sample of 15 unique toddlers in which five were measured at two different time points but were used as a sample of 20 independent cases (n = 27 unique children in the attentional processing section).

frontal gyri and posterior cingulate areas. Molfese and colleagues [33] in the first week of the experiment asked school-aged children participants (males only) to adjust their time in bed to 10 h per night; children slept an average of 9.3 ± 0.6 h during that week. In the following week, participants were instructed to follow a sleep routine that resulted in nine hours in bed; during that week the children participants slept an average of 8.4 ± 0.5 h [33]. However, for this study the habitual sleep before the experiment was not reported. The observational study by Hoyniak and colleagues [46] reported an average of 9.8 ± 0.7 h of sleep per 24 h in toddlers, but no significant results between sleep duration and the EEG-based outcome measures (P3 latencies and P3 amplitude) were found. However, in this sample of toddlers, irregular sleep was associated with longer target P3 latencies during an attentional task [46], indicating that these observational results suggest that irregular sleep is associated with less efficient attentional processing. Of note, in order to avoid assumption of independence in correlational analysis the study by Hoyniak and colleagues [46], which included 15 unique toddlers, five of whom were measured at two different time points, employed clustered regression to statistically account for longitudinal dependency.

Together, the two experimental studies suggest that sleep-related changes in activation in the parietal lobes during an attentional task may be expected. In toddlers and school-aged children irregular sleep and decreased sleep duration, respectively, was associated with differences in P3 latencies and amplitudes. The ERP, represented by the phasic changes in EEG as a result of a stimulus, is a non-invasive mean of evaluating temporal brain functioning of neural information processing.

Furthermore, findings in adolescents suggest that shorter sleep duration may be associated with compensatory brain mechanisms, increased activation of task positive and increased suppression of task negative brain regions, during a demanding attentional task in order to maintain performance. This brain homeostatic response to maintain performance during increased mental load, brought on by sleep restriction in this instance, upregulates processing power to the brain regions relevant task, and inhibits mental processes of irrelevant brain regions.

Risk, reward and/or impulsivity connectivity

Eight studies, including one cross-over trial [32] and seven observational studies (one longitudinal [35] and six cross-sectional studies [39–41,47–49]), examined the association between sleep and risk, reward and/or impulsivity connectivity in children. Sleep was assessed objectively using actigraphy in five of the eight studies [32,39,41,46,49]. All studies reported some significant findings between sleep (quality, duration, or timing), in school-

aged children and adolescents, and risk-taking, reward and/or impulsivity connectivity outcomes. In addition, the cross-over trial in an adolescent sample, by Robinson et al. [32], found a compensatory response to sleep deprivation (i.e., single night of 4 h of time in bed) that was expressed by the increased connectivity of key limbic and default-mode network structures including the posterior cingulate cortex and dorsolateral prefrontal cortex (dlPFC).

Collectively, inadequate sleep in school-aged children and adolescents was associated with heightened functional connectivity in brain regions involved with impulsivity and risk-taking, often observed in the dorsomedial PFC and dlPFC.

Emotion-dependent functional connectivity

Two recent cross-sectional [38,50] studies explored the association between sleep and emotion-dependent functional connectivity in school-aged children and adolescents (n = 34 participants). Both studies found a significant association between subjectively measured shorter sleep duration and higher emotional reactivity in the brain regions associated with emotion-dependent functional connectivity [38,50]. However, the study by Carlisi and colleagues [38], in an adolescent sample, reported mixed results; sleep duration, but not sleep quality (subjectively assessed via self-reported tiredness questionnaire), was associated with emotion-dependent functional connectivity.

These recent findings suggest that sleep duration of school-aged children and adolescents may be a factor in the association between sleep and emotion-dependent functionality connectivity, mainly observed in the dorsal anterior cingulate cortex.

Brain structures

Myelin water fraction

An experimental study [28], with a sample of 13 school-aged participants, reported a negative relationship between increased SWA in the parieto-occipital region and decreased myelin water fraction (measured by multi-component driven equilibrium single pulse observation of T1 and T2 [mcDESPOT]) in the bilateral optic radiation after a single night of acute sleep restriction (50% of habitual sleep 5.1 ± 0.1 h), compared with a night of habitual sleep (10.0 ± 0.1 h).

These findings suggest an association between white matter myelin content and local sleep need, for neural plasticity, in the children's developing brains. If myelin content is compromised (e.g., by slowed growth), brain functions may be altered as myelin plays a fundamental role in the speed of action potential in the central nervous system. Myelin water fraction can be defined as ratio of myelin water to total water in the brain [54,55]. An important advantage of mcDESPOT, over other magnetic resonance imaging (MRI) techniques (for a comprehensive review of MRI-based myelin imaging techniques see Alonso-Ortiz and colleagues [55]), is the increased speed at which it can capture data, that enables the measurement of whole brain myelin water fraction with high spatial resolution.

Global brain, grey and white matter volumes

A total of six observational studies, two longitudinal [34,36] and four cross-sectional [37,42,44,45] studies, investigated the association between sleep and brain grey, and/or white matter volumes. Together, all studies reported significant associations between sleep and global brain, grey and white matter volumes. The longitudinal study by Kocevska et al. [34], reported that persistent proxy-reported sleep disturbances from an early age (from 2 m to 6 y of life) were associated with lower global brain and grey matter volumes measured at 7 y old, while Telzer and colleagues' [36] longitudinal study focused on the association between greater sleep variability (subjectively measured) over time and less white matter integrity, measured during mid-to late-adolescence. Two cross-sectional studies, in school-aged children and adolescents, reported positive associations between SWA and grey matter volume [37,44] and cortical thickness [44]. The other two cross-sectional studies reported a positive association between subjectively measured weekday sleep duration, in school-aged children and adolescents, and grey matter volumes [42,45]. The study by Urrila and colleagues [42] also reported that in adolescents later bedtimes on weekends correlated with smaller grey matter volumes.

In school-aged children and adolescents, the positive association between SWA and grey matter volumes and cortical thickness were found in regions of the brain involved in executive function, sensory integration, language processing and motor functions. Additionally, in school-aged children the association between less weekday sleep duration and lower grey matter volumes in the bilateral hippocampal body, may suggest difficulty in learning and memory. In adolescents, the association found between later weekend bedtime and smaller grey matter volumes were observed in areas of the brain responsible for executive functions, cognitive control, and emotional control. The longitudinal findings suggesting that persisting sleep disturbance from an early age is associated with lower global brain volume and lower grey matter volumes in dlPFC is raising important questions as the functions of the dlPFC include important executive functions (e.g., planning, working memory, cognitive flexibility and inhibitory processes). Similarly, the regional longitudinal findings of lower white matter integrity in adolescents with increased sleep variability, may suggest decreased working memory capacity. However, how these associations between inadequate sleep and decreased cortical thickness, grey and white volumes directly relate to cognitive functions still remains unknown.

Cerebral blood supply

A single study [43] observed the association between sleep architecture during a nap and cerebral hemodynamics (measured by transcranial doppler sonography [TCD]) in partially sleep deprived school-aged children (n = 26). The study by Peng and colleagues [43] found that light sleep was associated with increased cerebral blood flow velocity (CBFV) of the middle and anterior cerebral arteries, while deep sleep was associated with reduced systolic CBFV in all vascular arteries.

The interpretation of these finding is difficult, since the regional CBFV during wakefulness were not measured. However, these findings may indicate that the observed increased CBFV during light sleep, compared to deep sleep, may be a homeostatic response to the increased metabolic brain demand imposed by the lack of sleep.

Discussion

In an effort to supplement and broaden the knowledge offered by the recently published systematic reviews on the relationship between sleep and cognitive function in the pediatric population [12–15], this systematic review was undertaken to review the associations between sleep and brain functions and structures in children and adolescents aged 1 to 17 y. The present review synthesized peer-reviewed scientific evidence from 24 studies (2091 participants [1972 participants from unique samples]) that included

both experimental (n = 7) and observational (n = 17) study designs. Among them, sleep was assessed subjectively in 37.5% of studies (n = 9) and was measured objectively (or both objectively and subjectively) in 62.5% of studies (n = 15). The present review compiled the evidence establishing associations between inadequate sleep and neuroanatomical structures, brain function and compensatory function mechanisms in apparently healthy children and adolescents. Imaging technologies, such as MRI and fMRI, have been instrumental research tools that have offered new insights in the relationships between sleep and neuroanatomical structures and functions. The studies included herein incorporated diverse measurements and an array of outcomes using a number of different neuroimaging techniques. The quality of the evidence ranged from moderate to very low. Collectively, the reviewed studies report some significant associations between inadequate sleep and corresponding differences in brain functions and/or structures. Although the research available to date on the topic supports and offers more insights on the importance of sleep for the developing brains of children and adolescents, precise conclusions that apply broadly cannot be drawn from these results. This is mainly due to the different stages of brain development during childhood years, and the diversity of the sleep variables and outcomes investigated. More research is needed to elucidate the mechanisms involved in the relationship between sleep and brain functions, and the neural plasticity and development of brain structures.

While more studies with larger sample sizes are needed to confirm these findings, an effect between acute mild sleep restriction (restriction of one hour per night for a week) and increased connectivity during attentional processing demands to maintain task performance was observed, compared with a week of ideal sleep duration in school-aged children [33] and adolescents [29]. The compensatory brain response to preserve performance during an attentional task following sleep restriction, may also explain the mixed findings reported by the recently published systematic reviews on the association between sleep and cognitive functions [13–15], since without brain function measurements (e.g., EEG or fMRI), the effect of sleep restriction on attentional processing (i.e., compensatory mechanism to preserve performance on an attentional task) may be missed. The cross-sectional findings [46] in this domain suggests an association between irregular sleep in toddlers, but not duration, and longer P3 event-related potential latencies, which suggest less efficient attentional processing.

The findings on the effect of sleep on memory consolidation processes suggest that sleep spindles, SWA and percentage spent in SWS after learning improve the memory consolidation connectivity processes in toddlers and school-aged children [27,30,31]. These findings are consistent with previous results from recent systematic reviews on sleep and cognitive functions [12,14]. In school-aged children and adolescents, findings suggest that shorter sleep duration, but not quality [38], was associated with greater emotion-dependent networks reactivity to negative emotions [38,50]. Specifically, in school-aged boys sleep duration was negatively associated with activation in the bilateral amygdala and PFC, cingulate, fusiform and occipital cortex when viewing negative faces compared to viewing neutral faces [50]. In adolescents, sleep duration was negatively correlated with BOLD neural response to negative faces in the dorsal anterior cingulate cortex and in the hippocampus [38]. The association between shorter sleep duration and increased amygdala reactivity was consistent with previous studies conducted in adults [56–58]. Mixed findings in the association between inadequate sleep (duration, variability, timing and/or quality) and increased risk, reward and/or impulsivity connectivity are also consistent with previous findings in adults [59]. However, risk taking and reward systems research in school-aged children and adolescents may be of greater importance than in adult populations, as evidence suggests that the risk-taking and reward centers of the brain are overactive during this period [60,61].

Compared to adulthood and childhood years, adolescence is a period prone to increased risk-taking behaviours [61]. While the exact brain mechanism for the increased propensity towards risky behaviours in adolescents remains debated, as to whether the striatum and its dopaminergic pathways are hypo- or hypersensitive to reward stimulus, there is very little doubt that the reward system undergoes important maturational changes that may lead to engaging in detrimental risky behaviours [60]. The need and motivation of adolescents to experience multiple new and intense stimuli to satisfy the rewards center of the brain has been associated with numerous detrimental health outcomes later on in life, including alcohol abuse, drug use, and smoking [62–65].

A brain structure study observed a negative relationship between habitual/restricted SWA ratio in school-aged children and myelin water fraction in the bilateral parietal optic radiation [28]. Additionally, results on the brain structure outcome also suggest that less sleep disturbances during early years [34], adequate weekday sleep duration in school-aged children and adolescents [42,45], and increased SWA in school-aged children and adolescents [37,44] are all associated with greater grey matter volumes. Although these findings are somewhat consistent with one another, a causal link cannot yet be established. Finally, in a study investigating associations between sleep architecture and cerebral blood flow, measured by video-electroencephalogram in sleep deprived school aged children, repported a positive association between the amount of non-rapid eye movement (NREM) sleep and increased CBFV in middle and anterior cerebral arteries [43]. Gaining an understanding of the mechanisms between sleep characteristics (timing, architecture, duration, and quality) and associated cerebral blood supply, grey, and white matter volumes development in the pediatric population, would be an important future endeavour to offer meaningful clinical relevance.

A greater level of consistency in defining and characterizing inadequate sleep is needed for this evolving field of research. Inadequate sleep can be defined as sleep disruption during a period of time that results in impairment of neurological and physiological functions [66]. The definition of inadequate sleep applies to one or multiple sleep characteristics being affected, such as the quantity (duration), timing, architecture, and the perceived quality of sleep. Moreover, it can be characterized in many temporal ways, this includes short-term (acute) or long-term (chronic), and partial (restriction) or near-total or total (deprivation) sleep loss. All experimental studies in the present review manipulated inadequate sleep by either choosing an acute sleep restriction (e.g., one week) intervention or acute sleep deprivation (e.g., one night) invention.

No studies to date, for obvious reasons, have looked at chronic sleep deprivation in this population, thereby limiting inferences to be made to more chronic situations. Evidence from animal studies suggest that chronic sleep deprivation leads to the suppression of the survival instinct, blunts maturation, impedes neural plasticity, and ultimately leads to early mortality [67,68]. Furthermore, research on the permanent adverse effects of chronic sleep loss on neurodevelopment is still minimal in humans, limiting our understanding of the long-term risk of chronic sleep restriction on the developing brain functions and structures in the pediatric population. However, animal studies have been instrumental at providing insights on the role of sleep in the development of brain functions and structures. Briefly, in rats, the effects of sleep deprivation are concordant with a range of effects of inadequate sleep (including acute sleep deprivation) in humans on cognitive functions [69]. Similarly to humans, animals also exhibit differential susceptibility to the effects of sleep deprivation, which is consistent with 'trait-like' susceptibility (inter-subject variability) [69].

Altering the circadian-clock (to 20 h: 10 h dark/ 10 h light cycles) of mice was shown to impact the dendritic length, and the complexity of neurons organization in the prelimbic region of the medial PFC [70]. These animals also showed decreases in cognitive flexibility, and changes in emotionality consistent with the brain structures affected [70]. Moreover, depriving young animals of rapid eye movement-sleep (REM) and NREM-sleep leads to the loss of brain plasticity, as quantified by the loss of brain volume [71–73]. In rats, the effect of suppression of REM sleep during early development is suggested to produce protracted behavioural and brain morphological abnormalities later in life [74]. Together, these animal studies emphasize the importance of sleep as a whole for proper brain development and functioning.

Investigating associations between sleep and the developing brain is complex, as results may be moderated or confounded by a number of factors. For instance, there may be important sex differences in brain structure volumes [75,76]. A systematic review and meta-analysis by Ruigrok and colleagues [75] has reported sex differences in overall brain volumes sustained from the early brain development stages of newborns to elderly years. However, none of the studies in the present review reported sex differences in the brain structures. Furthermore, neurobehavioral deficits varies significantly between individuals in response to sleep loss (i.e., trait-like differential vulnerabilities) [77], and intrinsic sleep needs varies between individuals and across developmental stages [78]. It is therefore important to have objective baseline measurements of the sleep, and to tailor the intervention on to each participant, as one intervention may not fit all.

This increased sleep requirement in the pediatric population may be partially related to the dynamically complex brain development processes that begin prenatally and continue postnatally into late adolescence [17]. For example, the myelin plasticity process begins in utero but continues throughout adolescent years [17]. Additionally, a MRI study has reported that the total brain volume more than doubles in the first year of life (increased by 101%) and increases an additional 15% during the second year [79]. Also, the cerebellum, compared with cortical hemispheres, shows disproportionate growth (increased by 240%) during the first year of life [60]. The early development of the cerebellum may be related to its essential functions, which include coordinating voluntary limb movements, ocular motor control, balance, walking, and non-motor higher cognitive functions [80]. This concords with a previous study providing evidence that myelination begins posteriorly before anterior brain regions [81]. Therefore, the neural plasticity of brain functions and its associated structures follows a specific sequence that builds upon previous developmental stages. A study conducted by Kurth and colleagues [82] mapped the changes in SWA (between 1 and 4.5 Hz) concentration that would appear to migrate with age as it is highest over posterior regions during preschool years and shifts progressively anteriorly to the central and frontal cortex in late adolescence. The shift in SWA concentration over specific areas of the brain predicted maturation of skills in the following order vision, visuomotor, simple motor, complex motor, language and cognitive control [82]. More research is needed to identify the mechanisms behind the observed clustering of SWA that parallels growth and brain development in children and adolescents.

Brain development and maturation periods are also accompanied with changes in sleep architecture [18]. A few studies have investigated the maturational changes for NREM and REM sleep cycles. Longitudinal trajectory changes in NREM-REM sleep cycles in preschoolers showed increases in NREM but not REM sleep episode durations [83]. A longitudinal study in adolescents revealed different trajectories that involved the shortening of NREM sleep episode durations and lengthening of REM sleep episode durations across adolescence [84]. Further investigation in these noticeable and normal changes into the relative proportion and functions of sleep stages in toddlers, pre-schoolers, school-aged children and adolescents is needed to fully understand its impact on neuro-developmental growth and maturational processes.

The hormone melatonin (mainly secreted by the pineal gland at night) is an important biochemical marker of the circadian clock and endogenous synchronizer of the sleep–wake cycle [85]. The knowledge of the regulating system involved in the secretion of melatonin comes from animal studies, and has been extrapolated to humans [85–87]. The circadian system is an hierarchical system with the central regulator in the suprachiasmatic nucleus of the hypothalamus [85,87,88]. In addition to helping sleep regulation, melatonin is involved in sleep thermoregulation, it appears to have a neurogenesis function, and a neuroprotective anti-oxidant function to protect against oxidative lipids [18,89–93]. Yet, much about the mechanisms between sleep disruption and melatonin in children and adolescents remains unknown, especially during the developmental stages of brain functions and structures.

Taken together, the potential sex differences, the variability in sleep needs, variability in the response to sleep loss, regional brain developmental stages, the age-related changes in sleep architecture (i.e., the cycling of NREM and REM sleep), melatonin secretion and other factors not discussed here (e.g., genetic, environmental, behavioural, hormonal, and other biochemical factors [for a comprehensive review see Jan et al. [18]]) require further research. Since they may all be important moderators or confounding factors in the association between sleep and neural plasticity in brain functions and structures development in the pediatric population. Additionally, the potential risk of chronic severe sleep disruption during the brain developmental stages are unknown but may have a permanent and cumulative effect on neuroanatomical structures and their associated functions.

The findings from the present review need to be interpreted in light of the following limitations. Foremost, the narrative synthesis prevents proper weighting of the reviewed studies. Additionally, the studies selected for this review are not without limitations. For instance, the sleep data in the observational studies were often based on proxy- and self-reports rather than objective measures, while some have used validated sleep questionnaires others have used questionnaires with unknown psychometric properties. Additionally, for many of the studies included in this review the participants were self-selected, the samples sizes from some studies were small, and thus prevented the use of important covariates (e.g., age, maturation status, energy expenditure, habitual sleep) in statistical analysis models. Finally, the majority of the studies included were correlational, precluding the possibility of making causal inferences about the impact of sleep on brain functions and structures in the developing brain of children and adolescents.

Conclusions

Overall, the evidence suggests that inadequate sleep may be negatively associated with various brain functions and structures in the developing brains of children and youth. Though not all brain function responses following short-term sleep loss are necessarily damaging, as it may be a homeostatic response to maintain task performance, yet the chronic effect of sleep restriction on brain functions remains unknown. We advocate caution in drawing conclusions grounded on an incomplete understanding of the

underlying mechanisms between chronic sleep loss and brain functions or brain structures in the pediatric population. Finally, based on these results, there is very little risk in taking a pragmatic approach in promoting healthy sleep practices in the pediatric population as chronic sleep loss may have negative consequences on the developing brains of children and is associated with other well-known adverse effects on health.

Practice points

1 Based on the current findings, when it comes to brain functions and structures, there is very little risk in continuing to recommend adequate sleep duration and a regular sleep schedule in the pediatric population.
2. It would be important for researchers to develop more tools that can be used by clinicians to efficiently and accurately identify sleep problems at an earlier age, as surveillance of sleep needs and problems is lacking. This could help identify the protracted negative consequences of inadequate sleep on brain functions and structures.
3. In the meantime, clinicians should continue to screen for sleep problems in the pediatric population, starting from an early age, as sleep may be important for brain functions and structures.

Research agenda

1. If possible, future research should focus on the relationships between inadequate sleep and cognitive functions, brain functions, and structures simultaneously as these relationships are currently unknown.
2. The effects of chronic mild sleep restriction on children's brain development have not been adequately studied, despite the prevalence of inadequate sleep in the pediatric population.
3. More research is needed to better address the causal pathways between inadequate sleep and brain development during the diverse stages of growth and maturation. In the neocortex, it has been demonstrated that the primary sensory and motor areas are the first to attain their peak cortical thickness, preceding both adjacent secondary areas, and polymodal areas [94]. Animal studies may be useful to better understand the causal pathways between chronic inadequate sleep and brain growth and related functions.
4. There is a need for more randomized controlled trials with adequate sample sizes aimed at testing the effect of sleep manipulations, mainly sleep extension, on brain functions and structures during these important periods of neurodevelopment.
5. Researchers should consider adding more sleep extension interventions in their research designs, to see if the effect of inadequate sleep are reversible.
6. Obtaining objective measurement of habitual sleep followed by longer (one week or more) sleep protocols that are individually tailored, and in naturalistic settings (at home) is recommended to elucidate the effect of chronic mild sleep loss and sleep extension/improvement on the developing brain functions and structures.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Authors' contributions

CD, JJW, KEG, MST, RG, SKW, KAC, MS and J-PC participated in the conception of the article. CD, JJW, RBF and J-PC screened the articles. CD, JJW and J-PC extracted the data. CD and JPC wrote the first version of the manuscript. All authors participated in the revisions of the manuscript, and read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.smrv.2018.08.003.

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2.5.3 Summary

The growing body of evidence from systematic reviews and studies on sleep and brain function in children and adolescents highlights the significant impact of sleep on cognitive function and brain structure. Despite variations in methodologies and limitations in the current literature, findings tend to show that inadequate sleep is associated with negative outcomes in brain function and structural development. This is particularly concerning in pediatric populations, where brain maturation is ongoing, and disruptions in sleep could lead to long-term cognitive and neurodevelopmental challenges.

The findings from Reynaud et al. [144], Short et al. [145], and de Bruin et al. [146] demonstrate the importance of adequate sleep across different age groups, though the heterogeneity in study designs and the lack of rigorous assessments of bias and quality limit the ability to draw definitive conclusions. Nonetheless, even with these limitations, there is evidence to suggest that ensuring sufficient sleep in children and adolescents is crucial for healthy brain function.

Our systematic review further adds to this understanding by examining the impact of sleep on both brain functions and structures in children and adolescents [14]. Included studies employed a variety of neuroimaging tools and techniques, such as MRI and fMRI, that played a significant role in obtaining the outcomes and providing insights into how sleep patterns are linked to neuroanatomical structures and brain functions [14]. However, the quality of evidence ranged from moderate to very low [14]. The findings highlight how insufficient sleep affects not only cognitive domains such as memory and attention but also neuroanatomical structures of the brain such as the hippocampus,

prefrontal cortex, and white matter integrity [14]. These regions are essential for executive functions, emotional regulation, and learning, all of which are vital [14]. This review supports the growing evidence that sleep is likely critical for brain development and underscores the need for further research to explore the complex relationships between sleep and brain health in pediatric populations [14].

2.6 Adolescents with T2D and at Risk for T2D and Brain Structures and Function

2.6.1 Introduction

The focus on healthy populations in studies presented in the previous section highlights the need to explore more vulnerable groups, such as adolescents at high risk for T2D. In this population, understanding how metabolic dysregulation interacts with sleep and brain function is of particular importance. Adolescents at risk for T2D may experience metabolic imbalances, such as insulin resistance and chronic inflammation, which, when combined with poor sleep, could exacerbate cognitive and neural deficits. These potential effects are particularly concerning due to the conceivable long-term cognitive and metabolic consequences, making early intervention essential for this high-risk population. While research has advanced our understanding of sleep's role in brain function and structure, the unique challenges faced by adolescents at high risk for T2D, or those already diagnosed, necessitate further investigation.

T2D is well-known for its broad impacts on organ systems, primarily through macrovascular and microvascular complications [149,150]. Significant advances in treatment, largely through improved glycemic control, blood pressure management, and lipid regulation, have allowed individuals with T2D to live longer [150,151]. However, as longevity increases, new complications are emerging, which are not fully addressed by current therapeutic strategies [150]. One such concern is the effect of T2D on brain structure and function, particularly regarding cognitive decline and the risk of dementia.

Most research on T2D and brain health comes from studies on adults who developed T2D during adulthood and some in elderly years [152]. These studies indicate that the

duration of diabetes plays a critical role in cognitive outcomes [153]. Chronic hyperglycemia is believed to promote cerebral microvascular disease, leading to brain atrophy and reductions in brain volume [150,154]. These structural changes are associated with cognitive impairments, particularly in memory and executive function. Moreover, individuals with T2D are at a significantly higher risk of developing dementia, with a 1.5 to 2.5 times greater risk of conditions such as Alzheimer's disease and vascular dementia compared to those without diabetes [150,154–156]. In addition, recent findings suggest a bidirectional relationship between insulin resistance and Alzheimer's disease pathology. Emerging evidence has led to Alzheimer's disease being conceptualized as "type 3 diabetes" due to the shared molecular and cellular mechanisms underlying insulin resistance and neuro degeneration, including impaired insulin signaling, oxidative stress, mitochondrial dysfunction, and inflammation of the brain [157].

The effects of T2D on brain health, however, go beyond chronic hyperglycemia. Recurrent episodes of severe hypoglycemia, common in individuals with T2D, can also have a profound impact on cognitive function and increase the risk of dementia [158]. A recent systematic review and meta-analysis shows a clear dose-response relationship between hypoglycemic events and dementia risk: one hypoglycemic event increases the risk of dementia by 29%, two events raise the risk by 68%, and three or more events nearly double the risk (RR = 1.99) [158]. These findings highlight the importance of managing both hyperglycemia and hypoglycemia, as both conditions can severely affect cognitive health.

In addition to poor glycemic control in both directions, several other risk factors are associated with cognitive decline in individuals with T2D. These include inflammatory mediators, dysregulation of the HPA axis, and rheological factors, such as changes in blood viscosity and flow [150]. These mechanisms may collectively contribute to the observed cognitive impairments and brain structural changes in people with T2D. Recent research shows that T2D is associated with smaller total and regional brain volumes, particularly in areas crucial for cognitive function, such as the hippocampus and prefrontal cortex, compared to individuals without T2D [159]. Brain atrophy rates are also higher in individuals with T2D, and these effects worsen with longer disease duration [159]. Interestingly, these changes appear to begin in young adulthood and become more severe over time, though they do not seem to be affected by biological sex [159].

Given these findings from adult studies, it is essential to extend this research to younger populations, particularly adolescents at high risk for T2D. Early onset of T2D could accelerate the cognitive and structural brain changes observed in adults, making early detection and intervention especially important. Understanding how T2D affects the developing brain in adolescents at risk for, or already diagnosed with, the disease could offer new avenues for prevention and treatment, potentially reducing the long-term burden of cognitive impairment associated with diabetes.

The following section explores the limited but growing evidence on brain structure and cognitive function deficits in adolescents at risk for, or living with, T2D. This focus on younger populations provides a foundation for understanding how early metabolic dysregulation impacts brain health and cognitive development, which is critical for informing future prevention and intervention strategies.

2.6.2 Evidence of brain structure deficits in adolescents with T2D and high risk for T2D

Limited knowledge exists regarding the potential negative impacts that T2D and the risk for T2D may have on the still-developing brain structures and functions in adolescents. Early studies have raised concerns, revealing associations not only in adolescents diagnosed with T2D but also in those with obesity, indicating structural brain differences, with adolescents with T2D already showing cognitive function impairments in several cognitive domains. This section builds on four key studies that predate our own work, which report that adolescents with T2D, compared to control groups, exhibit reduced grey matter volume, white matter integrity deficits affecting various brain regions, and signs of total cerebral atrophy [160–163]. Two studies investigated the association between T2D in adolescent and brain functions; they found that adolescents with T2D had impaired brain functions, compared to controls [161,164].

Two of these studies, conducted by Yau et al. and Bruehl et al. [160,161], examined the same cohort in cross-sectional, case-matched designs involving 18 adolescents with obesity and T2D and 18 adolescents with obesity but without T2D. These cross-sectional and case-matched studies included 18 adolescents with obesity and T2D compared to 18 adolescents with obesity without insulin resistance [160,161]. The groups were matched for key factors, such as age, sex, school grade, ethnicity, socioeconomic status, BMI, and waist circumference [160,161]. Yau et al. found that adolescents with T2D performed worse than controls on tests of intellectual functioning, verbal memory, and psychomotor efficiency, and exhibited reduced white matter volume, increased cerebrospinal fluid space, and reduced grey and white matter integrity [161]. Similarly, Bruehl et al. [160] discovered that adolescents with T2D had significantly

reduced hippocampal and prefrontal volumes, and higher rates of total brain atrophy compared to controls. These findings suggest that brain structure and function impairments in adolescents with T2D (aged 16.5 ± 1.9 years) manifest within approximately 2.5 years of diagnosis, long before the onset of macrovascular disease [160,161].

Both studies, however, shared important limitations. The potential inclusion of participants with insulin resistance in the control group could have confounded the results [160,161]. Furthermore, since both groups shared obesity as a common characteristic, it is difficult to discern whether the observed brain changes are related to T2D specifically or to obesity more generally. Notably, neither study comprehensively assessed sleep, despite administering a sleep questionnaire primarily focused on sleep apnea rather than broader sleep patterns or duration. This is an important oversight, as inadequate sleep has been shown to affect brain structures and functions and is linked to poor insulin resistance control in the pediatric population [1,14,144–146]. Another limitation was the lack of consideration for medication adherence and insulin resistance control, with 17% of participants not receiving anti-diabetic medications. This could introduce variability, as medication adherence and effective control of insulin resistance could significantly influence the severity of T2D and its impact on brain structures. In adults with T2D, poor glycemic control has been associated with cognitive dysfunction [150,154–156,165–167].

Rofey and colleagues [162] conducted a small-scale, cross-sectional, case-matched pilot study involving five adolescents with T2D, five adolescents with obesity but without T2D, and five healthy-weight adolescents. Adolescents with T2D had significantly

reduced grey matter volumes in the thalamus and caudate nucleus compared to the other groups [162]. Adolescents with obesity also had reduced grey matter volume in the caudate nucleus compared to healthy-weight adolescents, suggesting that obesity itself may contribute to brain structure deficits [162]. However, the small sample size and age distribution discrepancies between the groups (T2D group older than others) limit the interpretation of findings. Early pubertal development and puberty, independent of weight status, are risk factors for T2D in the pediatric population [168–171]. Additionally, insulin resistance and metformin adherence were not measured, and sleep assessment was again absent. Despite these challenges, the preliminary results cautiously suggest that T2D in adolescents is associated with impaired brain structures, and obesity may also be an independent risk factor.

Brady et al. [164] conducted a cross-sectional study examining the association between T2D, obesity, and cognitive functions in adolescents. The study included 20 adolescents with T2D and obesity, compared with 20 healthy adolescents, and assessed cognitive functions such as processing speed, working memory, verbal and semantic fluency, along with parent-reported executive function and problem behaviour [164]. Adolescents with T2D scored lower than controls on several cognitive tests, including working and verbal memory, as well as processing speed, with these impairments negatively correlated with the duration of T2D diagnosis [164]. However, differences in age, ethnicity, and family income between the groups are important considerations, as these are also risk factors for T2D in youth [99]. Sleep was again not considered as a covariate in the relationship.

Nouwen at al. [163] conducted the largest study to date, with 53 participants, comparing grey matter volumes and white matter integrity among adolescents with T2D, those with obesity, and healthy-weight controls. Adolescents with T2D and those with obesity had reduced grey matter volumes in the hippocampus, putamen, caudate, amygdala, and thalamus compared to healthy-weight controls [163]. Additionally, adolescents with T2D showed reduced white matter volume in several brain regions, which was correlated with higher BMI and insulin resistance [163]. However, limitations such as gender imbalance, potential insulin resistance in the obesity group, and lack of sleep or cognitive assessments limit the generalizability of these findings.

In summary, the four studies predating our own indicate that adolescents with T2D, and to a lesser extent those with obesity, exhibit structural impairments in brain regions critical for cognitive functions such as memory, attention, and executive function [160–163]. The prefrontal cortex and subcortical structures, including the thalamus and hippocampus, appear to be particularly affected. These brain regions play essential roles in executive functions, memory, emotional regulation, cognitive processing and more [172–176]. Although only two studies have directly examined cognitive function in adolescents with T2D, both report significant impairments compared to controls [161,164].

A more recent cross-sectional pilot study by Snyder and colleagues [177] examined the association between T2D, obesity, and cognitive function in adolescents, using domains such as intelligence quotient, spatial recognition, memory, attention, processing speed, and executive functions. The study tested three groups of children aged 12–17 years: children with T2D and obesity, children with obesity but without T2D, and healthy-weight

controls [177]. Children with T2D and obesity scored lower in intelligence quotient, visual-spatial, and executive domains compared to healthy-weight children [177]. These impairments correlated with adiposity and insulin resistance but not with A1C levels [177]. The small sample size and lack of accounting for sleep as a variable limit the findings, although the study addressed some previous limitations by testing insulin resistance and glucose control prior to cognitive assessments.

The limitations across these studies, including small sample sizes, lack of sleep assessments, and inconsistent control of insulin resistance, underscore the need for more comprehensive research. Future research should explore the potential mediating effect of improving sleep on cognitive function in adolescents at high risk for T2D with insulin resistance. Addressing sleep health in this population could have far-reaching benefits for both cognitive and metabolic health, making it a critical area for future study and intervention.

2.6.3 Summary

The link between T2D and cognitive decline, particularly dementia, is well-established in adults. Numerous studies have shown that adults with T2D are at a significantly increased risk of developing dementia, including both Alzheimer's disease and vascular dementia [150,154–156]. This heightened risk, which can be up to 2.5 times greater than in the general population, is thought to be driven by factors such as chronic hyperglycemia, cerebral microvascular disease, and recurrent hypoglycemia [150,153–156,158]. These metabolic disturbances contribute to structural brain changes, such as reduced grey matter volume, white matter integrity deficits, and accelerated brain atrophy [159]. However, the potential impact of T2D on the developing brains of

adolescents has only recently begun to be explored, and findings in this younger population raise similar concerns.

Emerging research in adolescents with T2D and those at high risk for the disease suggests that brain structure and function deficits may manifest much earlier than previously thought. Studies have revealed that adolescents with T2D exhibit structural impairments in critical brain regions, including the prefrontal cortex, hippocampus, and thalamus, which are involved in executive functions, memory, and emotional regulation [160–163]. In comparison to controls, adolescents with T2D perform worse on cognitive tests of memory, intellectual functioning, and processing speed [161,164]. These brain structural and function deficits appear within just a few years of diagnosis, long before the onset of classic macrovascular complications seen in adults with long-term diabetes.

Studies also suggest that obesity, a key risk factor for T2D, may independently contribute to brain structure differences in adolescents [162,163]. Grey matter volume reductions have been observed in adolescents with obesity, even in the absence of T2D, further complicating the understanding of the specific effects of T2D on brain health in youth. Despite these findings, the research is limited by small sample sizes, a lack of comprehensive sleep assessments, and inadequate monitoring of insulin resistance and medication adherence, factors that are crucial to understanding the full scope of T2D's impact on the adolescent brain.

Given the well-established connection between T2D and cognitive decline in adults, coupled with the emerging evidence from adolescent studies, there is a pressing need for more comprehensive research. Future studies must address these limitations by

incorporating larger sample sizes, detailed assessments of sleep, insulin resistance, and glycemic control, and longitudinal designs to track changes over time. The adolescent brain is still developing, and early metabolic dysregulation may have long-lasting consequences on cognitive function and brain structure. Understanding how sleep, metabolic control, and early interventions can mitigate these effects is essential for preventing long-term cognitive decline and promoting healthier brain development in adolescents at risk for T2D.

2.7 Sleep Intervention in Youth

2.7.1 Criteria for the study design

For the sleep intervention design in adolescents at risk for T2D, several key criteria were established to ensure practicality and scientific rigor. The intervention needed to be conducted in free-living conditions, allowing participants to stay in their natural environments to reflect real-world behaviours while minimizing the overall burden. A single site would acquire all the data. Additionally, sleep monitoring was required to be in free-living condition and objective, with participants not receiving any live feedback of the monitoring process, to avoid any biases that could influence their sleep patterns.

The intervention study needed to be crossover design and include three phases: baseline, followed by increased and decreased sleep manipulation periods that would be randomized and counterbalanced. A crossover design offers several benefits. One key advantage is that each participant acts as their own control, allowing treatment effects to be directly compared within individuals [178,179]. This approach eliminates variability between subjects, reducing the influence of covariates on the comparison [178,179]. As a result, imbalances in allocation that are common in randomized parallel studies are

less frequent in crossover designs [178,179]. Additionally, crossover studies are known for their high statistical power and efficiency, meaning they can achieve the same level of accuracy as parallel designs but with fewer participants [178,179]. Based on single-site and our knowledge of the available population meeting our criteria of adolescents at high risk for T2D in and around Ottawa, it was determined that a parallel design would not be advised. The manipulation phases were to be separated by a washout period to allow participants' sleep patterns to return to baseline, minimizing the risk of carryover effects [178,179]. A key consideration was balancing the study's length to minimize participant burden and confounding factors, while allowing for three OGTT time points after the habitual, increased, and decreased sleep periods. The baseline habitual sleep period needed to include a minimum two weekend nights and five week nights and no more than 10 nights total.

Since participants' weekdays wake-up times are fixed by school schedules, bedtimes would be the variable that is mainly manipulated. The study design and sleep duration schedule would also inherently affect sleep consistency and timing, which was taken into account in the study design. Laboratory visits were planned to be scheduled to start at a time that closely mimicked the participants' school start times to reduce any disruption to their normal routines.

Including both increased and decreased sleep manipulations in the study design was crucial to explore a comprehensive range of sleep behaviours in a high-risk adolescent population, which had not been previously done. Investigating both directions of sleep manipulation (increase and decrease) was essential for forming well-rounded, evidence-based sleep recommendations for adolescents at risk for T2D.

Moreover, by including both manipulation directions, adolescents were encouraged to maintain their habitual sleep patterns for the baseline week, ensuring they could either increase or decrease their time in bed in the first intervention week. Failure to adhere to their schedule during the first intervention week would result in dismissal from the study. However, if they completed the first intervention but failed to follow the second, their data would still be included using intention-to-treat analysis. To prevent participants from modifying their habitual sleep, the order of interventions was randomized, with allocation concealment using sealed envelopes. The order was only revealed during the first laboratory session after the baseline sleep period.

Another criterion of the study design was to replicate a sleep intervention that had previously been successful in a youth population. By following an approach with demonstrated efficacy, the focus would be on the outcomes without concerns about the feasibility of the sleep intervention itself. Overall, the intervention design aimed to be practical for participants while still yielding meaningful data on how sleep manipulation impacts adolescents at risk for T2D.

2.7.2 Two types of sleep manipulation

Two types of sleep manipulation interventions could meet the criteria for crossover studies. The first type involves fixed sleep duration manipulation, where the same time-in-bed is prescribed to all participants. Beebe and colleagues employed this method in two studies that examine the effects of both sleep restriction and sleep extension in adolescents, examining how these sleep manipulations affect behaviour and dietary intake through experimental crossover designs [180,181].

Both studies followed a 3-week sleep protocol, beginning five nights of baseline sleep (Monday to Friday nights), followed by two nights of self-selected bedtime on Saturday and Sunday nights, and then of five nights, Monday to Friday nights, of either sleep restriction (6.5 hours in bed) or healthy sleep (10 hours in bed) [180,181]. After the first intervention week, assessments occurred on the Saturday, followed by a 2-night washout period on Saturday and Sunday nights, before switching to the other condition for another five nights Monday to Friday nights, and a final assessment on the Saturday [180,181]. Sleep was monitored using both self-report and actigraphy [180,181].

In the 2008 feasibility study, Beebe et al. [181] tested the impact of a multi-night, at-home sleep manipulation protocol in 20 healthy adolescents aged 13.9 to 16.9 years. Participants and their parents completed behaviour rating questionnaires at the end of each intervention period. Sleep manipulation resulted in an average of 2.6 hours per night differences in sleep duration between the two sleep conditions, with participants averaging 6.1 hours per night of sleep during the sleep restriction period (a decrease of 90 minutes/night from baseline), and averaging 8.7 hours per night during the healthy sleep period (an increase of 66 minutes/night from) [181]. The sleep restriction phase led to significantly more behavioural issues, such as increased sleepiness, attention problems, irritability, oppositional behaviour, and difficulties with behaviour regulation and metacognition, as reported by parents [181]. Participants' self-reports reflected similar, though less pronounced, behavioural challenges [181]. This study demonstrated that a multi-night protocol incorporating both sleep restriction and extension are feasible in adolescents [181].

In the 2013 study, Beebe et al. [180] expanded their investigation to examine the impact of sleep manipulation on dietary intake in 41 adolescents aged 14 to 16 years. Dietary intake was assessed via 24-hour diet recall interviews [180]. Sleep manipulation resulted in an average of 2.6 hours per night difference in sleep duration between the two conditions, with participants averaging 6.3 hours per night in the restricted sleep condition (a decrease of 36 minutes/night from baseline) and 8.9 hours per night in the healthy sleep condition (an increase of 120 minutes/night from baseline) [180]. The results showed that adolescents consumed more high-glycemic foods, particularly desserts and sweets, during the sleep restriction condition compared to the healthy sleep condition [180]. There was also a trend toward higher caloric and carbohydrate intake during sleep restriction [180].

Both studies underscore that manipulating sleep duration in adolescents is possible and feasible, emphasizing the significant impact of manipulating sleep duration on behavioural and dietary outcomes in adolescents.[180,181]. While both studies had several strengths, there are limitations in the sleep manipulation methods used. Prescribing the same time-in-bed for all participants may not account for individual variability in sleep needs, as different individuals may require varying amounts of sleep to feel adequately rested. Consequently, the fixed time-in-bed approach may not reflect each participant's true sleep requirement, leading to potential inconsistencies in the effects of sleep manipulation and the outcomes.

Another limitation in both studies is the short washout period. A 2-night washout period may not be enough for participants to fully recover from the effects of five nights of sleep restriction or extension, which could result in carryover effects between the experimental

conditions. Insufficient recovery time might skew the results, particularly if the participants remain sleep-deprived or have not returned to their baseline sleep patterns before starting the next condition. A longer washout period would allow for recovery and returning to baseline sleep timing and offer a more accurate assessment of how each sleep manipulation independently affects behaviour and dietary intake, reducing the possibility of residual effects from the previous condition.

Furthermore, the washout period also included both a weekend and a weeknight, which may introduce additional variability. Adolescents typically have different sleep schedules on weekends compared to weekdays, which could further complicate the effectiveness of the washout period. They typically shift their sleep timing and try to catch up on sleep duration on weekend while having fixed wake times for school on weekdays. This inconsistency may reduce the effectiveness of the washout period and affect the validity of the subsequent sleep manipulation. A more standardized washout period, ideally consisting of several nights with consistent sleep schedules that account for both weeknights and weekends, would better ensure that participants return to their baseline sleep patterns, improving the generalizability of the findings.

Moreover, it is clear from the results that increasing sleep in adolescents is more challenging than decreasing it. Despite being prescribed 10 hours of time in bed, participants only achieved 8.9 and 8.7 hours of sleep in the healthy sleep condition, indicating it took them 66 and 78 minutes, respectively, to fall asleep. In contrast, during the sleep restriction condition, participants averaged 6.3 and 6.1 hours of sleep after being prescribed 6.5 hours of time in bed, taking only 12 and 24 minutes, respectively, to fall asleep. These differences in sleep latency likely account for the variation in sleep

efficiency, though this may not explain all the discrepancies. Additionally, adherence to the healthy sleep condition was not reported, making it difficult to assess how strictly participants followed the extended sleep protocol. This could further explain the observed differences in sleep outcomes.

The second type of crossover sleep intervention study is the individualized approach, where sleep manipulation is tailored to each participant's typical sleep duration. Hart et al. [182] conducted such a study in a pediatric population, investigating the effects of sleep manipulation on dietary intake, appetite-regulating hormones, food reinforcement behaviour, and weight in 37 children aged 8 to 11 years, nearly 30% of whom had overweight or obesity.

Hart and colleagues utilized a 3-week protocol, where participants slept their usual amount during the first 7 nights, then were randomized to either increased or decreased time in bed by 1.5 hours per night for the next 7 nights, and in the third week, participants completed the alternate sleep condition for the last 7 nights of the study [182]. Sleep was objectively measured using actigraphy (Actiwatch 2, Philips Respironics, Netherlands), and self-reported sleep diaries and call-ins were used to confirm the actigraphy data [182]. During each intervention week, participants completed three 24-hour dietary recalls (covering two weekdays and one weekend day) [182]. After each intervention week, at two time points, participants came into the laboratory 1 hour after waking, following an overnight fast, to measure leptin, ghrelin, weight, and food reinforcement [182].

The prescribed 3-hour gap in sleep manipulation resulted in an average of 2 hours and 21 minutes per night difference in sleep duration between the two conditions [182]. Results showed that an average sleep duration of 10.45 hours per night during the increased sleep duration week reduced calorie intake, lowered fasting leptin levels, and resulted in a modest weight reduction, compared to 7 nights of decreased sleep duration, where participants averaged 8.1 hours of sleep per night [182]. However, no changes were observed in food reinforcement or fasting ghrelin levels between the two sleep conditions [182].

The Hart et al. [182] study had several strengths, including their use of a tailored sleep manipulation protocol and its measurement of sleep duration. The study also mimicked naturalistic settings, was not overly long, and captured both weeknights and weekend nights [182]. Sleep manipulation was achieved solely by adjusting bedtimes, while wake times remained constant, and naps were not allowed [182]. The study was scheduled to avoid school vacations, which is important, as summer and vacation periods can significantly alter children's sleep patterns [182]. However, the absence of a washout period between sleep conditions may have influenced the results, as acknowledged by the authors [182]. A 7 nights washout period would have allowed for better recovery between conditions and could have enhanced the study protocol while maintaining a short study length.

Hart and colleagues [182] also incorporated daily communication with participants, monetary compensation, and structured laboratory assessments to ensure adherence. The combination of self-reports, proxy-reports, and objective measurements was particularly effective given the pediatric population [182]. One area for improvement

would be the inclusion of baseline measurements for outcome variables, as this would provide a clearer understanding of the clinical relevance of the manipulations [182]. Additionally, reporting on adherence to the sleep protocol would be beneficial, though the study design suggests adherence was likely high.

By incorporating the strengths of this study, such as individualized sleep manipulation, objective sleep monitoring, and close participant engagement, we can design a robust and methodologically sound crossover sleep manipulation study.

2.7.3 Summary

This section of the literature review discusses two types of sleep intervention methods used in youth crossover studies: fixed and individualized time-in-bed manipulation, with examples of each.

Fixed sleep duration manipulation standardizes the same time in bed for all participants, facilitating consistent comparisons between conditions. However, this approach does not account for individual sleep needs, which could result in inconsistent effects across participants. Studies by Beebe et al. employed this method to investigate sleep restriction and extension in adolescents [180,181]. Their findings showed that manipulating sleep duration was feasible but emphasized challenges such as a short washout period and variations in adherence, particularly with increasing sleep duration.

On the other hand, individualized sleep manipulation adjusts the time-in-bed based on each participant's typical sleep duration, allowing for a more tailored and personalized approach. This method requires a comprehensive baseline sleep assessment to inform

the manipulation. Hart et al. used this approach in their study on children aged 8-11 years, showing significant effects on dietary intake and metabolic outcomes [182]. However, the absence of a washout period was a limitation, potentially influencing the study results.

Both sleep manipulation methods are feasible for use in youth populations, with the fixed approach providing consistency across participants and the individualized approach offering a more tailored experience. The choice between these methods depends on whether consistency or personalization is prioritized. In an understudied population of high-risk adolescents with a wide age range, a personalized approach may be more appropriate to accommodate individual variability in sleep needs. While each study presented has its limitations, addressing these and incorporating their strengths could lead to more robust and effective sleep intervention designs, particularly for adolescents at risk for T2D.

2.8 Brain-Derived Neurotrophic Factor (BDNF)

2.8.1 Introduction

Brain-derived neurotrophic factor (BDNF) plays a crucial role in neuronal development, survival, and neuroprotection, especially under harmful conditions like cerebral ischemia [183,184]. It facilitates neurogenesis, primarily in brain regions such as the hippocampus, cortex, and hypothalamus, promoting the growth and differentiation of new neurons [185,186]. BDNF levels are notably reduced in neurodegenerative diseases like Parkinson's, Huntington's disease, and multiple sclerosis [187,188]. Besides its neuroprotective role, BDNF is involved in energy homeostasis, with both central and peripheral administration shown to suppress energy intake and reduce body weight [189].

BDNF expression peaks after birth and progressively declines into adulthood, regulated by neuronal activity, exercise, and stress [190–193]. Initially synthesized as pro-BDNF in the endoplasmic reticulum, it is processed into its mature form (mBDNF) through enzymatic cleavage, with pro-BDNF and mBDNF having opposing roles in cellular functions [194,195]. While mature BDNF binds to tropomyosin receptor kinase B (TrkB) receptors to promote cell survival, synaptic plasticity, and long-term potentiation, pro-BDNF tends to interact with the p75 neurotrophin receptor (p75NTR), inducing apoptosis, particularly under stress conditions [196,197]. This dual action highlights the complexity of BDNF in regulating both cell survival and death, depending on the context and receptor binding.

In mammals, BDNF exerts its effects through two main isoforms of the TrkB receptor: a full-length receptor (TrkB.FL) with both ligand-binding and intracellular signaling

domains, and a truncated receptor (TrkB.T1), which lacks kinase activity [183,198]. These isoforms are produced through alternative splicing, with each having distinct polyadenylation signals [183,198]. TrkB.FL is predominantly expressed in neurons within the central and peripheral nervous systems, where it mediates synaptic functions and neuronal plasticity [183]. On the other hand, TrkB.T1 has a broader distribution, including tissues outside the nervous system, such as the pancreas [183,199]. The expression of polyadenylated TrkB.T1 mRNA in the pancreas suggests that its presence and role in this organ are independent of direct neuronal input, pointing to BDNF's peripheral actions on metabolic functions, particularly insulin secretion [183].

The complex regulation of BDNF, influenced by transcriptional control, environmental factors, and epigenetic mechanisms, makes it a critical modulator of both neuroprotection and metabolic processes [186,200]. Its multifaceted functions and receptor specificity underscore BDNF's relevance in studying both neurodegenerative diseases and metabolic disorders like T2D, where BDNF may influence key regulatory mechanisms.

2.8.2 BDNF levels in humans displaying certain risk factors

The systematic review and meta-analysis (n=10) by Sandrini et al. [201] concluded that having obesity is not associated with lower levels of circulating BDNF compared to healthy weight controls. Many of the included studies did not adequately control for factors that could impact BDNF measurements [201]. For instance, important confounders such as smoking history, biological sex, pubertal status, ethnicity and BDNF genetic polymorphisms were not accounted for [201]. Furthermore, the small number of studies included in the review limits the impact of the findings and the

possibility of conducting meaningful sub-analyses. Additionally, the methods of BDNF collection and analysis varied across studies, introducing heterogeneity that could affect the results. Another key limitation was the wide age range of participants in some studies, which can naturally influence BDNF levels and contribute to greater variability in the findings [201]. More studies with better methodologies are needed to confirm these findings.

The study by Liu et al. [202] investigated the association between different glucose tolerance groups and serum BDNF levels in adults. Their results revealed that serum BDNF was higher in prediabetics compared to controls [202], while serum BDNF was lower in those with T2D compared to controls [202]. Another study found that plasma BDNF levels were lower in adults with T2D independently of obesity, compared to non-diabetic adults [203].

A study conducted in adolescents examined the relationship between BDNF and a composite z-score representing cardiovascular risk factors [204]. This composite score included key indicators such as the inverse of HDL-C, TG, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), waist circumference, and cardiorespiratory fitness (inversely represented) [204]. The findings revealed a significant positive association between serum BDNF levels and the composite z-score for cardiovascular risk across the entire cohort [204]. Notably, when the data were stratified by sex, distinct patterns emerged [204]. In male adolescents, higher BDNF levels were linked to an increase in the composite z-score, as well as positively associated with HOMA-IR and cardiorespiratory fitness [204]. In contrast, among female adolescents, BDNF levels showed a positive association with TG levels, while a negative

association was observed with waist circumference [204]. The authors concluded that these sex-specific differences suggest that BDNF may play a complex role in cardiovascular risk, potentially influencing different physiological pathways in males and females [204]. However, the observed sex differences in the association between BDNF and cardiovascular risk factors may be attributable to differences within the sample itself, as males and females exhibited significant disparities in several key risk factors. These variations could have influenced the relationship between BDNF levels and cardiovascular risk, potentially accounting for the distinct patterns seen between the sexes. Consequently, the differences in risk profiles between the sampled males and females should be considered when interpreting these findings.

In summary, the findings across multiple studies reveal a complex relationship between BDNF levels and various risk factors, including obesity, glucose tolerance, and cardiovascular health. While Sandrini et al. [201] found no clear link between obesity and lower BDNF levels, studies by Liu et al. [202] and Krabbe et al. [203] showed that BDNF levels are higher in prediabetics but significantly lower in individuals with T2D, independent of obesity. Pedersen et al. [204] highlighted sex-specific associations between BDNF and cardiovascular risk factors, suggesting that BDNF plays a nuanced role in metabolic health, potentially influencing different physiological pathways in males and females. Overall, these studies emphasize the need for more targeted research to better understand BDNF's role in metabolic conditions.

2.8.3 BDNF and sleep

The sleep-wake cycle consists of various neurophysiological states, including wakefulness, non-rapid eye movement (NREM) sleep with or without slow-wave activity

(SWA), and REM sleep. Serotonin, a neurotransmitter with numerous receptor types, plays a crucial role in regulating many essential and basic human functions, including neuroendocrine activity, reproductive activity, and the regulation of the sleep-wake cycle [205]. Notably, serotonin also promotes BDNF production [206–208]. In turn, BDNF enhances serotonergic signaling, creating a reciprocal feedback loop that supports neural plasticity and sleep regulation [205–207,209,210]. Animal studies have demonstrated that BDNF can influence both sleep deprivation and spontaneous wakefulness, emphasizing its role in sleep homeostasis [208,211]. Furthermore, BDNF expression during wakefulness is associated with increase SWA during subsequent sleep, a known marker of sleep pressure and need [212]. In humans, variations in BDNF levels have been linked to genetic differences, particularly in individuals carrying the Val66Met polymorphism [213]. This polymorphism is associated with reduced SWA during NREM sleep, further supporting BDNF's involvement in sleep regulation [213].

Chronic stress, observed in both animal studies and in mood disorders such as depression and anxiety, can disrupt sleep and reduce BDNF levels [214]. The hypothalamic-pituitary-adrenal HPA axis, which regulates the body's stress response, plays a significant role in this process [214]. Sleep disturbances often increase stress vulnerability, leading to a cycle that further depletes BDNF levels [205,215–219]. Insomnia, a common sleep disorder often associated with stress, affects 8.8% to 25.3% of Canadians aged 6 to 79 year, and closely associated with mood disorders such as depression and anxiety [220–222]. Studies indicate that individuals with insomnia exhibit significantly lower serum BDNF levels compared to healthy sleepers, with BDNF levels negatively correlated with insomnia severity [223,224]. These findings suggest that sleep

may mediate the relationship between stress and BDNF, potentially contributing to the onset of stress-related disorders.

Interestingly, acute stress, such as one night of sleep deprivation or partial sleep loss, induces a rapid increase in BDNF levels, highlighting a different response compared to chronic stress [208,225,226]. Studies on hippocampal plasticity demonstrate a biphasic response to stress: chronic stress leads to dendritic atrophy and decreased BDNF levels, while acute stress elevates BDNF levels, underscoring BDNF's critical role in stress-related hippocampal changes [227,228]. This biphasic stress model suggests that chronic stress disrupts the HPA axis, resulting in prolonged sleep disturbances and diminished BDNF levels [227,228]. Insomnia, in this context, further exacerbates BDNF depletion, while acute stressors like short-term sleep deprivation can temporarily elevate BDNF levels.

In summary, the sleep-wake cycle has a significant impact on BDNF levels. While chronic stress and sleep deprivation tend to reduce BDNF, acute stress can transiently increase its levels, revealing a complex interplay between sleep and BDNF regulation. Though the precise mechanisms remain unclear, the contrasting effects of chronic and acute stressors suggest an adaptive process in BDNF regulation in response to stress and sleep changes, with the lack of sleep itself acting as a significant stressor.

2.8.4 BDNF in glucose regulation: an novel pathway and its implications

In 2020, Fulgenzi et al. [183] uncovered a novel signaling pathway in mammals that links BDNF to the regulation of insulin secretion through β-cells in the pancreas. This pathway highlights BDNF’s role beyond its central functions, demonstrating its influence on

glucose homeostasis via peripheral actions on β-cells [183]. Specifically, BDNF binds to the TrkB.T1 receptor on β-cells, increasing intracellular Ca^{2+} levels, which in turn triggers insulin secretion [183]. Importantly, human β-cells show a greater sensitivity to BDNF, even at lower glucose levels, compared to mouse β-cells [183].

A critical aspect of the study was identifying skeletal muscle as a significant source of BDNF, which also impacts β-cell activity [183]. Mice with a skeletal muscle-specific BDNF knockout displayed metabolic impairments similar to those in TrkB.T1 knockout mice, underscoring the vital role of muscle-derived BDNF in glucose regulation [183]. This finding aligns with evidence showing that skeletal muscle can produce and secrete biologically active BDNF, especially during physical activity [229]. Muscle contraction not only boosts lipid oxidation but also promote insulin secretion [183]. These findings suggest that the secretion of BDNF during physical activity helps normalize blood glucose levels, contributing to the beneficial effects of exercise on glucose metabolism [183,189,229,230]. Additionally, the study notes that skeletal muscle can release BDNF even in the absence of physical activity, potentially preparing β-cells for insulin secretion ahead of a meal [183].

This discovery sheds light on the broader role of BDNF in energy balance and glucose regulation, offering new insights into its regulation of glucose homeostasis. However, one controversial finding from the study is the variability in BDNF levels depending on time of day and activity levels, which challenges the assumption that brain and circulating BDNF levels are consistently correlated. Béjot et al. [231] had earlier cautioned against this assumption, showing that brain and circulating BDNF levels were not correlated in post-stroke rats. However, their study's limitations, including the lack of

simultaneous glucose and insulin measurements and wide variability in the timing of blood and brain collections, leave room for further exploration [231].

While animal studies have demonstrated promising outcomes in stroke treatments involving BDNF manipulation [232–236], replicating these results in humans has proven challenging. Before the work of Fulgenzi et al. [183], many studies had overlooked the possibility that the TrkB.T1 and TrkB.FL pathways might function independently, which may explain certain inconsistencies in earlier research.

Post-stroke hyperglycemia is a common phenomenon, occurring in approximately 68% of stroke cases regardless of subtype or severity [237–240]. Although the mechanisms behind this glycemic dysregulation remain unclear, it is often attributed to acute stress responses or previously undiagnosed diabetes. Chaturvedi et al.'s [241] article raises concerns as they compared BDNF levels in stroke patients to those in healthy populations without risk factors. Stroke in the absence of risk factors is extremely rare, accounting for less than 1% of cases [242]. Such comparisons may confound interpretations of BDNF's role in stroke outcomes, including hyperglycemia.

Despite the prevalence of post-stroke hyperglycemia and the established sensitivity of human β-cells to BDNF, there is a scarcity of research exploring this relationship. One exception is the work by Otero-Ortega and colleagues, which found a negative correlation between BDNF levels and glucose within 24 to 48 hours after ischemic stroke, suggesting that BDNF could play a role in regulating glycemia post-stroke. [243]. However, further studies are needed to clarify the mechanisms and timing of BDNF's involvement in this process.

In summary, Fulgenzi et al. [183] identified a previously unknown mechanism by which BDNF regulates insulin secretion via β-cells, offering important insights into glucose homeostasis. BDNF binds to TrkB.T1 receptors on β-cells, promoting insulin secretion, with human β-cells exhibiting higher sensitivity. Skeletal muscle was identified as a key source of BDNF, particularly during exercise, underscoring its role in maintaining blood glucose levels and enhancing the metabolic benefits of physical activity. This research challenges the assumption that brain and circulating BDNF levels are always correlated, highlighting variability based on time of day and activity. Although evidence investigating BDNF's role in hyperglycemia remains limited, the available findings raise important questions, particularly for adolescents at high risk for T2D. In this population, chronic β-cell dysfunction and insulin resistance, rather than stroke injury, are primary drivers of hyperglycemia. Understanding how BDNF influences β-cell function and glucose regulation could offer new therapeutic approaches to slow the progression of T2D in adolescents.

2.8.5 Summary

BDNF plays a central role in neuronal development, survival, and neuroprotection, with effects that extend to energy regulation and metabolic processes. It is involved in neurogenesis and maintains neuronal integrity, particularly in brain regions such as the hippocampus and cortex. BDNF's regulation of glucose homeostasis, as demonstrated by Fulgenzi et al. [183], shows its influence on insulin secretion via β-cells, highlighting its peripheral metabolic functions. Skeletal muscle was identified as a crucial source of BDNF, especially during physical activity, where it helps regulate blood glucose levels and supports the metabolic benefits of exercise.

BDNF's role in metabolic health is further complicated by its relationship with risk factors such as obesity and T2D. While some studies, such as Sandrini et al. [201], did not find a clear association between obesity and lower BDNF levels, others reported lower BDNF in individuals with T2D. These findings indicate that BDNF levels may fluctuate based on different metabolic conditions and cardiovascular risk factors. Sex-specific differences in BDNF's relationship with metabolic health were also observed, as reported by Pedersen et al. [204], suggesting that BDNF's influence may differ in males and females.

Additionally, BDNF's relationship with sleep further underscores its importance in regulating both metabolic and neurophysiological processes. Chronic stress and sleep deprivation tend to reduce BDNF levels, exacerbating mood disorders like depression and anxiety. However, acute stress, such as short-term sleep deprivation, can transiently increase BDNF levels, reflecting a complex, biphasic response to stress and sleep disturbances. This relationship is particularly relevant for adolescents at high risk of T2D, where chronic stress and poor sleep may impair metabolic health, contributing to β-cell dysfunction and accelerating T2D development.

A key discovery by Fulgenzi et al. [183] introduced a novel signaling pathway involving BDNF's regulation of insulin secretion through TrkB.T1 receptors on β-cells. This finding highlights BDNF's broader role in glucose homeostasis and metabolic regulation, including its interactions with skeletal muscle during physical activity. This discovery challenges assumptions about the constant correlation between brain and circulating BDNF levels, showing that BDNF expression can vary based on factors like time of day and activity levels. Although much of the current research focuses on stroke-related

hyperglycemia, BDNF's role in regulating blood glucose in non-stroke populations, such as adolescents at risk for T2D, is a critical area for future study.

In conclusion, BDNF is a multifaceted regulator of neuronal and metabolic processes. Its involvement in glucose regulation, energy homeostasis, sleep, and stress responses makes it a key target for understanding and potentially mitigating metabolic disorders like T2D. Research targeting sleep manipulation and metabolic pathways in adolescents at high risk for T2D could lead to new therapeutic strategies aimed at improving insulin sensitivity, slowing the progression of T2D, and promoting overall metabolic health.

2.9 Measurement of Brain Functions in Adolescents at Risk for T2D

2.9.1 Introduction

Building on the topics discussed in Sections 2.5 and 2.6, this section explores neuropsychological cognitive function testing suitable for adolescents at risk for T2D. Considering the associations between sleep, metabolic dysregulation, and structural brain changes, it is essential to assess cognitive domains that may be particularly vulnerable in this population. These include executive function, attention, vigilance, processing speed, motor control, sensory processing, and working memory, each of which plays a crucial role in daily functioning and cognitive health. Testing these domains, especially in the context of sleep manipulations such as increased sleep duration, allows us to examine the interplay between sleep and metabolic factors on cognitive and neurological health in at-risk adolescents. This section outlines cognitive tasks designed to evaluate these areas, with a focus on engagement, minimal learning effects, and challenge. Tasks must be engaging and enjoyable to sustain participants' motivation over multiple sessions in a short timeframe, as low motivation could confound results. By assessing these domains, we aim to gain a more comprehensive understanding of how metabolic challenges and sleep affect cognitive outcomes, ultimately informing tailored interventions to support cognitive and neurodevelopmental health in this high-risk group.

2.9.2 Affective-shifting task go/no-go task paradigm

Research indicates that insufficient sleep in children and adolescents is associated with increased caloric intake and a preference for high-calorie foods [180,182,244]. This behaviour could reflect impaired inhibitory control, a core cognitive and executive

function that helps regulate impulses around food and influences healthy eating behaviours [245]. Inhibitory control, primarily governed by the prefrontal cortex, plays a critical role in flexible, goal-directed behaviour and decision-making [245]. Alongside inhibitory control, executive functions such as attention, working memory, and cognitive flexibility work together with the brain's reward system to shape immediate pleasures and motivations, both of which are central in decision-making affecting healthy and obesogenic behaviours [245–249].

In the context of childhood obesity, Reinert and colleagues [250] conducted a systematic review of the relationship between executive functions and obesity in children and adolescents [250]. The review, which included 31 studies found that adolescents with obesity (ages 13-18 years, represented in 11/31 studies) demonstrated lower inhibitory control, poorer mental flexibility, attention deficits, and weaker working memory compared to healthy-weight controls [250]. Among the studies included, most focused on inhibitory control (73.9%), followed by attention (21.7%), mental flexibility and working memory (13% each), and reward sensitivity (8.7%) [250]. Notably, the review did not adhere to systematic review standards, so the findings should be interpreted at the level of a scoping review, thus as indicative rather than conclusive. Additionally, it remains unclear whether any studies included controls for significant covariates such as sleep, which may differ across populations and could have notable effects on executive function. Nevertheless, these results point toward a possible association between obesity and executive function impairments in children and adolescents.

Additionally, the study by Pujol et al. [251] provide insights into how the brain's reward systems can influence reward-seeking behaviour. Using MRI, they observed that higher

BMI in a sample of 230 children aged 8–12 was associated with reduced connectivity between cortical and subcortical regions in the reward network, alongside increased integration between sensorimotor and parietal areas related to body image [251]. Children with obesity, unlike those classified as merely overweight, showed changes in the orbitofrontal cortex and amygdala [251]. These changes are similar to patterns observed in conditions involving compulsive eating, such as obsessive-compulsive disorder and Prader-Willi syndrome [251]. Such findings suggest that childhood obesity may involve reward system dysfunctions linked to behavioural control disorders rather than solely reflecting unhealthy dietary habits.

Further insights are provided by Boswell and Kober [252], who conducted a meta-analysis examining the predictive effects of food cue reactivity and cravings on eating behaviours and weight outcomes [252]. Their study, including 45 reports with 3,292 participants (25% under 18 years), found that food cue reactivity and cravings strongly predicted eating behaviours and subsequent weight gain ($r = 0.33$, CI: 0.27–0.38, $z = 10.7$, $p < .001$) [252]. Importantly, responses to visual food cues and direct food exposure showed similar, and stronger, predictive power than olfactory cues, highlighting the significant impact of visual stimuli on appetite and health [252]. Additionally, responses to food images effectively distinguished individuals with disordered eating patterns from those with typical eating behaviours, emphasizing the role of visual food cues in shaping eating habits [252]. These findings highlight the significant influence of visual food cues on eating behaviours and weight gain, particularly through their strong predictive power in distinguishing disordered from typical eating patterns.

Adding to this evidence, a study by Katsunuma et al. [253] examined the role of sleep in food-related reward processing. In healthy, normal-weight young males (average age 23.4 years), total sleep deprivation (39 hours) significantly increased activity in the food-related reward regions of the brain, resembling patterns observed in individuals with obesity [253]. These findings suggest that acute sleep deprivation enhances hedonic stimulus processing in the brain, independently driving the urge to consume food [253]. This highlights lack of sleep as a factor that may amplify reward responses, potentially contributing to overeating and reinforcing the role of sleep in regulating food-related impulse control.

Similarly, in a crossover study, Benedict and colleagues [254] examined the effects of one night of sleep deprivation versus a regular night of sleep on hunger, fasting plasma glucose, appetite ratings, and brain response to food images in 12 healthy, normal-weight young adult males (average age 22.3 years). Following sleep deprivation, participants showed increased activation in the right anterior cingulate cortex when viewing food images, regardless of the food's caloric content, their reported hunger before scanning, or fasting plasma glucose levels [254]. These findings suggest that acute sleep loss enhances hedonic processing in the brain, fueling a heightened desire to consume food independent of physiological hunger or glucose regulation [254].

While research remains limited, emerging evidence connects obesity and inadequate sleep with reduced executive functions, particularly inhibitory control. Reinert et al. [250] found that adolescents with obesity demonstrate lower inhibitory control, reduced mental flexibility, attention deficits, and weaker working memory compared to healthy-weight peers, indicating a link between obesity and executive function impairments in youth.

Similarly, Pujol et al. [251] observed that childhood obesity may involve dysfunctions in the brain's reward system, suggesting a resemblance to behavioural control disorders rather than solely unhealthy dietary habits, with obesity linked to altered connectivity in reward-related brain regions.

Food cue reactivity and cravings also play a crucial role. Boswell and Kober's [252] meta-analysis identified these as strong predictors of weight gain in both children and adults, finding that visual food cues and actual food exposure were especially influential, more so than olfactory cues, in driving appetite and eating behaviours. Furthermore, studies by Katsunuma et al. [253] and Benedict et al. [254] indicate that sleep deprivation in adults increases activity in brain regions associated with food-related rewards, mirroring patterns seen in obesity. This suggests that sleep loss enhances hedonic processing in the brain, independently driving food cravings without changes in physiological hunger or glucose levels.

These findings underscore the importance of exploring sleep manipulation, particularly sleep extension, and its impact on reward sensitivity and executive function in adolescents at high risk for T2D. The Affective Shifting Task (AST) presents a promising tool to evaluate how changes in sleep affect impulse control and reward sensitivity, offering valuable insights into potential interventions for improving dietary behaviours and reducing T2D risk in this vulnerable population [255–258]. The AST provides valuable insights into executive functions by assessing cognitive skills like response inhibition, attention, working memory, and cognitive flexibility [255–258]. An advanced adaptation of the go/no-go paradigm, the AST requires participants to adjust to changing stimulus-response rules every other block, engaging working memory and cognitive

flexibility as they recall and adapt to new rules [255–257]. Response inhibition is measured through commission errors (responses in "no-go" trials), while attention is assessed through omission errors (missed responses in "go" trials) [255]. Working memory, is assessed by looking at performance (i.e., number of errors and reaction time [RT]) in the repeated stimulus blocks compared to the new stimulus blocks [255]. RT on correct "go" trials serves as an additional indicator of general executive processing, offering a comprehensive view of complex cognitive function [255].

The AST incorporates food images alongside neutral object images, allowing for a direct comparison between responses to appetitive, reward-based cues and neutral, non-rewarding cues [255–258]. Food images act as conditioned stimuli, linked with the rewarding experience of eating, thereby activating neural pathways associated with appetite and craving [256,258–260]. In contrast, neutral object images provide a baseline to evaluate response patterns without the influence of reward cues [255–258].

The AST also minimizes the risk of a learning effect, as it employs a go/no-go task paradigm with a substantial set of unique food and object images [256,258]. This variation not only keeps the task engaging but also ensures that participants do not become overly familiar with specific stimuli, reducing potential bias in responses over repeated trials [255–258]. Additionally, the cognitive demands of the task, with its frequent shifts in stimulus-response rules and the detailed images help maintain participant focus and reduce the likelihood of boredom.

2.9.3 Chronic short sleep duration lengthens reaction time, but the deficit is not associated with motor preparation

Title:
Chronic short sleep duration lengthens reaction time, but the deficit is not associated with motor preparation

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RESEARCH ARTICLE

Chronic short sleep duration lengthens reaction time, but the deficit is not associated with motor preparation

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Summary

The purpose of this study was to investigate the association between chronic sleep duration and reaction time performance and motor preparation during a simple reaction time task with a startling acoustic stimulus in adults. This cross-sectional study included self-reported short sleepers ($n = 25$, ≤ 6 hr per night) and adequate sleepers ($n = 25$, ≥ 7.5 hr per night) who performed a simple reaction time task requiring a targeted ballistic wrist extension in response to either a control-tone (80 dB) or a startling acoustic stimulus (120 dB). Outcome measures included reaction times for each stimulus (overall and for each trial block), lapses, and proportion of startle responses. Chronic short sleepers slept on average 5.7 hr per night in the previous month, which was 2.8 hr per night less than the adequate sleepers. Results revealed an interaction between sleep duration group and stimulus type; the short sleepers had significantly slower control-tone reaction times compared with adequate sleepers, but there was no significant difference in reaction time between groups for the startling acoustic stimulus. Further investigation showed that chronic short sleepers had significantly slower control-tone reaction times after two blocks of trials lasting about 5 min, until the end of the task. Lapses were not significantly different between groups. Chronic short sleep duration was associated with poorer performance; however, these reaction time deficits cannot be attributed to motor preparation, as startling acoustic stimulus reaction times were not different between sleep duration groups. While time-on-task performance decrements were associated with chronic sleep duration, alertness was not. Sleeping less than the recommended sleep duration on a regular basis is associated with poorer cognitive performance, which becomes evident after 5 min.

KEYWORDS
alertness, chronic sleep duration, cognitive performance, reaction time, StartReact effect

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1 | INTRODUCTION

Numerous factors have been shown to modulate reaction time (RT) in apparently healthy individuals, including factors related to stimulus processing, such as stimulus type (Galton, 1899), intensity (Piéron, 1920; Wells, 1913) or number of possible stimuli (Hick, 1952), as well as factors related to response execution, such as task complexity (Henry & Rogers, 1960; Klapp, 2010), stimulus–response compatibility (Fitts & Deininger, 1954; Fitts & Seeger, 1953), mental acuity (Schweizer, 2001), age (Myerson et al., 2007) and the amount of sleep a person gets (Cote et al., 2009; Goel et al., 2009; Lim & Dinges, 2010; Van Den Berg & Neely, 2006). Sleep deprivation has been shown to have a strong influence on alertness and cognitive performance, affecting RT. Research, including the seminal work of Patrick and Gilbert published at the end of the 19th century (Patrick & Gilbert, 1896), highlighted a linear dose–response relationship in neurobehavioural deficits including slower RT, that was associated with up to 90 hr of sleep deprivation. More recently, a large meta-analysis of 70 studies (147 datasets) found that short-term sleep deprivation (19–48 hr) negatively affects cognitive domains like processing speed, complex attention, and working memory, with the most pronounced impact on simple attention, which showed the largest effect size (Lim & Dinges, 2010). Nonetheless, decrements in RT due to sleep deprivation for other domains such as processing speed, complex attention, and working memory also showed compelling moderate effect sizes despite substantial heterogeneity between the tasks (Lim & Dinges, 2010). These findings not only highlight the continued interest in understanding the role of sleep on cognitive performance, but more importantly emphasize the importance of sleep and its impact across many cognitive domains. While most studies focus on acute sleep deprivation or restriction, chronic sleep restriction, a more common form of sleep loss, remains relatively understudied.

Chronic sleep restriction is typically characterized as adults consistently receiving less than the recommended 7–8 hr of sleep per night (Chaput et al., 2020). In Canada and the USA, approximately one-third of adults do not meet the recommendations for minimum sleep duration per night (Chaput et al., 2017; Sheehan et al., 2019). Therefore, the first objective of this study was to investigate the association between *chronic* sleep duration and RT during a simple auditory RT task. This was accomplished by comparing RT in a sample of apparently healthy adults who were classified as chronic short sleepers (i.e. people who in the past month averaged a sleep duration that does not meet the sleep guidelines), versus adults who were classified as chronic adequate sleepers (i.e. people who in the past month averaged a sleep duration that meets the sleep guidelines).

As noted above, the negative effect of sleep deprivation on RT is often linked to deficits in alertness and time-on-task deficits (Mackworth, 1964). The Psychomotor Vigilance Task (PVT) is commonly used to measure these deficits, as tracking response latencies and errors over a 10-min period (Basner & Dinges, 2011; Dinges & Powell, 1985). However, the PVT does not assess preparedness for movement, leaving the influence of sleep duration on motor preparation processes unclear. One novel method to gauge preparation level is through the presentation of a startling acoustic stimulus (SAS) during a RT task. Research has shown that a prepared voluntary movement can be involuntarily triggered by a SAS at a very short latency (Carlsen et al., 2004a; Valls-Solé et al., 1995; Valls-Solé et al., 1999; Valls-Solé et al., 2008) when a startle reflex (Landis & Hunt, 1939) is elicited – a phenomenon known as the StartReact effect. Importantly, this effect occurs only when the movement is prepared in advance and when there are enough cognitive resources to maintain a high preparation level (Carlsen et al., 2004a; Drummond et al., 2013; Maslovat et al., 2015; Peters et al., 2022; Valls-Solé et al., 1999). Additionally, the StartReact effect is characterized by a high proportion of startle reflexes measurable via electromyography (EMG) over the sternocleidomastoid (SCM), and it does not exhibit quick habituation when a movement has been prepared (Blumenthal et al., 2005; Brown et al., 1991; Carlsen et al., 2003; Carlsen et al., 2004a).

Therefore, the second objective of the study was to utilize a SAS during a simple RT task in order to perform a comparative analysis of motor preparation level between chronic sleep duration groups (short versus adequate). It was hypothesized that if motor preparation deficits are associated with slowed RT in participants with chronic short sleep duration, both the SAS trials and control trial would be slower and the proportion of SAS trials with startle reflexes would be lower, compared with adequate sleepers. On the other hand, if RT on SAS trials and the proportion of SAS trials with startle reflexes are not significantly different between chronic short sleepers and adequate sleepers, then RT deficits would not be associated with motor preparation processes.

2 | METHODS

2.1 | Participants, exposure and comparator

The study was conducted and reported in accordance with the guidelines set forth by the Declaration of Helsinki, the ethical guidelines set by the University of Ottawa's Research Ethics Board, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Von Elm et al., 2007). Written informed consent was obtained from all participants. A convenience sample of apparently healthy adults was recruited at the University of Ottawa, Canada, between December 2018 and March 2019 to participate in this cross-sectional study.

To be eligible to participate, apparently healthy adults needed to be either chronic short duration sleepers (defined as self-reporting sleeping ≤ 6 hr per night on average in the previous month) or chronic adequate duration sleepers (defined as self-reporting sleeping ≥ 7.5 hr per night on average in the previous month). Sleep duration was subjectively assessed using the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). Additionally, in order to ensure that the night prior to testing was not atypical of their average sleep reported on the PSQI, participants also completed a short questionnaire asking about their previous night of sleep (i.e. bedtime, wake time, and length of time to fall asleep). If the night prior to testing was deemed atypical (i.e. > ± 30 min) of their monthly average sleep, participants were

ineligible to participate due to sleep variability as a possible confounder. No participants were excluded due to sleep variability. Participants were instructed to not consume any caffeine in the 2 hr preceding their testing session, as caffeine intake prior to testing may be a confounder. For those drinking coffee every morning, upon waking up, we made sure to schedule testing later in the day, disturbing daily routine and regular caffeine intake may also be a confounder. In addition to meeting the sleep duration group criteria to be eligible, participants were also required to have normal or adjusted to normal vision and hearing, to be fluent in English, and to have no upper right limb physical disorder or disability.

Based on previously reported effect sizes (Lim & Dinges, 2010), we determined that a total sample size of 46 (23 per group) would be sufficient for the present study, as it would provide 80% power at 0.05 level of significance (two-sided) to detect a 20% increase in RT in chronic short duration sleepers, which is a conservative increase in RT compared with acute sleep deprivation or restriction studies. Based on our sample size calculation, we decided to recruit two additional participants per group, to account for possible missing data. For this study, the exposure group was 25 chronic short duration sleepers and the comparator group was 25 chronic adequate duration sleepers. Although this was a convenience sample, everyone that was approached to participate in the study agreed.

2.2 | Experimental set-up

Participants were seated comfortably in front of a computer monitor set at eye-level ~1.5 m away. Their right arm rested in a custom-made manipulandum that placed their limb in ~30 degrees of shoulder abduction, 90 degrees of elbow flexion, and with their wrist in a semi-prone position so that their palm faced inwards. In order to isolate movement but not restrict the range of motion of the wrist joint, the participant's forearm was secured in the manipulandum armrest by a Velcro strap. A speaker was placed behind the participant's head, levelled with the ears at a distance of 30 cm. In order to minimize white and blue light exposure during testing, the task was conducted in a darkened room with the feedback display monitor set to night colours (Figure 1).

2.3 | Experimental procedures

The experimental task was a simple RT task that required participants to make a targeted wrist extension movement with the right hand in response to an auditory imperative stimulus. The control-tone consisted of a briefly presented single tone (1000 Hz, 100 ms duration, 80 ± 2 dB), and the SAS involved a brief intense white noise burst (25 ms duration, 120 ± 2 dB, < 1 ms rise time). The experiment included six blocks of 30 trials (including SAS trials), for a total of 180 experimental trials. The first two blocks contained no SAS trials, whereas in blocks 3–6, the ratio of SAS to control-tone trials was increased incrementally as follows: block 3: 1:15; block 4: 1:10; block 5: 1:6; block 6: 1:5. The number of SAS exposures for all participants

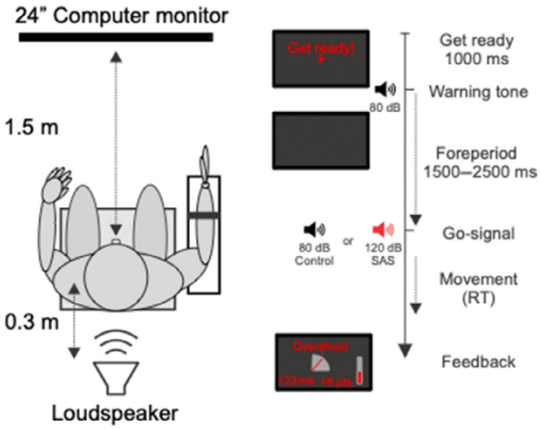


FIGURE 1 Schematic overhead view of participant set-up (left) and trial timing (right) for the simple reaction time (RT) task using a startling acoustic stimulus (SAS). Note trial timing represents the temporal sequence of events of a single trial, and illustrates visual prompts, stimuli, and feedback presented.

was 16 of the 180 total trials. SAS trials were pseudo-randomly interspersed (i.e. first two trials of a block could not be a SAS trial, and there were never two consecutive SAS trials) within their respective blocks. Prior to commencing the task, participants performed five familiarization trials that were not analysed.

To start each trial, participants were provided with a representation of their current wrist position as well as the location of the target for 1 s along with the words "Get Ready" on the computer screen. After this, the online feedback was removed, a warning tone (200 Hz, 100 ms duration, 80 ± 2 dB) was presented, and the screen was fully darkened. Following the warning tone, a variable foreperiod of 1500–2500 ms preceded the second auditory tone, which served as the "Go" signal (Figure 1). Following the auditory warning tone and display of "Get Ready" on the monitor, participants were instructed to prepare a right-handed 20 degree wrist extension movement from the starting position, and respond by releasing the prepared movement as quickly as possible when the second auditory tone was played. After each trial, terminal feedback was provided on the monitor for 3500 ms, which included displacement RT, proximity to the target (i.e. good, overshoot for movement > 25°, or undershoot for movement < 15°), and points awarded. To maintain motivation and task engagement, a cumulative point system was used in which participants received points for RTs on trials that were deemed fast (< 140 ms), and penalized for trials that were considered too slow (> 250 ms) or when participants anticipated and moved before the "Go" signal.

2.4 | Outcome measures

The primary outcome measure for cognitive performance was premotor RT in the right extensor carpi radialis, measured as the time between stimulus presentation and EMG onset of the muscle. EMG onset was

defined as an increase in the rectified and filtered signal exceeding two standard deviations from the baseline activation (mean of 100 ms of EMG prior to the Go-signal). Additionally, we also looked at the effect of time-on-task on RT performance. Time-on-task was defined as the observed RT performance during each of the trial block (blocks 1–6 for control-tone and blocks 3–6 for SAS tone) between the two chronic sleep duration groups. For time-on-task, it was decided that it would only be investigated if we found performance differences between the chronic sleep duration groups in the main analysis. Alertness was measured in terms of the number of lapses in the task and proportion of SAS trials with startle reflexes. Lapses were defined as trials where the participant had slow responses (RT > 500 ms), omissions and movement errors. For each participant, the proportion of SAS trials with a startle reflex was calculated as the number of SAS trials where an EMG burst was noted in SCM within 120 ms of the SAS (Carlsen et al., 2011), divided by the total number of SAS trials presented. For motor preparation, we used premotor RT in the right extensor carpi radialis in conjunction with EMG from the left SCM during the SAS trials. During the SAS trials, SCM was used as startle reflex indicator, and trials with no visible SCM activation were not used in the analyses as they are not indicative of high levels of preparation. Four participants' (two adequate and two short durations sleepers) SAS trials data were removed from the analyses as they did not startle.

2.5 | Recording equipment

Surface EMG was collected from the superficial muscle bellies of the right extensor carpi radialis (agonist), right flexor carpi radialis (antagonist) and left SCM (as an indicator of a startle reflex) using bipolar, preamplified parallel-bar electrodes (Delsys Bagnoli DE-2.1) connected via shielded cabling to an external amplifier (Delsys Bagnoli-8). To minimize electrical impedance, all electrode attachment sites were cleaned with abrasive skin gel (NuPrep) and alcohol wipes prior to attachment. The electrodes were aligned parallel to the muscle fibres and attached to the skin using adhesive double-sided tape. Finally, a reference electrode (Dermatrode HE-R) was placed on the right medial epicondyle. Unfiltered EMG were digitally sampled at 4000 Hz using a custom LabVIEW program and stored for offline analysis. Data collection was initiated by the computer on each trial beginning 1000 ms prior to presentation of the auditory Go-signal and continued for 3000 ms.

2.6 | Statistical analysis

Descriptive characteristics of the sample are presented for each group (chronic short sleepers versus chronic adequate sleepers), as well as for all participants overall. For normally distributed continuous variables, mean and standard deviation are reported, whereas *n* and percentage are reported for categorical variables. Data analyses were performed using SPSS statistical software (Version 29, SPSS, Chicago, IL, USA) and JASP (Version 0.18.3, JASP Team, Netherlands). All variables were examined for normality using the Shapiro–Wilk test, and no variables needed transformation. An independent *t*-test was performed to confirm a significant difference in sleep duration between the self-reported chronic short sleepers and chronic adequate duration sleepers. To ascertain the association between chronic sleep state, performance (RTs) and motor preparation (RT following the SAS), we performed a mixed-model analysis of variance (ANOVA) comparing the interaction between the two chronic sleep duration groups (short versus adequate sleepers) and the two Go-signals (control versus SAS). It was decided a priori that if a significant difference was found between chronic state groups and RT in response to one or both Go-signals, then secondary analyses using mixed-model ANOVAs would be used to determine the association between chronic sleep state and time-on-task (six blocks for regular Go and four blocks for startle Go). Additionally, for the post hoc analyses for the association between chronic sleep groups and time-on-task, it was also predetermined that we would only explore between group differences for each block of trials individually using Bonferroni correction (six comparisons for the control-tone, and four comparisons for the SAS tone). To determine the association between chronic sleep state and alertness, we conducted independent *t*-tests comparing lapses and the proportion of SAS trials with startle reflexes between chronic sleep duration groups. In cases where the assumption of sphericity was violated, Greenhouse–Geisser-corrected degrees of freedom were used to report the main effect. Finally, based on feedback from the peer-review process, we included two new analyses response variability and reciprocal response time (Basner & Dinges, 2011; Dinges et al., 1987). For each participant, standard deviations and reciprocal response time for each tone were calculated and analysed in the same manner as previously described for RT. Significant differences with a probability of less than 0.05 were considered significant. Significant interactions were decomposed using independent and paired *t*-tests with corrections for multiple comparisons using the Holm–Bonferroni method. Cohen's *d* or partial eta-squared (η_p^2) are reported where appropriate to provide an estimate of effect size (Cohen, 1988). Variations of the effects were verified for time of testing, age, education level, use of sleep medication and biological sex.

3 | RESULTS

3.1 | Descriptive characteristics

An independent *t*-test showed a significant difference in hours of self-reported sleep duration between our chronic short and adequate sleeper groups ($t_{48} = 6.2$, $p < 0.001$, $d = 0.68$), with a sleep duration difference between the two groups of 2 hr 47 min per night on average in the previous month (Table 1).

3.2 | Outcome measurement

Premotor RT observed for the two groups is shown in Figure 2. Analysis of mean premotor RT between sleep group and stimulus type showed a significant main effect of stimulus type ($F_{1,44} = 86.15$, $p < 0.001$, $\eta_p^2 = 0.66$), indicating that RT latencies observed following

TABLE 1 Descriptive characteristics of the sample by chronic sleep duration group and overall.

Variable	Chronic short sleepers ($n = 25$)	Chronic adequate sleepers ($n = 25$)	Total ($n = 50$)
Age in years	24.0 (4.2)*	21.8 (3.2)*	22.8 (3.8)
Self-reported sex, *n* (%)			
Female	16 (64)	15 (60)	31 (62)
Male	9 (36)	10 (40)	19 (38)
Self-reported handedness, *n* (%)			
Right-handed	24 (96)	25 (100)	49 (98)
Left-handed	1 (4)	0 (0)	1 (2)
Sleep duration (hr per night in the past month)	5.7 (0.7)*	8.5 (0.6)*	7.1 (1.6)
Mean total PSQI score	7.9 (3.2)*	4.2 (1.8)*	6.0 (2.9)
PSQI sleep efficiency percentage	91.3 (8.2)*	96.5 (2.3)*	93.9 (6.5)
Use of sleep medication, *n* (%)			
Not in the past month	22 (88)	20 (80)	42 (84)
Less than once a week	3 (12)	3 (12)	6 (12)
Once or twice a week	0 (0)	0 (0)	0 (0)
Three or more times a week	0 (0)	2 (8)	2 (4)
PSQI interpretation, *n* (%)			
Good sleep quality	5 (20)	17 (68)	22 (44)
Poor sleep quality	20 (80)	8 (32)	28 (56)
Sleep satisfaction percentage	44.2 (18.8)*	69.6 (16.2)*	56.9 (21.6)
Time of day of testing, *n* (%)			
Morning	8 (32)	8 (32)	16 (32)
Midday	8 (32)	6 (24)	14 (28)
Late afternoon	9 (36)	11 (44)	20 (40)

Note: Values are presented as means with standard deviations (SD) in brackets for normally distributed continuous variables, and *n* and percentage for categorical variables. A chronic short sleeper was defined as self-reporting an average sleep duration of ≤ 6 hr of sleep per night in the past month, while a chronic adequate sleeper was defined as self-reporting an average sleep duration of ≥ 7.5 hr of sleep per night in the previous month. A higher sleep satisfaction percentage means a more positive feeling towards the last night of sleep before testing. Good sleep quality represents a total PSQI score < 5, and a poor sleep quality represents a total PSQI score > 4.
Abbreviation: PSQI, Pittsburgh Sleep Quality Index.
*Significant differences between chronic sleep duration groups were observed ($p < 0.05$).

the SAS tone were significantly faster than the latencies following the control-tone. In addition, there was a significant main effect of chronic sleep group ($F_{1,44} = 5.25$, $p = 0.027$, $\eta_p^2 = 0.10$). However, these main effects were superseded by a significant interaction between the factors ($F_{1,44} = 5.97$, $p = 0.019$, $\eta_p^2 = 0.12$). Post hoc analysis of this interaction revealed that mean control-tone RT was significantly different between chronic sleep duration groups. Specifically, the adequate sleepers showed shorter latencies when responding to the control-tone (122.7 ms) compared with the short sleepers (156.0 ms; $p = 0.007$, $d = 0.68$). However, there was no significant difference in RT observed between sleep groups in response to the SAS ($p = 0.26$, $d = 0.34$; Figure 2). As expected, there was also a significant effect of stimulus type for both groups whereby the RTs observed following the SAS were significantly shorter than those following the control-tone ($p < 0.001$ for each paired *t*-test). Furthermore, we observed no significant main effect of sleep groups on response variability ($F_{1,44} = 1.72$, $p = 0.196$, $\eta_p^2 = 0.04$) or reciprocal response time ($F_{1,44} = 3.57$, $p = 0.07$, $\eta_p^2 = 0.08$). However, there were significant differences between tones for response variability ($F_{1,44} = 117.77$, $p < 0.001$, $\eta_p^2 = 0.73$) and reciprocal response time ($F_{1,44} = 94.72$, $p < 0.001$, $\eta_p^2 = 0.68$). Specifically, response variability was greater for the control-tone compared with the SAS tone, with a mean difference of 33.7 ms and 95% confidence interval between 27.46 and 39.98 ms. On the other hand, reciprocal response time was greater for the SAS tone compared with the control-tone, with a mean difference of 3.18 and 95% confidence interval between 2.52 and 3.84.

Secondary analysis investigating the association between chronic sleep duration group and RT performance to the control-tone as a function of time-on-task was tested by comparing control-tone RT as a function of trial block between the two sleep groups (Figure 3). Results revealed a significant effect of time (represented by the trial blocks) on control trial RT between the two sleep duration groups (Greenhouse–Geiser-corrected degrees of freedom; epsilon = 0.786; $F_{3.91,88.8} = 6.23$, $p < 0.001$, $\eta_p^2 = 0.12$). There was also a significant main effect of chronic sleep group ($F_{1,48} = 5.81$, $p = 0.020$, $\eta_p^2 = 0.11$). Preplanned comparisons with Bonferroni correction of control-tone RT between chronic sleep groups at each successive trial blocks revealed that the control-tone RT for trials in blocks 1 and

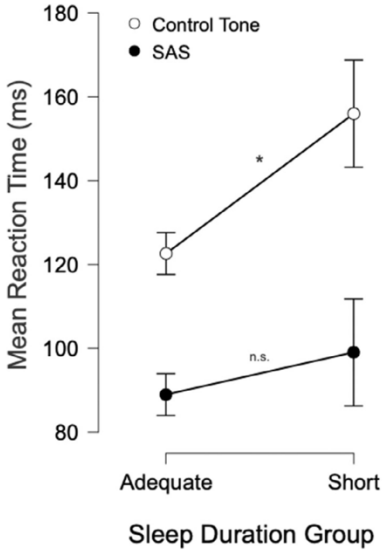


FIGURE 2 The association between chronic sleep duration group and mean premotor reaction time (RT) during a simple auditory RT task using a startling acoustic stimulus (SAS). A chronic short sleeper was defined as an individual self-reporting sleeping ≤ 6 hr per night in the previous month, while a chronic adequate duration sleeper self-reported sleeping ≥ 7.5 hr per night. Results for this figure were obtained using mixed-model ANOVA, two chronic sleep duration groups by two Go-signals. Error bars represent 95% confidence interval for each mean. *p-value < 0.05 for the interaction effect. ANOVA, analysis of variance; n.s., not significant.

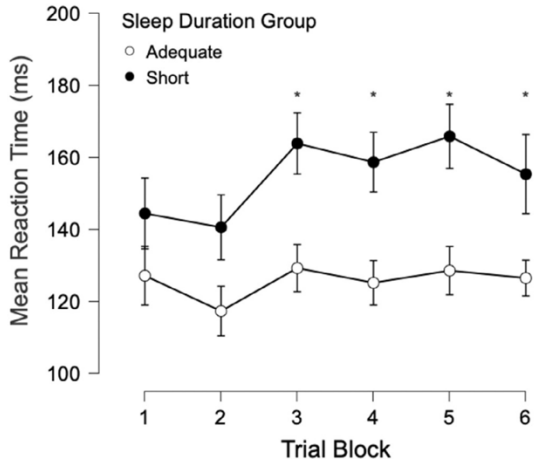


FIGURE 3 The association between chronic sleep duration group and mean premotor reaction time (RT) for the control-tone as a function of time-on-task, represented by trial block, during a simple auditory RT task. A chronic short sleeper was defined as an individual self-reporting sleeping ≤ 6 hr per night in the previous month, while a chronic adequate duration sleeper self-reported sleeping ≥ 7.5 hr per night. Results were obtained using a mixed-model ANOVA, two chronic sleep duration groups by six trial blocks. Error bars represent 95% confidence interval for each mean. *p-value < 0.05 for the comparison between the chronic sleep duration groups and at each individual trial block. ANOVA, analysis of variance.

2 were not significantly different between the two chronic sleep groups ($p > 0.05$); however, chronic short sleepers became significantly slower by approximately 26% (33.5 ms) in block 3 until the end of the task (blocks 3–6, all $p < 0.05$) compared with adequate sleepers.

The proportion of SAS trials where a startle reflex was observed in SCM was not significantly different between groups ($t_{48} = 0.71$, $p = 0.48$, $d = 0.20$). Analysis of the lapses also showed no significant difference between sleep groups ($t_{48} = -0.14$, $p = 0.89$, $d = 0.04$), in the mean number of lapses committed by adequate duration sleepers (16.6 lapses; SD = 8.4) versus short duration sleepers (16.9 lapses; SD = 10.2), representing an average error rate of ~9% for each group. No variations of the effect were found when taking age, level of education, biological sex, use of sleep medication or time of testing into account in the statistical models (all $p > 0.4$).

4 | DISCUSSION

The purpose of this study was to investigate the association between chronic sleep duration, RT performance and motor preparation during a simple auditory RT task with a SAS. Overall, this study showed that chronic short sleepers, who did not meet the recommended sleep duration guidelines in the past month, slept on average 2 hr 47 min less per night in the previous month than the adequate sleepers, those who met the recommended sleep duration guidelines in the past month. Chronic short duration sleepers showed lengthened RT as compared with chronic adequate sleepers (Figure 2). However, this effect does not appear to be a result of a deficit in motor preparation as inferred from the lack of significant differences between the two chronic sleep duration groups for the SAS tone RT (Figure 2), variability, reciprocal response time and the proportion of startle reflexes. Additionally, we found no association between chronic sleep state groups and alertness, measured via lapses. Finally, time-on-task (as a function of trial block) was found to be associated with an increase in the control-tone RT in chronic short sleepers compared with chronic adequate duration sleepers. Specifically, RT became significantly worse for the chronic short sleepers after completing two trial blocks, which represented only 5 min of actual work (Figure 3). Thus, the present study was not only able to investigate the association between chronic short sleep duration (a common form of sleep loss) and motor preparation, but was also able to quantify when time-on-task decrements occurred in this population.

According to the total PSQI results, five participants in the chronic short sleep duration group were considered good sleepers, while eight participants in the chronic adequate sleep duration group had poor sleep quality. The concept of sleep duration and adequacy is

crucial for understanding the interplay between sleep and cognitive function. Sleep duration refers to the total amount of time an individual spends asleep, and there are known individual differences in this trait (Webb & Friel, 1971). These differences may or may not be linked to functional variations, such as cognitive performance (Aeschbach et al., 1996). On the other hand, sustained sleep restriction, where an individual consistently gets less sleep than they need, has been shown to impact on cognitive function, particularly RT. This effect was first demonstrated in two landmark studies from two decades ago, that tested groups that were assigned 3, 5, 7 or 9 hr of time in bed for 7 nights (Belenky et al., 2003), and 4, 6 or 8 hr of time in bed for 14 nights (Van Dongen et al., 2003). These studies underscored the negative effects of prolonged sleep restriction on performance, highlighting the critical role of sufficient sleep in maintaining optimal cognitive function. In the present study, we recruited based on public health sleep duration recommendations, recognizing that most individuals with chronic short sleep duration would likely be sleep restricted, but we also acknowledge that individual sleep needs may vary. While long sleepers are less common, they can indicate other sleep issues that are associated with their own health risks (Chaput et al., 2020). These findings underscore the importance of promoting adequate sleep beyond just sleep duration for cognitive function and overall health. Importantly, we did not exclude mismatched good and poor sleeper from our sleep groups analyses, as our chronic sleep duration comparators were determined a priori and excluding them would have been less representative of our study population.

As previously mentioned, very few studies have explored the role of sleep restriction on motor preparation. Two recent studies have investigated how total sleep deprivation affects motor preparation. Fournier et al. (2020) placed particular emphasis on the impact of sleep deprivation (38 hr of wakefulness) compared with well-rested participants (10 hr of time in bed) on motor preparation during the coordination of multiple action plans. They found that sleep-deprived participants exhibited significant difficulties in preparing and executing motor actions, especially when these actions were part of an overlapping action plan. Similarly, a study by Song et al. (2023) investigated the effects of total sleep deprivation (36 hr of wakefulness) on motor preparation sub-stages during a visual search task. Using stimulus and response lateralized readiness potentials, they showed that total sleep deprivation impacted sensory integration but did not impact response execution (Song et al., 2023). Another study by Stojanoski et al. (2019) conducted a randomized crossover study to investigate the effects of mild acute sleep restriction (1 night of 5 hr of time in bed) compared with sleep extension (1 night of 9 hr of time in bed) on vigilance and cognitive processing. They measured indicators of reduced vigilance and perceptual and behavioural event-related potentials during a sustained PVT over an extended daytime period (Stojanoski et al., 2019). The study found that mild acute sleep restriction negatively affected the processing of visual stimuli, as measured by visual-evoked potentials, and reduced motor-related responses following the presentation of the stimulus, as measured by lateralized readiness potentials (Stojanoski et al., 2019). These findings and ours highlight that total sleep deprivation, short-term sleep and longer-term sleep restriction impact cognitive and motor functions that are essential to activities of daily living.

Slower RT in simple RT task paradigms has been linked to reduced readiness for movement after the Go-signal, possibly due to insufficient sleep. The two-process model of sleep regulation, published 40 years ago and still relevant today in sleep research, describes the homeostatic process (Process S) that regulates sleep pressure, and the circadian process (Process C) that tracks time of day (Borbély, 1982). Results from neuroimaging suggest that the fronto-parietal network is sensitive to Process S, while subcortical areas are sensitive to Process C (Muto et al., 2016). Our study found no RT variation based on testing time during the day, but we did not test throughout the 24-hr period. Despite chronic sleep duration affecting control trial RT, no significant differences were observed in RT for SAS trials or in the proportions of startle responses between the chronic sleep duration groups. This suggests that a deficit in motor preparation processes does not explain the link between RT decline and chronic short sleep. The involuntary triggering of a prepared movement by a SAS likely involved a subcortical pathway, which is said to be less affected by lack of sleep (Carlsen et al., 2004a; Carlsen et al., 2004b; Muto et al., 2016; Valls-Solé et al., 1999). The reticular activating system (RAS), known for regulating the sleep–wake cycle, fight-or-flight response and overall regulation of consciousness by a complex network that simultaneously connects the brainstem reticular formation all the way to the cerebral cortex, could be involved (Garcia-Rill, 2015; Paus, 2000). From the perspective of the RAS in our study, a SAS, considered an intense stimulus, can simultaneously activate both the ascending and the descending RAS and result in not only the release of the prepared movement at reflex-like latencies and a startle reflex, but also increase arousal at the cortical level. Because both response to the startle and the regulation of consciousness are mediated by the reticular formation, the lack of significant association between chronic sleep duration state and SAS trial RTs aligns with the notion that functioning in these neural pathways is preserved during bouts of sleep loss. While we have posited the two-process model of sleep regulation as a possible explanation for our interaction findings, we also acknowledge that other paradigms may be relevant, such as top-down and bottom-up regulation or vigilance decrement and local, use-dependent sleep. For a comprehensive review, see the work of Hudson et al. (2020).

In our study using a simple RT task with a warning signal before the Go-signal, participants could prepare consistently their movement ahead of time, unlike the more random PVT. While measuring motor preparation is harder in the PVT due to its randomness and longer stimulus intervals, preparation is still necessary before movement. Our results, based on responses to SAS trials, suggest that lack of sleep is not linked to movement preparation processes. Therefore, the longer latencies seen in our task and other PVT studies likely result from other processing stages. Additionally, we expected that pre-cueing participants to prepare for 1500–2500 ms would reduce differences in lapses between chronic sleep duration groups compared with a PVT. As expected, we found no

significant differences in lapses between the groups, with both having an average error rate of 9%.

Although the chronic short sleep group's RT performance to the control-tone was not consistently slower as compared with the chronic adequate sleep group, the short sleepers' performance significantly declined after only two trial blocks, which equated to 5 min of work. Specifically, the chronic short duration sleepers were, on average, ~35 ms slower during the final four blocks compared with adequate sleepers (Figure 3). Some neuroimaging studies suggest that sleep deprivation can lead to compensatory brain mechanisms that sustain performance despite the sleep loss (Drummond et al., 2001; Drummond et al., 2005; Drummond & Brown, 2001). To our knowledge, identifying the moment when RT degrades in chronic short duration sleepers is novel and could indicate when these compensatory mechanisms fail. Future research should further explore the effects of compensatory brain mechanisms associated with chronic short sleep.

If we consider lack of sleep as a stressor, there are several stress management responses and mechanisms that could also help explain the RT results. Briefly, during stress, the amygdala upregulates stress pathways in the hypothalamus and brainstem, leading to increased release of noradrenaline and dopamine (catecholamines; Arnsten, 2009). Under these circumstances, alertness regulation switches from a "top-down" control by the prefrontal cortex to a more sensory-driven "bottom-up" control that can desensitize the prefrontal cortex, prioritizing attention to more salient or intense stimulus (such as the SAS tone; Arnsten, 2009; Buschman & Miller, 2007). The observed increase in RTs for chronic short duration sleepers also coincided with the introduction of the SAS tone in the task (trial blocks 3–6). Considering our study design and the results, it is possible that stress responses also play a role in the interaction we found between our chronic sleep duration groups and stimulus type. However, further investigation is needed to fully understand the relationships between chronic sleep duration, stress responses and startling stimuli.

4.1 | Limitations

The findings of this study must be interpreted in the light of the following limitations. First, it is a cross-sectional study, so we cannot establish causal relationship, and further experimental studies are needed to confirm our results. Additionally, our sample was a sample of convenience, which could introduce a risk of selection bias and limit the generalizability of our findings. While we measured sleep subjectively using a reliable and validated questionnaire, future studies should use objective measure for a more accurate assessment of sleep duration and other sleep characteristics (e.g. variability, fragmentation, objective efficiency, wake-after-sleep onset, architecture and chronotype). Some participants in our short duration sleep group might not have been habitual short sleepers, despite meeting the sleep duration criteria, as their lack of sleep might have been due to temporary factors like academic demands. The ramp protocol used for presenting the SAS trials aimed to assess our research question without causing an immediate arousal spike. However, the lack of significant differences in RT for the SAS trials between the two chronic sleep groups could be attributed to other unmeasured factors, potentially confounding the assessment of time-on-task effect. More research with different SAS protocols is needed to confirm these results. Because the result is null, it may be suggested that there was insufficient power to detect the significant difference in RTs for the SAS trials, although the study was not underpowered for other effects of the SAS, such as the proportion of startle reflexes. This implies that motor preparation is not associated with chronic sleep duration. While we did not observe any variation in the effect based on time of testing, it is plausible that the time of day could influence the findings. Ideally, in future studies, establishing a uniform testing time based on individual's waking habits would be preferable. Sleep needs vary among individuals, not everyone is affected equally by lack of sleep, and sleep quality is also an important factor to consider. Some participants in the chronic adequate sleep group had sleep durations higher than recommended, potentially due to unmeasured sleeping issues that could have impacted these results. Therefore, large sample sizes or a within-subject experimental design would be preferable for such studies.

5 | CONCLUSION

In summary, our data reveal that individuals with chronic short sleep duration (less than 6 hr per night in the past month) exhibited significantly impaired voluntary RTs compared with those with chronic adequate sleep. However, we did not find a link between effective motor preparation and chronic sleep duration, suggesting that the impact of chronic short sleep primarily affects other processes. Additionally, while alertness (measured by lapses and startle responses) was not associated with chronic short sleep duration, time-on-task was, as indicated by chronic short sleepers showing a 25% slower RT after only 5 min of work despite being well prepared. This suggests that compensatory brain mechanisms may have limited resources to maintain performance before deficits appear. The specific mechanism underlying this association remains unknown but warrants further investigation. Those consistently sleeping less than 6 hr per night may benefit from increasing their nightly sleep duration to sustain faster reactions during extended periods of focus work.

AUTHOR CONTRIBUTIONS

Caroline Dutil: Conceptualization; methodology; data curation; formal analysis; project administration; writing – original draft; writing – review and editing; visualization. **Julia De Pieri:** Data curation; project administration; writing – review and editing. **Christin M. Sadler:** Writing – review and editing; visualization. **Dana Maslovat:** Methodology; conceptualization; software; writing – review and editing. **Jean-Philippe Chaput:** Conceptualization; methodology; writing – review and editing; supervision. **Anthony N. Carlsen:** Conceptualization; methodology; software; funding acquisition;

writing – review and editing; project administration; supervision; visualization; resources; data curation.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest relevant to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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In summary, our study aimed to explore the impact of chronic sleep restriction, a much more widespread form of lack of sleep, on RT and motor preparation [261]. Participants who identified as chronic short sleepers (n=25, with a self-reported average sleep duration of 5.7 hours per night) displayed significantly slower RTs when responding to control tone stimuli [261]. This effect became apparent after two blocks of trials and persisted until the end of the task, with the decline in performance emerging after approximately 5 minutes of engagement [261]. In contrast, chronic adequate sleepers (n=25, with a self-reported average sleep duration of 8.5 hours per night) maintained more stable RTs in response to the control tone [261]. However, no significant differences were observed between the groups in RT for the Startling Acoustic Stimulus (SAS), the number of lapses, or the proportion of startle reflex responses [261]. These findings suggest that while chronic short sleep is associated with slower RT during sustained tasks, it does not appear to impair motor preparation processes [261]. This could indicate that compensatory mechanisms help maintain performance over short periods; however, these resources are finite, and performance declines as they become depleted [261].

We noted several limitations, including the study's cross-sectional design, which limits causal inferences [261]. Additionally, sleep duration was assessed subjectively, which may be less accurate than objective measurements [261]. Also, sleep needs varies among individuals and lifetime, while participants met the short sleep duration criteria, some may have done so due to academic demands rather than as a long-term, habitual pattern [261]. The ramp protocol used for the presentation of the SAS could have influenced results [261]. There was notable variability in RT among short sleepers that could not be explained by factors such as sex, education level, or age [261]. A well

designed within-subject experimental design that directly manipulates sleep duration could address these limitations.

Mechanistically, clarifying the effects of sleep restriction by ruling out potential sources of delay, such as motor preparation, fills an important gap in the literature. By demonstrating that slowed RTs in short sleepers do not stem from deficits in motor readiness, future studies can infer that the delays likely originate in other stages of cognitive processing. This distinction is crucial for identifying where cognitive impairment occurs due to inadequate sleep, informing future research and interventions to mitigate these deficits.

The present thesis study offers a unique opportunity to expand our understanding of the effects of sleep duration on RTs and motor preparation in adolescents at high risk for T2D. Diabetic peripheral neuropathy is a common issue in youth with T2D, affecting more young males (39%) compared to females (27%), with those experiencing higher A1C levels and BMI being at the highest risk [262]. As such, central delays in RT may be compounded by peripheral delays in those with neuropathy. Gaining insight into how adequate sleep may help preserve RT in this population could be key to supporting better functional outcomes.

2.9.4 Balance in those with obesity and T2D

Diabetic peripheral neuropathy, a prevalent complication of T2D in adults, is linked to heightened postural instability, characterized by impaired balance and gait kinematics, and an increased risk of falls, potentially leading to severe limitations in daily activities [263]. In adolescents with T2D, the prevalence of peripheral neuropathy ranges between

22% and 39% [99,262,264]. Despite this, screening for peripheral neuropathy in adolescents with T2D is limited, and even fewer early screening efforts are conducted among adolescents at risk of developing T2D [99].

In addition to T2D, adults with obesity have been associated with poor postural control, during static balance, perturbed balance, and dynamic balance settings [265]. However, research on balance in children and adolescents with obesity presents mixed results. For instance, McGraw and colleagues [266] found that prepubescent boys aged 8–10 years with obesity demonstrated significantly greater sway area, primarily in the medial-lateral direction, compared to boys of normal weight. Similarly, Maślanko et al. [267] assessed balance in 166 children and adolescents aged 7–18 years and found that children and adolescents with obesity performed significantly worse on an unstable platform than their non-obese peers, though no significant differences were observed on a stable platform. Rusek and colleagues [268] studied a larger cohort of 1137 (49% girls) children and adolescents aged 7–15 and found that those with obesity exhibited better balance as indicated by reduced sway area, shorter center of gravity path length, and smaller deviations in the horizontal plane. Their results indicated that children and adolescents with obesity had better balance according to a reduce sway area, shorter path length of center of gravity, and smaller center of gravity deviations in the horizontal plane [268]. These studies primarily controlled for sex, age, and pubertal status, leaving other potential influencing factors unexamined. A systematic review by Han et al. [269] further underscores these discrepancies, indicating that while exercise and physical activity interventions generally improve locomotor and object-control skills in children and adolescents with overweight or obesity, the results for balance remain mixed and inconclusive. This variability in findings suggests that additional research is needed to

clarify how obesity affects balance in younger populations, considering potential confounding factors beyond those currently explored.

Recent evidence also highlights the impact of circadian rhythms and sleep loss on postural control. A systematic review by Izadi et al. [270], which included 49 studies (43% deemed high-quality), reported that 17 out of 21 studies found circadian rhythm significantly impacted postural control, and all 25 studies examining sleep deprivation/restriction noted impaired postural stability. Umemura et al. [271] additionally reported that in healthy adults, both acute and chronic sleep deprivation, and poor sleep quality were associated with impaired postural balance. The review by Umemura and colleagues [271] also noted that in terms of sensory perturbations, the visual conditions (i.e., eyes open vs. closed) had a greater effect on postural control than proprioceptive conditions (e.g., use of foam vs. hard surface) or dynamic balance tasks.

Balance during quiet standing requires complex interactions between sensory input (visual, vestibular, proprioceptive) and motor responses, relying on lower-level brain processes that function semi-automatically [272–276]. Postural control, defined as the ability to maintain the body's center of gravity within its base of support, can reveal factors related to postural instability and risk of falls [274,275,277–279]. Assessing quiet standing balance is an excellent complement to cognitive function tests, offering a more comprehensive understanding of the relationship between sleep and cognition and its impact on both cognitive and motor domains [280,281].

A force platform, commonly used to assess balance, registers three-dimensional ground reaction forces under the feet, allowing for calculation of key parameters such as centre

of pressure (CoP), postural sway, and balance stability [278,282–287]. During quiet standing, the CoP provides a measure of postural sway, tracking its variation over time, which is influenced by factors such as inherent noise within the human neuromotor system, the anticipatory search process, and control processes to maintain upright postural stability [288–291]. This approach could enhance the translational value of our study by linking the effects of sleep manipulation to functional outcomes and risk management strategies in adolescents at risk for T2D, addressing an important gap in the literature.

2.9.5 Summary

This section highlights the neuropsychological assessment of cognitive and motor functions critical to adolescents at risk for T2D, specifically focusing on executive functions, attention, motor control, and postural stability. Sleep disturbances and metabolic dysregulation in this population are linked to deficits in these cognitive domains, making it essential to explore how these factors affect cognitive and motor outcomes. Research suggests that both obesity and T2D are associated with impairments in inhibitory control, attention, and reward processing, which can contribute to obesogenic behaviours and may be further intensified by poor sleep.

Two cognitive tasks will be employed in this study to explore these effects:

1. AST: This task, an advanced version of the go/no-go paradigm, assesses executive functions including response inhibition, attention, working memory, and cognitive flexibility [255–258]. Participants will shift stimulus-response rules every two blocks, adapting to new instructions that involve appetitive food images and

neutral object images [255–258]. This corresponds to 4 conditions (2 block order x 2 image types). This design will help isolate working memory and the impact of reward sensitivity and inhibitory control in adolescents with sleep manipulation, providing insight into how altered sleep patterns may influence impulse control.

2. Dual-Task Paradigm: In this task, participants will complete a simple RT task with a SAS under dual-task conditions, while standing with their eyes open and closed. This setup will allow us to measure the effect of sleep manipulation on motor preparation, measured via RTs to the control and SAS tones, and postural stability via CoP under varying sensory conditions (eyes open vs. closed) [261,284,290–298]. Tracking RT and CoP under these four conditions (2 tones x 2 visual conditions) helps identify the specific effects of sleep manipulation on motor preparation and postural control, both of which are crucial in understanding functional impairments linked to T2D risk in adolescents.

Together, these tasks provide a comprehensive approach to evaluating the impact of sleep manipulation on cognitive and motor functions in adolescents at high risk for T2D, contributing to the development of targeted interventions and addressing several gaps in the current literature.

2.10 SMART2D Research Question and PICO, Manuscript Titles, Outcomes, and Hypotheses.

2.10.1 SMART2D overarching research question

Does increasing time-in-bed by 1.5 hours per night for a week, compared to habitual sleep duration and decreasing time-in-bed by 1.5 hours per night for a week, improve insulin sensitivity and brain functions in adolescents between 13 and 18 years presenting with risk factors for T2D?

2.10.2 SMART2D PICO

Population: Adolescents at risk for T2D between 13 and 18 years of age at the beginning of the study.

Intervention: Increasing sleep duration, by increasing time-in-bed by 1.5 hours for 7 nights, at home based on habitual sleep duration week.

Comparison: Decreasing sleep duration, by decreasing time-in-bed by 1.5 hours for 7 nights, and habitual sleep duration for 1 week.

Manuscript #1: Sleep and insulin sensitivity in adolescents at risk of type 2 diabetes: the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes randomized crossover study.

Primary ***Outcome***: Insulin sensitivity measured by Matsuda index.

Research hypothesis: We hypothesized that in our population of adolescents at high risk for T2D, increasing sleep duration for one week would result in significant improvements in IS compared to IS level following the habitual and decreased sleep weeks [299].

Manuscript #2: Effect of Sleep Duration Manipulation on Brain-Derived Neurotrophic Factor in Adolescents with Risk Factors for Type 2 Diabetes: A Secondary Analysis of the SMART2D Crossover Study.

*Primary **Outcome**:* BDNF

Research hypothesis: We hypothesized that BDNF levels would decrease following the week of decreased sleep duration compared to the other two weeks, with the week of increased sleep duration exhibiting the highest BDNF levels.

Manuscript #3: Effects of Sleep Duration Manipulation on Food-Related Impulsivity in Adolescents with Severe Obesity and High Risk for Type 2 Diabetes: Findings from a Randomized Crossover Study.

*Primary **Outcome**:* Performance metrics included RT on “go” trials, the number of commission errors on “no-go” trials, and the number of omission errors on “go” trials in each of the four conditions of the task.

Research hypothesis: We hypothesized that extending sleep would enhance task performance, indicated by a reduction in RT and errors, compared to the habitual and decreased sleep conditions.

Manuscript #4: Impact of Sleep Manipulation on Motor Preparation and Postural Control in Adolescents with Severe Obesity and High Risk for Type 2 Diabetes: A Crossover Study.

*Primary **Outcome**:* Performance metrics included RT during control and SAS trials, errors, and centre-of-pressure metrics for postural stability.

Research hypothesis: We hypothesize that sleep restriction will impair cortical contributions to postural adjustments while sparing subcortical reflexive responses, leading to increased postural sway and delayed voluntary RTs but preserved SAS-evoked responses, compared to sleep extension.

Chapter 3

Manuscript 1:

Sleep and Insulin Sensitivity in Adolescents at Risk of Type 2 Diabetes: the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes Randomized Crossover Study.

Title:

Sleep and insulin sensitivity in adolescents at risk of type 2 diabetes: the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes randomized crossover study.

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Sleep and insulin sensitivity in adolescents at risk of type 2 diabetes: the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes randomized crossover study

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Abstract

Study Objectives: To investigate the effect of increasing sleep duration for 1 week, compared to a week of habitual and decreased sleep, on insulin sensitivity (IS) in adolescents at risk for type 2 diabetes (T2D).

Methods: Adolescents, 13–18 years old, at risk for T2D, with obesity and other risk factors, were recruited for a randomized (1:1), open-label, sex-stratified crossover study, that manipulated time-in-bed to modify sleep duration (measured by actigraphy). Following a week of habitual (HB) sleep, time-in-bed was increased (IN) and decreased (DE) by 1 hour 30 min/night for 1 week, counterbalanced across participants (HBINDE or HBDEIN), and separated by a week of washout sleep. The main outcome measure was IS, obtained via 2-hour oral-glucose-tolerance-test conducted after each sleep week.

Results: Of the 43 participants recruited, 36 (84%) completed all sleep interventions (52.8% female, age = 15.1 years, body mass index = 99.9th percentile, order: HBINDE = 18 and HBDEIN = 18). On average, during the HB week, participants slept 7 hours 31 min/night; sleep duration was 1 hour 02 min/night higher during the IN week and 1 hour 19 min/night lower during the DE week. We found a significant effect of sleep week on IS with a large effect size. Following the IN sleep week, IS was 20% higher compared to after the HB and DE sleep weeks, but there was no significant difference in IS following HB versus DE sleep weeks.

Conclusions: Whenever possible, clinicians should empower youth at risk of T2D to improve their sleep duration, since even a modest increase in sleep duration of 1 h/night for 1 week can have a positive impact on IS in this population.

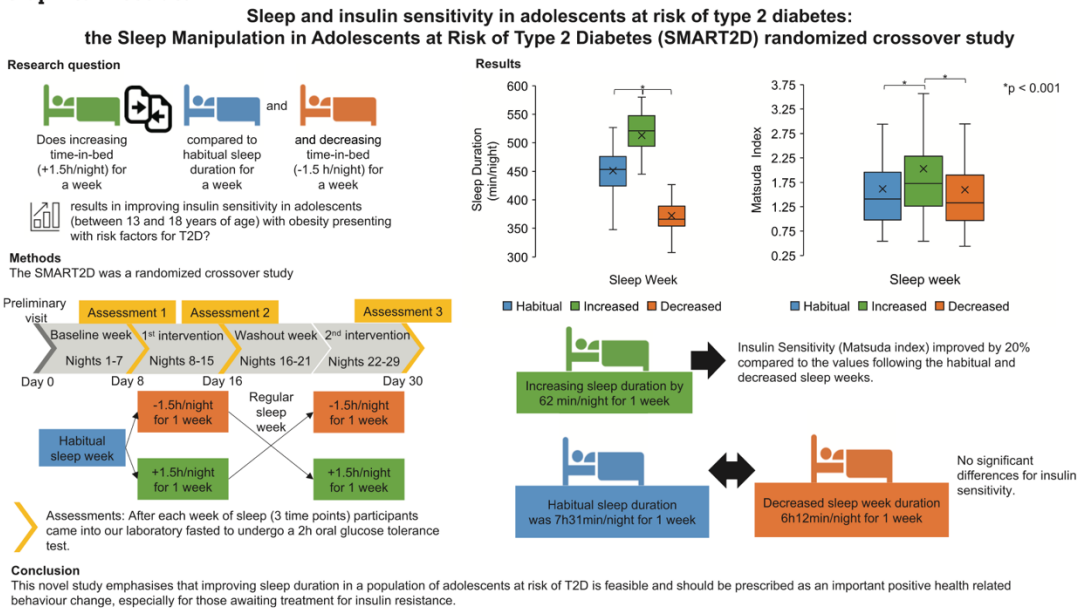
Clinical Trials: Sleep Extension and IS in Adolescents, https://clinicaltrials.gov/study/NCT03754036, November 23rd, 2018.

Trial registration: ClinicalTrials.gov (ID:NCT03754036).

Key words: adolescents; experimental study; insulin resistance; insulin sensitivity; obesity; sleep duration; sleep manipulation; type 2 diabetes

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Graphical Abstract



Statement of Significance

This unique study is the first to report that a short-term increase in sleep duration by 1 h/night for 1 week in adolescents at high-risk of type 2 diabetes improved insulin sensitivity (IS) by 20% compared to a week of habitual sleep and decreased sleep duration. These significant findings with large effect sizes were independent of many factors, including energy intake and physical activity. Notably, a 1 h/night increase in sleep duration for adolescents at high-risk for type 2 diabetes is feasible in the short-term and could be an effective non-pharmacological recommendation for the management of insulin resistance. Future work should investigate the mechanism(s) responsible for these results, and the longer-term (>1 week) impact of increasing sleep duration on IS in this population.

Introduction

In 2017, we reviewed the available evidence between sleep (duration, architecture, and quality) and biomarkers for type 2 diabetes in the pediatric population and found that inadequate sleep was associated with markers of insulin resistance [1]. The findings from our review were based largely on cross-sectional data and we noted that no study had tried to increase sleep duration in order to determine if it could improve insulin resistance in the pediatric population [1]. A recent systematic review examining the evidence between sleep interventions and glucose metabolism in adults found that five out of six experimental studies reported that a successful increase in sleep duration had a positive impact on insulin resistance and out of these five studies, two were conducted in short-sleeping adults with overweight or obesity [2]. Despite emerging evidence, adequate sleep remains an afterthought in the prevention and management of insulin resistance.

Adolescents aged 13 years are recommended to sleep 9–11 h/night and older adolescents should be getting 8–10 h/night, with consistent bedtimes and wakeup times [3]. Adolescents are particularly at risk of insufficient sleep, and while a myriad of contemporary contributors have been associated with short sleep in this population, excess weight is considered a primary risk factor [4–6]. The evidence, likely bi-directional, between poor sleep and increased adiposity is mounting in children and adolescents [7, 8]. While insufficient sleep is a more recent and often underrecognized public health concern, obesity on the other hand, according to the World Health Organization (WHO), has reached pandemic proportions; a 2022 WHO report showed that more than 340 million adolescents are affected worldwide, and there is no indication that obesity rates are plateauing or reversing [9]. Obesity has been linked to a number of noncommunicable diseases and comorbidities including mental health disorders, cardiovascular diseases, hypertension, musculoskeletal disorders, kidney failure, various forms of cancers, and type 2 diabetes [9].

Rates of diagnosis of type 2 diabetes have also risen dramatically amid the sharp increase in the prevalence of obesity in the pediatric population. According to global trends that were collected over a decade ago, the incidence rates for type 2 diabetes diagnosis in children and adolescents already ranged between 0 and 300 cases per 100 000 person/year depending on geographical location and ethnicity [10]. Once known as “adult onset” diabetes, type 2 diabetes is much more prevalent among youth and is associated with greater risk of comorbidity and premature mortality [11]. A recent systematic review and meta-analysis reported that

the prevalence of obesity in the pediatric population at type 2 diabetes diagnosis was 77.2% based on 30 studies published between 1992 and 2022 from various countries [12].

Considering that adolescents with obesity are likely to have poorer sleep and are at increased risk of developing type 2 diabetes and that no study to date has tried to improve sleep in this population in order to improve insulin sensitivity (IS), the following question was addressed: does increasing sleep duration for 1 week, compared to a week of habitual and a week of decreased sleep durations, result in improved IS in adolescents at risk of type 2 diabetes? We hypothesized that in our population of adolescents at risk for type 2 diabetes, increasing sleep duration for 1 week would result in significant improvements in IS compared to IS following the habitual and decreased sleep weeks.

Methods

The Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes (SMART2D) study was conducted at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Canada. The SMART2D study was designed, conducted, and reported in accordance with the ethical guidelines set forth by the Declaration of Helsinki, the Tri-Council established core principles for ethical research in humans (www.ethics.gc.ca), and the CONSORT statement [13–16]. See Supplementary Tables S1 and S2 for the completed CONSORT checklist. All experimental study protocols on human participants were approved by the Research Ethics Boards at CHEO and at the University of Ottawa (initial approval on April 5, 2017 and protocol modifications approved on October 26, 2018). The trial protocol was registered at ClinicalTrials.gov (on November 23, 2018 ID:NCT03754036). Piloting of the SMART2D protocol occurred in January 2019 and final modifications to the study protocols were completed in February 2019, with no modifications needed to the ethics documentation and no further modifications made to the protocols. SMART2D study recruitment started in April 2019 and ended in December 2021 (Figure 1).

Adolescent participants were either recruited from the referral or the discharge lists of CHEO's Center for Healthy Active Living (CHAL), a multidisciplinary pediatric weight management program. Adolescents currently enrolled in the CHAL program or another weight management program were not eligible to participate. Verbal and written explanations of the study protocols and associated risks were provided by a CHAL volunteer to all potential participants prior to obtaining written informed consent during a preliminary visit.

Population

SMART2D study enrolled participants who met the following inclusion criteria: age 13–18 years; no diagnosis of type 2 diabetes; no medical history of sleep disorders; no diagnosis of psychiatric disorders; can understand, speak, and read French and/or English; on average over the past month self-reported sleeping ≥6.5 hours but <9 hours per night; normal or corrected to normal vision; attended school in grades 8–12; lives within a 35 km radius from the hospital, no major disability that would prevent participation in the study; and one of the following three recruitment priorities to target adolescents at risk of type 2 diabetes. Recruitment priorities were chosen based on many of the screening criteria published by the Diabetes Canada Clinical Practice Guidelines Expert Committee on type 2 diabetes in children and

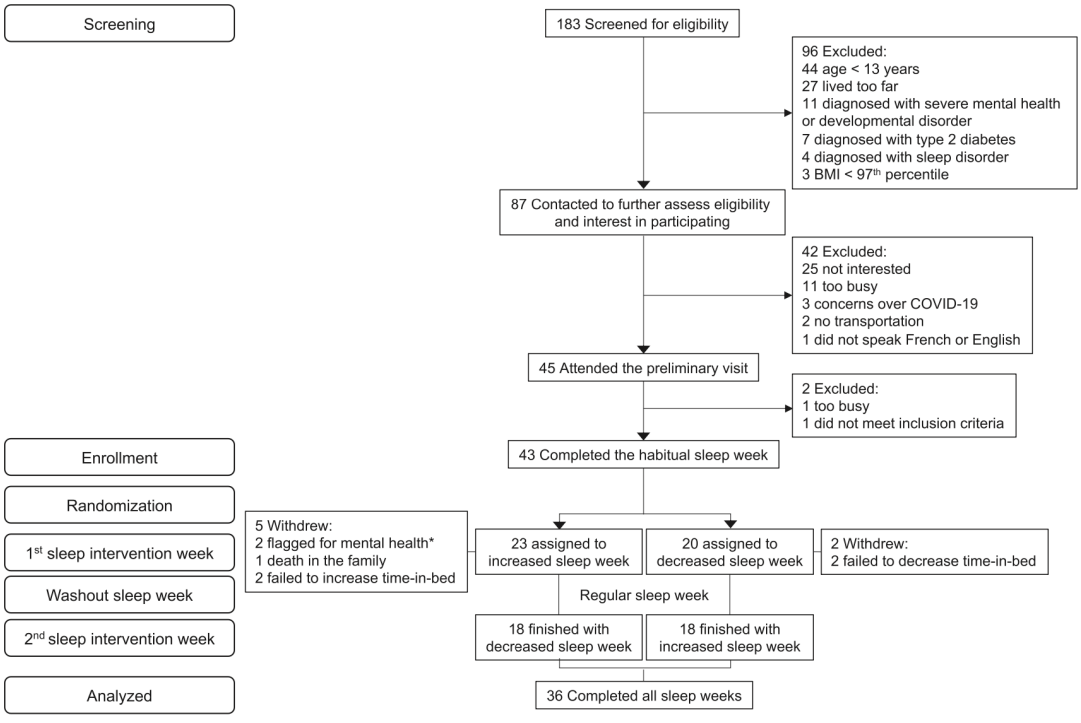


Figure 1. CONSORT flow diagram for the SMART2D study.

adolescents [17]: (1) have obesity, defined by the WHO as body mass index (BMI) > 97th percentile based on age and sex [18], and dyslipidemia indicated by one or more of the following values: triglycerides > 1.7 mmol/L, high-density lipoprotein (HDL) < 1 mmol/L, or non-HDL-C > 3.75 mmol/L, (2) have obesity and one or more of the following conditions: polycystic ovary syndrome (PCOS) and nonalcoholic fatty liver disease (NAFLD), and (3) have severe obesity, defined by the WHO as a BMI > 99th percentile based on age and sex [18]. All participants upon completing the study or upon withdrawal received $30 for each blood collection session and $5 per night for successfully following the time-in-bed schedule. Additionally, participants received a total of 40 hours of volunteering (volunteering is a requirement to graduate from high school in Ontario, Canada) for the good completion of their logs at home during each week of the study.

Intervention and comparisons

The intervention was increasing time-in-bed by 1.5 h/night for 1 week, based on the average sleep duration during the week of habitual sleep, to increase sleep duration.

The comparators were a week of habitual sleep duration and a week of decreasing time-in-bed by 1.5 h/night for 1 week to decrease sleep duration. The week of habitual sleep was added to the protocol as a comparator after the trial registration submission but before start of recruitment. Adding the habitual sleep assessment was essential so that we could determine whether increasing sleep duration could improve IS in an adolescent population at risk of type 2 diabetes. However, we also kept the decreasing sleep condition because having two comparators (habitual sleep duration and decreased sleep duration) was important, so that participants would not be tempted to restrict their sleep during the habitual sleep week. Participants needed to successfully increase or decrease their average time-in-bed during their first intervention in order to remain in the study as this is a within-participants study design and participants needed to be their own controls. However, if they passed the first intervention but failed the second their data remained in the analyses. The interventions, increasing and decreasing sleep weeks, were similar in that the participant received a sleep schedule with fixed daily bed- and wake-times but were different in terms of timing of the sleep schedule with a 3 h/night time-in-bed gap between the 2 sleep weeks and based on individual habitual sleep duration.

Outcome measurements

The Matsuda index [19], our primary outcome, was used as a marker of whole-body IS, while the Homeostasis Model Assessment (HOMA) [20], the computerized HOMA2 [21, 22], and the Quantitative IS Check Index (QUICKI) [23, 24] were used as secondary outcomes and as indicators of fasting insulin resistance. Other secondary outcome measurements included HOMA2 β-cell function % [21, 22] (used as an estimate of fasting insulin secretion) and HOMA2 sensitivity % [21, 22] (used as an estimate of fasting IS). Using trapezoidal integration calculations, we calculated the area under the curve (AUC) for early peak phase (between 0 and 30 minutes), for late peak phase (between 30 and 60 minutes), and total (between 0 and 120 minutes) for both glucose and insulin. The shape of the glucose curve was also dichotomized as being biphasic or not biphasic; to be classified as biphasic the glucose had to peak at either 30 or 60 minutes, and a second time at 120 minutes (increase from 90 to 120 minutes ≥ 0.25 mmol/L) [25]. Total cholesterol, HDL cholesterol, and triglycerides, were also used as secondary outcome measures while low-density lipoprotein cholesterol was removed as secondary outcome as it is not used to screen for insulin resistance [17]. During the peer-review process we added two more secondary outcome measurements for each week of sleep: the triglycerides to HDL ratio [26] and the single-point IS estimator (SPISE) [27] used as an indicator of fasting insulin resistance.

Trial design

The SMART2D study was a single-site, free-living conditions, randomized, open-label, and sex-stratified crossover study. This counterbalanced within-participants experimental design investigated the effect of sleep duration manipulation on type 2 diabetes risk profiles among high-risk adolescents aged 13–18 years.

Following a minimum of 7 nights of habitual sleep, participants completed two sleep duration intervention weeks that entailed increasing and decreasing time-in-bed by 1.5 h/night for 7 nights based on individual sleep duration during the habitual sleep week. This sleep manipulation was employed previously in children by Hart et al. [28]. The intervention weeks were separated by a washout week, during which participants were instructed to return to their habitual sleep schedule. Based on previous research we decided that 3 to 5 nights would be more than sufficient to prevent any carry-over effect [29, 30] but we opted for a length of 7 nights to maintain the same schedule for all the interventions. Randomization (1:1) and allocation concealment were created by a third party using a computer-generated block randomization (block size of two and four) for the order of the interventions (i.e. decreased sleep first or increased sleep first) and stratified by sex; then sealed in opaque envelops that were numbered for each sex. Participants and researchers were made aware of the order of the conditions after completing the week of habitual sleep. Following each week of sleep (i.e. 3 time points during the 1-month period), participants came into the laboratory for testing from 8 am and until 2:30 pm (see Figure 2 for the study design), which included a 2 hours oral-glucose tolerance-test (OGTT).

Potential harms

For the blood draws possible harms included: bleeding, fainting, dizziness, nausea, light headedness, discomfort, bruising, and infection/hematoma at the needle puncture site. These were mitigated by having a specialized nurse perform the insertion of the catheter, recording harms during the laboratory assessments on the data collection sheet, and, following each session, contacting participants in the evening and the next day via SMS text messages to ascertain the possibility of any new harms or assess the status of any lingering harms following the blood draws. Additionally, as part of the safety protocol, incidental findings related to the blood draws were disclosed to our pediatric endocrinologist, the adolescent participant, and with the participant's permission the information was also shared with their parent or legal guardian. While we excluded adolescents diagnosed with a psychiatric disorder, it was important to consider and mitigate the potential harm that our sleep intervention could have on participants' mental health. For the sleep intervention, since modifying sleep could worsen mood, emotional regulation, and increase risk of experiencing anxiety, during each assessment we also administered the Patient Health Questionnaire modified for adolescents (PHQ-A) [31]. A safety protocol was in place to respond promptly if a participant reported having any characteristics of suicidality (any answer other than "not at all" on question 9 of the PHQ-A) or a total score on the PHQ-A ≥ 15 representing moderately severe or

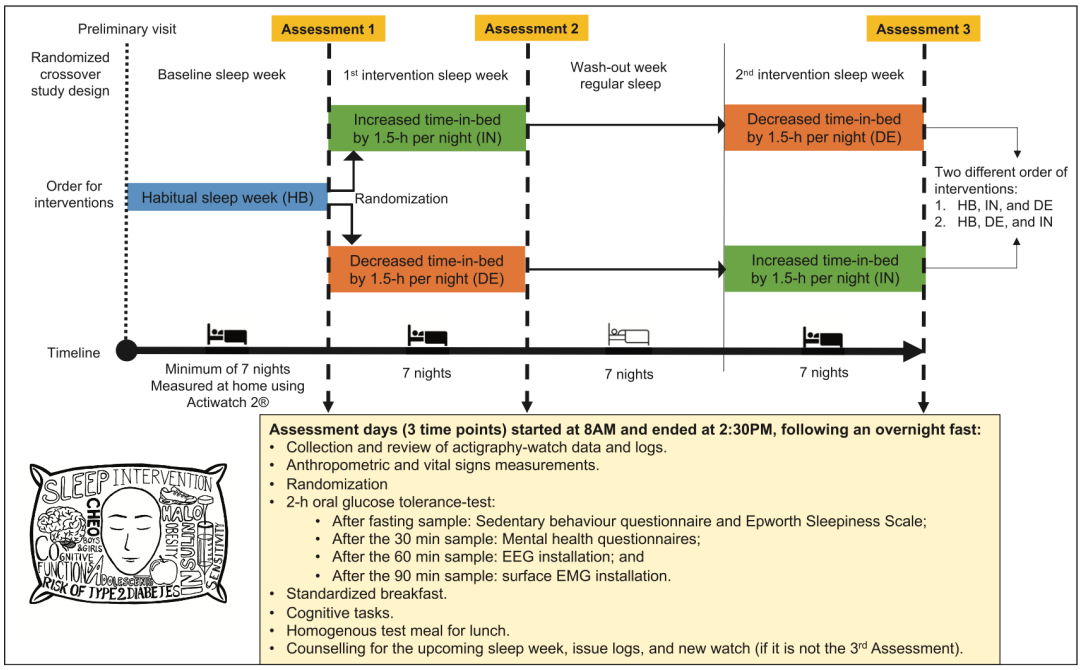


Figure 2. Overview of the SMART2D study's experimental protocol: a randomized crossover study design with timeline, assessments schedule, and tests.

severe depressive disorder or episode. Participants were encouraged to report any harm related to the study in person or during the daily communications via SMS text messages.

Preliminary visit

After obtaining written consent during the preliminary visit at CHEO, BMI percentile for age and sex [18] was verified by directly measuring height and weight using standardized protocols. Participants completed a screening questionnaire to assess other eligibility criteria and ascertain sociodemographic and descriptive characteristics. The screening questionnaire included, but was not limited to, date of birth, sex, self-reported gender, self-reported ethnicity/race, current school grade, list of current diagnoses, medication and supplements/vitamins taken, self-reported health quality, self-reported amount of moderate-to-vigorous physical activity per day, self-reported alcohol consumption, recreational drug use, and tobacco product use, highest education level attained by parents or legal guardians, and history of type 2 diabetes and other chronic diseases and conditions among immediate family members. The highest education level attained by parents or guardians was used as a proxy measure of socioeconomic status; coding of responses was done in accordance with a previous study [32]. Participants also completed the Pittsburgh Sleep Quality Index questionnaire [33] to measure self-reported sleep quality and problems, the 23-item Pediatric Quality of Life Inventory for 13–18 year-olds [34, 35] to assess health-related quality of life via self-report, the revised Three-Factor Eating Questionnaire to assess eating behaviors [36, 37], and a pubertal self-assessment questionnaire (that uses two sets of the five pictures with description to estimate Tanner stage) to assess sexual maturation [38]. At the end of the preliminary visit, participants were issued an actigraphy watch, and their SMART2D study booklet that contained basic study information, individualized study schedule, study staff contact information, reminder sheet, daily sleep and caffeine logs, and a 3-day food diary.

Sleep measurement

Sleep and daytime activity were objectively measured throughout the study, 24/7, using a research-grade sleep actigraphy watch (Actiwatch 2, Philips Respironics, Netherlands) worn on the non-dominant wrist. Watches were initialized to record in 1-minute epochs and to start recording 1 hour after the departure from their preliminary visit. Participants returned their watch and received a new watch during each visit to control for battery power; thus, a watch was issued at the preliminary visit for 7–10 nights to capture the habitual sleep week, another watch was issued following the habitual sleep week assessment for 7 nights to record the first intervention, and the final watch was issued after the first intervention week assessment for 14 nights to record the washout week and the second intervention. In order to capture habitual sleep accurately, including both week and weekend nights, participants who opted for weekend testing days had their preliminary visit scheduled during the week, giving us 8 to 10 nights of sleep data and a full picture of their weekend sleeping habits.

Habitual sleep duration obtained by the Actiware software version 6.0.9 (Philips Respironics, Netherlands) was then averaged and time-in-bed was increased and decreased by 1.5 h/night for 1 week for each intervention, respectively. Wakeup time during weekdays was set to the time that each participant needed to be up for school and weekend wakeup time could not be more than 2 hours later than their earliest wakeup time (this was to control

for sleep variability). Participants were also asked to not engage in any daytime napping, only engage in nighttime sleep, and not skip any night of sleep during the entire study (this was to prevent sleep fragmentation). Of note, the SMART2D study primarily manipulated time-in-bed to affect sleep duration, but the sleep manipulation protocol also controlled for sleep variability and fragmentation. Adherence to the sleep protocols was promoted by encouraging the adolescent participants to make the required changes to their sleep schedules by empowering them with tools (e.g. sleep hygiene counseling and goal setting), and daily support and reminders through SMS text messages. Total sleep time was used to compare sleep duration between each week of sleep. To remain in the study, participants needed to demonstrate that the average time-in-bed duration during their first intervention increased or decreased by at least 1 minute. If this was not achieved, their participation was terminated. If they passed their first intervention but failed the second, their data still remained in the analyses. As this was a within-participants study design, we wanted participants to demonstrate that they were trying to follow their sleep schedule and attempted to go to bed on time regardless of their success at actually increasing or decreasing their sleep duration.

Daytime non-wear-time of the actigraphy watch was captured by participants using the event marker button on the watch and noting the non-wear time interval in their sleep log. The watch was only removed for bathing, swimming, or participating in contact sports. For bedtime and wakeup times, participants also used the watch's event marker button and noted the times in their sleep log. Adherence to the sleep protocol was based on ± 10 minutes from the prescribed daily bedtime and wakeup time. The daily sleep log captured daily sleep satisfaction for each week of sleep, and daytime sleepiness was assessed using the Epworth Sleepiness Scale [39] administered in the laboratory after each week of sleep.

Assessment visits

Before blood collection.

After each week of sleep and an overnight fast (≥12 hours of fasting), the assessment visit commenced at 8:00 am. At the beginning of each assessment, the actigraphy watch and study logs were collected, downloaded, and verified for completeness and accuracy. Vital signs, resting blood pressure, resting heart rate, and pulse oximetry were measured twice, 1 minute apart, using an electronic vital signs monitor (Dinamap v100, GE Healthcare, USA), after a minimum period of 5 minutes of seated rest. Systolic and diastolic blood pressure percentile norms were obtained using mean blood pressure values, height percentile for age and sex, and exact age in months, as outlined in guidance from the National Institutes of Health [40]. After collecting vital signs, participants wearing shorts and a t-shirt without footwear and socks, were measured with our body composition scale (TBF-300A Total Body Composition Analyzer, Tanita Corporation, USA). After these measurements, the OGTT screening questionnaire was administered to confirm that participants were fasted overnight since 8:00 pm and not feeling ill, and then blood collection followed.

Blood collection.

After each week of sleep, SMART2D study participants underwent a 2-hour 75 g OGTT test with venous blood samples obtained through a catheter with saline lock. During each assessment visit, samples were obtained at baseline fasted, and four samples were obtained post-glucose consumption at 30, 60, 90, and 120 minutes for the analyses of serum glucose and serum insulin concentrations. At baseline, in addition to collecting blood samples for glucose and insulin analyses, we also collected additional blood to obtain total cholesterol, triglycerides, HDL-cholesterol, and HbA1c measurements for each week of sleep. The blood sample for glucose, total cholesterol, triglycerides, and HDL-cholesterol analyses was centrifuged immediately at 3000 rpm at 19°C for 10 minutes. The serum was stored at −80°C until assays were performed, no later than 3 weeks after collection. The blood sample for insulin analysis was clotted for 30 minutes at room temperature (19°C) before being centrifuged. Serum for the analysis of insulin was also stored at −80°C until assays were performed, no later than 4 months after collection. Frozen serum samples meant for the analysis of insulin were sent to the EORLA-The Ottawa General Hospital laboratory and were analyzed by electrochemiluminescence immunoassay on the Cobas e801 analyzer (Roche Diagnostics, Mannheim, Germany). All other blood samples were sent to the EORLA-CHEO laboratory. Total cholesterol, triglycerides, and HDL-cholesterol were measured using enzymatic colorimetric test while serum glucose was determined using an enzymatic reference method with hexokinase on an automated analyzer Cobras c501 module (Roche Diagnostic, Mannheim, Germany). A whole blood sample was collected and sent right away to the laboratory to determine HbA1c by capillary zone electrophoresis on the Sebia Capillarys 2 Flex Piercing Analyzer (Sebia, Lisses, France). All laboratory technicians were blinded.

Statistical analysis

It was calculated that a total sample size of 32 participants would provide 90% power at a 0.05 level of significance (two-sided) to detect a medium effect size, in a single group undertaking three measurements using repeated-measures ANOVA, within factors comparison, which in our estimation would represent 15% difference in IS. Therefore, it was decided that a total of 36 participants would be recruited, to account for ~10% of missing data. No interim analysis or stopping guidelines were applied for this study. Descriptive characteristics of our sample are presented as *n* and percentage for categorical variables, mean and standard deviation for normally distributed continuous variables, and median and range for continuous variables with skewed distribution. Data analyses were performed using SPSS statistical software (Version 29; SPSS Inc., Chicago, IL, USA). All variables were examined for normality using the Shapiro–Wilk test and the log was transformed when necessary. Repeated-measures ANOVA was conducted on total sleep time by sleep week to assess the success of the time-in-bed interventions. We also used repeated-measures ANOVA to investigate the effect of sleep week (three conditions: increased, habitual, and decreased) on our main outcomes, which consisted of measurements of IS, resistance, and secretion. If Mauchly's Sphericity Test was violated, Greenhouse-Geisser or Huynd-Feldt corrections were used to report the main effect of the model. Results are presented as means with standard deviation, 95% confidence interval, and *p*-values are reported and considered significant if the two-sided *p*-value was < 0.05. For significant main effects, Bonferroni post hoc pairwise comparisons method was used to determine the locus of the significant difference between the sleep weeks. Effect sizes are also reported as Cohen's *d* or partial eta-squared where appropriate, and characterized as small ($d = 0.2$ or $\eta^2_p = 0.01$), medium ($d = 0.5$ or $\eta^2_p = 0.06$), or large ($d = 0.8$ or $\eta^2_p = 0.14$) [41]. Variation of the effect was analyzed using linear mixed model

analysis for the order of the manipulations (to exclude the possibility of order or carryover effects), biological sex, pubertal maturation, socioeconomic status, recruitment priority, testing session occurring pre- or during the COVID-19 pandemic, and age.

Results

Recruitment

See Figure 1 for the CONSORT flow diagram which contains more details concerning our recruitment processes. Participants were prospectively enrolled until 36 completed both intervention weeks. Forty-three adolescents completed the habitual sleep week and assessment and were randomized into the increased ($n = 23$) or decreased ($n = 20$) sleep week as their first intervention. Of the 43 participants, seven withdrew: four failed or did not attempt to do the first sleep intervention ($n = 2$ increased and $n = 2$ decreased), where failure to modify time-in-bed on the first intervention led to the termination of participation; two were flagged for severe mental health concerns and were referred for immediate help and did not do any intervention to prevent further harm; and one experienced a death in the family and it was decided that withdrawing from the study was the best course of action. Three of the participants who failed to increase or decrease their time-in-bed reported doing so because they felt coerced to participate in the study by a parent and the fourth participant reported having serious gaming addiction and did not want to continue in the study.

Descriptive characteristics

Descriptive characteristics of the SMART2D study participants are summarized in Table 1. The seven participants who dropped out of the study were females ($n = 7$ self-identified as girls, $n = 3$ were non-Caucasian, mean age = 14.9 years, mean BMI percentile = 99.9, and mean pubertal score = 3.3). Out of the seven dropouts, $n = 3$ had dyslipidemia, $n = 3$ had a diagnosis of PCOS and/or NAFLD, and $n = 1$ had only a BMI greater than the 99th percentile for age and sex. Five out of the seven had a first-degree relative with a related chronic disease. Family income of the dropouts was as follows: $n = 2$ were from medium to medium-high income, $n = 3$ were from low to medium income, and $n = 2$ were from very low to low income. Dropouts were nonsmokers, they did not engage in recreational drugs, and they did not consume alcohol.

Sleep measurements

Results for the total sleep time are shown in Figure 3 and other sleep measurement results can be found in Supplementary Table S3. The effect of the time-in-bed manipulations on total sleep time resulted in significant differences between all sleep weeks with a large effect size $F(2,70) = 441.7$, $p < 0.001$, $\eta^2_p = 0.93$. Total sleep time increased on average by 1 hour 02 min/night during the increased sleep week and decreased by 1 hour 19 min/night during the decreased sleep week, compared to the mean total sleep time of 7 hours 31 min/night during the habitual sleep week. The time-in-bed manipulations protocol resulted in a mean total sleep time difference between the increased and decreased sleep weeks of 2 hours 21 min/night.

Main outcome measurements

The main outcome measurement results can be found in Figure 4 and Table 2. One participant was excluded from the main outcome result due to missing data. When significant, variation of the effect is reported. No significant order or carryover effects were found for any of our outcome measurements. Since age and pubertal maturation were highly correlated in our sample, $r(34) = 0.81$ $p < 0.001$, where the variation of the effect by age and pubertal maturation were significant, only pubertal maturation is reported.

We found a significant main effect of sleep week on Matsuda index (see Figure 4 and Table 2). IS, according to the Matsuda index, was significantly improved following the increased sleep week on average by 20.2% and 21.2% compared to values following habitual ($p < 0.001$) and decreased ($p < 0.001$) sleep weeks, respectively. The IS percentage, obtained from the computerized HOMA2 model using only fasting glucose and insulin levels, also revealed a significant main effect of sleep week, similar to the Matsuda index findings. IS percentage was significantly higher following the increased sleep week compared to the other 2 weeks of sleep; average IS was lower by 7.3% after the habitual sleep week and by 9.9% after the decreased sleep week (both $p < 0.001$). Findings pertaining to the estimation of insulin secretion using HOMA2 **β**-cell function percentage also showed a significant sleep week main effect; the percentage following the increased sleep week was lower (175.5%) than the percentages following the other 2 weeks of sleep, by 22.2% ($p = 0.003$) for the habitual week and 25.9% ($p = 0.002$) for the decreased sleep week. Additionally, SPISE index was significantly higher following the increased sleep week compared to the other 2 weeks of sleep. Lower SPISE index values are associated with greater risk of impaired glucose regulation. No significant differences were found between results obtained following the habitual and decreased sleep weeks across all of our main outcome measurements.

Similar trends were observed for the measurements used as indicators of hepatic insulin resistance where sleep week significantly impacted insulin resistance measured using HOMA, HOMA2, and QUICKI (see Table 2); however, both HOMA and HOMA2 also displayed significant variation of the effect in relation to pubertal maturity. More specifically, those in the earlier pubertal maturity stages 2 and 3 ($n = 18$) had significantly lower insulin resistance following the increased sleep week compared to the 2 other weeks of sleep while those in the later pubertal maturity stages 4 and 5 ($n = 18$) had significantly lower insulin resistance following the increased sleep week compared to only the value following the habitual sleep week. Post hoc analyses showed that those in the early pubertal maturity stages had significantly higher HOMA values following the decreased sleep week compared to those in the late pubertal maturity stages group; no other significant between-groups comparisons were found for HOMA or HOMA2. A low value on the QUICKI index indicates a trend towards insulin resistance, and our results showed that QUICKI index values were significantly lower following the habitual and decreased sleep weeks compared to the increased sleep week (both $p < 0.001$).

Early and late peak phase glucose AUCs and total glucose AUC all showed significant but more modest main effects of sleep week (see Table 2). The early phase glucose AUC was significantly smaller following the increased sleep week compared to the value following the decreased sleep week ($p < 0.003$), but not compared to habitual sleep week ($p > 0.05$). For the late peak phase glucose AUC, the AUC was significantly smaller following the increased sleep week (233.3 mmol/L*min) compared to the values associated with the habitual (6.4% higher $p = 0.034$) and decreased (6.8% higher $p = 0.012$) sleep weeks. The results for the total glucose AUC only showed a significantly smaller AUC following the increased sleep week compared with the total AUC following the habitual sleep week ($p = 0.049$). However,

Table 1. Descriptive Characteristics of SMART2D Study Participants by Full Sample, Order of Intervention, and Final Sample

Characteristics	Full sample *n* = 43	Order 1 *n* = 18	Order 2 *n* = 18	Final sample *n* = 36
Age in years	15.1 (1.3)	15.4 (1.5)	14.8 (1.1)	15.1 (1.3)
Self-reported sex n (%)				
female	26 (60.5)	9 (50)	10 (55.6)	19 (52.8)
male	17 (39.5)	9 (50)	8 (44.4)	17 (47.2)
Self-identification gender identity n (%)				
Girl	25(58.1)	8 (44.4)	10 (55.6)	18 (50.0)
Boy	16 (37.2)	9 (50)	7 (38.9)	16 (44.4)
Non-binary or genderqueer	2 (4.7)	1 (5.6)	1 (5.6)	2 (5.6)
Self-identification race and ethnicity n (%)				
Aboriginal (First Nations, Métis, or Inuk)	2 (4.7)	1 (5.6)	1 (5.6)	2 (5.6)
Asian or Asian Indian	4 (9.3)	2 (11.1)	2 (11.1)	4 (11.1)
Black people, African descent, or Caribbean	5 (11.6)	2 (11.1)	2 (11.1)	4 (11.1)
Caucasian or White people	24 (55.8)	10 (55.6)	10 (55.6)	20 (55.6)
Middle Eastern or North African	6 (13.9)	3 (16.7)	2 (11.1)	5 (13.9)
Hispanic, Latino, Spanish, South America	2 (4.7)	0 (0)	1 (5.6)	1 (2.8)
Proxy-socioeconomic status n (%)				
Very-low to low	12 (27.9)	6 (33.3)	4 (22.2)	10 (27.8)
Low to medium	17 (39.5)	8 (44.4)	6 (33.3)	14 (38.9)
Medium to medium–high	14 (32.6)	4 (22.2)	8 (44.4)	12 (33.3)
Self-reported pubertal maturity stage				
Female	3.2 (2–5)	3.4 (2–5)	2.9 (2–5)	3.2 (2–5)
Male	3.5 (2–5)	3.4 (2–5)	3.6 (2–5)	3.5 (2–5)
Family history of chronic condition/disease n (%)				
No	11 (25.6)	4 (22.2)	5 (27.8)	9 (25.0)
Yes	32 (74.4)	14 (77.8)	13 (72.2)	27 (75.0)
Self-reported smoking, vaping, or chewing tabacco *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Self-reported alcohol consumption n (%)				
Never	41 (95.4)	16 (88.9)	18 (100)	34 (94.4)
1 drink per month	1 (2.3)	1 (5.6)	0 (0)	1 (2.8)
2 drinks per month	1 (2.3)	1 (5.6)	0 (0)	1 (2.8)
Lifetime recreational drug use n (%)				
Never	40 (93.0)	17 (94.4)	16 (88.9)	33 (91.7)
1–2 times	2 (4.7)	0 (0)	2 (11.1)	2 (5.6)
10–19 times	1 (2.3)	1 (5.6)	0 (0)	1 (2.8)
Recruitment priority n (%)				
Priority 1	23 (53.5)	13 (72.2)	7 (38.9)	20 (55.6)
Priority 2	15 (34.9)	2 (11.1)	10 (55.6)	12 (33.3)
Priority 3	5 (11.6)	3 (16.7)	1 (5.6)	4 (11.1)
Stature in cm	166.9 (8.6)	167.8 (9.9)	166.8 (7.6)	167.3 (8.7)
Weight in kg	111.0 (16.6)	117.7 (18.4)	105.1 (12.1)	111.4 (16.6)
Resting heart rate in bpm	77.5 (9.1)	77.9 (9.4)	77.3 (9.7)	77.6 (9.4)
Systolic blood pressure in mmHg	116.9 (9.8)	117.9 (9.2)	114.5 (10.9)	116.2 (10.1)
Diastolic blood pressure in mmHg	65.9 (8.1)	66.6 (8.2)	65.3 (6.6)	65.9 (7.4)
Blood pressure normative interpretation n (%)				
Normal	26 (60.5)	10 (55.6)	12 (66.7)	22 (61.1)
Elevated	12 (27.9)	6 (33.3)	4 (22.2)	10 (27.8)
Stage 1 hypertension	5 (11.6)	2 (11.1)	2 (11.1)	4 (11.1)

Table 1. Continued

Characteristics	Full sample *n* = 43	Order 1 *n* = 18	Order 2 *n* = 18	Final sample *n* = 36
BMI in kg/m^2	39.8 (4.9)	41.8 (5.9)	37.7 (3.1)	39.8 (5.1)
BMI z-score	3.77 (0.7)	4.01 (0.8)	3.45 (0.4)	3.73 (0.7)
BMI percentile	99.94 (0.06)	99.96 (0.04)	99.92 (0.08)	99.94 (0.07)
Fat mass percentage	47.6 (6.1) *n* = 42	48.3 (8.0) *n* = 17	46.9 (4.4) *n* = 18	47.6 (6.3) *n* = 35
Basal metabolic rate in kcal/day	2189.1 (429.3) *n* = 42	2257.3 (454.2) *n* = 17	2134.8 (413.8) *n* = 18	2194.3 (431.9) *n* = 35
PSQI score	6.2 (2.4)	5.9 (2.3)	6.1 (2.4)	6.0 (2.3)
Sleep difficulty *n* (%)	33 (76.7)	13 (72.2)	15 (83.3)	28 (77.8)
Epworth Sleepiness Scale	8.2 (4.1)	8.1 (4.0)	8.1 (4.0)	8.1 (4.0)
Excessive amount of daytime sleepiness *n* (%)	13 (30.2)	6 (33.3)	5 (27.8)	11 (31.4)
Three-factor eating scores				
Percentage for cognitive restraint	30.9 (8.9)	32.9 (9.1)	29.6 (9.4)	31.3 (9.3)
Percentage for emotional eating	30.1 (22.6)	28.2 (24.3)	32.4 (21.6)	30.3 (22.7)
Percentage for uncontrolled eating	33.2 (15.8)	31.8 (15.0)	34.6 (17.9)	33.2 (16.4)
Pediatric Quality of Life Inventory	71.8 (10.7)	71.3 (12.2)	73.3 (10.3)	72.3 (11.2)
Self-reported health quality n (%)				
Poor	6 (14.0)	1 (5.6)	3 (16.7)	4 (11.1)
Average	17 (39.5)	9 (50)	6 (33.3)	15 (41.7)
Good	18 (41.8)	7 (38.9)	8 (44.4)	15 (41.7)
Excellent	2 (4.7)	1 (5.6)	1 (5.6)	2 (5.6)
Self-reported amount of MVPA min/day	19.5 (0-60)	20.0 (0-60)	20.6 (0-40)	20.3 (0-60)
Meeting daily physical activity guideline *n* (%)	1 (2.3)	1 (5.6)	0 (0)	1 (2.8)
Self-reported amount of screen time on a week day min/day	176.0 (77.5)	177.5 (91.4)	175.4 (65.1)	176.4 (78.2)
Self-reported amount of screen time on a weekend day min/day	213.6 (142.2)	244.3 (199.9)	179.9 (59.3)	211.9 (148.9)
Meeting daily screen time guideline on a week day *n* (%)	6 (14.0)	3 (16.7)	3 (16.7)	6 (16.7)
Meeting daily screen time guideline on a weekend day *n* (%)	8 (18.6)	4 (22.2)	3 (16.7)	7 (19.4)
Tested when in relation to COVID-19 pandemic n (%)				
Prior	22 (51.2)	12 (66.7)	8 (44.4)	20 (55.6)
During	21 (48.8)	6 (33.3)	10 (55.6)	16 (44.4)

Data are mean or median with standard deviation or range in bracket, unless otherwise indicated. Order 1 represents HBINDE and order 2 is HBDEIN, which represents the order of the interventions; both orders started with a week of habitual sleep (HB), followed by either the increased (IN) or decreased (DE) sleep week and completing the alternate intervention after a week of washout sleep. The full sample size is 43 participants and the final sample size is 36 participants or 18 for each intervention order, unless otherwise indicated. For family history of chronic condition/disease, "no" represents no history among first degree relatives, while "yes" represents one or both parent(s) reporting having one or more related chronic condition(s)/disease(s). For self-reported alcohol consumption and lifetime recreational drug use, only categories with responses were reported. Recruitment priorities were defined as follows: "priority 1," having obesity (BMI percentile > 97th) and dyslipidemia; "priority 2," having obesity (BMI percentile > 97th) and nonalcoholic fatty liver disease and/or polycystic ovary syndrome; and "priority 3," having severe obesity (BMI percentile > 99th). Blood pressure normative interpretation according to the American Academy of Pediatrics Clinical Practice Guidelines based on sex, age, and height. Sleeping difficulty was determined by a score ≥5 on the PSQI. Excessive amount of daytime sleepiness was determined by a score >10 on the Epworth Sleepiness Scale. Those who self-reported engaging in at least 60 minutes of MVPA per day met the physical activity guideline as per the Canadian 24-Hour Movement Guidelines for Youth. Those who self-reported engaging in no more than 2 hours of recreational screen time per day during both week and weekend days met the screen time portion of the sedentary behavior guideline as per the Canadian 24-Hour Movement Guidelines for Youth.
Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; PSQI, Pittsburgh Sleep Quality Index; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes.

when dichotomizing the shape of the glucose curves as being biphasic, generally considered to be the shape that represents healthy processing of glucose, versus non-biphasic curves, we found that there was a statistically significant effect of sleep week on the proportion of biphasic glucose curves. Post hoc analyses revealed a significant increase in the proportion of participants who displayed a biphasic glucose curve after the increased sleep week; 40.0% (representing 10 additional participants) compared to 11.4% following both the habitual and decreased sleep weeks.

We also analyzed the AUC for the insulin for the early and late peak phases, as well as total insulin. Findings showed a significant and modest main effect of sleep week on the AUC for the insulin during the early peak phase and total insulin AUC but no significant main effect of sleep week on the AUC for the insulin during the late peak phase (Table 2). The early peak phase insulin AUC was only significantly smaller following the increased sleep week compared to the value obtained following the decreased sleep week ($p = 0.041$). For the total insulin AUC, the value following the increased sleep week was significantly

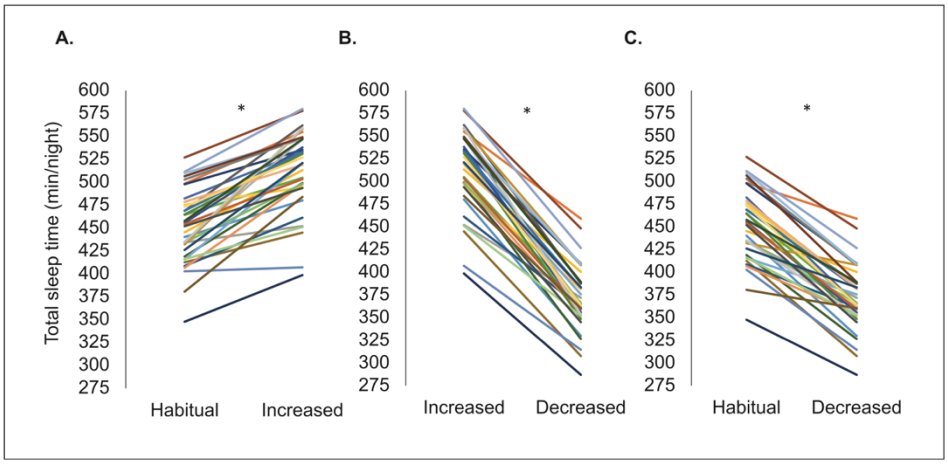


Figure 3. SMART2D study: effect of increasing time-in-bed by 1.5 h/night for one week, compared to a week of habitual sleep duration and a week of decreasing time-in-bed by 1.5 h/night, on total sleep time in adolescents at risk of type 2 diabetes (n = 36). (A) Average total sleep duration in min/night during the habitual and increased sleep weeks for each participant; (B) Average total sleep duration in min/night during the increased and decreased sleep weeks for each participant; and (C) Average total sleep duration in min/night during the habitual and decreased sleep weeks for each participant. *All conditions are significantly different from one another $p < 0.001$ based on post hoc test following a significant main effect, tested using repeated-measures ANOVA, of sleep per week on the average total sleep duration in minutes per night.

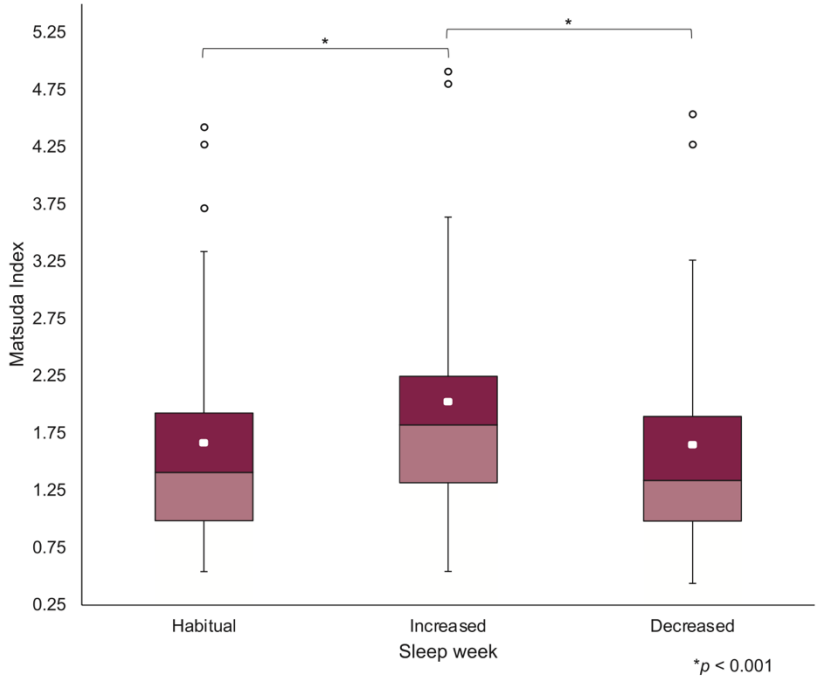


Figure 4. Box and whisker plots of the Matsuda Index, primary outcome, for each week of sleep during the SMART2D study. For each box and whisker plot, the mean is represented by the small white rectangle, the middle horizontal line represents the median, the bottom less opaque rectangle is the lower quartile, the top more opaque rectangle is the upper quartile, and the whiskers at the bottom represents the minimum values, the whiskers at the top represent 1.5 times the interquartile range, and the small transparent circles represent the outliers.*The Matsuda Index obtained following the increased sleep week is significantly higher (improved), $p < 0.001$, compared to the values obtained following the other 2 sleep weeks.

Table 2. SMART2D Study Results: Effect of Increasing Time-in-bed by 1.5 Hour/Night for One Week, Compared to a Week of Decreasing Time-in-bed by 1.5 Hour/Night and a Week of Habitual Sleep, on Fasting Blood Profile and Insulin Sensitivity/Resistance Measurements in Adolescents at Risk of Type 2 Diabetes ($n = 36$)

	Sleep week			*Main effect* and *df*	P-value	Effect size (*d* or η^2p)
	Habitual	Increased	Decreased			
Fasting blood profile						
HbA1c (%)	5.42 (0.25) [5.33, 5.51]	5.39 (0.29) [5.29, 5.48]	5.39 (0.28) [5.30, 5.49]	0.72 (2,70)	0.49	0.02
HbA1c (mmol/mol)	35.8 (2.9) [34.9, 36.8]	35.4 (3.3) [34.3, 36.5]	35.4 (3.3) [34.3, 36.5]	1.01 (2,70)	0.37	0.03
HDL (mmol/L)	1.12 (0.27) [1.01, 1.20]	1.08 (0.27) [0.99, 1.17]	1.08 (0.27) [0.99, 1.17]	1.53 (2,70)	0.22	0.04
Triglycerides (mmol/L)	1.48 (0.59)* [1.28, 1.68]	1.23 (0.57) [1.04, 1.42]	1.49 (0.6)* [1.23, 1.97]	11.4 (2,70)	0.001	0.25
Triglycerides to HDL ratio	1.47 (0.84)* [1,18, 1.75]	1.26 (0.81) [0.99, 1.54]	1.49 (0.79)* [1.22, 1.76]	5.9 (2,70)	0.004	0.14
Total cholesterol (mmol/L)	4.22 (0.72)† [3.97, 4.46]	3.99 (0.73) [3.75, 4.24]	4.11(0.86) [3.82, 4.40]	4.3 (HF:1.7,60.0)	0.02	0.11
Fasting glucose (mmol/L)	5.34 (0.32) [5.23, 5.45]	5.27 (0.36) [5.15, 5.39]	5.41 (0.40)‡ [5.27, 5.54]	4.7 (2,70)	0.01	0.12
Fasting insulin (pmol/L)	195.8 (91.3)§ [164.9, 226.6]	158.1 (77.2) [132.0, 184.3]	219.1 (118.3)§ [179.1, 259.2]	17.3 (GG:1.6,54.8)	0.001	0.33
Outcome measurements						
Matsuda Index $n = 35$	1.62 (0.97)§ [1.28, 1.95]	2.03 (1.06) [1.66, 2.39]	1.60 (0.99)§ [1.26, 1.94]	16.1 (2,68)	0.001	0.32
HOMA	6.56 (3.09)§ [5.51, 7.60]	5.10 (2.55) [4.24, 5.96]	7.60 (4.36)§ [6.12, 9.07]	15.3 (GG:1.5,52.4)	0.001	0.30
HOMA2	3.56 (1.53)§ [3.04, 4.08]	2.84 (1.28) [2.41, 3.27]	3.82 (1.77)§ [3.22, 4.42]	20.7 (2,70)	0.001	0.37
HOMA2 β-cell function (%)	197.7 (62.5)‖ [176.5, 218.8]	175.5 (59.7) [155.3, 195.7]	201.4 (62.7)‖ [180.2, 222.6]	10.0 (2,70)	0.001	0.22
HOMA2 sensitivity (%)	35.4 (20.7)§ [28.4, 42.5]	42.7 (20.8) [35.7, 49.8]	32.8 (17.6)§ [26.9, 38.8]	21.6 (2,70)	0.001	0.38
QUICKI	0.339 (0.027)§ [0.330, 0.348]	0.350 (0.026) [0.341, 0.359]	0.333 (0.024)§ [0.325, 0.341]	23.4 (2,70)	0.001	0.40
SPISE	3.43 (0.73) § [3.18, 3.67]	3.54 (0.77) [3.28, 3.80]	3.40 (0.71) § [3.16, 3.64]	11.6 (2,70)	0.001	0.25
Early peak phase glucose AUC (mmol/L*min)	206.8 (22.8) [199.1, 214.5]	198.9 (21.1) [191.7, 206.0]	209.3 (22.7)¶ [201.6, 217.0]	6.4 (2,70)	0.003	0.16
Late peak phase glucose AUC (mmol/L*min)	249.3 (43.6)* [234.5, 264.0]	233.3 (38.4) [220.3, 246.3]	250.4 (45.3)* [235.0, 265.7]	6.0 (2,70)	0.004	0.15
Total glucose AUC $n = 35$ (mmol/L*min)	899.5 (153.7)# [846.7, 952.3]	849.1 (133.6) [803.3, 895.0]	890.2 (156.1) [836.6, 943.8]	4.0 (2,68)	0.022	0.11
Early peak phase insulin AUC (pmol/L*min)	25892.9 (1380.2) [21216.8, 30569.0]	22639.2 (12817.7) [18302.3, 26976.0]	25923.8 (14767.9)‡ [20927.0, 30920.5]	3.3 (2,70)	0.048	0.09
Late peak phase insulin AUC (pmol/L*min)	47126.7 (27222.6) [37915.9, 56337.5]	40707.5 (26300.4) [31808.7, 49606.3]	46347(26665.8) [37324.7, 55369.5]	3.2 (HF:1.6,55.9)	0.058	0.09
Total insulin AUC $n = 35$ (pmol/L*min)	164802.4 (103258.4)* [129331.9, 200272.9]	136431.9 (96506.1) [103280.9, 169582.9]	158271.4 (104227.1)* [122468.2, 194074.7]	3.8 (GG:1.4,46.5)	0.045	0.10
Biphasic glucose curve $n = 35$ (%)	11.4§	40.0 OR: 5.2 [1.5, 17.8]	11.4§	14.3 (2)	0.01	0.39

Data are means with standard deviation in brackets and 95% CI lower and upper limits in the square brackets. Main effect for most analyses are from repeated-measures ANOVA, *F*-value with degrees of freedom in brackets, *p*-value and effect size as partial eta-squared are presented. Main effect for the proportion of participants who displayed a biphasic glucose curve was obtained using Friedsman's test and post hoc analysis was conducted using Wilcoxon signed-rank test with Bonferroni correction.

*Habitual and decreased sleep weeks are significantly different from the increased sleep week $p < 0.05$.
†Habitual sleep week is significantly different from increased sleep week $p = 0.001$.
‡Decreased sleep week is significantly different from increased sleep week $p < 0.05$.
§Habitual and decreased sleep weeks are significantly different from increased sleep week $p < 0.001$.
‖Habitual and decreased sleep weeks are significantly different from increased sleep week $p < 0.01$.
¶Decreased sleep week is significantly different from increased sleep week $p = 0.003$.
#Habitual sleep week is significantly different from increased sleep week $p < 0.05$.

Abbreviations: AUC, area under the curve; df, degrees of freedom; GG, Greenhouse-Geisser correction; HDL, high-density lipoprotein; HF, Huynh-Feldt correction; HOMA, Homeostasis Model Assessment; HOMA2, computerized Homeostasis Model Assessment, OR, odds ratio; NA, not applicable; QUICKI, Quantitative Insulin Sensitivity Check Index; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; SPISE, single-point insulin sensitivity estimator.

smaller than the values obtained following the 2 other sleep weeks (habitual: $p = 0.010$ and decreased: $p = 0.048$).

We found no significant main effect of sleep week on HbA1c or HDL. A significant main effect of sleep week was found for triglycerides. Specifically, following the increased sleep week, average triglycerides were significantly lower by 16.9% ($p < 0.001$) and 18.0% ($p = 0.001$) compared to the averages following the habitual and decreased sleep weeks, respectively. Similarly, triglycerides to HDL ratio was significantly lower following increased sleep week by 14.3% ($p = 0.03$) and 15.4% ($p = 0.007$) compared to the average ratio following the habitual and decreased sleep weeks, respectively. Total cholesterol was also found to be significantly affected by sleep week, but only total cholesterol following the increased sleep week was significantly lower by an average of 0.23 mmol/L ($p = 0.001$) than the value following the habitual sleep week.

A significant interaction between sleep week and pubertal maturation was found for fasting glucose $F(2,70) = 4.7$, $p = 0.013$, $\eta^2_p = 0.12$; the post hoc analysis revealed that those in the pubertal maturation stages 2 and 3 ($n = 18$) had significantly higher fasting glucose following the decreased sleep week (5.51[95% CI: 5.33 to 5.69] mmol/L) compared to the habitual and increased sleep weeks (5.33[95% CI: 5.18 to 5.48] mmol/L, $p = 0.018$ and 5.27 [95% CI: 5.10 to 5.44] mmol/L, $p = 0.002$, respectively) but no significant differences in fasting glucose between sleep weeks were found for those in pubertal maturation stages 4 and 5 ($n = 18$, $p > 0.4$). Fasting insulin analysis also exposed a significant interaction effect between sleep week and pubertal maturation, corrected by Huynh-Feldt $F(1.74,59.3) = 4.39$, $p = 0.021$, $\eta^2_p = 0.11$. Those in pubertal maturation stages 2 and 3 had significant differences in fasting insulin levels between all sleep weeks, with the fasting insulin following the increased sleep week significantly lower (176.0 [95% CI: 140.6 to 211.4] pmol/L) compared to the fasting insulin values following the habitual (224.3 [95% CI: 183.6 to 264.9] pmol/L, $p < 0.027$) and decreased sleep weeks (264.8 [95% CI: 213.8 to 315.8] pmol/L, $p < 0.001$). Also, further interaction investigations revealed that those in the early pubertal maturation stages 2 and 3 ($n = 18$), compared to those in the late maturation stages 4 and 5 ($n = 18$), had significantly higher fasting insulin levels following the habitual (stage 4 and 5 163.8 [95% CI: 120.8 to 206.8] pmol/L) and decreased (stage 4 and 5 168.1 [95% CI: 114.2 to 222.0] pmol/L) sleep weeks ($p < 0.05$), but no significant differences were found for the fasting insulin values between pubertal maturation groups following the increased sleep week (stage 4 and 5 138.2 [95% CI: 100.8 to 175.6] pmol/L). Based on the total cholesterol and HbA1c results two participants were flagged for incidental findings (harm), these results were reported to the participants, their parents (with participants' permission), and our pediatric endocrinologist. However, their results remained in our analyses.

Discussion

The SMART2D study investigated the effects of manipulating sleep duration, by increasing and decreasing time-in-bed by 1.5 h/night for 1 week, based on a week of habitual sleep, on IS in adolescents who displayed risk factors for type 2 diabetes. Adolescent participants were highly adherent (>80%, see Supplementary Table S3 for more details) to their prescribed sleep schedule. The key finding indicates that, in this high-risk population of adolescents, even a small average increase in sleep duration of 1 hour 02min/night for a single week resulted in significant improvements in IS, while decreasing sleep duration on average by 1 hour 19 min/night during the decreased sleep week had no impact on IS/resistance.

Additionally, following the increased sleep week, there was a higher proportion of participants (an additional 28.6%) who displayed a biphasic glucose curve indicative of better insulin secretion and greater sensitivity. Improvement in insulin resistance, based on fasting values, due to increased sleep duration was even more prominent in the participants who were less physically mature.

Descriptive characteristics

The adolescent participants displayed many known risk factors for type 2 diabetes. These included having severe obesity [17, 42], being of pubertal age (mean age = 15.1 years) [42], coming from very-low to low-income families (27.8%) [43], identified as non-Caucasian and being from ethnoracial backgrounds that are at higher risk for type 2 diabetes (44.4%) [17, 42, 44], presented with dyslipidemia, polycystic ovary syndrome and/or nonalcoholic fatty liver disease syndrome (88.9%) [17, 45–47], had a first degree relative with a related chronic disease diagnosis or condition (75%), presented with resting blood pressure that is considered elevated to stage 1 hypertension (38.9%) [17, 48] and were hypoactive (97.2%). These modifiable and non-modifiable risk factors for youth onset type 2 diabetes have been well documented in the literature and continuing to raise awareness seems sensible considering that the rates of diagnosis continue to increase.

Sleep results

The prescribed 3-hour difference in time-in-bed between the two sleep manipulation weeks resulted in an average nightly sleep duration difference of 2 hours 21 minutes as assessed by actigraphy, indicating that the time-in-bed manipulation protocol was successful at changing nightly sleep duration in our sample of adolescents at risk of type 2 diabetes. This nightly sleep duration gap between our two sleep manipulation weeks is similar to the results obtained by Hart et al. in apparently healthy children ages 8 to 11 years old [28]. Additionally, the significant decrease in night-to-night sleep duration variability during the two sleep manipulation weeks, compared to the habitual sleep week, coupled with the high adherence to the sleep schedule for bedtime and wake-up time are further evidence demonstrating that participants were making an effort to follow their prescribed sleep schedule. These sleep results reinforce the feasibility of this type of sleep intervention in adolescents at risk of type 2 diabetes.

Fasting blood results

Total cholesterol was only significantly higher following the habitual sleep week by 5.5% on average compared to following the increased sleep week. Increasing sleep by 1 h/night for 1 week improved triglycerides on average by 16.9% and 23.1% compared to the values obtained following the habitual and decreased sleep weeks, respectively. A large cross-sectional study reported that higher levels of triglycerides were associated with elevated sleep disorder and moderately correlated with HOMA in U.S. adults [49]. However, a cross-sectional study conducted in children and adolescents ($n = 133$, 13.2 years mean age, 66% female) found the reverse association where short sleep duration was associated with lower triglycerides and higher HDL-cholesterol levels [50]. We found no significant relationship between sleep week and HDL or HbA1C.

Less physically mature participants displayed an elevated metabolic reaction to lack of sleep; specifically, fasting glucose level in this group was significantly higher following the week of decreased sleep compared to the 2 other weeks of sleep. In more physically mature participants, no significant differences were

found. Additionally, for the fasting insulin results, those in the early maturation stages showed significantly higher insulin levels following the habitual and decreased sleep weeks, compared to the increased sleep week, but not those who were more physically mature. Glucose homeostasis can be maintained by β-cell compensatory insulin secretion especially needed when IS decreases. While this may not be so evident in our fasting results, despite changes in sleep duration, fasting glucose values remained within normal ranges for all conditions, which could suggest that higher insulin secretion compensated for lower IS following the habitual and decreased sleep weeks. This result was more pronounced in those who were in the earlier stages of puberty. More research should be done to understand the role of physical maturation on the risk of type 2 diabetes in adolescents.

Main outcomes

The main outcome for this study was IS measured using the Matsuda index. IS was significantly improved by approximately 20% following the increased sleep week compared with the values obtained following the habitual and decreased sleep weeks, with a large effect size. Additionally, when looking at the shape of the glucose curve during the 2-hour glucose challenge period, increasing sleep duration improved the shape of the glucose curve in 10 participants who did not display a biphasic glucose curve following the other weeks of sleep. These results are novel and collectively indicate that increasing sleep duration in adolescents at risk of type 2 diabetes had a positive effect on both β-cell function and IS during a glucose challenge, compared to the measurements obtained following the habitual and decreased sleep weeks. However, the mechanism for this change remains unknown.

There are several possible pathways that could explain the positive effect that increasing sleep had on IS in our sample of adolescents at risk of type 2 diabetes. Briefly, the suppression of sympathetic nervous system (SNS) activity and/or of the hypothalamic-pituitary-adrenal (HPA) axis drive are likely contributors [1]. The SNS is known to play a role in the level of circulating insulin, glucagon, and leptin; it regulates peripheral insulin resistance and adipocyte function. The HPA axis drive regulates the multifaceted neuroendocrine response to a stressor and can be inferred by measuring cortisol and growth hormone levels throughout the day or looking at inflammatory markers. Our lower triglycerides results following the increased sleep week, compared to the other weeks of sleep, could indeed point towards the suppression of the SNS activity output [51]. To confirm this theory, in addition to measuring triglycerides, measurements of white and brown adipose tissues could provide further insights [51]. However, we cannot rule out a decrease in HPA axis drive, as we did not measure any of the typical associated markers. Measuring HPA axis drive markers, properly, would have added significant impacts on our participants and was ruled out early in the planning process of the present study.

Of note, we found no significant differences between habitual sleep and decreased sleep weeks across all of our main outcomes. A recent systematic review and meta-analysis reported that IS, measured by Matsuda index ($n = 7$ studies, mean age ranging from 16.8 to 26 years old, with a total sample size of 108, with interventions ranging from 1 to 5 nights of sleep restrictions), was significantly lower following sleep restriction [52]. However, these sleep restriction studies were not conducted in populations with severe obesity or already presenting with risk factors for type 2 diabetes. In a population already at risk of type 2 diabetes and lacking sleep, it is possible that decreasing sleep further did not create additional metabolic stress. A recent large cross-sectional study ($n = 4101$, mean age = 53.0 years, 24.2% female) reported that adults with prediabetes ($n = 862$) had elevated serum C-reactive protein (CRP) compared to adults with normal glucose tolerance [53]. However, that study did not control for sleep. Another recent cross-sectional study conducted in adults ($n = 60$ prediabetes, mean age = 41.0 years, 46.7% female) with and without prediabetes, reported that CRP levels were significantly higher in people with prediabetes and sleep disturbance predicted CRP levels [54]. In future studies, to better understand mechanisms between sleep and glucose homeostasis in a population at risk of type 2 diabetes, we would recommend measuring CRP. Additionally, we cannot discount that during the decreased sleep week, while sleep duration decreased on average by approximately 80 min/night, other sleep characteristics did improve; for instance, there was no sleep fragmentation, lower nightly sleep variability, and improvement in certain aspects of sleep efficiency. Improvement in these other sleep characteristics during the decreased sleep week may have counterbalanced a sleep curtailment effect on insulin resistance.

Variation of the effect based on physical maturity was found for some of the calculations that utilized fasting glucose and insulin values, namely HOMA and HOMA2 but not QUICKI. QUICKI values were significantly lower following the habitual and decreased sleep weeks compared to the increased sleep week; these results revealed that the average QUICKI following the habitual and decreased sleep weeks are indicative of insulin resistance but not the average results following the week of increased sleep [24]. Not many studies have investigated the role of pubertal changes on IS. A longitudinal study conducted with overweight Hispanic youth ($n = 253$, mean age = 11.1 years at baseline, 43.5% female) revealed that compensatory changes in insulin secretion failed after Tanner stage 3 [55]. Our IS results, based on the 2-hour oral-glucose challenge, are more or less in line with the results from this longitudinal study, as we found no variation of effect for sex or physical maturation. Based on our results, relying solely on fasting insulin and glucose measurements may lead to erroneous conclusions and an incomplete picture of glucose homeostasis in this population; thus, whenever possible, a glucose challenge should be used in adolescents presenting with risk factors for type 2 diabetes.

By manipulating sleep duration, we anticipated that we would impact other daily behaviors that might have an effect on IS, namely energy balance. In terms of energy intake, we found no significant difference in the total amount of calories (average of 1950 kcal/day) or proportions of macronutrients (carbohydrates 46%, proteins 18%, and fats 36%) consumed between our weeks of sleep (data not shown). This is contrary to a recent study by Morrison and colleagues and the study by Hart and colleagues who conducted randomized crossover studies to manipulate sleep duration in apparently healthy children [28, 56]. Morrison et al. increased and decreased children's ($n = 59$, mean age = 10.3 years, 52% female) time-in-bed by 1 h/night for 1 week, which resulted in a total sleep time difference between the two sleep manipulation weeks of 59.5 min and found that total energy intake, carbohydrates, and total sugar consumption were significantly ($p < 0.05$) lower during the increased sleep week, compared to the decreased sleep week, by 86.3 kcal/day, 14g/day, and 7g/day, respectively [56]. Hart et al. results revealed that during the increased sleep week apparently healthy children ($n = 37$, mean age = 9.6 years, 43% female) reported consuming significantly less calories, compared to the decreased sleep week, by 134 kcal/

day; however, similar to our findings, found no significant difference in macronutrient consumption [28]. In our experience, our adolescents had very little control over most meal preparation or mealtime portions and, in future studies, it may be more pertinent to focus on snacks and beverage consumption, a segment of the energy intake that a population of adolescents has more control over.

As for the other side of the energy balance equation, the energy output, we found that energy output per hour of wakefulness was higher during the increased sleep week compared to the habitual sleep week ($p = 0.01$, $\Delta = 21.7$ activity count/h/day, representing a 6.8% increase) but not compared to the decreased sleep week ($p = 0.10$) (data not shown). As for the total energy output, it was significantly higher during the decreased sleep week compared to the habitual (12.8% less activity) and increased (10.3% less activity) sleep weeks (both $p = 0.001$), but no significant differences were found in total activity count between the habitual and increased sleep weeks ($p = 0.38$). A randomized crossover study conducted with short-sleeping adolescents ($n = 18$, mean age = 15.1 years, 67% female) by Van Dyk and colleagues increased sleep duration for 2 weeks compared to 2 weeks of habitual sleep, based on a week of baseline sleep, and revealed that an increase in sleep duration of 71 minutes/school night, compared to the 2 weeks of habitual sleep, did not significantly impact the amount of light or moderate-to-vigorous physical activity [57]. Another recent randomized crossover study that compared 1 week of 6.5 h/night to 1 week of 9.5 h/night of time-in-bed in adolescents ($n = 90$, mean age = 15.7 years, 67% female) revealed no changes in moderate-to-vigorous physical activity between sleep weeks despite the gap of 1.5 hours between the 2 sleep weeks [58]. Considering our energy balance findings, it would be doubtful that it had much impact on the relationship between increased sleep and IS improvement, as we did not find any significant difference in energy intake. The highest total energy output was during the decreased sleep week, and the relative energy output was only significantly higher during the increased sleep week compared to the habitual sleep week.

Strengths and Limitations

The study design, protocols, and conduct of the SMART2D study are collectively a strength of this work. No significant differences were found for any of our variables between those who participated in the study before versus during the pandemic. However, it is important to note that recruitment was much more difficult during the COVID-19 pandemic.

While we recruited participants who did not have type 2 diabetes based on chart review, it is possible that some of our participants did develop type 2 diabetes between the time of their charted assessment and enrollment into the study. However, since this is a within-participants study design, it should not impact findings too profoundly. We reported our incidental findings (two of our participants) to our physician specialist, a pediatric endocrinologist. Their results remained in our analyses.

In the days prior to engaging in the OGTT, participants were not instructed to consume an adequate amount of carbohydrates, which could have impacted the findings. However, meeting the threshold of consuming at least 150 g of carbohydrates per day (600 kcal/day) in this high-risk population of adolescents is typically not a concern. We also measured their food intake via a 3-day food log and found no significant difference between all 3 weeks of sleep for the total calories or proportion of carbohydrates (approximately 900 kcal/day) consumed.

Although all significant improvements in IS can be mainly attributed to the increased sleep duration, an important limitation pertains to the sustainability of our results beyond a single week of increased sleep duration. Further investigation is needed to ascertain the possibility of a dose–response relationship between increasing sleep on IS over a longer duration in this population. However, as the first study of its kind in this population, the single-week randomized and counterbalanced sleep manipulation protocol was a strength, as it minimized the impacts on participants, tried to control for many variables that longer studies are unable to account for, and also ensured that participants did not manipulate their habitual sleep duration as they needed to be able to increase and decrease their sleep duration.

Having a large number of females in the study is also a strength; inclusivity and representation are key to having better generalizability. No variability of effect was found for biological sex.

The HOMA2 computer model for insulin resistance is an improvement over the classic HOMA insulin resistance calculation; however, in our sample, it had some limitations as 7/108 (6.5% of all samples, $n = 1$ habitual, $n = 1$ increased and $n = 5$ decreased) of our fasting insulin blood samples were > 400 pmol/L, the upper limit for the computerized HOMA2 value calculations.

Finally, although it is feasible to increase sleep in this population, our most successful participants were those who were highly engaged with the study staff and found intrinsic motivation to change their habits. Beyond the offered extrinsic motivation in the form of monetary compensation and verbal encouragement, unlocking intrinsic motivation is key for any behavior modification and more studies should report on participant's motivation.

Conclusion

In summary, we found that increasing sleep duration in a population of adolescents who do not get enough sleep nightly and are presenting with many risk factors for type 2 diabetes can have an important positive impact on their IS. More research should be done to understand the physiological mechanisms behind this relationship that ideally will be multi-site and will include a longer period for the increased sleep duration manipulation. In the meantime, this proof-of-concept study highlights that increasing sleep duration in adolescents at risk of type 2 diabetes is feasible and should be considered in the cocktail of behavior modifications that are needed to reduce the risk factors for type 2 diabetes. Continuing to have an evidence-based and holistic approach to manage the risks that insulin resistance poses in the pediatric population is of great importance.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Disclosure Statement

Nonfinancial disclosure: None. No potential conflicts of interest relevant to this article were reported.

Author's Contribution

CD, GSG, SH, RG, MST, DP, and J-PC conceived the study design. J-PC obtained funding. CD led the study and was supervised by J-PC. IP, RBF, AE, and CMS assisted CD with the data collection and data entry. CD conducted the data analysis. CD and J-PC have ownership of the data. CD prepared the graphical abstract, tables, figures, and wrote the manuscript. All authors critically reviewed the manuscript.

Data Availability

The data underlying this article cannot be shared publicly due to ethical reasons as it poses a risk for the privacy of the individual participants. The data and full protocol will be shared on reasonable request to the corresponding author.

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3.1 Supplementary Material

3.1.1 Supplementary Table S1. CONSORT checklist of information to include when reporting randomised crossover trials: Filled out for the study titled: Sleep and insulin sensitivity in adolescents at risk of type 2 diabetes: the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes a randomized crossover study.

Section/topic	Item No	Description	Page No*
Title†	1a	Identification as a randomised crossover trial in the title	1
Abstract†	1b	Specify a crossover design and report all information outlined in table 2	2 and see table 2 below
Introduction:			
Background‡	2a	Scientific background and explanation of rationale	4-6
Objectives‡	2b	Specific objectives or hypotheses	5-6
Methods:			
Trial design†	3a	Rationale for a crossover design. Description of the design features including allocation ratio, especially the number and duration of periods, duration of washout period, and consideration of carry over effect	9-10
Change from protocol‡	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	None, see p.6 and 9 for clarifications
Participants‡	4a	Eligibility criteria for participants	6-7

Section/topic	Item No	Description	Page No*
Settings and location‡	4b	Settings and locations where the data were collected	6
Interventions†	5	The interventions with sufficient details to allow replication, including how and when they were actually administered	8-14 and Figure 2
Outcomes‡	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	9, 10, 15, 16
Changes to outcomes‡	6b	Any changes to trial outcomes after the trial commenced, with reasons	9
Sample size†	7a	How sample size was determined, accounting for within participant variability	17
Interim analyses and stopping guidelines‡	7b	When applicable, explanation of any interim analyses and stopping guidelines	17
Randomisation:			
Sequence generation‡	8a	Method used to generate the random allocation sequence	10
Sequence generation‡	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10

Section/topic	Item No	Description	Page No*
Allocation concealment mechanism‡	9	Mechanism used to implement the random allocation sequence§ (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation†	10	Who generated the random allocation sequence,§ who enrolled participants, and who assigned participants to the sequence of interventions	10
Blinding‡	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9, 16
Similarity of interventions‡	11b	If relevant, description of the similarity of interventions	8
Statistical methods†	12a	Statistical methods used to compare groups for primary and secondary outcomes which are appropriate for crossover design (that is, based on within participant comparison)	16-18
Additional analyses‡	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	18
Results			
Participant flow (a diagram is strongly recommended)†	13a	The numbers of participants who were randomly assigned, received intended treatment, and were	Figure 1

Section/topic	Item No	Description	Page No*
		analysed for the primary outcome, separately for each sequence and period	
Losses and exclusions†	13b	No of participants excluded at each stage, with reasons, separately for each sequence and period	18, Figure 1
Recruitment‡	14a	Dates defining the periods of recruitment and follow-up	6
Trial end‡	14b	Why the trial ended or was stopped	18
Baseline data†	15	A table showing baseline demographic and clinical characteristics by sequence and period	Table 1
Numbers analysed†	16	Number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1, Table 1, and Table 2
Outcomes and estimation†	17a	For each primary and secondary outcome, results including estimated effect size and its precision (such as 95% confidence interval) should be based on within participant comparisons.¶ In addition, results for each intervention in each period are recommended	Table 2 19-24
Binary outcomes‡	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 2

Section/topic	Item No	Description	Page No*
Ancillary analyses‡	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	19-21, 23
Harms†	19	Describe all important harms or untended effects in a way that accounts for the design (for specific guidance, see CONSORT for harms32)	10-11, 18, and 24
Discussion:			
Limitations†	20	Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses. Consider potential carry over effects	33-34
Generalisability‡	21	Generalisability (external validity, applicability) of the trial findings	33-35
Interpretation‡	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	31-32
Other information:			
Registration‡	23	Registration number and name of trial registry	35
Protocol‡	24	Where the full trial protocol can be accessed, if available	36

Section/topic	Item No	Description	Page No*
Funding‡	25	Sources of funding and other support (such as supply of drugs), role of funders	35

CONSORT=Consolidated Standards of Reporting Trials.

- ** Note: page numbers are optional depending on journal requirements.*
- *† Modified original CONSORT item.*
- *‡ Unmodified CONSORT item.*
- *§ Random sequence here refers to a list of random orders, typically generated through a computer program. This should not be confused with the sequence of interventions in a randomised crossover trial, for example receiving intervention A before B for an individual trial participant.*
- *¶ A within participant comparison takes into account the correlation between measurements for each participant because they act as their own control, therefore measurements are not independent.*

3.1.2 Supplementary Table S2. Information to include in abstract of report of randomized crossover trial: extension of CONSORT for abstracts Filled out for the study titled: Sleep and insulin sensitivity in adolescents at risk of type 2 diabetes: the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes a randomized crossover study

Item	Description	
Title*	Identification of study as a randomized crossover trial	Yes
Trial design*	Description of the trial design (crossover trial and number of periods)	Yes
Methods:		
Participants†	Eligibility criteria for participants and the settings where the data were collected	Yes
Interventions*	Interventions intended for all participants	Yes
Objective†	Specific objective or hypothesis	Yes
Outcome†	Clearly defined primary outcome for this report	Yes
Randomization*	How participants were allocated to sequences	Yes

Item	Description	
Blinding (masking)*	Whether or not participants, care givers, and those assessing the outcomes were blinded to intervention	Yes
Results:		
Numbers randomized*	Number of participants randomized to each sequence	Yes
Recruitment†	Trial status‡	Yes
Numbers analyzed*	Number of participants analyzed	Yes
Outcome*	For the primary outcome, the estimated effect size and its precision based on within participant comparisons	Yes
Harms†	Important adverse events or side effects	No, there is no room in a 250 words abstract for this.
Conclusions†	General interpretation of the results	Yes
Trial registration†	Registration number and name of trial register	Yes
Funding†	Source of funding	Yes

CONSORT=Consolidated Standards of Reporting Trials.

- * Modified original CONSORT item.
- † Unmodified CONSORT item.
- ‡ This is applicable to conference abstracts.

3.1.3 Supplementary Table S3. The SMART2D study: effect of increasing time-in-bed by 1.5h/night for one week, compared to a week of habitual sleep duration and decreasing time-in-bed by 1.5h/night for one week, on sleep characteristics in adolescents at risk of type 2 diabetes (n=36).

	Sleep Week					
	Habitual	Increased	Decreased	Main effect and df	p-value	Effect Size *(d or η^2_p)*
Sleep Characteristics						
Adherence to the sleep protocol (%)	NA	87.3 (19.3) [80.7, 93.8]	82.1 (24.3) [73.8, 90.4]	0.94 (35)	0.35	0.23
Total sleep time (min/night)	451.2 (39.9)* [437.7, 464.7]	513.2 (44.2)* [498.2, 528.1]	372.0 (36.1)* [359.8, 384.3]	441.7 (2,70)	0.001	0.93
Week night total sleep time (min/night)	442.2 (43.2)* [427.5, 456.8]	506.8 (48.6)* [490.3, 523.2]	365.6 (41.0)* [351.8, 379.5]	380.1 (2,70)	0.001	0.92
Weekend night total sleep time (min/night)	472.9 (62.1)* [451.9, 493.9]	528.1 (44.2)* [513.2, 543.1]	388.4 (55.5)* [369.6, 407.1]	81.6 (HF:1.8,63.3)	0.001	0.70
Night-to-night sleep duration variability (min/night)	65.1 (26.7) [56.1, 74.1]	37.9 (17.6)† [31.9, 43.8]	46.5 (31.7)† [35.7, 57.2]	17.1 (2,70)	0.001	0.33
Objective sleep efficiency (%)	86.1 (3.9)‡ [84.8, 87.4]	83.6 (4.3) [82.1, 85.1]	87.4 (3.5)‡ [86.2, 88.5]	14.5 (2,70)	0.001	0.29
Wake after sleep onset (number)	46.4 (13.7)* [41.7, 51.0]	57.2 (14.2)* [52.4, 62.0]	33.0 (8.9)* [30.0,36.0]	81.5 (2,70)	0.001	0.70
Amount of wakefulness (%)	10.2 (2.8)§ [9.2, 11.1]	11.2 (2.8)§ [10.2, 12.1]	8.7 (2.4)§ [7.9, 9.6]	25.4 (2,70)	0.001	0.42
Amount of stillness (%)	88.8 (2.7)§ [87.9, 89.7]	87.5 (2.5)§ [86.7, 88.4]	90.3 (2.2)§ [89.5, 91.0]	26.0 (2,70)	0.001	0.43
Midpoint of Sleep (time: h:mm:ss)	3:48:54 AM (1:04:23)‖ [3:27:53, 4:09:56 AM]	2:56:44 AM (0:52:55) [2:39:28, 3:14:02 AM]	4:08:45 AM (0:51:49)‖ [3:51:56, 4:25:48 AM]	35.3 (HF:1.7,58.6)	0.001	0.50
Daytime sleepiness (score)	8.1 (3.9)* [6.8, 9.4]	5.1 (3.8)* [3.9, 6.4]	12.0 (4.5)* [10.5, 13.5]	44.2 (2,70)	0.001	0.56
Sleep satisfaction (score)	2.9 (0.7)* [2.7, 3.2]	3.8 (0.8)* [3.6, 4.1]	2.2 (0.6)* [2.0, 2.4]	53.4 (2,70)	0.001	0.60

Meeting sleep duration recommendation (%)	11.1*	77.8*	0*	49.1 (2)	0.001	0.56

Note. Data are means with standard deviation in brackets and 95% CI lower and upper limits in the square brackets. Main effect for most analyses are from repeated measures ANOVA, F-value with degrees of freedom in brackets, p-value and effect size as partial eta squared are presented. Main effect and effect size for the percentage of adherence to the protocol were obtained using paired-sample t-test and Cohen's d, respectively. Adherence to the sleep protocol was based on ±10 minutes from the prescribed daily bedtime and wakeup time. A higher score in the sleep satisfaction denotes increased satisfaction with the nightly sleep. While a higher score in the Epworth Sleepiness Scale represents greater daytime dysfunction. Main effect for meeting sleep duration recommendation was obtained using Friedsman's test and post-hoc analysis was conducted using Wilcoxon signed-rank test.

**All conditions are significantly different from one another p<0.001.*
†Both sleep intervention weeks are significantly different from the habitual sleep week p<0.01.
‡Habitual and decreased sleep weeks are significantly different from the increased sleep week p<0.05.
§All conditions are significantly different from one another p<0.05.
‖Habitual and decreased sleep weeks are significantly different from increased sleep week p<0.001.

Abbreviations: df, degrees of freedom; HF, Huynh-Feldt correction; NA, not applicable.

Chapter 4

Manuscript 2:

Effect of Sleep Duration Manipulation on Brain-Derived Neurotropic Factor in Adolescents with Risk Factors for Type 2 Diabetes: A Secondary Analysis of the SMART2D Crossover Study.

4.1 Abstract

Study Objective: We examined the effect of sleep duration manipulation on serum brain-derived neurotrophic factor (BDNF) levels in adolescents at risk for type 2 diabetes (T2D).

Methods: This randomized (1:1), sex-stratified, crossover study manipulated sleep duration, measured by actigraphy, by increasing (IN) and decreasing (DE) time-in-bed by 1.5 h/night for 1 week, separated by a week of washout sleep, based on an initial week of habitual (HB) sleep duration. After each week of sleep, fasted blood samples were collected for analysis of serum BDNF.

Results: Adolescent participants (n=36, 52.8% female, mean age=15.1±1.3 y) with severe obesity (>99th BMI percentile) successfully increased and decreased their sleep duration by 1:02 h/night and 1:19 h/night, respectively, based on a week of HB sleep duration (mean=7:31 h/night). Increasing sleep duration resulted in a significant (~14%) decrease in serum BDNF compared to the HB and DE weeks, while no significant differences were observed between the HB and DE weeks.

Conclusion: This study is among the first to demonstrate that sleep duration manipulation influences serum BDNF levels in adolescents at risk for T2D. The observed decrease in BDNF levels during the IN week, coupled with previously reported improvements in insulin sensitivity, suggests that increasing sleep duration may modulate circulating BDNF in a way that supports glucose regulation. These findings underscore the potential of sleep as a low-cost, non-invasive intervention for improving metabolic outcomes in high-risk adolescents.

4.2 Background

Recent neuroimaging studies have highlighted concerning associations between obesity, insulin resistance and T2D with reduced structural brain integrity in adolescents [160–163], mirroring patterns observed in older adults with these conditions. Adults with insulin resistance face an increased risk of early cognitive decline and neurodegenerative diseases such as dementia and Alzheimer's disease [300,301]. While these observations are well-documented in adults, the mechanisms underlying structural brain abnormalities in both adolescents and adults remain speculative. In particular, studies on brain structure abnormalities in adolescents with obesity, insulin resistance, and T2D have largely overlooked the role of sleep.

Research indicates that a significant proportion of adolescents fall short of achieving the recommended sleep duration, both in Canada and globally, with substantial variation in estimates [24,28,302]. For example, research shows that approximately 30% of adolescents in high-income European countries and Canada fail to meet recommended sleep durations on school nights, while this figure rises to 73% among U.S. adolescents [24,28,302]. This widespread sleep deficiency is particularly concerning given its association with obesity and other health complications [16,30]. A systematic review and meta-analysis found a 57% increased risk of obesity in children and adolescents with short sleep duration, while longer sleep duration appeared protective [303]. The relationship between sleep duration and obesity is likely bidirectional: insufficient sleep exacerbates metabolic dysregulation, leading to weight gain, which in turn disrupts sleep patterns [1,16,30]. Adolescents with obesity are therefore at an heightened risk of short sleep duration, which has also been linked to impaired cognitive performance, brain structural changes, and worsened metabolic outcomes [1,14,30].

One potential link between metabolic dysfunction and adverse brain changes is lower levels of BDNF [192,203]. BDNF, a neurotrophin expressed in both the central and peripheral nervous systems, crosses the blood-brain barrier bidirectionally and plays critical roles in neurogenesis, synaptic plasticity, and neuronal integrity [304,305]. It also plays a role in metabolic processes, including glucose homeostasis, fat metabolism, and appetite regulation [192,306]. Circulating BDNF levels are often lower in adults with obesity and T2D compared to healthy individuals [307], suggesting a potential mechanistic role in the interplay between metabolic and neurological health. Chronic sleep deprivation, and insomnia, has also been associated with decreased BDNF levels, potentially impairing the brain's adaptability and repair mechanisms [208,223,308]. Experimental evidence on animal models suggests that sleep fragmentation or deprivation reduces hippocampal BDNF levels, negatively impacting learning and memory processes [309–311]. Interestingly, while chronic sleep disturbances decrease BDNF, acute sleep deprivation may temporarily elevate its levels, potentially as an adaptive response to acute stress or metabolic challenges [208].

Given the prevalence of short sleep duration among adolescents and its association with obesity, insulin resistance, and T2D, as well as the link between these conditions and reduced structural brain integrity, it is crucial to investigate the effects of sleep manipulation on BDNF levels in this high-risk population. Therefore, the present secondary analysis of a randomized crossover study aimed to examine the effects of three separate weeks of sleep duration (extension, restriction, and habitual sleep) on BDNF concentrations in adolescents at risk for T2D. We hypothesized that BDNF levels would decrease following the week of decreased sleep duration compared to the other

two weeks, with the week of increased sleep duration exhibiting the highest BDNF levels.

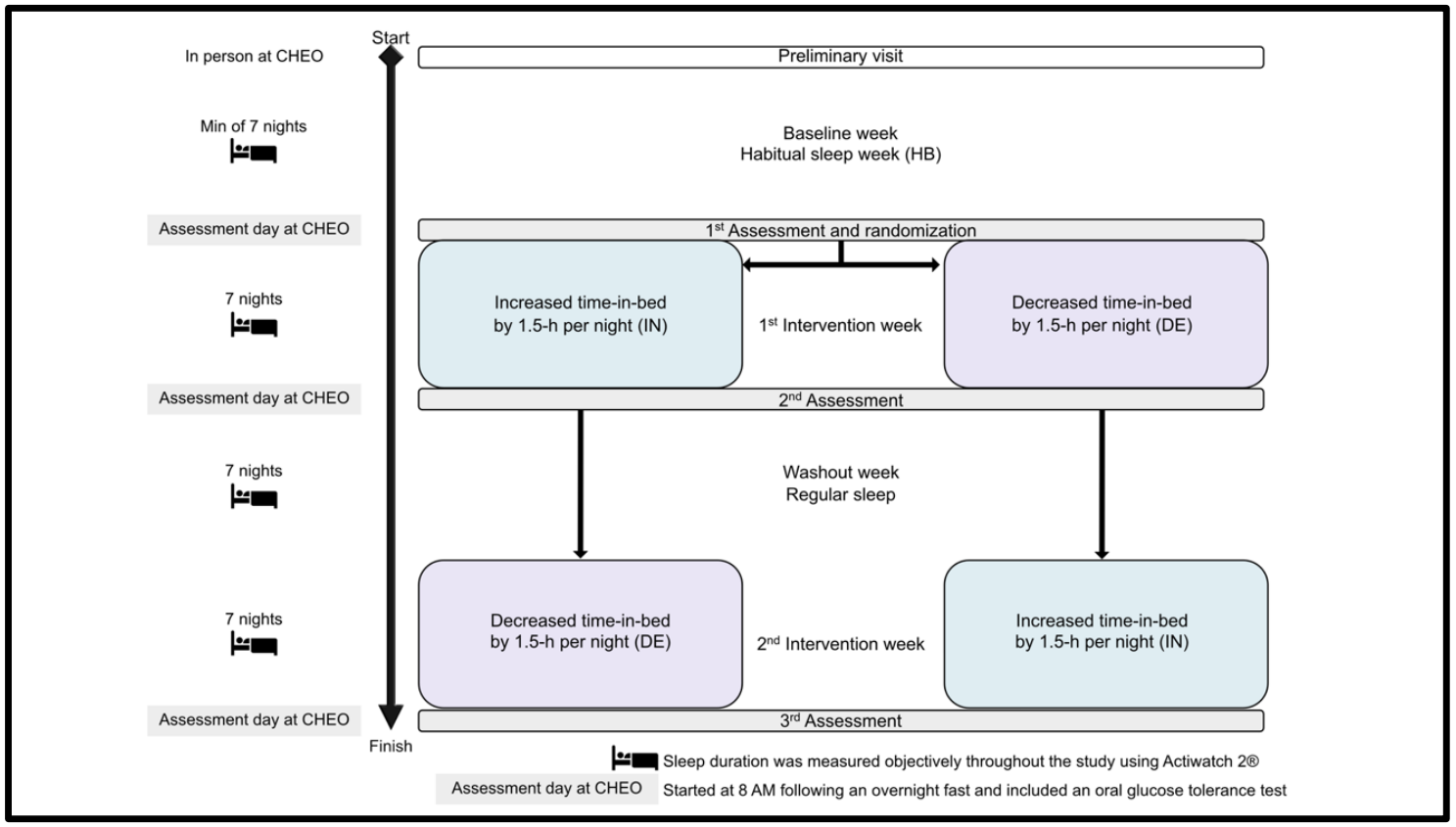
4.3 Methods

4.3.1 Study design and procedures

The study design including detailed recruitment methods, protocols, dropouts, and the sleep intervention protocols for the SMART2D study have been previously reported in Dutil et al. [299]. Briefly, the experimental study protocols on human participants for the SMART2D study were approved by the Research Ethics Boards at the Children's Hospital of Eastern Ontario (CHEO) and at the University of Ottawa, Canada. We obtained written informed consent from all adolescents, which was witnessed by a parent/legal-guardian and a study staff.

Figure 2 is a depiction of the SMART2D study design and timeline for the participants. The SMART2D study was a randomized and sex-stratified crossover study conducted in Ottawa, Canada (single-site), and in free-living conditions; which was developed, powered, and conducted to investigate the effect of sleep manipulation on insulin sensitivity in adolescents at high risk for T2D (ClinicalTrials.gov ID:NCT03754036). In the present secondary data analysis, we investigated the effect of increasing and decreasing time-in-bed by 1.5 h/night for 1 week based on a week of habitual sleep duration and separated by a week of washout sleep, on serum BDNF in our high-risk population of adolescents. For the entire month of the study, participants' sleep duration at night and activity count during hours of wakefulness were measured objectively by Actiwatch 2® (Philips Respironics, Netherlands) worn 24/7 on the non-dominant wrist. Randomization (1:1) was created by a third party using the block method and allocation

concealment (in envelops that were opaque and numbered for males and females separately) to deliver the order of the interventions. All participants started with the habitual sleep week (HB), consisting of at least 2 weekend nights and 5 week nights. At the end of the HB week, participants came to the laboratory for their first assessment and received the order for their first sleep intervention, which was either increasing (IN) or decreasing (DE) time-in-bed by 1.5 h/night for 1 week based on their average sleep duration during the HB week. At the end of the first intervention week (IN or DE), participants came to the laboratory for their second assessment, which was followed by a week of washout sleep (returning to the HB duration after a recovery period). After the washout week, participants did the alternate sleep manipulation schedule for their second intervention week (DE or IN) and at the end of the week they came to the laboratory for their third and last assessment. This study design resulted in two different orders for the interventions: HB, IN and DE or HB, DE and IN with 3 time points for the assessments during a 1-month period (see Figure 2 for the study design and Dutil et al. [299] for more details).



4.3.2 Figure 2. SMART2D randomized crossover study design.

Note. This study design depicts two possible orders for the SMART2D participants: HB, IN and DE or HB, DE, and IN. The in-person preliminary visit and assessment day at CHEO were conducted in our laboratory. The first sample of the oral glucose tolerance test, was the fasting sample which included the collection for serum BDNF levels analysis.

Abbreviations: CHEO, Children's Hospital of Eastern Ontario; DE, decreased; HB, habitual; IN, increased; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes.

4.3.3 Participants

Thirty-six adolescents with severe obesity and at high-risk for T2D completed the SMART2D study between April 2019 and December 2021. The inclusion criteria were as follows: (i) aged 13 to 18 years old, (ii) at high risk for T2D (3 categories of recruitment priority based on severity of the risks factors), (iii) no diagnosis of T2D, sleep disorders or severe psychiatric disorders, (iv) fluent in English or French, (v) in the past month self-reported an average sleep duration > 6:30/night but < 9:00/night, (vi) attended school in grades 8-12, (vii) lived in close proximity to CHEO (35 km radius), and (viii) normal or corrected to normal vision and no major disability that would prevent the participant from performing our neuro-motor cognitive tasks. Participants received monetary compensation for participating in the SMART2D study. During the preliminary visit, the adolescents completed a screening questionnaire to assess eligibility criteria and obtained important descriptive characteristics. More information on inclusion and exclusion criteria can be found in Dutil et al. [299].

4.3.4 Outcome measurement

Serum BDNF samples were obtained from venous blood samples at the end of each week of sleep (3 time points). Blood samples were collected following a 12-hour overnight fast, prior to the start of an oral glucose tolerance test for the SMART2D study [299]. After a 30-minute clotting period, blood samples were centrifuged for 10 minutes at 3,000 rpm and 17°C to separate the serum. The serum was then aliquoted into cryogenic vials and stored at −80°C until assayed. Human serum BDNF concentrations were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (BEK-2211, Biosensis®, Australia) for each week of sleep (HB, IN, DE). During the assay process, serum samples were diluted 1:100 with the provided assay buffer. All

samples were assayed in duplicate following the manufacturer's instructions (see www.biosensis.com), and all three sessions for individual participants were tested on the same plate to minimize inter-assay variability. The coefficient of variation for all samples was under 10% (mean = 4.1% and SD = 2.9%) and reported as the average of the two duplicate measurements.

4.3.5 Statistical analysis

Descriptive characteristics are presented as mean and standard deviation for normally distributed continuous variables, median and range for skewed distribution of continuous variables, and as *n* and percentage for categorical variables. Analyses were performed using SPSS statistical software (Version 29; SPSS Inc., Chicago, IL, USA) and JASP (Version 0.17.3, Amsterdam, Netherlands). All variables were examined for normality using the Shapiro-Wilk test. Repeated-measures ANOVA was used to investigate the effect of sleep week (three conditions: HB, IN, and DE) on serum BDNF. If Mauchly's Sphericity Test was violated, appropriate corrections were applied using Greenhouse-Geisser or Huynh-Feldt corrections. Results are presented as means with standard deviations, 95% confidence intervals, and *p*-values are reported and considered significant if the two-sided *p*-value was <0.05. For significant main effects, Bonferroni post-hoc pairwise comparisons method was used to determine the locus of the significant difference between the sleep weeks. Effect sizes are also reported as partial eta-squared, and characterized as small (η^2_p=0.01), medium (η^2_p=0.06), or large (η^2_p=0.14) [312]. Variation of the effects were analysed using linear mixed model analyses for the order of the manipulations (to exclude the possibility of order or carryover effects), age, biological sex, pubertal maturation, socioeconomic status,

recruitment priority, testing session occurring pre- or during the COVID-19 pandemic, and physical activity.

4.4 Results

Table 1 shows the descriptive characteristics of the sample. Adolescents (n=36, mean age = 15.1 years, 47.2% male, 5.6% self-identified as being non-binary or genderqueer, and 44.4% self-identified as being non-white) had severe obesity (99.94th BMI percentile) and presented with numerous risks factors for T2D including 88.9% of participants with dyslipidemia, non-alcoholic fatty live disease, and/or polycystic ovary syndrome. Sixteen of the 36 participants (44.4%) were tested during the COVID-19 pandemic.

Table 2 shows the impact that the 1.5 h/night time-in-bed manipulations had on sleep duration. The time-in-bed manipulation resulted in significant sleep duration differences between all three weeks of sleep, $F(2,70)=441.7$, $p<0.001$, $\eta^2_p=0.93$. During the HB sleep week participants slept 7:31/night on average, during the IN sleep week the average sleep duration increased to 8:33/night, and during the DE sleep week the average sleep duration decreased to 6:12/night. The prescribed 3-hour per night time-in-bed difference between the two sleep manipulation weeks resulted in an average sleep duration difference of 2:21/night.

4.4.1 Table 1. Descriptive characteristics for the SMART2D study participants.

Characteristics	Order IN first *n* = 18	Order DE first *n* = 18	Total *n* = 36
Age in years	15.4 (1.5)	14.8 (1.1)	15.1 (1.3)
Sex, self-reported *n* (%):			
male	9 (50)	8 (44.4)	17 (52.8)
female	9 (50)	10 (55.6)	19 (47.2)
Gender identity, self-identification *n* (%):			
boy	9 (50)	7 (38.9)	16 (44.4)
girl	8 (44.4)	10 (55.6)	18 (50.0)
non-binary or genderqueer	1 (5.6)	1 (5.6)	2 (5.6)
Race and ethnicity, self-identification *n* (%):			
Aboriginal (First Nations, Métis and Inuit peoples)	1 (5.6)	1 (5.6)	2 (5.6)
Asians or Asian Indian	2 (11.1)	2 (11.1)	4 (11.1)
Black people, African or Caribbean descent	2 (11.1)	2 (11.1)	4 (11.1)
Caucasian or White people	10 (55.6)	10 (55.6)	20 (55.6)
Middle Eastern or North African	3 (16.7)	2 (11.1)	5 (13.9)
Hispanic, Latino, Spanish, South America	0 (0)	1 (5.6)	1 (2.8)
Proxy-socioeconomic status *n* (%):			
very-low to low	6 (33.3)	4 (22.2)	10 (27.8)
low to medium	8 (44.4)	6 (33.3)	14 (38.9)
medium to medium-high	4 (22.2)	8 (44.4)	12 (33.3)

Pubertal maturity stage (score), self-reported:			
male	3.4 (2-5)	3.6 (2-5)	3.5 (2-5)
female	3.4 (2-5)	2.9 (2-5)	3.2 (2-5)
Recruitment priority *n* (%):			
Priority 1: obesity > 97th percentile WHO and dyslipidemia	13 (72.2)	7 (38.9)	20 (55.6)
Priority 2: obesity > 97th percentile WHO and NAFLD and/or PCOS	2 (11.1)	10 (55.6)	12 (33.3)
Priority 3: severe obesity > 99th percentile WHO	3 (16.7)	1 (5.6)	4 (11.1)
BMI percentile WHO	99.96 (0.04)	99.92 (0.08)	99.94 (0.07)
Testing occurred *n* (%):			
prior to the COVID-19 pandemic	12 (66.7)	8 (44.4)	20 (55.6)
during the COVID-19 pandemic	6 (33.3)	10 (55.6)	16 (44.4)

Note. Unless otherwise indicated as n (%), data are presented as mean or median with standard deviation or range in bracket, respectively. Order IN first signifies that participants following the habitual sleep week were randomized into starting with the increased sleep week (IN), while Order DE first indicate that participants following the habitual sleep week were randomized into starting with the decreased sleep week (DE). Total, indicate the total of participants that completed both interventions.

Abbreviations: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; WHO, World Health Organization.

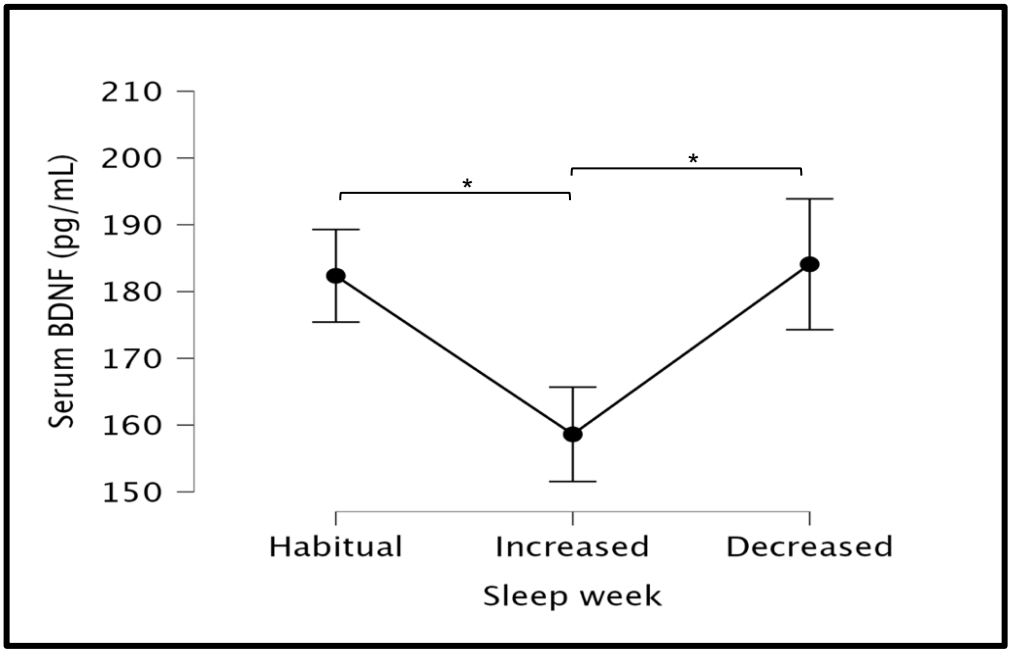
4.4.2 Table 2. Effect of time-in-bed manipulation during the SMART2D crossover study on sleep duration.

	Sleep Week			Main effect (df)	p-value	Effect Size (η^2_p)
	HB	IN	DE			
Sleep duration in hh:mm/night	07:31 (00:40)* [07:18, 07:45]	08:33 (00:44)* [08:18, 08:48]	06:12 (00:36)* [06:00, 06:24]	441.7 (2,70)	<0.001	0.93
Week night sleep duration in hh:mm/night	07:22 (00:43)* [07:08, 07:37]	08:27 (00:49)* [08:10, 08:43]	06:06 (00:41)* [05:52, 06:20]	380.1 (2,70)	<0.001	0.92
Weekend night sleep duration in hh:mm/night	07:53 (01:02)* [07:32, 08:14]	08:48 (00:44)* [08:33, 09:03]	06:28 (00:56)* [06:10, 06:47]	81.6 (HF:1.8,63.3)	<0.001	0.70

Note. For each sleep week, data on the first line are means with standard deviation in brackets and on the second line in the square brackets are the 95% confidence intervals lower and upper limits. Repeated measures ANOVAs were used and the F-value with degrees of freedom (df) in brackets, p-value and effect size as partial eta squared (η^2_p) are reported for each analysis.
**All sleep weeks are significantly different from one another p < 0.001.*

Abbreviations: DE, decreased; df, degrees of freedom; HB, habitual; HF, Huynh-Feldt correction for significant Mauchly's Test of sphericity; IN, increased; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes.

Figure 3 presents the effect of sleep week on serum BDNF levels. We found a significant effect of sleep week on serum BDNF levels, corrected by Greenhouse-Geisser $F(1.62,56.7) = 12.905$, $p = 0.001$, $\eta^2_p = 0.27$. The post-hoc analysis revealed that the serum BDNF level was significantly lower following the increased sleep week (158.6 [95% CI:142.7 to 171.0] pg/mL, SD = 41.1 pg/mL), compared to the habitual and decreased sleep weeks (183.3 [95% CI:163.8 to 194.2] pg/mL, and 184.7 [95% CI: 168.4 to 197.4] pg/mL, $p < 0.001$, respectively), but no significant difference was found between serum BDNF levels following the habitual and decreased sleep weeks ($p > 0.05$). Analyses showed no evidence of order or carryover effects ($p > 0.8$) and no variation of this effect for the following variables: biological sex, pubertal maturation, socioeconomic status, severity of T2D risk factors, testing session occurring pre- or during the COVID-19 pandemic, ethnicity, physical activity count, or age ($p>0.4$ for all).



4.4.3 Figure 3. Effect of sleep manipulation on serum BDNF levels in adolescents with obesity and high risk for type 2 diabetes.

*Note: *Represents significant differences (p<0.001). Error bars represent 95% confidence intervals. No significant differences were found between the habitual sleep duration week and the decreased sleep week.*

4.5 Discussion

The purpose of this study was to examine the effects of short-term sleep manipulation on serum BDNF levels in adolescents with severe obesity and at high risk for T2D. As previously presented, time-in-bed manipulation was successful as participants increased their sleep duration by an average of 1:02 h/night during the IN sleep week and reduced their sleep by 1:19 h/night during the DE sleep week, based on their average sleep duration during the HB week [299]. Contrary to our hypothesis, serum BDNF levels were significantly lower following the IN week compared to the HB and DE sleep weeks, while no significant differences were observed between HB and DE conditions. To our knowledge, this is the first study to experimentally manipulate sleep and measure BDNF levels in adolescents at high risk for T2D.

BDNF has been implicated in sleep regulation and may serve as a mediator between waking activities and homeostatic sleep responses [208,313,314]. Evidence from animal models demonstrate that BDNF levels rise during wakefulness, inducing sleep pressure and contributing to the intensity of SWA during subsequent NREM sleep [205,213,315]. As SWA reflects sleep need and pressure, its correlation with BDNF expression underscores the neurotrophins role in maintaining sleep homeostasis [313,315,316]. In humans, the Val66Met polymorphism of BDNF has been linked to impaired SWA intensity, particularly after extended wakefulness, further supporting its role in sleep regulation [213]. However, stress-related activation of the HPA axis may disrupt BDNF levels and potentially degrade sleep function [67,208].

Compared to IN, the higher BDNF levels following the HB and DE weeks in our high risk population of adolescents may represent an adaptive stress response to maintain

wakefulness during inadequate sleep and mild sleep restriction, respectively. Previous studies suggest that BDNF induces spontaneous wakefulness and may act as part of a broader stress adaptation mechanism. Increased BDNF levels under these conditions may help counteract the physiological challenges of reduced sleep duration by supporting arousal and metabolic stability.

The interplay between inadequate sleep, stress, and BDNF dynamics underscores the complexity of sleep regulation and its broader implications for health. Most mechanistic pathways suggest that inadequate sleep acts as a stressor, activating networks that collectively promote weight gain, insulin resistance, and an increased risk of T2D [1,53,317–319]. Hormonal shifts, particularly those involving the HPA axis, also play a critical role in the metabolic effects of inadequate sleep [1]. Sleep deprivation elevates cortisol levels, a hallmark of HPA axis activation [1,320,321]. Cortisol, while essential for managing metabolism and stress adaptation, can negatively impact glucose regulation when elevated for prolonged periods [1,68,322]. Elevated cortisol promotes gluconeogenesis in the liver, reduces insulin sensitivity, and inhibits insulin secretion by pancreatic β-cells, impairing glucose metabolism and exacerbating insulin resistance [69,323,324]. Additionally, elevated cortisol levels contribute to abdominal fat storage and increased appetite, often for calorie-dense foods, compounding the risk of weight gain and insulin resistance over time [1,30,73].

These hormonal and behavioural adaptations highlight the critical role of the HPA axis in mediating the effects of inadequate sleep on metabolic health. Notably, these disruptions align with our primary outcome findings, which have shown that insulin sensitivity was significantly improved following the IN week compared to the other two weeks of sleep,

but insulin sensitivity was not significantly different following the HB and DE weeks [299]. The lower BDNF levels and improved insulin sensitivity following the IN week suggest that adequate sleep in a high-risk population of adolescents may mitigate the metabolic consequences of HPA axis activation while promoting glucose regulation.

Fulgenzi et al. [183] demonstrated that skeletal muscle-derived BDNF modulates insulin secretion and glucose clearance during hyperglycemia. They identified a regulatory function of BDNF acting on metabolism independently of its central nervous system role [183]. Additionally, they highlighted that muscle-derived BDNF may mediate glucose metabolism in response to daily behaviours such as exercise and feeding [183]. Walsh and Tschakovsky's [325] review emphasizes that in healthy individuals, the type, intensity, and duration of exercise are crucial factors influencing BDNF levels and the magnitude of their increase. However, following acute exercise the increase in BDNF is relatively transient, with BDNF levels returning to normal within 30-60 minutes post exercise [325–328]. The transient nature of BDNF post-exercise may suggest a role in glucose homeostasis, with the effect potentially being more detectable in individuals with metabolic dysregulation.

Rodriguez et al. [329] investigated the effect of high-intensity interval exercise compared to continuous moderate-intensity exercise on BDNF expression in a small sample (n = 12) of adult males with and without obesity. Their findings revealed that participants with obesity exhibited significantly higher baseline serum BDNF levels compared to their lean counterparts, and that high-intensity interval exercise elicited greater BDNF response in those with obesity [329]. Serum BDNF levels remained significantly higher in participants with obesity one hour post-exercise compared to those without obesity

[329]. Additionally, high-intensity interval exercise increased blood lactate and cortisol levels overall, though participants with obesity had lower blood lactate levels but showed no difference in cortisol levels relative to participants without obesity [329]. Although the study did not assess insulin sensitivity or control for behavioural factors such as caloric intake, feeding time, or sleep, the results suggest that obesity may alter the regulation of circulating BDNF in response to physiological stressors. This has important implications for interpreting BDNF findings in behavioural studies, particularly those involving populations with severe obesity. More research is needed to better understand how BDNF functions in individuals with metabolic dysfunctions and how it may respond differently to behavioural interventions in this context.

In the present study, adolescents with severe obesity exhibited lower BDNF levels following the increased sleep week, during which insulin sensitivity was also highest [299]. Conversely, BDNF levels were elevated during the habitual and decreased sleep weeks, when insulin sensitivity was reduced [299]. These findings align with the work by Fulgenzi and colleagues [183], who demonstrated that skeletal muscle derived BDNF modulates insulin secretion and glucose clearance, suggesting a mechanistic link between BDNF and metabolic regulation. The inverse pattern observed in our data further supports the idea that behavioural modulation, here via sleep, can influence BDNF levels and associated metabolic outcomes. Taken together, the findings of Fulgenzi et al. [183] and Rodrigez et al. [329] underscore the complexity of interpreting circulating BDNF levels in individuals with obesity and highlight the importance of considering both baseline metabolic state and behavioural context when evaluating the relationship between BDNF, sleep and metabolism in high-risk youth.

4.5.1 Strengths and limitations

This study has several notable strengths. The randomized crossover design minimized inter-individual variability, providing robust evidence for the effects of short-term sleep manipulation on serum BDNF levels and metabolic outcomes. The use of objective sleep measurements ensured reliable assessment of sleep duration, while controlling for the timing of blood sampling and feeding reduced potential confounders. To our knowledge, this is the first study to experimentally manipulate sleep in adolescents at high risk for T2D while examining both neurotrophic and metabolic outcomes.

However, the findings should be interpreted considering some limitations. The relatively small sample size may limit generalizability, and the short duration of the intervention may not capture long-term effects of sleep manipulation. Future studies with larger, more diverse cohorts and extended interventions are needed. While serum BDNF provides valuable insights, it may not fully reflect central BDNF activity. Including neuroimaging or cerebrospinal fluid analyses could provide deeper insights into central mechanisms. Additionally, other sleep characteristics, such as architecture, quality, and variability, should be investigated for their potential role in metabolic and neurotrophic regulation. Lastly, this study focused on adolescents with severe obesity at high risk for T2D, a vulnerable population. While this focus is a strength, it limits applicability to populations without obesity or metabolic risk factors. Future research should explore whether these findings extend to other groups, including healthy-weight adolescents and adults.

4.5.2 Conclusion

Our study provides novel insights into the relationship between sleep manipulation and serum BDNF levels in adolescents with severe obesity and additional risk factors for T2D. To our knowledge, this is the first study to experimentally manipulate sleep and

evaluate its effects on BDNF in this vulnerable population. The observed lower BDNF levels following the IN sleep week suggests that sleep duration may modulate peripheral BDNF dynamics, potentially reflecting an adaptive response linked to metabolic regulation. These findings add a new dimension to the existing literature, which has predominantly focused on central nervous system BDNF, by highlighting the potential role of skeletal muscle-derived BDNF in response to behavioural changes such as sleep extension.

The relationship between BDNF and insulin sensitivity observed in this study provides a mechanistic explanation for our findings. The highest insulin sensitivity coincided with the lowest BDNF levels during the IN week, while the HB and DE sleep weeks, characterized by higher BDNF levels, were associated with lower insulin sensitivity. These results align with emerging evidence suggesting that skeletal muscle-derived BDNF plays a critical role in glucose regulation, potentially serving as a key mediator in the interplay between sleep and metabolic health. However, as highlighted by Rodriguez et al. [329], individuals with obesity may show altered baseline BDNF level and exaggerated responses to behavioural stimuli such as exercise, possibly reflecting compensatory or dysregulated mechanisms. This underscores the importance of interpreting changes in circulating BDNF within the context of metabolic status and behavioural conditions, including sleep.

Our findings underscore the importance of adequate sleep duration in modulating BDNF and its downstream metabolic effects. Increasing sleep may serve as a low-cost, non-invasive intervention to improve metabolic outcomes, particularly in adolescents with risk factors for T2D that extend beyond obesity, such as impaired insulin resistance. In a society where access to pediatric endocrinologists can be challenging due to long wait

times, promoting sleep duration as a modifiable behaviour may offer an accessible and practical strategy to support metabolic health. Encouraging sleep extension could empower families and healthcare providers to take preventive action, reducing reliance on specialized care and addressing metabolic risks earlier.

Chapter 5

Manuscript 3:

Effects of Sleep Duration Manipulation on Food-Related Impulsivity in Adolescents with Severe Obesity and High Risk for Type 2 Diabetes: Findings from a Randomized Crossover Study.

5.1 Abstract

Study Objectives: This study investigated the impact of sleep extension and restriction on food image-related impulsivity in adolescents with risk factors for type 2 diabetes (T2D).

Methods: In this randomized, sex-stratified crossover study, adolescents aged 13–18 years with severe obesity and additional T2D risk factors were recruited. Sleep duration, measured objectively, was manipulated by increasing and decreasing time-in-bed by 1.5 hours per night for one week, based on a habitual sleep week and separated by a one-week washout period (two possible orders). The Affective Shifting Task, a go/no-go task using food and object images with a shifting “go” stimulus every second block, assessed behavioural inhibition and impulsivity. Reaction time (RT), commission errors, and omission errors were analyzed across four conditions: food images in new (FiNb) and repeated blocks (FiRb), and object images in new (OiNb) and repeated blocks (OiRb).

Results: Thirty-six adolescents (52.8% female, age=15.1y, BMI=99.9th percentile) participated. Based on an average habitual sleep duration of 7h31min/night, the sleep manipulation created a 2h21min/night difference between the two manipulation weeks. RTs were significantly shorter following the increased sleep week compared to the decreased sleep week but were not different from habitual RTs. RTs were shorter for Fi compared to Oi across all sleep durations, with no differences by block type (Nb vs. Rb). Significant interaction effects were observed for commission and omission errors, which were highest following decreased sleep, lower after habitual sleep, and minimal following increased sleep. More errors occurred in Nb compared to Rb across all weeks. Following decreased and habitual sleep weeks, participants committed more omission errors on Oi and more commission errors on Fi. Errors were minimal following increased sleep, with no differences between Fi and Oi.

Conclusion: Extending sleep duration in high-risk adolescents improved performance by reducing errors and enhancing cognitive functions across all task dimensions. This improvement eliminated biases between stimulus types, underscoring the critical role of adequate sleep in supporting inhibitory control and effective response regulation.

5.2 Background

Over the past 15 years, the study of food impulsivity has expanded substantially. Food impulsivity, defined as the tendency toward impulsive food choices, is characterized by a reduced capacity to regulate food intake, especially in the presence of highly processed, calorie-dense foods rich in sugar and fat [330]. Such foods are often readily accessible and act as potent rewards, enhancing the likelihood of impulsive eating behaviours. This behaviour is driven by an immediate desire for gratification and is linked to an increased risk of obesity [330–334].

Food impulsivity is a complex construct influenced by genetic, psychological, and environmental factors [335–340]. Genetic predispositions can heighten impulsivity, making some individuals more inclined toward impulsive eating [339]. Psychological factors, such as stress, anxiety, and depression, also play a significant role, as individuals may use food as a coping mechanism in response to these emotions [333,334,341,342]. Additionally, environmental aspects, such as the ubiquity of unhealthy foods and the constant promotion of these options, can exacerbate food impulsivity by triggering cravings and promoting excessive consumption [340,343,344]. Social and cultural norms further influence eating behaviours by creating social pressures to indulge in unhealthy foods, especially in communal settings [345,346]. Certain parenting practices related to food, such as restricting foods or pressuring children to eat (e.g., requiring them to finish their plates before being able to leave the table), have been associated with higher weight status and the development of unhealthy weight-related behaviours in children and adolescents [347].

The link between sleep and food impulsivity has recently garnered attention as a potential contributing factor [254,348–351]. Inadequate sleep has been shown to disrupt the regulation of appetite-regulating hormones, like leptin and ghrelin, heightening hunger and intensifying craving for high-calorie foods [16,348,352,353]. However, there is not enough evidence to consistently link inadequate sleep to leptin and ghrelin levels in the pediatric population, as reports have shown conflicting results [354–356]. Additionally, lack of sleep can impair brain functions, particularly affecting regions of the brain responsible for decision-making and impulse control, making individuals more likely to engage in impulsive and unhealthy eating behaviours [14,146,254,349–351]. These findings suggest that adequate sleep may be able to play a protective role against food impulsivity, highlighting the need to address sleep duration in interventions aimed at promoting healthier eating habits within high-risk groups.

According to the World Health Organization 160 million children and adolescents aged 5-19 years were living with obesity in 2022, and since the 1990s the adolescent obesity rates have quadrupled [357–359]. Globally, the prevalence of childhood obesity is approximately 5.6% in girls and 7.8% in boys; yet, while obesity rates have plateaued in many high-income countries, they continue to increase in low- to middle-income countries [38]. Adolescents grappling with severe obesity may be especially vulnerable to food impulsivity [30,360]. The physiological transformations inherent to adolescence, coupled with societal pressures that endorse unhealthy eating practices, can intensify impulsivity and contribute to overconsumption of food and increase the risk of obesity. This population faces unique challenges in weight and health management, underscoring the importance of addressing food impulsivity in interventions targeting adolescents with obesity.

There is a high prevalence of lack of sleep in the adolescent population ranging between 30-70% in high-income countries [24,28,302], which could further exacerbate food impulsivity. Understanding the role of sleep duration in food impulsivity among adolescents with severe obesity is therefore crucial.

The present study aimed to explore the intricate relationship between sleep duration, inhibition, and food impulsivity in a high-risk population of adolescents with severe obesity and elevated risk for T2D. We manipulated sleep duration by increasing and decreasing time in bed by 1.5 hours per night for one week (within-subjects study design), relative to each participant's habitual sleep and separated by one week of washout sleep. While directly measuring food impulsivity is challenging, response inhibition to food cues serves as a valuable proxy. The AST, developed by Meule et al. [255–258], is a robust tool for assessing food impulsivity through a go/no-go paradigm. In this task, participants respond to two types of stimuli: food images, considered salient stimuli, and non-food images, regarded as more neutral stimuli. Using the AST, we assessed how sleep manipulation changed behavioural inhibition and impulsivity in response to food cues. We hypothesized that extending sleep would enhance task performance, indicated by a reduction in RT and errors, compared to the habitual and decreased sleep conditions.

5.3 Methods

5.3.1 Participants and Research Design

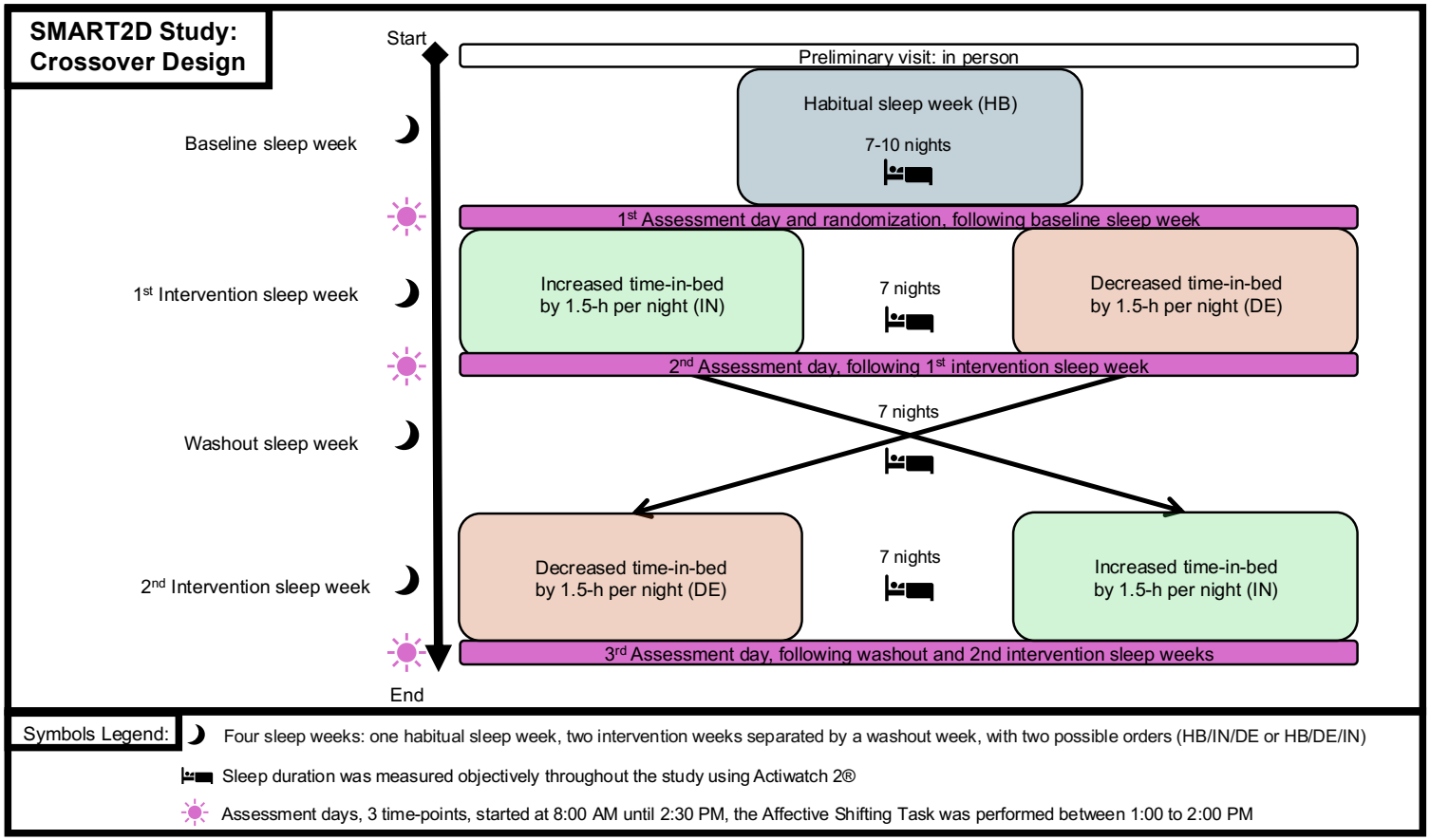
Thirty-six adolescents with severe obesity and at high-risk for T2D completed the SMART2D study [299]. This randomized and sex-stratified crossover study was conducted in Ottawa, Canada, as a single-site under free-living conditions [299].

Detailed methodology, including randomization procedures, recruitment strategies, intervention protocols, dropout management, and participant compensation, was previously published [299]. The study received ethical approval from the Research Ethics Boards at the CHEO and the University of Ottawa, Canada [299].

Participants were recruited between April 2019 and December 2021 [299]. Written informed consent was obtained from all participants, witnessed by a parent/legal guardian and a study staff member [299]. Eligibility was confirmed in person at CHEO during the preliminary visit and included the following criteria: (i) be aged between 13 and 18 years, (ii) be at high risk for T2D without a diagnosis of T2D, (iii) not have a diagnosis of sleep or severe psychiatric disorder, (iv) self-report an average sleep duration of more than 6.5 hours but less than 9 hours per night in the past month, (v) have normal or corrected-to-normal vision, (vi) not have a major disability that would prevent them from performing the neurocognitive tasks, (vii) attend school in grades 8-12, (viii) live withing a 35 km radius of CHEO, and (ix) be fluent in English or French [299].

Each participant completed four sleep weeks as part of the SMART2D study: HB, IN, DE, and washout [299]. The two intervention weeks (IN and DE) were randomized (order: HB-IN-DE or HB-DE-IN) and separated by 7 nights of washout sleep [299]. Participants were assessed at three different time points, at the end of each HB, IN, and DE sleep week. In-person assessments occurred at CHEO from 8:00 AM to 2:30 PM, with the Affective Shifting Task performed between 1:00 and 2:00 PM [299].

Sleep duration was objectively measured throughout the study using an Actiwatch 2® (Philips Respironics, Netherlands) worn on the non-dominant wrist, complemented by subjective reporting via sleep logs [299]. The HB week consisted of a minimum of 7 nights, including at least 2 weekend nights and 5 weeknights, during which participants' baseline sleep habits were recorded [299]. Participants then underwent their first assessment day and received their randomized first sleep intervention (IN or DE) [299]. The sleep manipulation weeks adjusted time-in-bed by ±1.5 hours per night relative to each participant's HB average sleep duration [299]. This was done by manipulating bedtime while keeping wake-up time mostly constant. Following the first intervention week, participants completed their second assessment day and proceeded to one week of washout sleep [299]. After the washout week, participants completed the alternate intervention week and their final assessment day [299]. See *Figure 4* for the graphical representation of the SMART2D randomized crossover study design.



5.3.2 Figure 4. Study design overview for the SMART2D randomized and sex-stratified crossover study.

Note. Visual representation of the within-subject and free-living condition study design, including sleep manipulation weeks (habitual, increased, and decreased), washout periods, and testing sessions for SMART2D participants.

Abbreviations: DE, decreased; HB, habitual; IN, increased; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes.

5.3.3 Affective Shifting Task

The AST, a go/no-go task utilizing pictures of food and neutral everyday objects as stimuli, was used in this study [257]. Images for the task were sourced from the *Food-Pics_Extended* database, which consists of standardized images on a white background specifically designed for experimental research on eating and appetite [256,258]. Images containing definitive grasp elements (e.g., utensils, mugs with handles) were flipped 90 degrees horizontally if the handle or grasp was not oriented to the right side.

The task comprised 16 experimental blocks, each containing 20 trials, for a total of 320 trials. Stimuli included an equal number of food and object images (160 food images and 160 object images), with food stimuli encompassing beverages (e.g., milk, orange juice) as well as healthy (e.g., fruits, vegetables, proteins) and unhealthy (e.g., highly-processed foods, chocolates, candies, cakes) food options [255–258]. Among the 16 blocks, eight designated food images (Fi) as the target “go” stimulus, while the other eight designated object images (Oi) as the target “go” stimulus [255–257]. In each block, the non-target stimulus served as the distractor (“no-go”) in a 1:1 target-to-distractor ratio [255–257]. The “shifting” aspect of the AST involves alternating the go stimulus between food and object images every two blocks, creating both new and repeated stimulus blocks conditions [255–258]. By requiring participants to suppress or initiate responses based on alternating “go” and “no-go” stimuli, the task assesses complex cognitive processes such as response inhibition, cognitive flexibility, working memory and attentional control, all key elements of executive functions. The frequent shift between food and neutral object images go signals enables researchers to evaluate how effectively individuals adapt to changing cues and resist impulsive responses [255,257].

The target “go” stimulus alternating every two blocks, created two levels of task complexity and resulted in four task conditions: FiNb, OiNb, FiRb, and OiRb [255–257]. New-stimulus blocks (Nb) required participants to reverse the stimulus-response association established in the previous block, while repeated-stimulus blocks (Rb) required them to maintain the same stimulus-response association [255–257]. The two possible starting block types thus resulted in two possible block orders: either FFOOFFOOFFOOFFOO or OOFFOOFFOOFFOOFF, which were randomized and counterbalanced across participant and sleep week. To ensure the first block was considered an Nb, each session began with a practice block of 10 trials, where the “go” stimulus was opposite to the first experimental block. A full list of the *Food-Pics_Extended* images that were used is available in Supplementary Material 1 [256,258].

5.3.4 Participant Setup and Task Execution

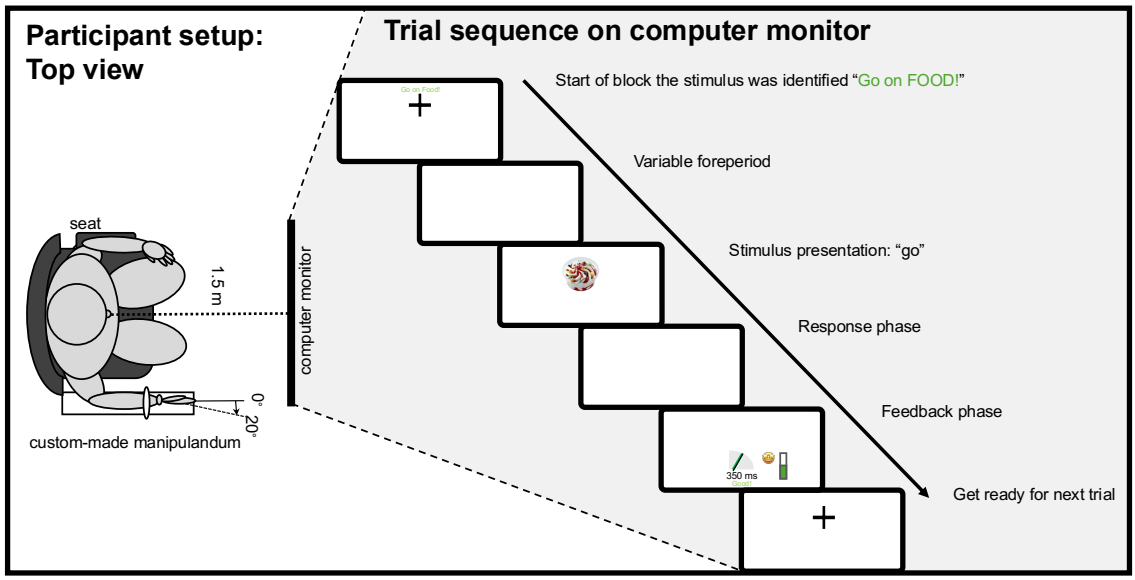
Participants were seated 1.5 meters from a computer monitor set at eye-level. Their right arm rested on a custom-made manipulandum positioned as a chair armrest, allowing wrist extension and flexion while the forearm was stabilized with a Velcro strap.

Participants were instructed to perform a brisk, 20 degree extension of their right wrist as quickly as possible in response to the “go” stimulus but to withhold movement and maintain a neutral wrist position when presented with the “no-go” distractor stimulus. Before each block, participants were informed of the current “go” stimulus via a display of “Go on FOOD” or “Go on OBJECT” above a fixation cross on the monitor. Each trial began with a fixation cross displayed for 1000 ms, followed by a blank screen (foreperiod) lasting 1000-1750 ms. Subsequently, the stimulus (either “go” or “no-go”)

appeared for 500 ms, followed by a blank screen for 1500 ms. Feedback was then displayed for 3.5 s before the next trial began. This sequence repeated until all 20 trials in a block were completed, and the process continued across all 16 blocks. On “go” trials feedback included RT, movement accuracy, and points earned or deducted. Accuracy feedback was either the word “Good” or “Bad” presented in green or red text, respectively, depending on whether the extension movement was within +/- 6 deg of the target. A single point was provided when RT was less than 400 ms, and accuracy was good, and a single point was removed if RT was greater than 600 ms and accuracy was bad, or if no movement was made. Otherwise, no points were awarded. On no-go trials a single point was awarded for correctly withholding the movement and a single point was removed for incorrectly responding. Positive points were accompanied by a “happy stary eyed” face emoji icon appearing on the screen, negative points were accompanied by a “sad” face emoji, and zero points awarded were accompanied by a “neutral flat line-mouth” face emoji. Points were provided to increase motivation and task engagement and were not analyzed.

Angular wrist movements were captured using a potentiometer attached to the pivot of the manipulandum. Surface electromyography (EMG) was collected from the right extensor carpi radialis and flexor carpi radialis muscles using biploar preamplified EMG electrodes (Delsys DE-2.1) connected to an external amplifier (Delsys Bagnoli). A grounding electrode (Easy@home) was attached to the right medial epicondyle. Electrode sites were cleansed using conductive paste (Nuprep) and alcohol wipes to decrease impedance. All data were digitally sampled at 4000 Hz (National instruments PCIe-6024). Task execution and data collection were managed using custom-made LabVIEW programs (National Instruments Inc., USA). Data recording for each trial began

1000 ms before stimulus presentation and continued for 2000 ms after, for a total sampling duration of 3000 ms. See *Figure 5* for a depiction of the participant setup and visual task sequence.



5.3.5 Figure 5. SMART2D participant setup for the Affective Shifting Task and visual trial sequence.

Note. Image 0025 from Food-Pics_Extended was used for this visual [256,258].

5.3.6 Outcome Measures

Performance metrics in the AST include commission errors (responses to no-go stimuli), which reflect the participant's level of inhibitory control and impulsivity, particularly toward salient (food) versus neutral (non-food) images [255,257]. Omission errors (failure to respond to go stimulus) provide insights into attention, working memory, and cognitive flexibility, with comparison across new and repeated stimulus blocks offering a deeper understanding of adaptability to changing cues [255,257]. RT further reveals processing speed and impulse control across these four conditions [255,257]. Altogether, the AST provides a comprehensive measure of an individual's ability to

regulate responses in the presence of image-related food cues, essential for understanding impulsive eating behaviours.

Thus, in the present study, the primary outcomes of this task were premotor RT on “go” trials, the number of commission errors on “no-go” trials, and the number of omission errors on “go” trials in each of the four conditions (FiNb, FiRb, OiNb, and OiRb) across the three sleep weeks (HB, IN, and DE) [255]. Premotor RT for “go” trials was determined based on the onset of EMG activity the right extensor carpi radialis muscle. EMG onset was defined as the point when filtered and rectified EMG activity exceeded two standard deviations above the mean baseline signal for at least 20 ms [293]. A “go” trial was included in the analysis if the movement was initiated within 850 ms of the “go” stimulus presentation and achieved a minimum wrist extension of 5 degrees.

Omission errors were defined as the failure to produce the targeted movement within 850 ms of the “go” stimulus or if the time-to-peak movement exceeded 300 ms, indicating hesitation. Commission errors were defined as wrist extension movements exceeding 2 degrees following the presentation of a “no-go” stimulus. To ensure consistency in reporting, results are discussed in terms of the image presented rather than the task designation (“go” vs. “no-go”). For example, a commission error on a food image refers to a response being made to a food image when the target “go” stimulus was an object. Conversely, an omission error on a food image refers to a failure to respond to a food image when it was the target “go” stimulus.

Finally, for this task, we also aimed to examine the potential impact of sleep manipulation on movement kinematics, specifically time-to-peak displacement and

angular movement displacement. Time-to-peak displacement was defined as the time, measured in milliseconds, from the initiation of movement to the point at which maximum displacement was reached. Angular movement displacement was defined as the difference, measured in degrees, between the neutral wrist position (the starting position) and the final position achieved during the task. Participants were instructed to perform a 20-degree wrist extension in response to the “go” stimulus, and this measure quantified the rotational movement from the neutral starting position to the endpoint.

5.3.7 Statistical Analysis

The sample size for the larger SMART2D study was determined using a power analysis targeting insulin sensitivity as the primary outcome [299]. Descriptive statistics are presented as mean and standard deviation for normally distributed continuous variables and as count and percentage for categorical variables. Statistical analyses were performed using SPSS (Version 30; SPSS Inc., Chicago, IL, USA) and JASP (Version 0.17.3, Amsterdam, Netherlands). Normality was assessed using the Shapiro-Wilk test. Repeated-measures ANOVA was conducted to evaluate total sleep time across sleep weeks and assess the effectiveness of the time-in-bed manipulations [299]. To examine the impact of sleep manipulation on inhibitory control and food impulsivity, repeated-measures ANOVAs were used to analyze premotor RT and error count (omission and commission) with 4 levels of task condition (FiNb, OiNb, FiRb, and OiRb), and 3 levels of sleep (HB, IN, and DE). Kinematic variables, including time-to-peak and movement displacement in degrees, were also analyzed across sleep weeks and conditions using repeated-measures ANOVAs. For sphericity violations identified by Mauchly’s test, Greenhouse-Geisser or Huynh-Feldt corrections were applied. Results are reported as means with standard deviations, 95% confidence intervals, and p-values, with

significance set at $p<0.05$. Post-hoc comparisons were adjusted using Bonferroni corrections, with comparisons determined a priori.

For significant interaction effects, simple main effects tests were applied using repeated-measures ANOVAs conducted to analyze all four conditions within a single sleep week, individual conditions across sleep weeks, and collapsed analyses based on image type (Fi vs. Oi) and block type (Nb vs. Rb). Effect sizes are reported as Cohen's (d) and partial eta-squared (η^2p), categorized as small ($d = 0.2$ and $\eta^2p = 0.01$), medium ($d = 0.5$ and $\eta^2p = 0.06$), or large ($d = 0.8$ and $\eta^2p = 0.14$) [312].

Finally, linear mixed models were used to assess variations related to the order of sleep manipulations (to account for order or carryover effects). These analyses were employed to examine potential covariates such as age, maturity, biological sex, socioeconomic status, recruitment priority (see *Table 3*), and whether testing occurred pre- or during the COVID-19 pandemic. These covariates were included in analyses and reported only if statistically significant.

5.4 Results

5.4.1 Table 3. Descriptive characteristics of SMART2D study participants overall and by order of intervention.

Characteristics	Overall n = 36	HBINDE order n = 18	HBDEIN order n = 18
Age (y)	15.1 (1.3)	15.4 (1.5)	14.8 (1.3)
Biological sex *n* (%):			
male	17 (47.2)	9 (50.0)	10 (55.6)
female	19 (52.8)	9 (50.0)	8 (44.4)
Gender self-identification:			
boy	16 (44.4)	9 (50)	7 (38.9)
girl	18 (50.0)	8 (44.4)	10 (55.6)
non-binary or genderqueer	2 (5.6)	1 (5.6)	1 (5.6)
Ethnicity self-identification n (%)			
Asian or Asian Indian	4 (11.1)	2 (11.1)	2 (11.1)
Black people, African descent, or Caribbean	4 (11.1)	2 (11.1)	2 (11.1)
First Nations, Métis, or Inuk	2 (5.6)	1 (5.6)	1 (5.6)
Middle Eastern or North African	5 (13.9)	3 (16.7)	2 (11.1)
Hispanic, Latino, Spanish, South America	1 (2.8)	0 (0)	1 (5.6)
White or Caucasian	20 (55.6)	10 (55.6)	10 (55.6)
Recruitment priority *n* (%):			
priority 1	20 (55.6)	13 (72.2)	7 (38.9)
priority 2	12 (33.3)	2 (11.1)	10 (55.6)
priority 3	4 (11.1)	3 (16.7)	1 (5.6)
BMI percentile	99.94 (0.07)	99.96 (0.04)	99.92 (0.08)
Tested when in relation to COVID-19 pandemic *n* (%):			
prior	20 (55.6)	12 (66.7)	8 (44.4)
during	16 (44.4)	6 (33.3)	10 (55.6)
Handiness *n* (%):			
right	33 (91.7)	16 (88.9)	17 (94.4)
left	3 (8.3)	2 (11.1)	1 (5.6)

Note. Data are presented as mean with standard deviation or as counts with percentages. For a more extensive list of characteristics on this sample see Dutil et al. [299]. In both order (HBINDE and HBDEIN), participants began with a week of habitual sleep (HB), followed by either

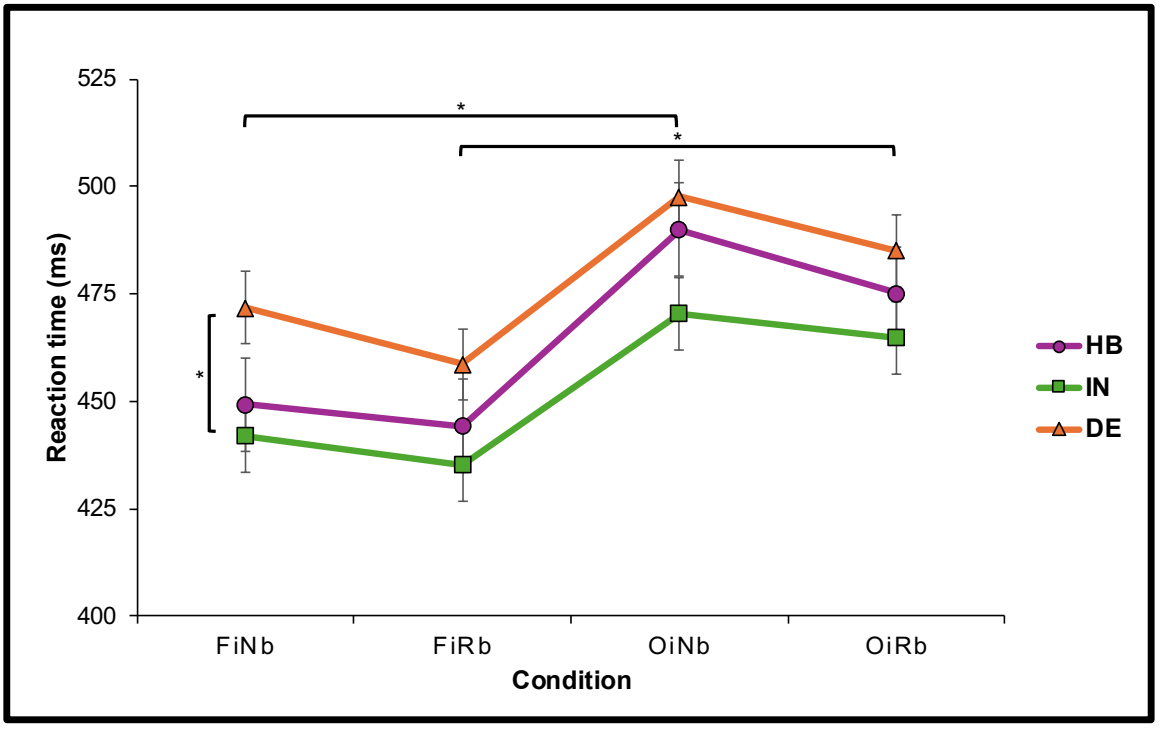
the increased sleep week (IN) or decreased sleep week (DE), and completed the alternate intervention after a washout week. Recruitment priorities were categorized as follows: "priority 1" included individuals with obesity (BMI percentile > 97th) and dyslipidemia; "priority 2" encompassed those with obesity (BMI percentile > 97th) along with non-alcoholic fatty liver disease and/or polycystic ovary syndrome; and "priority 3" focused on individuals with severe obesity (BMI percentile > 99th).

Thirty-six participants completed the sleep intervention and the AST. Basic characteristics of the SMART2D sample are presented in *Table 3*. Participants were on average 15.1 years old, 42.7% were male, 5.6% of participants (including one male and one female) identified as genderqueer or non-binary, and 44.4% identified as non-white, reflecting diverse ethnocultural backgrounds. Additionally, most participants were right-handed (91.7%). Furthermore, 88.9% of the sample exhibited significant risk factors for T2D, including having severe obesity (>99th percentile), insulin resistance, dyslipidemia, non-alcoholic fatty liver disease, and/or polycystic ovary syndrome. None of the potential covariates, such as age, maturity, biological sex, socioeconomic status, recruitment priority, and whether testing occurred pre- or during the COVID-19 pandemic, were significantly associated with any of our outcome variables (all $p > 0.4$). Additionally, according to the linear mixed models, none of the outcomes were impacted by an order or carryover effects (all $p > 0.28$).

The main findings from the SMART2D study have confirmed the effectiveness of the sleep manipulation protocol [33]. Relative to the baseline habitual sleep duration of 7 hours and 31 minutes, the protocol successfully manipulated total sleep time, increasing sleep by an average of 62 minutes per night during the increased sleep week and reducing it by an average of 79 minutes per night during the decreased sleep week, creating a nightly difference of 2 hours and 21 minutes between the two intervention weeks [299].

See *Figure 6* for a graphical representation of the analysis of RT across sleep weeks and task conditions. Repeated-measures ANOVA indicated a significant effect of sleep week on RT, $F(2, 2) = 6.94$, $p = 0.002$, $\eta^2p = 0.17$. Post-hoc examination of this effect revealed that participants exhibited significantly slower RTs following the decreased sleep week compared to the increased sleep week (DE - IN mean difference = 25.1 ms, 95% CI[8.6,41.7], $p = 0.001$, $d = 0.39$), but not compared to the habitual sleep week ($p = 0.096$). No significant differences in RT were observed between the habitual sleep and increased sleep weeks ($p = 0.096$).

A second main effect for RT, the task condition, was also significant $F(2.3, 5) = 52.31$, $p < 0.001$, $\eta^2p = 0.60$, with sphericity violations corrected using Huynh-Feldt. Post-hoc tests indicated that all conditions were significantly different from one another. The shortest RTs occurred for “go” signals involving food images compared to object images (FiNb - OiNb: mean difference = -31.6 ms, 95% CI[-41.3, -21.9], $p < 0.001$, $d = 0.49$ and FiRb - OiRb: mean difference = -29.9 ms, 95% CI[-38.6, -19.3], $p < 0.001$, $d = 0.45$). Additionally, RTs were slower in new-stimulus blocks compared to repeated-stimulus blocks (FiNb - FiRb: mean difference = 8.4 ms, 95% CI[-1.3, 18.0], $p = 0.022$, $d = 0.13$ and OiNb - OiRb: mean difference = 11 ms, 95% CI[1.3, 20.6], $p = 0.006$, $d = 0.17$).



5.4.2 Figure 6. Reaction times across sleep weeks and task conditions in SMART2D participants.

Note. Graphical representation of premotor reaction times for correct "go" responses in SMART2D participants in a within-subject design across each sleep week (habitual, increased, decreased) and task condition (FiNb, OiNb, FiRb, OiRb). Differences were analyzed using repeated-measures ANOVA, highlighting significant effects of sleep manipulations and task types ($p < 0.01$). Reaction times were only significantly different between the DE and IN sleep weeks. All sleep conditions displayed shorter RTs on Fi compared to Oi and Rb compared to Nb.*

Abbreviations: ANOVA: analysis of variance; DE: decreased sleep duration week; Fi: Go-stimulus with food images; HB: habitual sleep duration week; IN: increased sleep duration week; Nb: new stimulus block; Oi: Go-stimulus with object images; Rb: repeated stimulus block; and SMART2D: Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes.

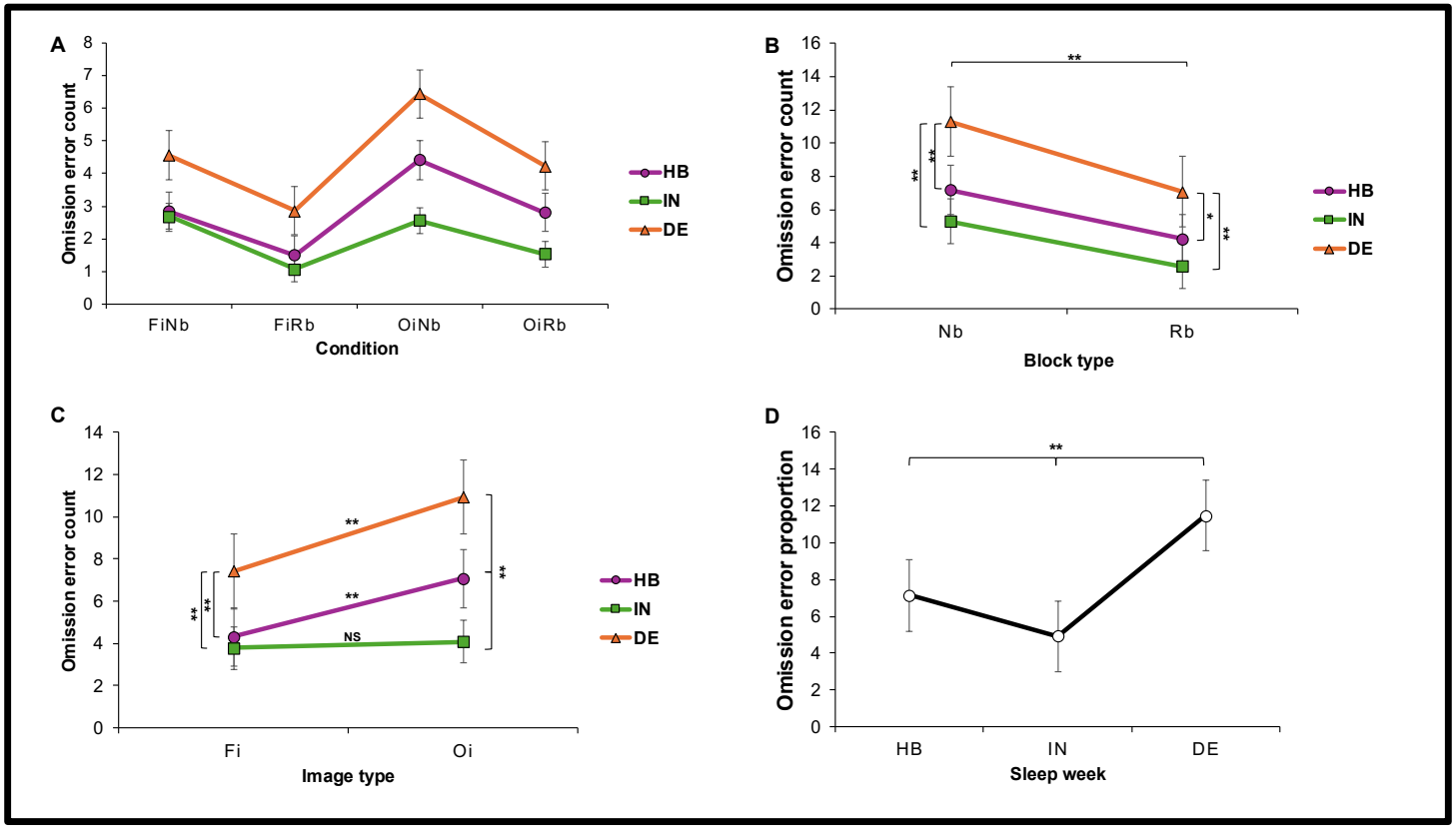
In terms of omission error counts, the main effects of sleep week and task condition were significant ($p < 0.001$ for both). Additionally, a significant interaction was found between sleep week and task condition $F(5.6, 20) = 3.26$, $p = 0.006$, $\eta^2p = 0.09$, with sphericity violations corrected using Huynh-Feldt (see *Figure 7A*).

To investigate this interaction, omission error counts were collapsed across block type (Nb vs. Rb) (see *Figure 7B*). No interaction effects were observed; however, significant main effects were found for both sleep week ($F(1.4, 2) = 25.0$, $p < 0.001$, $\eta^2p = 0.42$) and block type ($F(1,1) = 63.4$, $p < 0.001$, $\eta^2p = 0.64$), indicating their independent impact on omission errors. Post-hoc tests revealed that overall higher count of omission errors were committed following the decreased sleep week (DE - HB: mean difference = 3.5, 95% CI[1.6, 5.3], $p < 0.001$, $d = 0.64$ and DE - IN: mean difference = 5.3, 95% CI[3.4, 7.1], $p < 0.001$, $d = 0.97$, followed by the habitual week (HB - IN: mean difference = 1.8, 95% CI[-0.9, 3.6], $p = 0.022$, $d = 0.33$), and the fewest omission errors were committed following the increased sleep week. Across all sleep weeks, significantly more omission errors were committed in new-stimulus blocks (Nb - Rb: mean difference = 3.3, 95% CI[2.4, 4.1], $p < 0.001$, $d = 0.61$) compared to repeated-stimulus blocks.

To further investigate the interactions, omission error counts were collapsed across image type (food vs. objects), revealing an interaction effect $F(1.5, 2) = 10.92$, $p < 0.001$, $\eta^2p = 0.24$, (see *Figure 7C*). Post-hoc tests indicated that participants made significantly more omission errors on both food and object images following the decreased sleep week compared to the other two weeks (DE Fi – IN Fi: mean difference = 3.6, 95% CI[1.1, 6.2], $p < 0.001$, $d = 0.69$, DE Fi – HB Fi: mean difference = 3.1, 95% CI[0.6, 5.6], $p = 0.005$, $d = 0.59$, DE Oi – IN Oi: mean difference = 6.9, 95% CI[4.3, 9.3], $p < 0.001$, $d = 1.31$, and DE Oi – HB Oi mean difference = 3.9, 95% CI[1.3, 6.4], $p < 0.001$, $d = 0.74$). While no significant differences occurred for omission errors on food images between the habitual and increased sleep weeks, omission errors on object images were significantly different (HB Fi – IN Fi: mean difference = 0.53, 95% CI[-2.0, 3.0], $p = 1.00$, $d = 0.1$, and HB Oi – IN Oi: mean difference = 3.0, 95% CI[0.5, 5.5], $p = 0.008$, $d = 0.57$).

Following both the habitual and decreased sleep weeks, participants committed more omission errors on object images than food images (HB Fi – HB Oi: mean difference = -2.8, 95% CI[-4.3, -1.2], $p < 0.001$, $d = 0.53$, and DE Fi - DE Oi: mean difference = -3.5, 95% CI[-5.1, -2.0], $p < 0.001$, $d = 0.67$). However, following the increased sleep week, participants made the fewest omission errors, with no significant differences between food and object images (IN Fi – IN Oi mean difference = -0.3, 95% CI[-1.9, 1.2], $p = 1.00$, $d = 0.06$).

Finally, the proportion of omission errors varied significantly across sleep week (F (1.4, 2) = 24.9, $p < 0.001$, $\eta^2p = 0.42$) (see *Figure 7D*). All sleep weeks differed significantly, with the least proportion of omission errors committed following the increased sleep week (IN - DE: mean difference = -6.6%, 95% CI[-8.9, -4.2], $p < 0.001$, $d = 1.1$ and IN - HB: mean difference = -2.2%, 95% CI[-4.5, 0.1], $p = 0.023$, $d = 0.35$), followed by the habitual sleep week (HB - DE: mean difference = -4.4%, 95% CI[-6.7, -2.0], $p < 0.001$, $d = 0.70$), and the highest proportion of omission errors occurred following the decreased sleep week (mean = 9.2%, 95% CI[7.5,10.9]).



5.4.3 Figure 7. Omission error counts and proportions across sleep week and task conditions in SMART2D participants.

Note. Panel A: Interaction effects between sleep week and task condition on omission error counts. Panel B: Main effects of sleep week and block type (new vs. repeated stimuli) on omission error counts. Panel C: Interaction effects of sleep week and image type (food vs. objects) on omission error counts. Panel D: Proportions of omission errors across sleep weeks.

Abbreviations: DE: decreased sleep duration week; Fi: Go-stimulus with food images; HB: habitual sleep duration week; IN: increased sleep duration week; Nb: new stimulus block; NS: not significant; Oi: Go-stimulus with object images; Rb: repeated stimulus block; and SMART2D: Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes.

In terms of commission error counts, the findings were similar but mirrored in reverse to those observed for omission errors. Both main effects of sleep week and task condition were significant ($p < 0.001$ for both). Additionally, a significant interaction was found between sleep week and task condition $F(4.4, 20) = 9.1$, $p < 0.001$, $\eta^2p = 0.21$ (see *Figure 8A*).

Once again to investigate this interaction, commission error counts were collapsed across block type (Nb vs. Rb) (see *Figure 8B*). While no interaction effects were observed, significant main effects were found for both sleep week ($F(1.5, 2) = 50.2$, $p < 0.001$, $\eta^2p = 0.59$) and block type ($F(1,1) = 118.0$, $p < 0.001$, $\eta^2p = 0.77$), indicating their independent impact on commission errors. Post-hoc tests revealed that all relevant comparisons were significantly different, with the lowest commission error counts committed following the increased sleep week during repeated-stimulus blocks and the highest commission error counts were committed following the decreased sleep week during new-stimulus blocks (Nb – Rb: mean difference = 6.9, 95% CI[5.7, 8.2], $p < 0.001$, $d = 0.75$). Overall, the most commission errors were committed following the decreased sleep week (DE - HB: mean difference = 3.3, 95% CI[1.2, 5.4], $p < 0.001$, $d = 0.36$ and DE - IN: mean difference = 8.6, 95% CI[6.5, 10.7], $p < 0.001$, $d = 0.93$), followed by the habitual week (HB - IN: mean difference = 5.3, 95% CI[3.2, 7.4], $p < 0.001$, $d = 0.57$), and the fewest omission errors were committed following the increased sleep week.

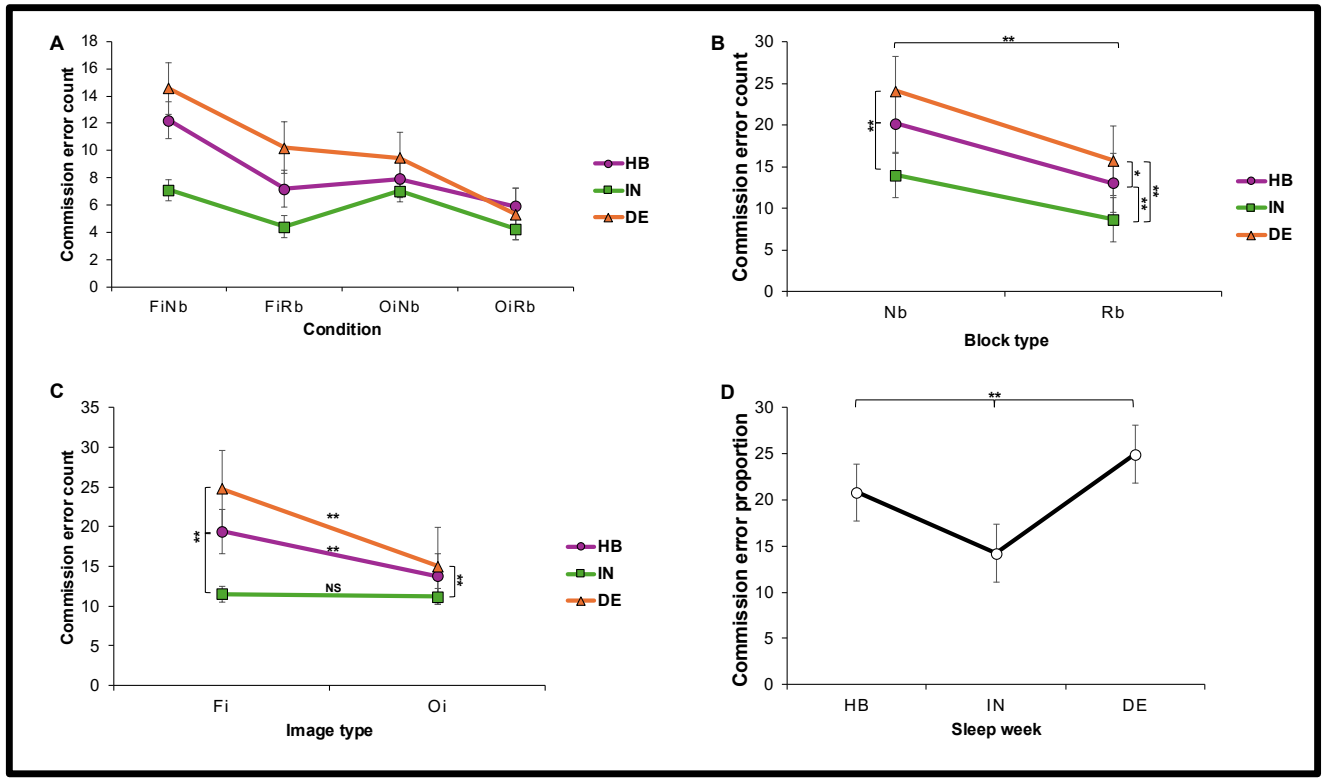
When collapsing commission error counts across image type (food vs. objects), an interaction effect was observed $F(2, 2) = 30.7$, $p < 0.001$, $\eta^2p = 0.47$, (see *Figure 8C*). The pattern was reversed as compared to omission errors. Post-hoc tests indicated that food-image commission errors differed significantly across all three sleep weeks, with the most food-image commission errors occurring following the decreased sleep week and the fewest following the increased sleep

week (DE Fi – HB Fi: mean difference = 13.3, 95% CI[10.2, 16.5], $p < 0.001$, $d = 1.46$, DE Fi – IN Fi: mean difference = 5.4, 95% CI[2.2, 8.5], $p < 0.001$, $d = 0.59$, and HB Fi – IN Fi: 7.9, 95% CI[4.8, 11.1], $p < 0.001$, $d = 0.87$). Participants committed the fewest commission errors following the increased sleep week, with no significant differences between food and object images (IN Fi – IN Oi: mean difference = 0.31, 95% CI[-2.3, 2.9], $p = 1.00$, $d = 0.03$). This pattern of no significant differences in error rates is mirrored across both error types (omission and commission) during the increased sleep week. For object images, commission errors were significantly different only between the increased and decreased sleep weeks (IN Oi - DE Oi: mean difference = -3.9, 95% CI[-7.0, -0.7], $p = 0.005$, $d = 0.43$). No significant differences were found for commission errors on object images between the habitual and increased sleep weeks or the habitual and decreased sleep weeks.

Finally, the proportion of commission errors varied significantly across sleep week (F (1.5, 2) = 50.1, $p < 0.001$, $\eta^2p = 0.58$; see *Figure 8D*). All sleep weeks differed significantly, with the lowest proportion of commission errors occurring following the increased sleep week (14.2%, IN - DE: mean difference = -10.7%, 95% CI[-13.4, -8.1], $p < 0.001$, $d = 0.98$ and IN - HB: mean difference = -6.6%, 95% CI[-9.3, -4.0], $p < 0.001$, $d = 0.61$). This was followed by the habitual sleep week (20.8%, HB - DE: mean difference = -4.1%, 95% CI[-6.8, -1.5], $p < 0.001$, $d = 0.38$). The highest proportion of commission errors, 24.9%, occurred following the decreased sleep week.

In terms of kinematic measurements, time-to-peak displacement did not differ significantly between sleep week or task condition (sleep week: F (1.7, 2) = 3.2, $p = 0.055$, $\eta^2p = 0.08$; condition: F (2.5, 5) = 0.7, $p = 0.54$, $\eta^2p = 0.02$). The mean time-to-peak was 157.1 ms (SD = 28.1) and with a coefficient of variation of 17.9% across participant. Similarly, movement

displacement in degrees showed no significant differences between sleep week or task condition (sleep week: F (1.8, 2) = 3.0, p = 0.062, η^2p = 0.06; conditions: F (3, 5) = 2.0, p = 0.12, η^2p = 0.05). The mean movement displacement was 22.6° (SD = 2.8) and with a coefficient of variation of 12.2% across participants.



5.4.4 Figure 8. Commission error counts and proportions across sleep weeks and task conditions in SMART2D participants.

Note. Panel A: Interaction effects between sleep weeks and task conditions on omission error counts. Panel B: Main effects of sleep weeks and block types (new vs. repeated stimuli) on omission error counts. Panel C: Interaction effects of sleep weeks and image types (food vs. objects) on omission error counts. Panel D: Proportions of omission errors across sleep weeks.

Abbreviations: DE: decreased sleep duration week; Fi: Go-stimulus with food images; HB: habitual sleep duration week; IN: increased sleep duration week; Nb: new stimulus block; NS: not significant; Oi: Go-stimulus with object images; Rb: repeated stimulus block; and SMART2D: Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes.

5.5 Discussion

To our knowledge, this study is the first to investigate the effect of sleep duration manipulation on food-related impulsivity in adolescents with severe obesity and at high risk for T2D (n = 36, 47% male, mean age = 15.1 years, 44% from ethnodiverse background). Using a sex-stratified, randomized, crossover design, we systematically evaluated the cognitive and behavioural impacts of increased, decreased, and habitual sleep durations. The successful sleep intervention created a 2-hour and 21-minutes difference in sleep duration between the two intervention weeks. For more detailed results on the sleep manipulation, see Dutil et al. [299].

The present findings demonstrate that decreased sleep duration significantly impaired cognitive processing. Following the decreased sleep week, participants exhibited slower RTs compared to the increased sleep week, although RTs were not significantly different from the habitual sleep week. Cognitive flexibility was notably impaired, as evidenced by increased omission errors, particularly on neutral object images compared to salient food images, and during new blocks with changing stimuli compared to repeated blocks with consistent stimuli. Across all sleep conditions, participants committed more errors on new-stimulus blocks than on repeated-stimulus blocks, highlighting the added cognitive demands posed by novel stimuli. However, RTs remained unaffected by block type, suggesting that cognitive speed was less sensitive to stimulus novelty than accuracy.

Decreased sleep led to poorer inhibitory control and heightened impulsivity toward food-related stimuli, as reflected by increased commission errors, compared to the other two weeks of sleep. These errors were significantly more frequent for food images than neutral object images and occurred more often in new blocks compared to repeated

blocks. The overall proportion of both omission and commission errors was highest following the decreased sleep week and progressively decreased with longer sleep durations. Notably, during the decreased and habitual sleep weeks, participants committed more omission errors on object images than food images, reflecting impaired mental flexibility and working memory as they struggled to “go” on neutral stimuli. Conversely, during these same sleep weeks, commission errors were more frequent for food images than for object images, indicating reduced inhibitory control in the presence of more salient stimuli.

In contrast, increased sleep duration improved cognitive and behavioural outcomes. While RTs were significantly shorter compared to the decreased sleep week only, the most notable effects were seen in the interactions between sleep week and omission and commission errors. Increased sleep significantly reduced both error types compared to the two shorter sleep duration weeks. Importantly, the biases between food and object images observed during the habitual and decreased sleep weeks were no longer evident after the increased sleep week. This suggests that sufficient sleep restored inhibitory control and cognitive balance across stimuli types, supporting adaptive decision-making processes.

Movement kinematics, including time-to-peak displacement and angular movement displacement, remained stable throughout the study and were unaffected by sleep manipulation. This stability indicates that the observed cognitive and behavioural impairments were specific to higher-order processes underlying impulsivity, attention, and working memory, rather than basic motor control.

The distinct error patterns between food and object images highlight the interplay between sleep duration, inhibitory control, and cognitive demands in suppressing impulsive behaviours toward salient stimuli such as food. These findings underscore the critical importance of adequate sleep in supporting key cognitive functions, including processing speed, attention, working memory, cognitive flexibility, and inhibitory control, particularly in adolescents at high risk for T2D.

A recent narrative review by de Klerk et al. [361] emphasized inhibitory control as a promising treatment target for obesity. The review findings highlighted that individuals with obesity, compared to healthy-weight individuals, demonstrate poorer food-specific inhibitory control, particularly when hungry, and exhibit lower activation in inhibitory brain regions [361]. However, most behavioural studies included in the review focused on adult, with one exception [361–370]. Findings from stop-signal tasks unrelated to food yielded mixed results: half of the studies reported slower RTs in adults with obesity compared to normal-weight adults, while the other half found no differences [363,364,366,367]. A single study employing a non-food-related go/no-go task found that young adults with obesity exhibited slower RTs compared to normal-weight young adults, though accuracy did not differ [362]. For go/no-go tasks involving food images, findings were inconsistent. One study in middle-aged and older adults (n = 30, age range 42–70 years, mean BMI = 31.9 kg/m²) reported null results, likely influenced by the small sample size and age variability [369]. Two other studies reported that both adults with and without obesity responded faster to food-related targets than neutral stimuli, though error rates differed: one study found higher error rates in participants with obesity, while the other reported no group differences [365,370].

Evidence in youth is more limited. Batterink et al. [368] examined 35 adolescent girls (mean age = 15.7 years) with BMIs ranging from normal weight to severe obesity using a go/no-go task [368]. The study reported a negative correlation between BMI and RT (RT; $r = -0.54$, $p = 0.001$) and a positive correlation between BMI and commission errors ($r = 0.50$, $p = 0.002$) [368]. However, the task lacked a control condition to isolate the specific effects of food cues on inhibitory processes. Importantly, none of these studies accounted for the role of sleep, despite substantial evidence linking obesity to poor sleep quality and duration. Obesity has been shown to increase the odds of poor sleep by 46% (OR = 1.46, 95% CI [1.24, 1.72]) compared to healthy-weight individuals [51].

Our findings, obtained in a population of adolescents with severe obesity, demonstrate that sleep durations below the recommended 8-10 hours per night [18] negatively impact inhibitory control and cognitive function. Both the decreased and habitual sleep weeks resulted in poorer performance, characterized by more omission errors on object images, reflecting impairments in mental flexibility and working memory, and more commission errors on food images, indicative of reduced inhibitory control. It was only following the increased sleep week that these biases between food and object images disappeared, highlighting the stabilizing effect of sufficient sleep on cognitive performance. These results emphasize that both acute sleep restriction and chronic mild sleep insufficiency are confounding factors in studies investigating cognitive impairments, particularly in high-risk populations. Addressing sleep insufficiency is crucial, as sleep is a modifiable risk factor that profoundly influences inhibitory control, mental flexibility, and decision-making processes in adolescents with obesity at high risk for T2D.

A recent sleep manipulation crossover study, by DiFrancesco and colleagues (2024), in healthy adolescents (n = 39 , mean age = 16.0 ± 1.1 years, 56.4% female) demonstrated that 5 nights of restricted sleep (6.5 hours per night) heightened activation in reward-related brain regions associated with dopaminergic drive when participants viewed food images, compared to their responses after 5 nights of healthy sleep (9 hours per night) [371]. Interestingly, despite these neural changes, sleep manipulation did not alter participants' subjective ratings of food appeal [371]. Consistent with our findings, this study highlights that obtaining adequate sleep may serve as a protective strategy to reduce food saliency, curb impulsivity, and mitigate the effects of an obesogenic environment. In our high-risk population of adolescents with severe obesity, sufficient sleep improved inhibitory control and minimized errors, reducing the cognitive biases toward food-related stimuli. During periods of restricted sleep, such as exams or high-stress situations, managing the availability of unhealthy foods may help mitigate overeating caused by heightened sensitivity in the mesolimbic reward network. This approach is particularly relevant for vulnerable populations, such as ours, where sleep insufficiency could exacerbate cognitive vulnerabilities and food impulsivity.

5.5.1 Limitations

This study has several limitations that should be acknowledged. First, the sample size, while adequate for detecting within-subject differences, was relatively small (n = 36) and may limit the generalizability of the findings to broader populations of adolescents with severe obesity and at high risk for T2D. Future studies with larger and more diverse cohorts are needed to confirm these results.

Second, while the randomized crossover design minimized individual variability and strengthened causal inferences, the study relied on a relatively short-term sleep manipulation protocol. A longer-term sleep extension intervention would be valuable to investigate whether sustained increases in sleep duration produce cumulative or more pronounced effects on cognitive and behavioural outcomes.

Third, the sleep manipulation occurred under free-living conditions, which enhanced external validity but may have introduced variability in adherence to the prescribed sleep schedules. Although objective monitoring (e.g., actigraphy) in conjunction with sleep logs was used to verify sleep duration and measure adherence, participants' home environments and routines could have influenced the results.

Fourth, the study did not include a control group of adolescents without obesity and without risk factors for T2D. Including such a group in future studies would help isolate the specific contributions of obesity and metabolic risk to the observed effects of sleep manipulation, distinguishing them from the broader impacts on cognitive and behavioural outcomes.

Finally, while this study highlights the effects of sleep duration on food-related impulsivity behaviours, further research could investigate the neural mechanisms underlying these changes. Studies employing neuroimaging techniques could offer valuable insights into the involvement of reward-related and inhibitory control regions in mediating the behavioural outcomes observed with sleep manipulation.

5.5.2 Conclusion

This novel study provides valuable first-of-its-kind evidence on the impact of sleep manipulation on cognitive and behavioural functioning in adolescents with severe obesity and at high risk for T2D. The findings emphasize the critical role of adequate sleep in mitigating cognitive vulnerabilities, such as impaired mental flexibility, reduced inhibitory control, and heightened impulsivity toward food-related stimuli. Increased sleep duration not only improved cognitive processing and behavioural outcomes but also eliminated the bias between salient and neutral stimuli, restoring cognitive balance and adaptive decision-making.

These results underscore the importance of prioritizing sufficient sleep as part of intervention strategies aimed at improving cognitive and behavioural health in this high-risk population. By integrating behavioural and neural approaches, future studies can contribute to developing more effective obesity prevention and treatment strategies that account for the critical role of sleep. In the meantime, promoting adequate sleep duration and minimizing the visibility and availability of highly processed, calorie-dense foods rich in sugar and fat may help mitigate food impulsivity and enhance cognitive control, particularly in adolescents with obesity.

5.6 Supplementary Material

5.6.1 Supplementary Table S4. List of Food-Pics_Extended images used in the SMART2D study. As per the usage guidelines for the Food-Pics_Extended image bank, the identification number of each image used is reported.

Food images: 0001, 0002, 0004, 0008, 0010, 0016, 0022, 0023, 0025, 0026, 0028, 0032, 0033, 0034, 0041, 0045, 0046, 0048, 0052, 0060, 0061, 0065, 0066, 0067, 0073, 0076, 0078, 0080, 0085, 0087, 0089, 0093, 0097, 0104, 0107, 0109, 0110, 0114, 0115, 0117, 0127, 0133, 0138, 0139, 0140, 0141, 0145, 0154, 0157, 0169, 0172, 0180, 0181, 0189, 0192, 0194, 0196, 0199, 0202, 0206, 0212, 0215, 0219, 0221, 0226, 0227, 0229, 0244, 0248, 0283, 0286, 0287, 0289, 0293, 0294, 0295, 0296, 0297, 0298, 0299, 0310, 0311, 0313, 0317, 0321, 0325, 0327, 0330, 0332, 0335, 0339, 0341, 0347, 0349, 0351, 0353, 0354, 0358, 0361, 0363, 0366, 0372, 0373, 0374, 0376, 0394, 0396, 0398, 0403, 0417, 0424, 0435, 0456, 0465, 0469, 0470, 0471, 0483, 0488, 0489, 0492, 0500, 0507, 0511, 0515, 0528, 0547, 0551, 0558, 0560, 0564, 0573, 0577, 0581, 0587, 0593, 0602, 0655, 0662, 0664, 0665, 0666, 0670, 0676, 0677, 0679, 0680, 0693, 0704, 0705, 0712, 0715, 0716, 0721, 0723, 0737, 0823, 0829, 0832, 0878.
Non-food images: 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1022, 1023,1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1035, 1036, 1038, 1039, 1043, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1055, 1056, 1058, 1059, 1060, 1080, 1083, 1084, 1085, 1086, 1092, 1094, 1095, 1096, 1098, 1112, 1113, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1187, 1188, 1194, 1195, 1198, 1199, 1200, 1202, 1207, 1208, 1209, 1210, 1211, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1221, 1222, 1223, 1225, 1229, 1231, 1232, 1234, 1236, 1237, 1238, 1239, 1240, 1241, 1242, 1243, 1245, 1246, 1247, 1248, 1249, 1250, 1252, 1256, 1258, 1259, 1260, 1261, 1262, 1263, 1264, 1265, 1266, 1267, 1268, 1269, 1270, 1271, 1272, 1273, 1275, 1276, 1277, 1278, 1279,1286, 1293, 1297, 1302, 1313, 1314.

Chapter 6

Manuscript 4:

Impact of Sleep Manipulation on Motor Preparation and Postural Control in Adolescents with Severe Obesity and High Risk for Type 2 Diabetes – A Crossover Study.

6.1 Abstract

Background: Sleep restriction has been shown to impair cognitive and motor performance, but its effects on postural control remain poorly understood, particularly in adolescents with severe obesity at risk for type 2 diabetes (T2D). Given the high prevalence of poor sleep in this population, investigating the impact of sleep manipulation on cognitive-motor integration is critical.

Objective: This study examined the effects of sleep manipulation on reaction time (RT) and postural stability in a dual-task paradigm involving a simple RT task with a startling acoustic stimulus (SAS) while standing with eyes-open and eyes-closed.

Methods: Using a randomized crossover design, adolescents aged 13–18 years completed two one-week sleep conditions: increased (+1.5h) and decreased (−1.5h) time-in-bed, based on a week of habitual sleep. RT and postural control were assessed under four conditions: control tone eyes-closed, control tone eyes-open, SAS tone eyes-closed, and SAS tone eyes-open.

Results: Sleep restriction significantly impaired voluntary RT in control trials but had no effect on SAS-evoked responses. Postural stability was also affected, with greater sway and peak velocity observed following sleep restriction, particularly during the movement phase and in SAS trials. Sleep restriction exacerbated postural instability in eyes-closed conditions, highlighting the role of visual input in balance control.

Conclusion: Compared to a week of increased sleep duration, decreasing sleep duration for one week resulted in longer response latencies to the control tone but not the SAS tone, suggesting that the sleep-induced delay stems from response execution rather than motor preparation. Additionally, postural stability was impaired following the decreased sleep week, particularly in response to the SAS tone, compared to the increased sleep week. Chronic sleep restriction in adolescents at high risk for T2D may heighten fall risk by impairing neuromuscular coordination, slowing RTs, and reducing the ability to recover from postural perturbations.

6.2 Background

Adolescence is a critical period for neurodevelopment, yet it is also a stage marked by increased vulnerability to chronic sleep insufficiency. Biological factors, such as delayed circadian rhythms, and environmental pressures, including academic demands, screen exposure, and social obligations, contribute to widespread inadequate sleep in this population [25,372–374]. A substantial proportion of adolescents fail to meet the recommended 8–10 hours of sleep per night [24,28,302,375,376], with chronic sleep restriction linked to impairments in attention, executive function, and response inhibition; key domains for academic success and overall well-being [14,146,280,377].

Beyond its impact on cognition, sleep insufficiency may pose greater risks for adolescents with severe obesity and those at high risk for T2D. Obesity and metabolic dysfunction have been associated with alterations in brain structure and function, including reduced cortical thickness, compromised white matter integrity, and executive function deficits [160–163,378–380]. Furthermore, adolescents with T2D exhibit structural and cognitive impairments, particularly in regions governing attention, memory, and motor control, raising concerns about long-term neurodevelopmental consequences [160–163,380]. Given the crucial role of sleep in metabolic regulation and cognitive function, insufficient sleep in this high-risk group may further exacerbate neural deficits and cognitive-motor impairments.

Our previous study examined the impact of habitual sleep duration on RT performance in adults using a simple RT task with a SAS [261]. Chronic short sleepers (≤6 hours per night, n = 25) and adequate sleepers (≥7.5 hours per night, n = 25) performed ballistic wrist extensions (20°) in response to either a control tone (80 dB) or a SAS (120 dB)

[261]. Our cross-sectional habitual sleep duration study aimed to determine whether chronic insufficient sleep affected motor preparation, as indexed by RT differences between voluntary (control tone) and involuntary (SAS) responses [261]. Results revealed a significant interaction between sleep duration and stimulus type. Short sleepers exhibited longer RTs following the control tone than adequate sleepers, but SAS-evoked RTs did not differ between groups, suggesting intact motor preparation despite sleep restriction [261]. Lapses and alertness levels were comparable, indicating that the performance deficits were not due to general wakefulness impairments [261]. These findings suggest that habitual short sleep affects voluntary RT performance over time, likely reflecting deficits in response execution or sustained attention rather than basic motor readiness [261].

We posited that the preserved SAS-evoked RTs stem from the subcortical nature of the response, which may be less susceptible to sleep-related impairments [261,292,297,381,382]. The reticular activating system, a neural network regulating sleep–wake cycles, arousal, and motor responses, likely plays a role in this preserved function [261,383,384]. By integrating sensory input through brainstem pathways, the reticular activating system enables a SAS to trigger a startle reflex, elicit movement at reflex-like latencies, and enhance cortical arousal [383,384]. Given that both startle reflexes and arousal regulation are mediated by the brainstem, these neural pathways may remain functionally preserved despite chronic sleep restriction [261].

To further investigate how sleep duration affects cognitive-motor interactions, incorporating postural control, a motor function with both subcortical and cortical contributions, may provide additional insights. While early research emphasized

subcortical structures (e.g., brainstem and basal ganglia) in balance maintenance [385,386], more recent evidence highlight cortical involvement (e.g., supplementary motor area, premotor cortex, and cerebellum) in anticipatory postural adjustments [273,387–389]. The prefrontal and parietal cortices also contribute to postural control in response to unexpected perturbations [390], while sensory integration for postural sway involves the parietal association cortex, insular vestibular cortex, and extrastriate body area [391]. The brainstem coordinates postural control via the reticulospinal and vestibulospinal tracts [392–394], while regions such as the midbrain and cerebellar locomotor areas regulate posture and locomotion [393,395]. The basal ganglia-brainstem loop further modulates automatic balance control through GABAergic projection [394,396].

Given the shared reliance on subcortical pathways between SAS-evoked responses and postural control, a dual-task paradigm combining these processes could clarify how sleep affects cognitive-motor integration, particularly in adolescents at high risk for T2D. By requiring participants to maintain postural control while performing an RT task with a SAS under varying conditions (e.g., standing with eyes-open vs. eyes-closed), we can assess whether sleep duration manipulation modulates compensatory mechanisms engaged when postural demands increase. This approach extends our previous findings by determining whether the preserved SAS response in sleep-restricted individuals generalizes to other predominantly subcortical motor functions, such as balance control. Using a randomized crossover design, adolescents will undergo both sleep duration restriction and extension conditions, allowing us to directly examine the effects of sleep duration on cognitive-motor interactions. We hypothesize that sleep restriction will impair cortical contributions to postural adjustments while sparing subcortical reflexive

responses, leading to increased postural sway and delayed voluntary RTs but preserved SAS-evoked responses, compared to sleep extension. These findings will provide critical insights into how sleep modulates cognitive-motor function in high-risk adolescents, informing strategies to mitigate the impact of chronic sleep insufficiency on neurodevelopment and metabolic health.

6.3 Methods

6.3.1 Ethical Approval and Study Design

The SMART2D study received ethical approval from the Research Ethics Boards at the CHEO and the University of Ottawa, Canada. Written informed consent was obtained from all participants, with a parent or legal guardian and a study staff member serving as witnesses. Data collection took place between April 2019 and December 2021. This randomized, sex-stratified crossover study was conducted under free-living conditions in Ottawa, Canada. Thirty-six adolescents with severe obesity and at high risk for T2D completed the study. Detailed protocols, including randomization procedures, recruitment strategies, intervention design, dropout management, and participant compensation, have been described elsewhere (see Dutil et al., [299]).

Eligible participants were adolescents aged 13–18 years, fluent in French or English, and at high risk for T2D without a formal diagnosis (meeting one of three recruitment categories; Table 4) [299]. They self-reported an average sleep duration of 6.5–9 hours per night over the past month and had normal or corrected-to-normal vision, no auditory impairments, and no significant physical disabilities that would interfere with task performance [299]. Exclusion criteria included diagnosed sleep disorders or severe psychiatric conditions [299]. All participants were enrolled in grades 8–12, lived within a

35-km radius of CHEO, and met screening criteria during the preliminary visit [299]. Compared to the overall SMART2D sample, two participants declined to complete this task (n = 34).

6.3.2 Sleep Intervention

Sleep duration was objectively measured using Actiwatch 2® devices (Philips Respironics, Netherlands) worn on the non-dominant wrist, supplemented by participant sleep logs. The study began with a baseline HB sleep week, requiring a minimum of 7 nights, including at least 2 weekend nights and 5 weeknights. Participants' average sleep duration during this period informed the time-in-bed adjustments for subsequent intervention weeks.

For the sleep manipulations, time-in-bed was IN and DE by 1.5 hours per night for one week each, with the intervention order randomized and stratified by sex. Two intervention orders were possible: HB-IN-DE or HB-DE-IN. Bedtimes were adjusted to achieve the target time-in-bed durations while maintaining consistent wake-up times aligned with participants' regular school schedules. The two sleep manipulation weeks were separated by a 7-night washout period to allow participants' sleep patterns to stabilize. Assessments were conducted at three time points, following the HB serving as baseline, and the IN, and DE weeks as the sleep duration manipulation weeks.

6.3.3 Experimental Task Procedures

Motor preparation and postural control while standing were assessed using a dual-task paradigm that combined a simple RT task with a SAS, utilizing two distinct sounds, under two sensory conditions eyes-open and eyes-closed. Participants completed the

assessments while standing barefoot on a force platform in a quiet, temperature-controlled room. To ensure consistency, the floor surrounding the force platform was elevated to match its height, creating a level surface (Figure 9).

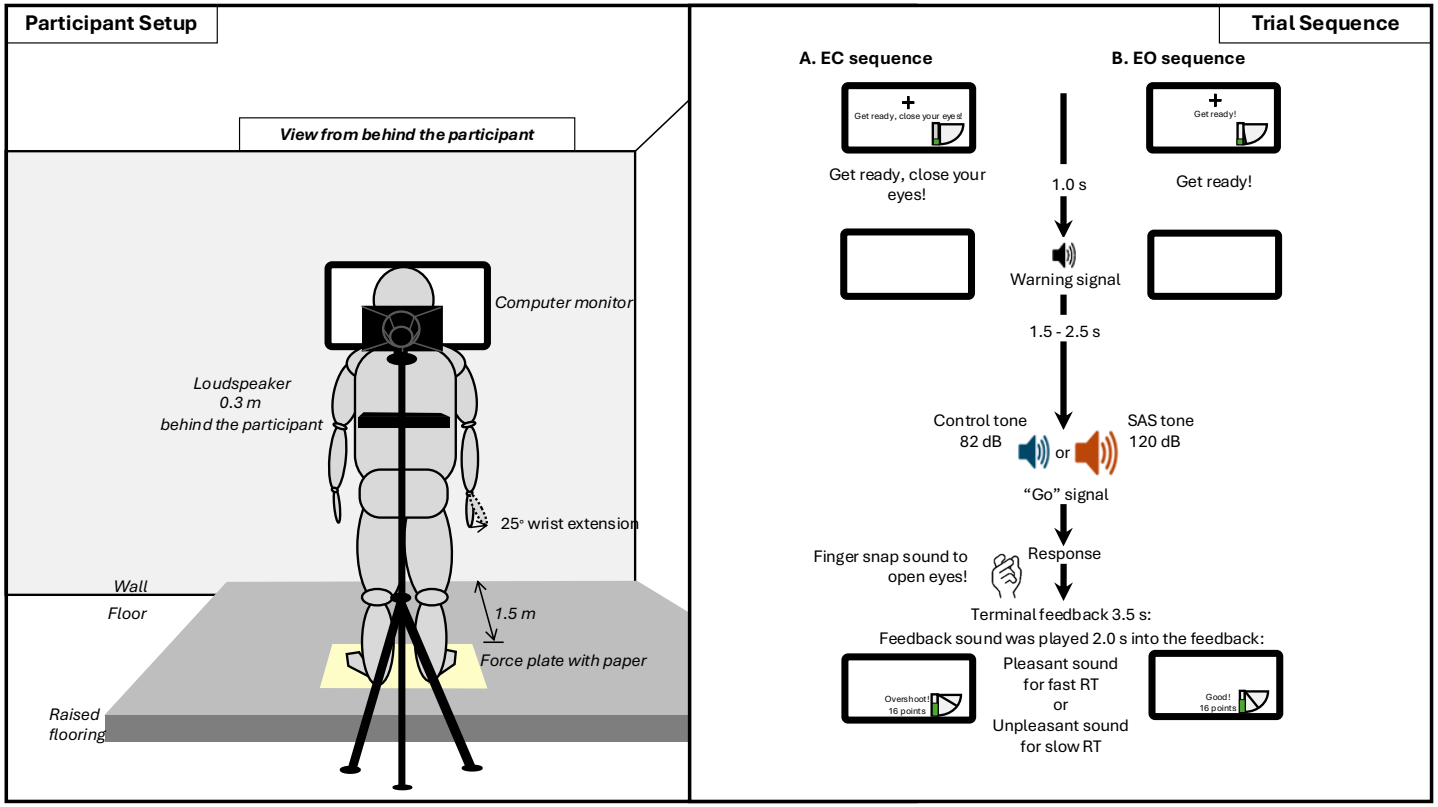
Participants' posture was standardized based on the initial posture recorded during their baseline HB assessment. During this session, participants were instructed to select a comfortable posture that they could maintain for one hour. Their feet were required to be positioned with half above the horizontal midline of the force platform and one foot on each side of the vertical midline. The position of their feet was traced and used consistently across all three assessments. The stance was approximately shoulder-width apart, with their hands resting at their sides. A 24-inch monitor was positioned 1.5 meters ahead at eye level to present task instructions and stimuli, and a tripod-mounted loudspeaker was placed 30 cm behind the participant, aligned with their ears, to deliver auditory stimuli. A twin axis electrogoniometer (SG110, Biometrics $_{Ltd}$, Newport, UK) was attached to the participant right wrist to measure wrist extension/flexion, according to manufacturer's operating manual.

The RT task required participants to perform a targeted wrist extension movement (25 degrees) with their right hand as quickly as possible in response to an auditory "go" stimulus. The go-stimuli included a control tone (1000 Hz, 100 ms duration, 80 ± 2 dB) and a SAS, consisting of an intense white noise burst (25 ms duration, 120 ± 2 dB, <1 ms rise time). Participants performed the task under four conditions: control tone with eyes-closed (C_EC), control tone with eyes-open (C_EO), SAS tone with eyes-closed (SAS_EC), and SAS tone with eyes-open (SAS_EO). First, participants completed four control blocks of 20 trials, where only the control tone was presented. Each visual

condition (eyes-open and eyes-closed) was tested in two of these blocks, which were randomized and counterbalanced for each sleep manipulation week. Following the control blocks, participants completed four experimental blocks of 32 trials, with a 1:3 ratio of SAS to control tone trials. The visual conditions in the experimental blocks followed the same order as the control blocks. Before starting the task each week, participants performed five practice trials for each visual condition to familiarize themselves with the task setup.

Each eyes-open trial began with a fixation cross, the words “Get ready!” and a real-time angular position of the participant’s right wrist displayed on the computer monitor, allowing them to return to the starting position (0°). After this, a warning tone (200 Hz, 100 ms duration, 80 ± 2 dB) was presented, and the screen turned blank, marking the preparation phase where participants were instructed to prepare their movement ahead of the “go” signal. Following the warning tone, a variable foreperiod of 1500–2500 ms preceded the second auditory tone, which served as the “go” signal. Participants were instructed to prepare during the warning phase and to respond to the “go” signal by making a 25° wrist extension movement as quickly and accurately as possible from the starting position. They were required to hold the movement at the target position until receiving terminal feedback at the end of the trial before resetting for the next trial. Terminal feedback was presented on the monitor for 3500 ms and included displacement RT, proximity to the target (categorized as “good,” “overshoot” for movements >40°, or “undershoot” for movements <10°), and points awarded. This visual feedback was accompanied by auditory RT feedback: a “pleasant chime” for fast RTs (<160 ms) and a “sad sound” for RTs deemed too slow (>220 ms) that were played at 2 s after visual feedback onset. Participants also earned points for RTs that were fast

(<160 ms), while points were deducted for RTs that were too slow (>220 ms) or for anticipatory movements performed before the “go” signal. A cumulative point system was implemented to maintain task motivation and engagement but it was not analysed. Each eyes-closed trial began similarly, with a fixation cross and the words “Get ready, close your eyes!” displayed on the monitor. Participants then closed their eyes as instructed and completed the trial under the same conditions as eyes-open. After completing the wrist extension and holding the movement at the target, participants waited for an audio cue (a “finger snap” sound) to open their eyes and view the feedback before resetting for the next trial.



6.3.4 Figure 9. Participant setup and trial sequence for a dual-task involving motor preparation during quiet standing following sleep manipulation in adolescents with severe obesity and high risk for type 2 diabetes.

Note. Participants were tested at three time points: baseline following a week of habitual sleep (HB) and after each sleep manipulation (increased and decreased sleep). Participant setup (left panel): Participants stood barefoot on a raised platform aligned with the force plate, using a standardized stance traced on a sheet of paper during the HB week and replicated across all testing sessions. A computer monitor in front of the participant displayed visual cues and a fixation cross, while a loudspeaker positioned behind them delivered auditory signals. Trial sequence (right panel): sequence A illustrates the trial structure for Eyes-Closed (EC) trials, whereas sequence B depicts Eyes-Open (EO) trials. The "go" signal was either a control tone or a startling acoustic stimulus (SAS).

6.3.5 Data Acquisition

EMG was collected from the superficial muscle bellies of the right extensor carpi radialis (prime mover), right flexor carpi radialis (antagonist), and the left orbicularis oculi ([OOc], as an indicator of the startle reflex). Bipolar, pre-amplified parallel-bar electrodes (Delsys Bagnoli DE-2.1) were used, connected via shielded cables to an external amplifier (Delsys Bagnoli-8). To minimize electrical impedance, the skin at electrode attachment sites were cleaned using abrasive gel (NuPrep) and alcohol wipes. Electrodes were aligned parallel to the muscle fibers and secured using adhesive double-sided tape. A reference electrode (Dermatrode HE-R) was placed on the right medial epicondyle. Postural stability data and ground reaction forces were collected using a force platform (KISTLER type 9286BA, Kistler Instruments AG, Winterthur, Switzerland) connected to an electric amplifier (KISTLER type 9865E, Kistler Instruments AG, Winterthur, Switzerland). Raw EMG and force platform signals were digitally sampled at 4000 Hz (PCIe-6321, National Instrument Inc. Austin, TX, USA) using a custom LabVIEW program enabling simultaneous acquisition and synchronized storage of both datasets for offline analysis. For each trial, data collection began 1000 ms prior to the presentation of the auditory “go” signal and continued for 4000 ms.

6.3.6 Outcome Measures

The primary outcome measure was premotor RT, defined as the time interval between stimulus presentation and the EMG onset of the right extensor carpi radialis muscle. EMG onset was identified as an increase in the rectified and filtered signal exceeding two standard deviations above the baseline activation, represented by the mean EMG

activity 100 ms prior to the “go” signal.

Motor preparation was evaluated using premotor RT during SAS trials where startle reflex was recorded, characterized by an EMG burst in the left OOc within 120 ms of the SAS [293]. These trials assessed the ability to release a prepared movement at a very short latency under startling conditions [292,297,298].

Alertness was measured by the proportion of errors defined as lapses during the task and the proportion of SAS trials with a startle reflex. Errors included trials with slow RTs (>600 ms), omissions (no movement), and incomplete movement (< 5 degrees of displacement). The proportion of SAS trials with a startle reflex was calculated as the percentage of trials with an OOc EMG burst relative to the total number of SAS trials [292,397].

Postural control was analyzed using ground reaction forces to compute CoP trajectories and associated metrics derived from force and moment data from a 2s windows around the go-signal representing 1s prior (during the preparation phase of the movement) and 1s after the “go” signal [286]. CoP metrics included time-domain measures such as sway area (95% confidence ellipse), path length, peak positive and negative velocities in the anterior-posterior (AP), and medial-lateral (ML) directions, as well as variability assessed using root mean square (RMS) sway in AP and ML [277,286,398,399].

Two participants from the larger SMART2D study opted out of this task, while four others were unable to complete it due to feeling unwell and requiring extended breaks during the first assessment week (HB), resulting in a significant number of missing trials, with at

least one full condition absent. Additionally, seven other participants, while completing all conditions, had missing trials due to the need for extended breaks before resuming the task. The increased variability in performance during the HB week, including slower RTs on control trials and less prepared movements, was likely due to a combination of nervousness and lack of hydration before the assessment. Notably, none of the participants reported similar discomfort during the sleep manipulation weeks (IN and DE). Given these factors and the potential for learning and order effects, outcome comparisons were restricted to the two sleep manipulation weeks, with the HB week serving as a familiarization phase. However, results from the HB week are presented in Table 5 for reference (n = 30).

6.3.7 Statistical Analysis

Descriptive statistics were calculated for all variables. Sleep data across conditions were analyzed using a repeated-measures ANOVA to confirm the effectiveness of the time-in-bed manipulations. Changes in outcomes metrics were analyzed using a 2 sleep manipulation (IN vs. DE) × 4 task condition (four sensory conditions: C_EC, C_EO, SAS_EC, SAS_EO) repeated-measures ANOVA to examine the effects of sleep manipulation on cognitive-motor performance. Greenhouse-Geisser or Huynh-Feldt corrections were applied for violations of sphericity. Bonferroni-adjusted post-hoc comparisons were conducted to further investigate significant interactions, and effect sizes were reported as partial eta-squared (η^2p) [312]. Linear mixed models were used to assess the influence of potential covariates, including age, sex, and socioeconomic status, on cognitive and postural outcomes. No covariate had a significant impact on any of our findings (all $p > 0.41$). Statistical significance was set at $p < 0.05$. All analyses

were conducted using SPSS (Version 30; SPSS Inc., Chicago, IL, USA) and JASP (Version 0.19.3, Amsterdam, Netherlands).

6.4 Results

6.4.1 Descriptive Characteristics

The descriptive characteristics of the sample (n = 34) are presented in Table 4, both overall and by order of intervention. Participants were randomized and counterbalanced to start with either decreased sleep duration (DE first, n = 17) or increased sleep duration (IN first, n = 17).

6.4.1.1 Table 4. Descriptive characteristics of study participants (n = 34).

Characteristics	Total *n* = 34	DE First *n* = 17	IN First *n* = 17
Age in years mean (SD)	15.1 (1.3)	14.8 (1.0)	15.5 (1.5)
Self-reported sex *n* (%):			
female	17 (50.0)	9 (52.9)	8 (47.1)
male	17 (50.0)	8 (47.1)	9 (52.8)
Self-identification gender identity *n* (%):			
girl	16 (47.05)	9 (52.9)	7 (41.2)
boy	16 (47.05)	7 (41.2)	9 (52.9)
non-binary or genderqueer	2 (5.9)	1 (5.9)	1 (5.9)
Self-reported pubertal maturity stage mean (range):			
female	4 (2-5)	4 (2-5)	4 (2-5)
male	4 (2-5)	4 (2-5)	4 (2-5)
Self-identification race and ethnicity *n* (%):			
Aboriginal (First Nations, Métis, or Inuk)	1 (2.9)	0 (0.0)	1 (5.9)
Asian or Asian Indian	4 (11.8)	2 (11.8)	2 (11.8)
Black people, African descent, or Caribbean	4 (11.8)	2 (11.8)	2 (11.8)
Caucasian or White people	19 (55.9)	10 (58.8)	9 (52.9)
Middle Eastern or North African	5 (14.7)	2 (11.8)	3 (17.6)
Hispanic, Latino, Spanish, South America	1 (2.9)	1 (5.9)	0 (0.0)
Proxy-socioeconomic status *n* (%):			
very-low to low	10 (29.4)	4 (23.5)	6 (35.3)
low to medium	14 (41.2)	6 (35.3)	8 (47.1)
medium to medium-high	10 (29.4)	7 (41.2)	3 (17.6)
Family history of chronic condition/disease *n* (%):			
apparently healthy parent(s)	9 (26.5)	5 (29.4)	4 (23.5)
one or both parent(s) reported having one or more chronic condition/disease	25 (73.5)	12 (70.6)	13 (76.5)
Recruitment priority *n* (%):			
priority 1: obesity > 97th percentile and dyslipidemia	18 (52.9)	6 (35.3)	12 (70.6)
priority 2: obesity >97th percentile and NAFLD and/or PCOS	12 (35.3)	10 (58.8)	2 (11.8)
priority 3: obesity > 99th percentile	4 (11.8)	1 (5.9)	3 (17.6)
Stature in cm	167.4 (8.9)	166.8 (7.8)	168.0 (10.2)
Weight in kg	112.0 (16.6)	106.1 (11.6)	117.9 (18.9)
BMI in kg/m^2	40.0 (5.0)	38.1 (2.7)	41.8 (6.1)

BMI *z*-score	3.75 (0.7)	3.50 (0.37)	4.01 (0.75)
BMI percentile	99.95 (0.04)	99.94 (0.04)	99.96 (0.04)
Fat mass percentage	47.9 (6.1)	46.8 (4.3)	48.9 (7.5)
PSQI score	6.12 (2.3)	5.88 (2.4)	6.35 (2.3)
PSQI score > 5 showing sleep difficulty *n* (%)	23 (67.6)	11 (64.7)	12 (70.6)
Tested when in relation to COVID-19 pandemic *n* (%):			
prior	19 (55.9)	8 (47.1)	11 (64.7)
during	15 (44.1)	9 (52.9)	6 (35.3)
Handedness *n* (%):			
left	3 (8.8)	2 (11.8)	1 (5.9)
right	31 (91.2)	15 (88.2)	16 (94.1)

Note. Characteristics are presented as mean, median, or counts (n) with standard deviation, range, or percentage shown in bracket. Sample size is 34 participants, which is a subsample of the overall SMART2D sample size. Abbreviations: MVPA, moderate-to-vigorous physical activity; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; PSQI, Pittsburgh Sleep Quality Index.

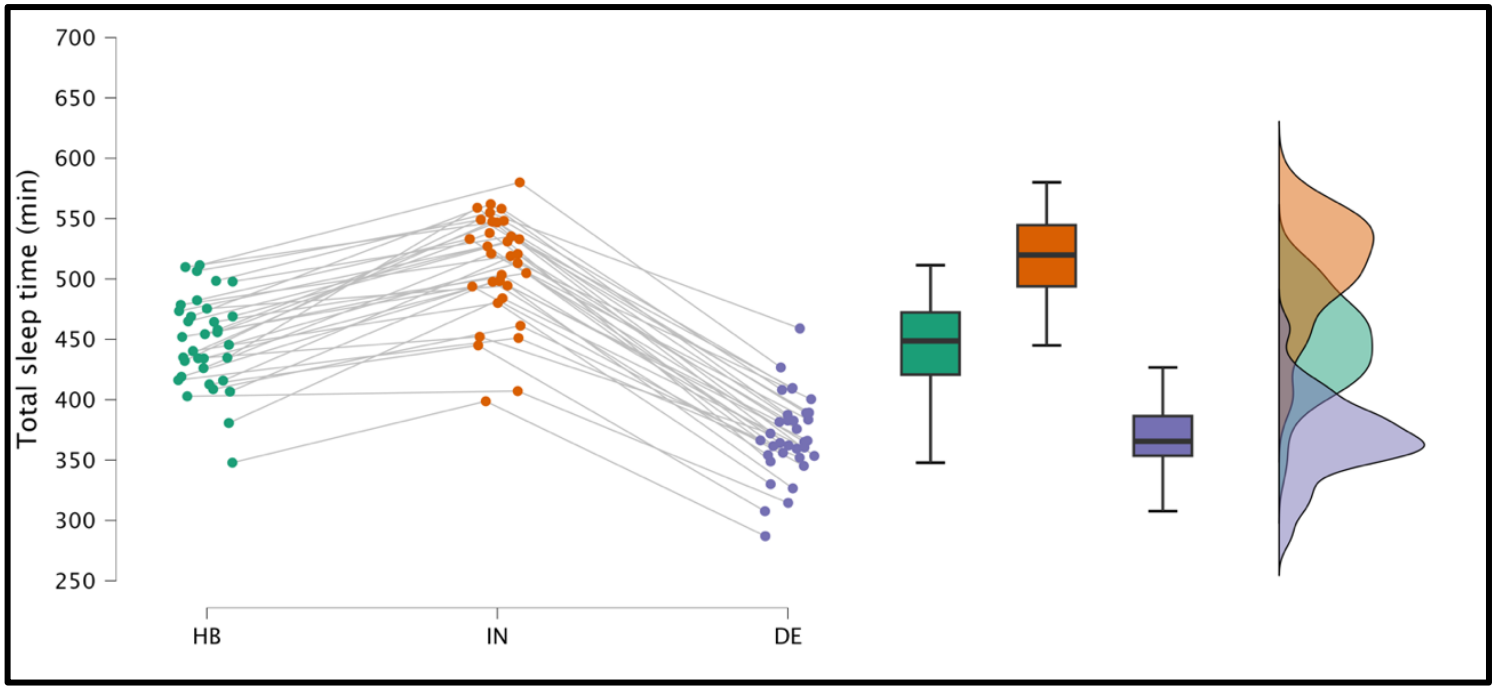
The study included 34 adolescents (50% female) with a mean age of 15.1 years (SD: 1.3). Participants exhibited severe obesity and key risk factors for T2D, with a mean BMI of 40.0 kg/m² (SD: 5.0), a BMI z-score of 3.75 (SD: 0.7), and a fat mass percentage of 47.9% (SD: 6.1). Additionally, 73.5% reported a family history of chronic disease. Regarding sleep measures, 67.6% of participants reported poor sleep quality (PSQI > 5). Approximately 55.9% of participants were tested before the COVID-19 pandemic, while 44.1% were tested during the pandemic.

6.4.2 Sleep Manipulation

Analysis of total sleep time (TST) revealed a significant main effect of sleep condition ($F(2, 66) = 398.99$, $p < 0.001$, $\eta^2_p = 0.92$), confirming the effectiveness of the sleep manipulation (Figure 10), and indicating that 92% of the variance in total sleep time was explained by the sleep condition, The mean difference in TST between the sleep extension and sleep restriction manipulation was 141.5 minutes (95% CI: 129.2, 153.8 whereby during the sleep extension condition (IN), participants increased their sleep by an average of 1 hour 3 minutes per night compared to habitual sleep ($p < 0.001$), achieving a mean TST of 8 hours 30 minutes. Conversely, during the sleep restriction condition, participants slept 6 hours 9 minutes per night, reducing their sleep by 1 hour 18 minutes compared to habitual sleep ($p < 0.001$).

Regarding adherence (were in bed at the prescribed time ± 5 minutes) to the assigned sleep conditions, participants adhered to the sleep extension manipulation 86.6% (SD: 19.6%) of the time and to the sleep restriction manipulation 81.5% (SD: 25.9%) of the time. A paired t-test ($t(33) = 0.87$, $p = 0.390$, $d = 0.15$, 95% CI: -0.190, 0.486) indicated no significant difference in adherence between conditions, suggesting that participants

maintained a similar level of adherence regardless of whether they were extending or restricting their sleep.

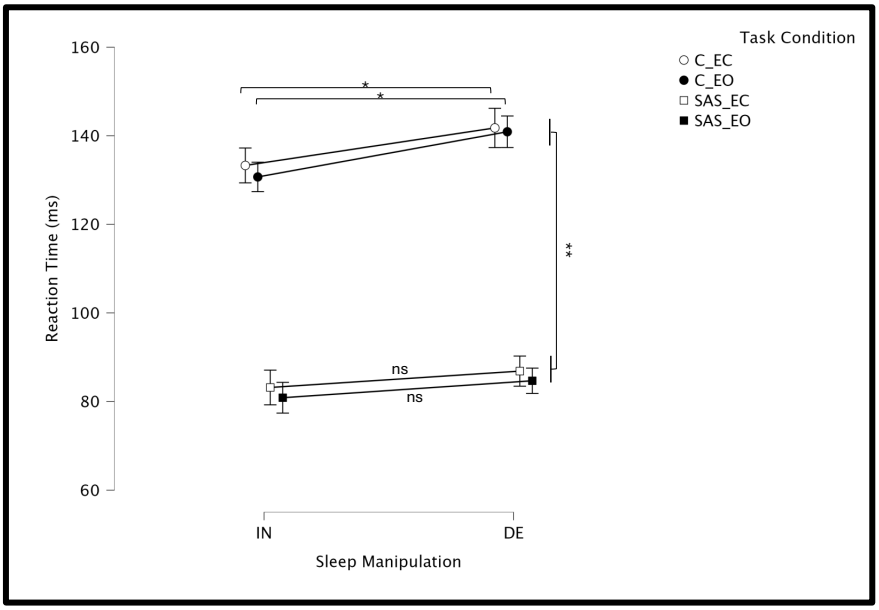


6.4.2.1 Figure 10. Total sleep time across habitual and sleep manipulation weeks, including increased and decreased sleep conditions.

Note. The figure illustrates total sleep time (TST) across the habitual (HB), increased (IN), and decreased (DE) sleep weeks. Individual participant data are shown with connecting lines, highlighting within-subject changes in sleep duration. Boxplots summarize group-level distributions, and the density plot provides an overview of TST variation across conditions. This figure plot was produced in JASP (Version 0.19.3, Amsterdam, Netherlands).

During the washout sleep week, participants slept 7 hours and 41 minutes (SD: 51.4 minutes) per night, compared to the 7 hours and 27 minutes during the HB baseline sleep week. There was no statistically significant difference between the two weeks ($t(33) = -1.80$, $p = 0.082$, $d = -0.308$), though participants who underwent sleep restriction first appeared to extend their sleep during the washout period, likely to compensate for prior sleep loss. This suggests that while the washout period was effective in allowing participants to return to their habitual sleep patterns, some variability in sleep recovery was observed.

6.4.3 Simple RT Primary Task



6.4.3.1 Figure 11. Reaction time across sleep manipulation conditions.

Note. This figure illustrate reaction time (RT) performance across sleep manipulation conditions, comparing increased sleep (IN) and decreased sleep (DE) weeks. The four task conditions – control tone with eyes-closed (C_EC), control tone with eyes-open (C_EO), startling acoustic stimulus with eyes-closed (SAS_EC), and startling acoustic stimulus with eyes-open (SAS_EO) – are displayed. Error bars represent the 95% confidence interval of the mean. (*) denotes a significant main effect of sleep manipulation on control tone RTs, (ns) indicates no significant differences for SAS trials, and (**) highlights a significant main effect of task condition between control and SAS trials. This figure plot was produced in JASP (Version 0.19.3, Amsterdam, Netherlands).

Repeated measures ANOVA revealed a significant interaction effect, $F(3, 99) = 5.44$, $p = 0.002$, $\eta^2_p = 0.15$, between the two sleep manipulation weeks and four task conditions (Figure 11). Specifically, the sleep duration manipulation differentially affected RT based on the type of auditory stimulus, but not the visual condition. RTs within the sleep week did not differ between the eyes-closed and eyes-open conditions. However, RTs for control tone conditions were significantly shorter following the increased sleep week compared to the decreased sleep week (IN-DE C EC: -8.5 ms, 95%CI[-14.2,-2.7] ms, $p < 0.001$, $d = -0.54$; and IN-DE C EO: -10.2 ms, 95%CI[-15.9,-4.4] ms, $p < 0.001$, $d = -0.65$). In contrast, RTs for the SAS trial did not significantly differ between sleep conditions.

Additionally, repeated measures ANOVA (n = 30) across all three sleep weeks (HB, IN, and DE) revealed the same interaction effect, $F(3.3, 97.0) = 18.3$, $p < 0.001$, $\eta^2_p = 0.39$, confirming that the effect of sleep week on RT varied by task condition. Specifically, RTs for control trials significantly different across all three sleep weeks, with the longest RTs occurring during the HB week and significantly decreased after both sleep manipulation weeks (IN-HB: -17.1 ms, 95% CI [-24.4, -9.8]; DE-HB: -10.4 ms, 95% CI [-17.0, -3.8]). RTs were shortest following the increased sleep week, followed by the decreased sleep week. However, RTs in SAS trials remained unchanged across sleep conditions, and no significant differences were observed between eyes-open and eyes-closed conditions. Since the HB week served as the first assessment, potentially introducing order, learning or adaptation effects, primary outcome comparisons were limited to the two sleep manipulation weeks. Additional results for the HB week are presented in Table 5.

6.4.3.2 Table 5. Habitual sleep week, baseline results for RT during the dual-task paradigm.

	Mean (SD)	Statistic (*df* effect, *df* error)	Sample size	*p-value*	Effect size
RT (ms)		HF: 144.4 (1.8, 51.7)	30	<0.001	0.83
*C_EC	159.9 (37.8)				
**C_EO	158.9 (29.0)				
SAS_EC	87.2 (12.5)			*, **	
SAS_EO	83.4 (7.9)			*, **	
Intraindividual Variability in RT (ms)		HF: 131.2 (2.4, 69.0)	30	<0.001	0.82
*C_EC	61.4 (20.4)				
**C_EO	61.2 (21.4)				
SAS_EC	14.0 (9.5)			*, **	
SAS_EO	11.6 (3.7)			*, **	
Error Percentage		HF: 61.2 (1.7, 48.0)	30	<0.001	0.68
*C_EC	5.5 (5.3)				
**C_EO	5.0 (3.2)				
SAS_EC	41.5 (24.3)			*, **	
SAS_EO	47.8 (28.3)			*, **	
Total Displacement (degree)		HF: 7.89 (2.5, 71.5)	30	<0.001	0.21
†C_EC	29.0 (6.2)				
‡C_EO	28.9 (6.7)				
SAS_EC	31.7 (8.3)			†,‡	
SAS_EO	31.9 (7.7)			†,‡	
OOc Onset (ms)		16.8 (1, 29)	30	<0.001	0.37
§SAS_EC	38.3 (4.4)				
SAS_EO	40.7 (4.0)			§	
Total Percentage of Startle	64.8 (20.6)		30		

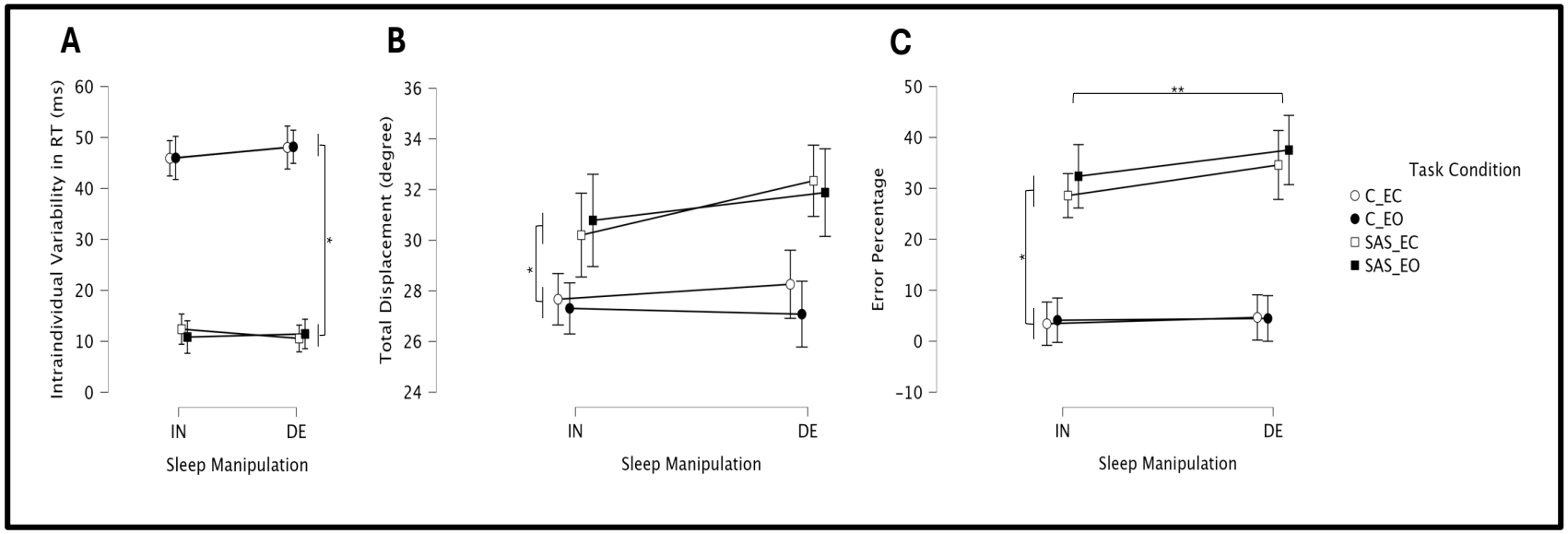
Note: Results from repeated measures comparing the conditions are presented, except for the total percentage of startle, which represents the percentage of orbicularis oculi onset among all startle tone trials. The sample size for the habitual sleep week included 30 participants, with no missing values across all four conditions. Effect size is reported using partial eta squared.

Statistical significance markers:
(*) shows significant difference between C EC and both (p < 0.001) SAS EC and SAS EO,
(**) shows significant difference between C EO and both (p < 0.001) SAS EC and SAS EO,
(†) shows significant difference between C EC and both (p < 0.05) SAS EC and SAS EO,
(‡) shows significant difference between C EO and both (p < 0.05) SAS EC and SAS EO, and
(§) shows significant difference between SAS EC and SAS EO (p < 0.001).

Abbreviations: C EC, control tone and eyes-closed condition; C EO, control tone and eyes-open condition; dƒ, degrees of freedom; HF, Huynh-Feldt correction; ms, milliseconds; OOc, orbicularis oculi; RT, reaction time; SAS EO, startling acoustic stimulus tone and eyes-open condition; SAS EC, startling acoustic stimulus tone and eyes-closed condition; SAS EO, startling acoustic stimulus tone and eyes-open condition; and SD: standard deviation.

Intraindividual variability in RTs and total displacement remained consistent across sleep manipulation weeks, $F(1, 33) = 0.90$, $p = 0.34$, $\eta^2_p = 0.03$, and $F(1, 33) = 0.90$, $p = 0.35$, $\eta^2_p = 0.03$, respectively, both indicating small effect sizes (Figure 12A, 12B). However, errors told a different story, participants made significantly more mistakes following the decreased sleep week compared to the increased sleep week, F(1, 33) = 5.3, p = 0.028, η²p = 0.14. With more sleep, participants made fewer errors (IN-DE mean difference = -3.2%, 95% CI [-6.0, -0.4]%, p = 0.028, d = 0.18) (Figure 12C).

The proportion of SAS trials where a startle response was observed (burst of EMG in OOc) did not significantly differ between the sleep manipulation weeks, $t(33) = -0.03$, $p = 0.98$, $d = -0.004$, with an average startle response rate of 75.6% (SD: 20.5%).



6.4.3.3 Figure 12. Effect of sleep manipulation on reaction time variability, total displacement and error percentage.

Note. This figure illustrates the effects of sleep manipulation on (A) intraindividual variability in reaction time (RT), (B) total displacement (degrees), and (C) error percentage across the increased sleep (IN) and decreased sleep (DE) weeks. The four task conditions: control tone with eyes-closed (C_EC), control tone with eyes-open (C_EO), startling acoustic stimulus with eyes-closed (SAS_EC), and startling acoustic stimulus with eyes-open (SAS_EO) are displayed. Error bars represent the 95% confidence interval of the mean. (*) indicates a significant main effect of task condition between control and SAS tones, while (**) denotes a significant main effect of sleep manipulation on error percentage. These figure plots were produced in JASP (Version 0.19.3, Amsterdam, Netherlands).

6.4.4 Postural Control

6.4.4.1 95% Confidence Ellipse

The 95% confidence ellipse area (calculated during the 1 second prior to the “go” signal), reflecting postural sway variability during motor preparation, was not significantly affected by sleep manipulation, $F(1, 33) = 0.29$, $p = 0.59$, $\eta^2p = 0.009$ (Table 6). However, task condition had a significant effect, $F(1.9, 64.0) = 37.37$, $p < 0.001$, $\eta^2p = 0.53$. Post hoc comparisons revealed significantly larger sway areas in eyes-closed trials than eyes-open trials for both control (C_EC > C_EO, $p < 0.001$, $d = 0.54$) and SAS (SAS_EC > SAS_EO, $p < 0.001$, $d = 0.63$) trials.

A significant interaction between sleep manipulation and task condition was found for the 95% confidence ellipse area in the 1-second before and after the “go” signal, $F(1.8, 60.3) = 3.28$, $p = 0.049$, $\eta^2p = 0.090$ (Table 7). Sleep manipulation had no significant effect on control tone trials (C_EC and C_EO), with no difference between increased and decreased sleep weeks (IN-DE C_EC: -13.03 mm², 95% CI [-37.02, 10.96], $p = 0.284$, $d = -0.18$; IN-DE C_EO: mean difference = -14.17 mm², 95% CI [-38.16, 9.81], $p = 0.244$, $d = -0.19$). However, in SAS trials, postural sway was significantly greater following decreased sleep compared to increased sleep (IN-DE SAS_EC: -46.92 mm², 95% CI [-70.91, -22.94], $p < 0.001$, $d = -0.64$; IN-DE SAS_EO: -40.24 mm², 95% CI [-64.22, -16.25], $p = 0.001$, $d = -0.55$), confirming that sleep restriction disproportionately increased sway in SAS conditions. Additionally, a significant main effect of sleep manipulation was observed, $F(1, 33) = 10.79$, $p = 0.002$, $\eta^2p = 0.25$, with greater sway after decreased sleep (DE-IN: 28.59 mm², 95% CI [10.88, 46.30], $p = 0.002$, $d = 0.39$). Task condition also had a significant main effect, $F(2.03, 66.86) = 15.63$, $p < 0.001$, $\eta^2p = 0.32$.

6.4.4.2 Root Mean Square

A significant main effect of sleep manipulation was found on RMS AP sway during motor preparation (calculated during the 1 second prior to the "go" signal), $F(1, 33) = 8.25$, $p = 0.007$, $\eta^2_p = 0.20$, with greater sway following decreased sleep (mean difference = -0.24 mm, 95% CI [-0.41, -0.07], $p = 0.007$, $d = -0.28$; Table 6). Task condition also had a significant effect, $F(3, 99) = 50.79$, $p < 0.001$, $\eta^2_p = 0.61$, with greater sway in eyes-closed trials (C_EC > C_EO, $p < 0.001$, $d = 1.02$; SAS_EC > SAS_EO, $p < 0.001$, $d = 0.96$).

A similar pattern emerged for RMS AP sway in the 1-second before and after the "go" signal, $F(1,33) = 7.79$, $p = 0.009$, $\eta^2_p = 0.19$ (Table 7). Participants exhibited greater sway following decreased sleep (IN-DE: -0.50 mm, 95% CI [-0.87, -0.14], $p = 0.009$, d = -0.30). Task condition remained a significant factor, $F(1.97, 64.89) = 67.67$, $p < 0.001$, $\eta^2_p = 0.67$, with all task conditions being significantly different from one another (all $p < 0.01$). Sway was greatest in eyes-closed conditions SAS_EC vs. SAS_EO (SAS_EC-SAS_EO = 1.62 mm, 95% CI [1.09, 2.14], $p < 0.001$, $d = 0.96$) and C_EC vs. C_EO (C_EC-C_EO = 1.30 mm, 95% CI [1.02, 1.59], $p < 0.001$, $d = 0.78$).

For RMS ML sway during the motor preparation phase, sleep manipulation had a significant effect, $F(1, 33) = 5.57$, $p = 0.024$, $\eta^2_p = 0.14$, with greater sway after decreased sleep (IN-DE: -0.15 mm 95% CI [-0.28, -0.02], $p = 0.024$, $d = -0.28$; Table 6). Task condition was observed also impacted ML sway, $F(3, 99) = 5.16$, $p = 0.002$, $\eta^2_p = 0.14$, with greater sway in C_EC vs. C_EO ($p = 0.002$, $d = 0.28$), while no significant differences were found between SAS_EC and SAS_EO.

During the 1-second before and after the “go” signal, RMS ML sway remained greater after the decreased sleep, $F(1,33) = 9.35$, $p = 0.004$, $\eta^2_p = 0.22$ (Table 7; IN-DE = -0.43 mm, 95% CI [-0.72, -0.15], $p = 0.004$, $d = -0.35$). Task condition was also a significant factor, $F(2.1, 67.7) = 20.33$, $p < 0.001$, $\eta^2_p = 0.38$, with all task conditions being significantly different from one another (all $p < 0.05$). Sway was greatest in SAS_EC, followed by SAS_EO, then C_EC, with the lowest sway in C_EO.

6.4.4.3 Total Path Length

Total path length during the motor preparation phase (calculated during the 1 second prior to the “go” signal) was significantly affected by sleep manipulation, $F(1,33) = 8.34$, $p = 0.007$, $\eta^2p = 0.20$, with longest path length during the decreased sleep week (IN-DE = -1.46 mm, 95% CI [-2.49, -0.43], $p = 0.007$, $d = -0.26$; Table 6). Task condition also had a significant effect, $F(3,99) = 51.28$, $p < 0.001$, $\eta^2p = 0.61$), eyes-closed conditions (C_EC, SAS_EC) resulted in significantly longer path length than eyes-open conditions (C_EO, SAS_EO). Greater total path length in C_EC vs. C_EO ($p < 0.001$, $d = 0.65$) and SAS_EO ($p < 0.001$, $d = 0.67$). Similarly, SAS_EC exhibited significantly greater path length than C_EO ($p < 0.001$, $d = -0.71$) and SAS_EO ($p < 0.001$, $d = 0.72$). No significant differences were found between C_EC and SAS_EC or between C_EO and SAS_EO.

Sleep manipulation had no significant effect on total path length during the 1-second before and after the “go” signal, $F(1,33) = 0.30$, $p = 0.590$, $\eta^2p = 0.01$; Table 7. However, task condition was significant, $F(3,99) = 33.83$, $p < 0.001$, $\eta^2p = 0.51$, with SAS_EC showing the longest path length, followed by SAS_EO, then C_EC, and shortest in C_EO. Post-hoc comparisons confirmed that SAS_EC had a significantly longer path

length than all other conditions (all p < 0.001), and SAS_EO had a significantly longer path length than C_EO (p < 0.001). Additionally, C_EC had a significantly longer path length than C_EO (p < 0.001), but no significant difference was observed between C_EC and SAS_EO (p = 0.07).

6.4.4.4 Peak Positive Velocity

Peak positive velocity in the AP direction, during the motor preparation phase (calculated during the 1 second prior to the "go" signal) was significantly affected by sleep manipulation, $F(1,33) = 5.82$, $p = 0.022$, $\eta^2_p = 0.15$, with higher values during the decreased sleep week compared to the increased sleep week (IN-DE: -1.99 mm/s, 95% CI [-3.66, -0.31], $p = 0.022$, $d = -0.19$; Table 6). Task condition was also significant, $F(3, 99) = 46.72$, $p < 0.001$, $\eta^2_p = 0.586$, with post hoc comparisons revealing that peak positive velocity was significantly higher in the eyes-closed conditions compared to the eyes-open conditions, regardless of stimulus type. Specifically, C_EC showed significantly higher peak velocity than C_EO (C_EC-C_EO: 7.72 mm/s, 95% CI [5.09, 10.34], $p < 0.001$, $d = 0.74$), and SAS_EC was also significantly higher than SAS_EO (SAS_EC-SAS_EO: 8.58 mm/s, 95% CI [5.96, 11.21], $p < 0.001$, $d = 0.83$). No significant differences were found between the control and SAS trials within the same visual condition (C_EC vs. SAS_EC: p = 1.000; C_EO vs. SAS_EO: $p = 1.000$).

There was no significant main effect of sleep manipulation on peak positive velocity in the AP direction during the 1-second before and after the "go" signal, $F(1,33) = 2.94$, $p = 0.096$, $\eta^2_p = 0.082$ (Table 7). However, There was a significant main effect of task condition, $F(3,99) = 26.72$, $p < 0.001$, $\eta^2_p = 0.45$, with post hoc comparisons revealing that SAS_EC had significantly higher peak positive velocity than C_EC ($p < 0.001$),

C_EO ($p < 0.001$), and SAS_EO ($p < 0.05$). Additionally, SAS_EO had significantly higher velocity than C_EC ($p < 0.01$) and C_EO ($p < 0.001$), but no significant difference was found between C_EC and C_EO ($p = 0.051$).

Peak positive velocity in the ML direction was significantly lower during the increased sleep week compared to the decreased sleep week during the motor preparation, $F(1, 33) = 40.35$, $p < 0.001$, $\eta^2_p = 0.55$ (Table 6). Post hoc analysis confirmed that velocity was significantly reduced in the IN week (IN-DE: -4.66 mm/s, 95% CI [-6.15, -3.17], $p < 0.001$, $d = -0.65$). A significant main effect of task condition was observed ($F(3, 99) = 8.44$, $p < 0.001$, $\eta^2_p = 0.20$). Post hoc comparisons revealed that peak velocity was significantly higher in the eyes-closed condition compared to the eyes-open condition for control trials (C_EC-C_EO: 2.01 mm/s, 95% CI [0.38, 3.60], $p = 0.006$, $d = 0.28$). No significant differences were found between control and SAS trials within the same visual condition (C_EC vs. SAS_EC: $p = 0.881$; C_EO vs. SAS_EO: $p = 0.516$).

There was a significant main effect of sleep manipulation on peak positive velocity in the ML direction during the 1-second before and after the “go” signal, $F(1,33) = 4.87$, $p = 0.034$, $\eta^2_p = 0.13$ (Table 7). Participants exhibited higher peak positive velocity in the ML direction during the 1-second before and after the “go” signal following decreased sleep compared to increased sleep (DE-IN: 7.17 mm/s, 95% CI [0.56, 10.8], $p = 0.034$, $d = 0.31$). There was also a significant main effect of task condition, $F(3,99) = 29.78$, $p < 0.001$, $\eta^2_p = 0.47$. Post hoc comparisons showed that peak positive velocity in the ML direction was significantly greater in SAS_EC compared to C_EC (SAS_EC-C_EC: 20.23 mm/s, 95% CI [12.21, 28.26], $p < 0.001$, $d = -0.89$) and C_EO (SAS_EC-C_EO: 22.06 mm/s, 95% CI [14.03, 30.08], $p < 0.001$, $d = -0.97$). Peak positive velocity in the

ML direction was also greater in SAS_EO vs. C_EC (SAS_EO-C_EC: 17.51 mm/s, 95% CI [9.49, 25.54], $p < 0.001$, $d = -0.77$) and SAS_EO vs. C_EO (SAS_EO-C_EO: 19.34 mm/s, 95% CI [11.31, 27.36], $p < 0.001$, $d = -0.85$). There was no significant difference between SAS_EC and SAS_EO ($p = 1.000$) or between C_EC and C_EO ($p = 1.000$).

6.4.4.5 Peak Negative Velocity

Peak negative velocity in the AP direction during the motor preparation phase (calculated during the 1 second prior to the "go" signal) was significantly lower in the increased sleep week compared to the decreased sleep week, $F(1, 33) = 5.12$, $p = 0.030$, $\eta^2_p = 0.13$ (Table 6). Post hoc comparisons confirmed that peak negative velocity was significantly less during the increased sleep week (DE-IN: 1.77 mm/s, 95% CI [0.18, 3.36], $p = 0.030$, $d = 0.22$). Task condition was also significant $F(3, 99) = 37.29$, $p < 0.001$, $\eta^2_p = 0.53$. Post hoc comparisons revealed that eyes-closed conditions resulted in significantly higher negative peak velocity compared to eyes-open conditions for both control and SAS trials. Specifically, peak negative velocity was significantly higher in C_EC vs. C_EO (C_EC-C_EO: -6.80 mm/s, 95% CI [-9.29, -4.32], $p < 0.001$, $d = -0.83$) and in SAS_EC vs. SAS_EO (SAS_EC-SAS_EO: -6.98 mm/s, 95% CI [-9.46, -4.50], $p < 0.001$, $d = -0.85$), but no significant difference was observed between control and SAS trials within the same visual condition (C_EC vs. SAS_EC: $p = 1.000$; C_EO vs. SAS_EO: $p = 1.000$).

There was a significant interaction between sleep manipulation and task condition on peak negative velocity in the AP direction during the 1-second before and after the "go" signal, $F(3,99) = 6.98$, $p < 0.001$, $\eta^2_p = 0.18$ (Table 7). Post hoc analyses revealed that sleep manipulation had no significant effect on control tone trials (C_EC and C_EO),

meaning that peak negative velocity in these conditions was not significantly different between increased and decreased sleep weeks (C_EC: p = 0.139, and C_EO: p = 0.187). However, a strong sleep manipulation effect emerged for SAS tone trials, where peak negative velocity was significantly greater following decreased sleep compared to increased sleep (IN-DE SAS_EC: 25.02 mm/s, 95% CI [16.73, 33.31], $p < 0.001$, d = 1.03 and IN-DE SAS_EO: 22.39 mm/s, 95% CI [14.11, 30.68], $p < 0.001$, d = 0.92). These results confirm that decreased sleep had a disproportionate effect on SAS trials, whereas control tone trials were unaffected by sleep condition. There was also a significant main effect of sleep manipulation, $F(1,33) = 36.27$, $p < 0.001$, $\eta^2_p = 0.52$, with participants exhibiting greater peak negative velocity following decreased sleep compared to increased sleep (IN-DE: 14.80 mm/s, 95% CI [9.80, 19.80], $p < 0.001$, d = 0.61). Additionally, there was a significant main effect of task condition, $F(3,99) = 25.97$, $p < 0.001$, $\eta^2_p = 0.44$.

Peak negative velocity in the ML direction during the motor preparation phase was significantly lower during the increased sleep week compared to the decreased sleep week $F(1, 33) = 12.93$, $p = 0.001$, $\eta^2_p = 0.28$ (Table 6). Post hoc analysis confirmed that peak negative velocity in the ML direction was lower during the IN week (IN-DE = 2.41 mm/s, 95% CI [1.05, 3.78], $p = 0.001$, $d = 0.30$) (Table 6). Task condition was also significant $F(3, 99) = 51.55$, $p < 0.001$, $\eta^2_p = 0.61$. Post hoc comparisons showed that eyes-closed conditions resulted in significantly higher negative peak velocity compared to eyes-open conditions. Specifically, C_EC had a significantly higher peak negative velocity than C_EO (C_EC-C_EO: -4.03 mm/s, 95% CI [-5.31, -2.75], $p < 0.001$, d = -0.51) and SAS_EC vs. SAS_EO (SAS_EC-SAS_EO: -4.34 mm/s, 95% CI [-5.62, -3.06], $p < 0.001$, d = -0.55), but no significant difference was found between control and SAS

trials within the same visual condition (C_EC vs. SAS_EC: p = 1.000; C_EO vs. SAS_EO: p = 1.000).

There was a significant interaction between sleep manipulation and task condition on peak negative velocity in the ML direction during the 1-second before and after the “go” signal, $F(3,99) = 4.51$, $p = 0.005$, $\eta^2_p = 0.12$ (Table 7). Post hoc analyses showed that sleep manipulation had no significant effect on control tone trials (C_EC and C_EO), as peak negative velocity did not significantly differ between increased and decreased sleep weeks (C_EC: p = 0.342, and C_EO: p = 0.230). However, a strong sleep manipulation effect emerged for SAS tone trials, where peak negative velocity was significantly greater following decreased sleep compared to increased sleep (IN-DE SAS_EC: 20.96 mm/s, 95% CI [11.28, 30.63], $p < 0.001$, $d = 0.80$; IN-DE SAS_EO: 19.33 mm/s, 95% CI [9.65, 29.00], $p < 0.001$, $d = 0.74$). These findings suggest that decreased sleep had a disproportionate effect on SAS tone trials, whereas control tone trials remained stable across sleep conditions. There was also a significant main effect of sleep manipulation, $F(1,33) = 14.13$, $p < 0.001$, $\eta^2_p = 0.30$, with participants exhibiting greater peak negative velocity in the ML direction following decreased sleep compared to increased sleep (IN-DE = 12.71 mm/s, 95% CI [5.83, 19.58], $p < 0.001$, $d = 0.49$). Additionally, there was a significant main effect of task condition, $F(3,99) = 20.08$, $p < 0.001$, $\eta^2_p = 0.38$.

6.4.5.6 Table 6. Postural stability measurements during the motor preparation phase, before the "go" signal, dual-task paradigm.

	Increased				Decreased				
	C_EC (SD)	**C_EO (SD)**	**SAS_EC (SD)**	**SAS_EO (SD)**	**C_EC (SD)**	**C_EO (SD)**	**SAS_EC (SD)**	**SAS_EO (SD)**	***p*-value**
95% confidence ellipse area (mm^2)	41.8* (28.5)	27.5* (21.2)	42.5** (33.8)	24.0** (20.5)	42.9* (26.9)	28.4* (24.0)	43.1** (25.7)	28.2** (30.6)	0.59
Root Mean Square of Anteroposterior Sway (mm)	2.32* (0.78)	1.45* (0.64)	2.29** (1.00)	1.50** (0.77)	2.53* (0.94)	1.63* (0.68)	2.62** (1.09)	1.75** (0.94)	0.007
Root Mean Square of Mediolateral Sway (mm)	0.89* (0.45)	0.73* (0.46)	0.78 (0.49)	0.69 (048)	0.97* (0.57)	0.83* (0.59)	0.99 (0.60)	0.90 (0.64)	0.024
Total Path Length (mm)	16.98* (4.54)	12.99* (4.56)	16.45** (5.57)	12.70** (4.59)	17.59* (5.45)	14.26* (5.37)	18.71** (7.27)	14.41** (6.84)	0.007
Peak Positive Velocity in Anteroposterior direction (mm/s)	28.80* (9.11)	19.86* (8.62)	27.96** (10.75)	18.36** (8.27)	28.35* (9.62)	21.86* (8.35)	30.13** (13.60)	22.57** (13.20)	0.022
Peak Positive Velocity in Mediolateral direction (mm/s)	14.43* (6.80)	12.18* (5.68)	14.89** (6.54)	13.01** (5.60)	18.52* (7.52)	16.75* (6.94)	19.84** (8.43)	18.03** (9.26)	< 0.001
Peak Negative Velocity in Anteroposterior direction (mm/s)	-25.93* (8.76)	-18.11* (6.71)	-25.12** (8.31)	-18.26** (6.23)	-26.46* (7.62)	-20.67* (11.92)	-27.24** (11.92)	-20.13** (7.31)	0.030
Peak Negative Velocity in Mediolateral direction (mm/s)	-17.82* (7.51)	-14.06* (6.23)	-18.05** (7.50)	-14.00** (6.15)	-20.53* (9.81)	-16.23* (7.32)	-20.72** (9.85)	-16.09** (8.32)	0.001

Note. Means and standard deviations (SD) are presented for the four task conditions: Control tone with Eyes-Closed (C_EC), Control tone with Eyes-Open (C_EO), Startling Acoustic Stimulus tone with Eyes-Closed (SAS_EC), and Startling Acoustic Stimulus tone with Eyes-Open (SAS_EO), across the two sleep manipulation weeks for the 1-second prior to the "go" signal. The p-values in the table represent the main effect of sleep manipulation on each respective postural and velocity measure during the motor preparation phase.

Statistical significance markers:
(*) Significant difference between C_EC and C_EO ($p < 0.01$).
(**) Significant difference between SAS_EC and SAS_EO ($p < 0.01$).

6.4.5.7 Table 7. Postural stability measurements during the 1-second motor preparation phase and 1-second following the "go" signal in a dual-task paradigm.

	Increased				Decreased				
	C_EC (SD)	**C_EO (SD)**	**SAS_EC (SD)**	**SAS_EO (SD)**	**C_EC (SD)**	**C_EO (SD)**	**SAS_EC (SD)**	**SAS_EO (SD)**	***p*-value**
95% confidence ellipse area (mm^2)	81.70* (48.90)	49.66*,†† (23.21)	100.43*,†,†† (42.32)	65.78†,†† (36.69)	94.73* (48.52)	63.83*,†† (35.27)	147.35*,†,†† (50.02)	106.02†,†† (47.60)	0.002
Root Mean Square of Anteroposterior Sway (mm)	4.24§§ (1.27)	2.99§§ (1.04)	4.80§§ (1.45)	3.44§§ (1.21)	4.65§§ (1.45)	3.29§§ (1.30)	5.70§§ (1.85)	3.83§§ (1.89)	0.009
Root Mean Square of Mediolateral Sway (mm)	2.08§§ (0.86)	1.84§§ (0.79)	2.53§§ (1.13)	2.23§§ (1.07)	2.25§§ (1.10)	2.08§§ (1.11)	3.17§§ (1.50)	2.91§§ (1.59)	0.004
Total Path Length (mm)	42.86* (18.06)	34.55*,** (17.12)	54.93*,† (29.41)	44.60**,† (25.57)	41.10* (19.88)	34.09*,** (19.10)	58.28*,† (32.06)	47.60**,† (28.03)	0.59
Peak Positive Velocity in Anteroposterior direction (mm/s)	41.35‡,‡‡ (15.43)	31.94‡,‡‡ (12.78)	65.08‡ (39.11)	53.94‡,‡‡ (31.95)	43.28‡,‡‡ (16.74)	34.21‡,‡‡ (15.78)	78.13‡ (41.17)	63.34‡,‡‡ (45.06)	0.096
Peak Positive Velocity in Mediolateral direction (mm/s)	29.07§,‡‡ (11.39)	26.21§,‡‡ (10.02)	44.72§ (25.01)	42.72‡‡ (24.17)	31.20§,‡‡ (13.10)	30.42§,‡‡ (16.00)	56.02§ (37.94)	53.15‡‡ (29.14)	0.034
Peak Negative Velocity in Anteroposterior direction (mm/s)	-34.89‡,‡‡ (10.70)	-26.27‡,‡‡ (8.05)	-49.44‡ (20.69)	-36.22‡,‡‡ (22.64)	-41.12‡,‡‡ (12.23)	-31.83‡,‡‡ (13.54)	-74.46‡ (43.70)	-58.62‡,‡‡ (37.34)	< 0.001
Peak Negative Velocity in Mediolateral direction (mm/s)	-29.69§,‡‡ (11.05)	-26.52§,‡‡ (11.31)	-40.87§ (17.00)	-37.02‡‡ (16.03)	-34.34§,‡‡ (13.85)	-32.41§,‡‡ (14.30)	-61.82§ (39.76)	-56.35‡‡ (42.10)	< 0.001

Note. Means and standard deviations (SD) are presented for the four task conditions: Control tone with Eyes-Closed (C_EC), Control tone with Eyes-Open (C_EO), Startling Acoustic Stimulus tone with Eyes-Closed (SAS_EC), and Startling Acoustic Stimulus tone with Eyes-Open (SAS_EO), across the two sleep manipulation weeks during the 1-second motor preparation phase and 1-second following the "go" signal. The p-values in the table represent the main effect of sleep manipulation on each respective postural and velocity measure during the 1-second motor preparation phase and 1-second following the "go" signal.

Statistical significance markers:
(*) Significant difference between C_EC, C_EO, and SAS_EC $p < 0.01$.
(**) Significant difference between C_EO and SAS_EO $p < 0.01$.

(†) Significant difference between SAS_EC and SAS_EO $p < 0.01$.
(††) Significant difference between C_EO and (SAS_EO and SAS_EC) $p < 0.05$.
(‡) Significant difference between SAS_EC and (C_EC, C_EO, and SAS_EO) $p < 0.05$.
(‡‡) Significant difference between SAS_EO and (C_EC and C_EO) $p < 0.01$.
(§) Significant difference between SAS_EC and (C_EC and C_EO) $p < 0.01$.
(§§) All task conditions are significantly different $p < 0.05$

6.5 Discussion

Our study population of adolescents at risk for T2D exhibited substantial burden of risk factors for the disease [99,299]. These overlapping risk factors emphasize the importance of early interventions targeting sleep to assess its impact cognitive functions. In the present study, we investigated the effect of sleep manipulation on motor preparation and postural control.

The sleep manipulation effectively altered sleep duration, with participants increasing sleep by 63 minutes during the increased sleep manipulation week and reducing it by 78 minutes during the decreased sleep manipulation week, based on an habitual sleep duration of 7 hours and 27 minutes. This created a 2 hour and 21 minutes gap between the two sleep manipulation weeks. These findings align with previous studies in youth, demonstrating that children and adolescents can reliably adjust their sleep duration in controlled experimental settings [182,400].

Overall, decreasing sleep duration led to longer RTs in response to the control tone but not the SAS tone, increased error rates, and greater RMS sway, total path length, and peak positive and negative velocities during the motor preparation phase, particularly in eyes-closed trials, compared to the increased sleep manipulation week. Additionally, during the 1 second before and after the “go” signal, decreased sleep also resulted in increased 95% confidence ellipse area, RMS sway, and peak negative velocities, as well as higher peak positive velocities in the ML direction but not in the AP direction, particularly in SAS trials, compared to increased sleep manipulation week.

6.5.1 Sleep Manipulation Effect on Simple RT Task Performance

Sleep manipulation significantly affected RTs, particularly in control tone trials, where RTs were longer following the decreased sleep week. This suggests that sleep restriction impaired basic cortical information processing speed. However, this effect was absent in SAS trials, indicating that automatic motor responses to startle stimuli remain robust despite sleep restriction. Additionally, RTs did not differ between eyes-closed and eyes-open conditions, suggesting that visual context had no influence on response latency. These findings align with our previous work [261], which demonstrated that chronic short sleepers exhibited longer RTs to control tones but showed no deficits in SAS-evoked responses, supporting the idea that a prepared movement involuntarily triggered, likely mediated by subcortical pathways, are resistant to sleep-related impairments.

Although direct comparisons of auditory RTs between eyes-open and eyes-closed conditions are limited, related research offers insights into how eye closure affects sensory processing and attention. For instance, Wöstmann et al. [401] investigated the impact of eye closure on auditory attention and found that closing the eyes increased alpha oscillatory power (~10 Hz), a neural signature of attentional focus. However, despite this neural modulation, behavioural performance in auditory tasks did not improve, suggesting that eye closure does not necessarily enhance auditory perception or response speed [401]. This aligns with our findings, where RTs remained unchanged between eyes-open and eyes-closed conditions, reinforcing the notion that visual context does not modulate auditory RT under well-controlled task conditions. This contrasts with prior research in the somatosensory domain, where eye closure was found to reduce perceptual detection at threshold levels [402,403]. The key difference, aside from

population, may be task difficulty and sensory modality. Both Wöstmann et al.'s [401] auditory task and the present study used stimuli well above sensory detection thresholds, ensuring high performance regardless of eye closure. Our results extend this understanding to motor responses, indicating that eye closure does not meaningfully affect the latency of either voluntary or startle-evoked movements. This supports the idea that the mechanisms driving auditory-motor responses are robust to visual input, at least in the context of simple, prepared, and well-learned reaction tasks.

Error rates were also affected by sleep manipulation, with participants committing more errors following the decreased sleep week compared to the increased sleep week. This suggests that sleep loss impaired task accuracy, particularly for SAS tone trials, where the difference was most pronounced. These findings contrast with our previous work [261], where chronic short sleepers did not exhibit higher error rates despite showing slower RTs to control tones.

The increase in SAS trial errors suggests that motor preparation remains necessary for response accuracy, even when the StartReact effect facilitates movement execution. This aligns with findings from psychomotor vigilance task research, which show that sleep deprivation reduces cortical excitability, leading to slower and more variable responses [404]. Additionally, sleep loss is known to increase microsleeps and attentional lapses, impairing the ability to sustain focus on an upcoming response [405]. Despite explicit instructions to prepare, participants in the decreased sleep week may have experienced brief lapses that resulted in delayed or incorrect responses. These findings suggest that while participants may remain capable of initiating a fast motor response through preserved subcortical pathways, sleep loss compromises the cortical

control processes needed to maintain response accuracy, even in individuals instructed to anticipate the stimulus.

In contrast, intraindividual RT variability and total displacement did not significantly differ between sleep conditions. The proportion of SAS trials eliciting a startle reflex did not significantly differ between sleep conditions, aligning with our previous cross-sectional findings [261]. However, these results extend prior work by demonstrating that neuromotor reactivity to startling stimuli remains unaffected by acute sleep manipulation.

Overall, these findings suggest that sleep restriction slows cognitive-motor responses and increases errors, but does not affect intraindividual RT variability, total displacement, or startle responses. The differential impact of sleep manipulation on voluntary versus reflexive responses highlights the greater vulnerability of controlled cognitive-motor processes to insufficient sleep and likely excludes motor preparation as the cause of the delays [261].

6.5.2 Sleep Manipulation Effect on Postural Stability Performance

Our findings indicate that sleep manipulation significantly influenced both postural control and RT, but in distinct ways. Sleep restriction impaired RT in control trials but had no effect on SAS trials, suggesting that voluntary response execution is more vulnerable to sleep loss than automatic StartReact responses.

Notably, the effects of sleep manipulation on postural control varied depending on the period tested. During the motor preparation phase (1 second before the “go” signal),

postural instability was more pronounced in eyes-closed vs. eyes-open trials following decreased sleep week. However, during the combined motor preparation and movement phase (1 second before and after the “go” signal), sleep restriction had a greater impact in SAS vs. control trials, suggesting that recovery from startle-evoked perturbation was more challenging compared to the increased sleep week.

According to limited resource theories of attention [406–410], interference occurs when two tasks compete for attentional resources, leading to performance decrements. Given that sleep loss reduces attentional capacity [146,405], postural stability was likely more vulnerable during movement execution rather than during motor preparation alone. While the StartReact effect resulted in shorter RTs in SAS trials, the imperative stimulus triggered the response before participants could engage in postural adjustments. However, this does not necessarily imply greater instability. Instead, the challenge may arise in the transition from movement execution to postural recovery, particularly under sleep curtailment and conditions of reduced visual input.

Previous research has shown that postural instability worsens under conditions of increased cognitive load [406,411–415], particularly when attention is divided between cognitive and motor tasks while others have found no such effect [416–419]. However, the StartReact effect does not necessarily impose cognitive load in the same way. Instead of requiring sustained attentional control, SAS bypasses cortical processing and elicits a pre-prepared movement through subcortical pathways. As a result, the postural demands in SAS trials may not stem from cognitive interference but rather from the biomechanical consequences of executing a rapid, reflexive movement. Unlike a voluntary movement, which allows for gradual acceleration and concurrent postural

adjustments, SAS-evoked responses occur abruptly, likely requiring distinct neuromuscular strategies to maintain stability.

Sensory contributions further shape these effects. Vision plays a stabilizing role in postural control [398,420,421], and the increased sway observed in eyes-closed trials suggests a greater reliance on visual input for balance, particularly under sleep-restricted conditions. Previous studies have shown that sleep loss alters visual system processing [422,423], potentially impairing the integration of visual information needed to guide postural adjustments [424–426]. The greater instability observed in eyes-closed SAS trials suggests that in the absence of visual feedback, participants relied more heavily on vestibular and proprioceptive cues, which may be more vulnerable to the effects of sleep restriction. This reliance on non-visual sensory inputs may explain why postural instability was most pronounced when movement execution was required, as visual feedback plays a critical role in real-time corrections.

The influence of sleep loss on postural stability became evident in several key measures. The 95% confidence ellipse area, a measure of sway variability, was significantly larger following sleep restriction, particularly in SAS trials during the movement phase. Similarly, RMS sway in the AP and ML directions was significantly greater following sleep restriction in both phases, with the most pronounced effects occurring during movement execution. These findings indicate that sleep restriction exacerbates postural instability, particularly when external perturbations are introduced. A few studies have reported similar effects, with sleep deprivation leading to increased postural sway and decreased stability. For instance, Robillard et al. [427] found that 25 hours of sleep deprivation resulted in greater body sway magnitude and velocity during

upright stance, indicating compromised postural control. Similarly, Aguiar and Barela [428] observed that sleep-deprived individuals exhibited impaired adaptation of sensorimotor coupling in postural control when exposed to changes in visual information, leading to reduced stability. This aligns with our findings that postural instability was more pronounced when participants lacked visual input, suggesting that sleep restriction impairs the ability to integrate multisensory cues for balance.

Finally, neuromuscular alterations may further contribute to sleep-related instability. Sleep deprivation has been associated with increased musculoskeletal stiffness [429,430] and reduced muscle sympathetic nerve activity [431], both of which could impair rapid postural adjustments. Additionally, some evidence suggests that sleep loss may increase antagonist muscle co contraction during balance tasks, potentially as a compensatory strategy to enhance joint stability at the expense of movement fluidity and responsiveness. For instance, studies using EMG analyses during postural tasks have shown greater simultaneous activation of agonist and antagonist muscles under conditions of fatigue or sleep deprivation, leading to stiffer movement patterns and reduced adaptability [432,433]. This increased co contraction may reflect a shift toward more conservative motor control strategies when cortical contributions are impaired, which could help explain the slower or less accurate adjustments observed in our postural stability findings following the decreased sleep week compared to the increased sleep week. In our study, the increased peak negative sway velocities and greater confidence ellipse area following the decreased sleep week support this interpretation, suggesting that participants may have adopted a stiffening strategy to compensate for reduced postural control efficiency under sleep restricted conditions, including in response to the SAS perturbation.

Overweight and obesity may further exacerbate these neuromuscular challenges, as excess body weight alters postural control by increasing mechanical demands and modifying sensorimotor integration [266,434,435]. Prior research has shown that children with obesity exhibit greater postural sway and increased reliance on visual feedback for balance, particularly in conditions with reduced sensory input [266,434]. The present findings align with these observations, as postural instability was most pronounced in eyes-closed SAS trials, particularly following sleep restriction. Additionally, previous studies have reported that overweight and obese individuals demonstrate slower transition times in sit-to-stand tasks and reduced efficiency in dynamic balance tasks, which may be attributed to increased inertia and reduced relative muscular strength [434,436]. These biomechanical constraints, coupled with sleep restriction, may heighten the risk of falls and instability in this population, particularly under conditions requiring rapid postural adjustments. Future research should explore how obesity-related neuromuscular adaptations interact with sleep loss to influence postural control and fall risk in high-risk populations.

6.5.3 Limitations and Future Research

Although this study provides valuable insight into the effects of sleep manipulation on postural control and RT, several limitations should be considered. First, the sample consisted of adolescents with severe obesity, a population at high risk for T2D, which enhances the clinical relevance of our findings but may limit their generalizability to other groups. Future research should explore whether similar impairments occur in adolescents with lower BMI percentiles or in adults, while also comparing high-risk

populations with healthy individuals to determine whether obesity and metabolic risk factors exacerbate the effects of sleep loss on cognitive-motor performance. Additionally, the study was conducted under controlled laboratory conditions, which, while ensuring precision in measurement, may not fully capture the complexities of real-world dual-task scenarios, such as walking while responding to auditory cues or reacting to unexpected environmental changes. Investigating these effects in dynamic postural tasks, such as gait assessments or obstacle navigation, could provide a more ecologically valid understanding of how sleep loss affects stability and movement in everyday life. Future studies should also consider the role of environmental factors, such as lighting conditions or surface stability, to better understand the interplay between sleep deprivation and postural control under different sensory and biomechanical constraints.

Another limitation is the relatively short duration of sleep manipulation, which, although sufficient to produce measurable effects, may not reflect the chronic sleep deficits experienced by many adolescents. Longitudinal studies assessing the cumulative impact of habitual sleep restriction on postural control and cognitive-motor performance are warranted. Furthermore, individual differences in sleep need and resilience to sleep loss were not explicitly examined. Future studies could explore whether baseline sleep quality, habitual sleep duration, or genetic factors influence susceptibility to postural instability following sleep restriction.

Finally, the underlying neural mechanisms remain to be fully elucidated. Functional neuroimaging studies could help clarify how sleep deprivation affects the integration of sensory inputs for postural control, particularly in the absence of visual feedback.

Additionally, interventions such as strategic naps, caffeine consumption, or exercise should be investigated as potential countermeasures to mitigate the observed impairments.

6.5.4 Conclusion

These findings underscore that decreasing sleep in adolescents at risk for T2D negatively impacts the latency of a voluntary prepared movement and postural stability while standing, compared to increasing sleep. The broader implications of sleep restriction on cognitive-motor performance are particularly relevant in real-world scenarios where individuals must maintain balance while responding rapidly to environmental stimuli. Adolescents with obesity may be at heightened risk of falls when sleep is restricted, as the combination of impaired postural control and delayed response times could hinder their ability to recover from unexpected perturbations. This concern is further exacerbated by their elevated risk for T2D, as diabetes-related complications such as retinopathy and peripheral neuropathy may further impair visual input and proprioceptive feedback, making postural stability even more precarious. These findings highlight the need for interventions that promote adequate sleep as part of broader strategies aimed at improving neuromotor function and reducing fall risk in at-risk youth.

Chapter 7

Global Discussion

7.1 Study Motivation and Broader Implications

The SMART2D study emerged from the need to understand how sleep duration impacts metabolic health in a high-risk adolescent population. Previous research primarily relied on a few cross-sectional and experimental studies conducted in healthy pediatric populations [1], leaving gaps in knowledge. Given that many adolescents fail to meet recommended sleep durations [22,24–26,28,375], understanding sleep's role in glucose metabolism is critical for shaping prevention and intervention strategies.

Additionally, this study extends beyond metabolic health by exploring the link between sleep and cognitive functions, an area understudied in youth with or at risk for T2D. Limited evidence exists regarding the potential negative impacts that T2D and the risk for T2D may have on the still-developing brain structures and functions of adolescents. Adolescents with T2D, compared to control groups, exhibit reduced grey matter volume, white matter integrity deficits affecting various brain regions, and signs of total cerebral atrophy [160–163]. Evidence from adult populations suggests that T2D is associated with cognitive deficits and Alzheimer's disease [150,154–156,437], yet little is known about these effects in adolescents. The SMART2D study provides new insights into this relationship by examining sleep-induced changes in cognitive performance and neurophysiological markers.

Sleep duration manipulation in the pediatric population has been shown to be feasible [180–182]. However, choosing the right approach for our population was crucial, requiring a balance between practicality and scientific rigor. Given the broad age range of participants in the SMART2D study (13-18 years old), we opted for an individualized sleep manipulation design rather than a fixed sleep duration manipulation. This method

was informed by the previous work of Hart et al. [182], which utilized a 3-week protocol, where children participants in free-living conditions maintained their habitual sleep for the first 7 nights, were then randomized to either increased or decreased time-in-bed by 1.5 hours per night for the next 7 nights, and subsequently completed the alternate sleep manipulation for the last 7 nights of the study.

Many of the study design elements from Hart et al. [182] were incorporated into the SMART2D study design, including the time-in-bed manipulation (+1.5h and -1.5h for one week each based on 7 nights of baseline sleep) in free-living conditions, objective sleep measurement using actigraphy, manipulation of bedtime while keeping wake time fixed, using self-reported sleep diaries, scheduling interventions outside of school vacation, daily contact with participants, combining self-reported and objective outcome measures, standardized laboratory visit timing, and the use of compensation to enhance adherence. However, the SMART2D study also introduced additional methodological refinement to increase ecological and external validity. We included an assessment following the baseline week to provide a more comprehensive picture of habitual sleep patterns before initiating the intervention, because we expected that our population would have sleep curtailment. Furthermore, to minimize potential carryover effects and allow participants' sleep to return to baseline, we incorporated a one-week washout period between the two sleep manipulation weeks.

The study was conducted during an unprecedented period, as the COVID-19 pandemic posed significant challenges to research involving human participants. Recruitment and data collection were particularly demanding, with pandemic-related restrictions leading to extended timelines and requiring rigorous safety protocols.

Despite these obstacles, the study persevered, underscoring the resilience of both researchers and participants. The pandemic also highlighted the importance of sleep, as disruptions in daily routines, increased screen time, and stress affected sleep patterns globally [438–440]. The findings from SMART2D are especially relevant in this context, reinforcing the role of sleep in metabolic and cognitive health during times of heightened stress and uncertainty.

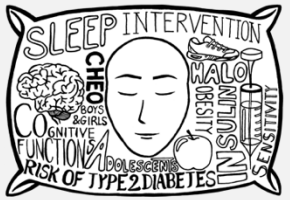
7.2 Purpose of the SMART2D Study

The purpose of the SMART2D study was to determine whether increasing time-in-bed by 1.5 hours per night for one week, compared to a week of habitual sleep duration and a week of decreasing time-in-bed by 1.5 hours per night, improves insulin sensitivity, cognitive markers and functions in adolescents aged 13–18 years at high risk for T2D. By investigating both sleep extension and restriction in a randomized crossover design, this study aimed to provide insight into the role of sleep duration as a modifiable factor in metabolic and cognitive health in a vulnerable population.

7.3 Summary of Findings

This research was inspired by the growing evidence linking inadequate sleep to metabolic dysfunction and cognitive impairments, particularly in youth with elevated obesity and diabetes risk.

SMART2D Study Key Findings Highlighted:



- **Feasibility of Sleep Manipulation:** The study confirmed that sleep duration can be effectively modified in a free-living population of adolescents at risk for T2D, with strong adherence (> 80%) to both sleep extension and restriction protocols. The time-in-bed prescription created a gap of 3 hours between the increased and decreased sleep manipulation, resulting in a 2-hour and 21-minute sleep duration difference.
- **Insulin Sensitivity**: A modest increase in sleep duration (+1h02min per night) for one week resulted in a significant (~20%) improvement in insulin sensitivity, while sleep restriction (-1h19min per night) in a population not meeting the sleep duration recommendation had no significant effect. This highlights the potential of sleep extension as an intervention for metabolic health in at-risk adolescents.
- **Glucose Regulation**: Following the increased sleep week, a greater proportion of participants displayed a biphasic glucose response (from 11% to 40%), indicative of improved insulin secretion and greater insulin sensitivity, particularly in those who were less physically mature. In those participants, a one-week sleep increase changed their glucose curve from unhealthy to healthy.
- **BDNF:** Increasing sleep duration led to a significant (~14%) decrease in serum BDNF levels compared to habitual and decreased sleep weeks. The highest insulin sensitivity coincided with the lowest BDNF levels, suggesting that sleep may modulate circulating BDNF in a way that supports glucose regulation.
- **Food-Cue Behavioural Inhibition:** Sleep restriction impaired response inhibition, particularly in the presence of food-related stimuli. Participants committed significantly more errors in the food-related impulse control task following restricted sleep duration compared to habitual and increased sleep weeks. Sleep extension improved inhibitory control and reduced impulsivity toward food cues. This improvement eliminated biases between food and object images seen in both the habitual and decreased sleep weeks, underscoring the critical role of adequate sleep in supporting inhibitory control and effective response regulation.
- **Cognitive Function and Motor Performance:** Sleep restriction led to slower RT, increased commission and omission errors, and impaired cognitive flexibility. Increasing sleep restored cognitive balance, reduced errors, and improved performance on tasks requiring response inhibition.
- **Postural Stability and Dual-Task Performance:** Sleep restriction impaired postural control. Increased sleep improved postural stability and RT to control trials, reinforcing the role of sleep in neuromotor function.

7.3.1 Figure 13. SMART2D study key findings highlighted.

Note. SMART2D Logo drawing credit to Salomé Aubert and concept by Caroline Dutil.

7.4 Recent Research Building on the SMART2D Approach

The SMART2D trial demonstrated that even modest improvements in sleep duration can significantly impact metabolic health and cognitive physiological and behavioural outcomes. Adolescents with severe obesity and at risk for T2D who extended their sleep by approximately 60 minutes per night for one week improved their insulin sensitivity by about 20% [299], showed a 14% reduction in circulating BDNF, and exhibited improved inhibitory control and reduced impulsivity toward food cues compared to both their habitual and decreased sleep weeks. Increased sleep duration also led to shorter RT in both simple and complex RT tasks and improved multiple measures of postural stability compared to a week of decreased sleep duration.

Over the last 2–3 years, several peer-reviewed studies have expanded on this approach, examining how sleep affects metabolic outcomes (such as insulin resistance and glucose metabolism) and cognitive or behavioural functions. A summary of the key findings, methodologies, and implications from these recent studies and how they relate to or build upon SMART2D findings is provided below.

7.4.1 Sleep Manipulation and Metabolic Outcomes

Multiple recent studies have used sleep manipulation (either extension or restriction) to assess its effects on metabolic health, echoing the SMART2D experimental approach: Hartescu et al. [441] conducted a randomized controlled trial examining the effects of a six-week sleep extension intervention in overweight adult men with habitually short sleep (<6.5 hours per night). Participants increased their time in bed and slept approximately 72 minutes longer per night, which led to significant reductions in insulin resistance (measured by HOMA-IR) as well as lower systolic and diastolic blood pressure [441].

The inclusion of both a control group and a population with overweight strengthens the evidence that sleep extension can produce meaningful cardiometabolic benefits in at risk adults. The rationale for manipulating sleep in adolescents at risk for T2D was partly informed by earlier work by Leproult et al. [55], who demonstrated that sleep extension improved insulin sensitivity in young adults following a 6-week sleep intervention that increased sleep by ~45 minutes per night. At the time, no similar studies had been conducted in the pediatric population, making Leproult et al.'s findings a key reference in the development of the SMART2D study. By contrast, Al Khatib et al. [442] found no significant changes in fasting insulin or glucose concentrations in healthy adults whose sleep was extended by only ~20 minutes per night during a 4-week intervention. These contrasting results suggest that both the magnitude of sleep extension and total sleep duration may be critical in achieving positive metabolic health outcomes. The SMART2D findings align more closely with those of Hartescu et al. [441] and Leproult et al. [55], indicating that a meaningful increase in sleep duration, rather than minor adjustments, is needed to elicit improvements in insulin resistance.

Zuraikat and colleagues study [443] took the opposite approach, investigating the impact of chronic sleep restriction on metabolic outcomes. In a randomized crossover trial including 38 healthy women, participants completed two 6-week conditions: one with adequate sleep (≥7 hours per night) and another with bedtimes delayed to limit sleep to approximately 6.2 hours per night [443]. Chronic mild sleep curtailment significantly impaired glucose metabolism, raising fasting insulin and HOMA-IR levels by ~12–15% compared to adequate sleep [443]. Importantly, women did not gain weight during this short period, so the decline in insulin sensitivity was independent of adiposity [443].

Furthermore, the effect was more pronounced in postmenopausal women, suggesting that certain groups may be more vulnerable to sleep restriction and at heightened risk for metabolic dysfunction [443].

Beyond insulin measures, dietary intake is another key metabolic outcome influenced by sleep duration. Tasali and colleagues [444] conducted a randomized controlled trial, in free-living conditions. Participants (80 adults with overweight, habitually <6.5h sleep) were randomized to either a 2-week sleep extension condition (8.5h time-in-bed) or a 2-week of habitual sleep duration condition (control) [444]. The sleep-extension group increased their sleep duration by ~1.2 h per night which led to a decrease in caloric intake of ~270 kcal/day and a modest reduction in weight, compared to control [444]. Participants who slept longer also consumed fewer energy-dense, high-glycemic foods in the evening, which is a pattern that could promote better long-term weight and glycemic control [444].

A randomized controlled trial by Hart et al. [445] tested a behavioural sleep intervention in children aged 8–11 years (n = 78) who habitually slept < 9.5 h per night. The intervention successfully increased sleep duration by 40 minutes per night for the 8-week intervention compared to controls. While no significant differences in BMI or caloric intake were found between groups, post-hoc analyses revealed that children who increased their sleep by at least 30 minutes per night showed reduced fat intake and lower BMI after two months [445]. These findings suggest that even small increases in sleep duration could support long-term weight management, highlighting sleep as a promising target for early obesity prevention efforts [445]. Targeting sleep duration in prepubescent children may be particularly beneficial, as establishing healthy sleep

habits early could help mitigate the accumulation of metabolic risk factors that often emerge or intensify during adolescence.

SMART2D did not observe significant dietary intake changes due to sleep manipulation (possibly due to the short intervention duration and reliance on self-reported diet logs). However, participants consumed significantly fewer calories during the ad libitum lunch following the habitual sleep week compared to both sleep manipulation weeks, with no significant differences between the increased and decreased sleep conditions.

Collectively, these trials demonstrate that adjusting sleep duration, either by increasing or decreasing it, has measurable effects on metabolic health markers such as insulin resistance, blood sugar regulation, blood pressure, energy balance, and dietary choices. These studies build upon SMART2D's findings by investigating a range of populations, including adults and adolescents, as well as healthy and at-risk individuals, while also utilizing longer intervention periods. The consistent evidence across diverse groups highlights the importance of incorporating sleep-focused interventions into comprehensive strategies for promoting metabolic health and preventing disease.

7.4.2 Insulin Sensitivity and Glucose Metabolism in Adolescents

Recent research has increasingly focused on adolescence, a critical period for metabolic health, to further examine the relationship between sleep and glucose regulation. The SMART2D study provided experimental evidence that improving sleep enhances insulin sensitivity in at-risk teens. Recent observational studies have reinforced and extended these findings.

A longitudinal study following ~350 late-adolescents over two years investigated whether habitual sleep patterns predict the development of insulin resistance [446]. Using wrist actigraphy, researchers found that chronic short sleepers (i.e., those who consistently slept at least one hour less than the recommended duration) were 2.74 times more likely to develop insulin resistance over time compared to their peers who achieved adequate sleep [446]. Similarly, adolescents with very late sleep timing (i.e., a delayed circadian phase) had 2.63 times higher odds of developing insulin resistance than those with earlier sleep midpoints (1 to 3 AM) [446]. These associations held even after adjusting for changes in body fat, indicating sleep duration and timing independently influence glucose metabolism in youth [446]. Such results align with SMART2D's causal trial showing that short sleep (both during the habitual and decreased sleep week) leads to poorer insulin sensitivity, which suggests that even in free-living settings, teens who don't get enough sleep are on a path toward metabolic dysfunction.

Cross-sectional research has further reinforced the connection between poor sleep and metabolic risk in adolescents. A cross-sectional analysis of the same adolescent cohort found that shorter sleep duration and later weekday sleep midpoints were associated with higher insulin resistance (HOMA-IR), with these associations being stronger in girls than boys [447]. Another cross-sectional study of 124 adolescents with metabolic syndrome classified participants based on self-reported sleep duration (<8 hours vs. >8 hours per night) and found that shorter sleep was negatively associated with insulin sensitivity [448].

Additionally, research on ~150 adolescents with obesity investigated the relationship between metabolism, melatonin secretion, and sleep behaviours [449]. Findings

revealed that adolescents with insulin resistance (n = 101) had significantly lower nocturnal melatonin levels than those without insulin resistance [449]. Moreover, melatonin secretion was negatively associated with uric acid and triglyceride levels, even after adjusting for sex, age, and Tanner stage [449]. These findings suggest that both sleep duration and underlying circadian factors play an important role in metabolic regulation in adolescents.

Recent adolescent-focused research further supports the critical role of sleep in metabolic health during this developmental stage. Sufficient sleep may serve as a protective factor against insulin resistance, while chronic insufficient sleep and circadian misalignment may accelerate early metabolic changes. These findings expand upon the SMART2D approach, demonstrating that the benefits of sleep extension are observable not only in controlled experimental conditions but also in real-world adolescent populations over time. They highlight the importance of prioritizing healthy sleep habits in youth as a strategy to mitigate the risk of prediabetes and T2D.

7.4.3 Sleep's Role in Behavioural and Cognitive Functions

Adequate sleep is not only vital for metabolic regulation but also for optimal behavioural and cognitive functioning. Expanding on SMART2D's experimental manipulation approach, other researchers have examined how changing sleep duration affects adolescents' brain function, mood, and behaviour.

A recent randomized crossover study investigated the cognitive effects of acute sleep restriction in adolescents, focusing on how adiposity influences cognitive vulnerability [450]. In this study, 61 teenagers (ages 14–19) underwent two sleep conditions: one

night of adequate sleep (~9 hours) and one night of severe sleep restriction (~4 hours), with at least two nights of washout sleep in between before switching conditions [450]. Findings revealed that adolescents with overweight or obesity experienced significant cognitive impairments following sleep restriction, whereas their normal-weight peers maintained stable cognitive performance [450]. Specifically, sleep deprivation in higher-adiposity teens resulted in slower processing speed, reduced working memory, impaired cognitive flexibility, and weaker inhibitory control (measured via the Stroop test) [450]. These impairments were not observed in normal-weight adolescents, suggesting that youth with obesity may be more susceptible to cognitive deficits from insufficient sleep [450]. This study reinforces the role of adequate sleep in learning, memory, and executive function, particularly for those already facing metabolic health risks. However, given the short intervention duration (one night of sleep manipulation), further research is needed to determine whether longer sleep interventions yield sustained cognitive benefits.

Beyond acute cognitive effects, research suggests that chronic sleep deprivation may have lasting impacts on brain development and mental health. A longitudinal study analyzing data from the Adolescent Brain Cognitive Development (ABCD) cohort examined how consistent short sleep (<9 hours per night) affects neurocognitive and emotional health over time [451]. At baseline, researchers matched 3,021 children (ages 9–10) based on their sleep patterns and followed a subset of 749 matched pairs for two years [451]. Results showed that children who consistently slept less than 9 hours per night had higher levels of depression, anxiety, and impulsivity compared to those who met sleep duration recommendations [451]. These sleep-deprived children also performed worse on memory, decision-making, and problem-solving tasks and exhibited

reduced gray matter volume in brain regions associated with learning and cognitive control [451]. Notably, these differences persisted over the two-year follow-up, indicating that the effects of chronic insufficient sleep on cognitive and emotional health are long-lasting rather than temporary [451].

This large-scale observational study complements experimental research by highlighting both the immediate and long-term consequences of insufficient sleep in adolescents. While short-term lab-based studies, such as Stager et al. [450], demonstrate acute cognitive impairments from sleep loss, longitudinal data from Yang et al. [451] suggest that chronic inadequate sleep disrupts brain development and psychological well-being. Together, these findings underscore the importance of sleep for attention, memory, emotional regulation, and cognitive health throughout adolescence.

By demonstrating that adequate sleep supports both metabolic health and cognitive-behavioural functioning, recent research reinforces the importance of integrating sleep interventions into broader adolescent health strategies. Just as SMART2D showed that sleep extension enhances insulin sensitivity, cognitive performance, and postural stability, growing evidence suggests that sufficient sleep may also promote better academic achievement, emotional resilience, and long-term neurodevelopmental health. Recognizing sleep as a foundational component of both physical and mental well-being could inform future preventive efforts aimed at optimizing adolescent health outcomes.

7.4.4 Sleep Duration Interventions in High-Risk Populations

Several recent studies have focused on high-risk populations to assess how sleep interventions might mitigate metabolic and cognitive risks in those most susceptible to

adverse health outcomes. This aligns with SMART2D's approach, which prioritized adolescents with severe obesity and elevated T2D risk as a population that could benefit the most from sleep modification.

Recent findings suggest that adolescents with obesity may be more vulnerable to cognitive impairment following sleep restriction compared to their peers with normal weight. As noted above, Stager et al. [450] found that when sleep was restricted for a single night, adolescents with high adiposity exhibited notable declines in cognitive performance, while those with normal weight showed minimal effects. Given these findings, targeting sleep improvement in adolescents with obesity may be particularly beneficial, as it could help prevent or mitigate cognitive deficits that may impact academic performance and daily functioning.

In adults, sleep interventions have mainly focused on habitually short sleepers or those with pre-existing metabolic risk factors. For example, Hartescu et al. [441] examined the effects of sleep extension in men with obesity and chronic short sleep and found that increasing sleep duration led to significant improvements in insulin resistance and blood pressure. Similarly, Zuraikat et al. [443] investigated the impact of imposed sleep restriction in postmenopausal women, a group already at heightened cardiometabolic risk. Their study revealed that even a moderate reduction in sleep duration resulted in marked declines in insulin sensitivity, highlighting how certain populations may be more vulnerable to metabolic dysfunction due to insufficient sleep [443].

These findings underscore the importance of tailoring sleep interventions to those who stand to gain the most, particularly individuals with obesity, metabolic risk, or chronically

short sleep. Research suggests that even modest increases in sleep duration, which can be achieved through strategies like bedtime adjustments, sleep hygiene counseling, and structured interventions can yield measurable health benefits.

By extending research on sleep duration interventions to a range of high-risk populations, these studies build on the SMART2D framework, demonstrating that improving sleep is a viable and impactful strategy for metabolic and cognitive health across different life stages. Whether targeting adolescents with obesity, adults with chronic sleep deficits, or individuals at heightened cardiometabolic risk, sleep interventions could serve as a critical component of disease prevention and health promotion. The consistency of positive findings across diverse groups strengthens the case for incorporating sleep-focused strategies alongside traditional lifestyle interventions like diet and exercise in clinical and public health settings.

7.4.5 Implications for Future Research and Practice

The convergence of findings from SMART2D and other recent studies highlights critical avenues for future research and public health strategies aimed at leveraging sleep as a modifiable factor in metabolic and cognitive health.

7.4.5.1 Extending Intervention Duration for Sustained Benefits

Most sleep intervention studies, including SMART2D, have focused on short-term effects, typically ranging from one to eight weeks. While these studies demonstrate significant metabolic improvements, such as enhanced insulin sensitivity within a single week of increased sleep, the long-term sustainability of these benefits remains uncertain. Future research should extend intervention durations and track participants

over several months or years to assess whether sustained sleep extension leads to lasting improvements in A1C, weight regulation, and reduced incidence of T2D. Longitudinal studies could also determine whether habitual short sleepers who adopt longer sleep durations experience permanent metabolic improvements or if benefits diminish over time. Establishing these long-term effects is essential for integrating sleep interventions into preventive healthcare models.

7.4.5.2 Investigating Biological Mechanisms Underpinning Sleep-Metabolism Links

While strong evidence supports a causal relationship between sleep duration and metabolic health, the specific biological mechanisms underlying this link require further investigation. Future studies should focus on identifying the mechanisms through which sleep loss and sleep extension influence metabolic, neuroendocrine, and cognitive processes.

Key areas of investigation include:

- **Autonomic nervous system regulation** and its impact on insulin sensitivity and glucose metabolism.
- **Dysregulation of appetite-related hormones** such as leptin, ghrelin, and GLP-1, which may contribute to increased energy intake with insufficient sleep.
- **Altered beta-cell function and pancreatic insulin secretion**, especially relevant in youth, potentially leading to higher insulin resistance.
- **Neurocognitive impairments** due to inadequate sleep, with neuroimaging studies indicating disruption in brain network connectivity and its relationship to impulse control and decision-making.
- **Inflammation, oxidative stress, and the gut microbiome**, which play key roles in metabolic homeostasis and could be affected by inadequate sleep.

Clarifying these pathways will help explain why certain high-risk groups, such as adolescents with obesity, are more susceptible to the adverse effects of inadequate sleep. Understanding these mechanisms will also enable more targeted interventions tailored to specific physiological processes.

7.4.5.3 Targeted Sleep Interventions for High-Risk Groups

Recent findings suggest that certain populations, including adolescents with obesity and individuals with prediabetes or metabolic syndrome, may derive greater metabolic and cognitive benefits from sleep interventions compared to those without underlying risk factors.

T2D is increasingly diagnosed at younger ages, with an average onset of 13.7 years in Canadian youth [99]. Many children under 13 already exhibit risk factors but were ineligible for the SMART2D study due to age restrictions. Future research should examine whether sleep interventions implemented before puberty, when habits are still forming, could mitigate metabolic risks before they become entrenched. Younger children may be more receptive to behaviour changes, making sleep interventions a promising strategy for early risk reduction.

Additionally, research should move beyond sleep duration alone to explore other sleep characteristics that may impact metabolic outcomes, such as sleep timing, sleep efficiency, and circadian alignment. Trials investigating interventions that promote earlier bedtimes, more consistent sleep schedules, and reduced social jet lag could provide further insights into how optimizing sleep patterns benefits at-risk populations.

7.4.5.4 Integrating Sleep into Broader Lifestyle and Prevention Programs

Growing evidence supports the need to incorporate sleep health into mainstream prevention and lifestyle interventions for obesity and metabolic disorders. Traditional weight management programs focusing solely on diet and physical activity may be more effective when combined with sleep interventions, given sleep's role in appetite regulation, energy metabolism, and behavioural self-regulation. Potential strategies include:

- **Adding sleep education to obesity prevention programs,** promoting earlier bedtimes, reducing screen exposure before sleep, and improving sleep consistency.
- **Implementing community-based programs and school initiatives** to promote youth sleep heath at s population level.
- **Exploring policy-driven solutions**, such as delaying school start time to better align with adolescent circadian rhythms.
- **Utilizing wearable sleep-tracking technology**, to provide real-time feedback and behavioural coaching for personalized sleep improvements.

Given that many sleep interventions are feasible, low-cost, and non-invasive, integrating sleep education into clinical care, public health initiatives, and school-based programs could play a role in long-term disease prevention. For adolescents with obesity, improving sleep may serve as a more approachable and empowering lifestyle modification, offering a sense of control and self-efficacy. Unlike physical activity, which can be intimidating or socially challenging in school settings, particularly among peers with lower body weight, adjusting sleep habits may provide a more accessible and sustainable entry point for health improvement.

7.4.5.5 Public Health and Policy Considerations

At a broader level, the increasing prevalence of adolescent sleep deprivation and its associated consequences, ranging from metabolic dysfunction to mental health challenges, necessitate a shift in how society values and prioritizes sleep. Future research quantifying the long-term economic and healthcare burden of chronic sleep deprivation could drive policy changes in areas such as:

- **Adjusting school start times** to better accommodate adolescent sleep needs.
- **Implementing sleep education programs** within pediatric healthcare and school curricula.
- **Developing public health guidelines** aimed at reducing evening screen time and limiting artificial light exposure before sleep.
- **Establishing workplace and academic accommodations** that support adequate sleep in young adults.

By prioritizing sleep as a public health concern, these policy shifts could reduce the long-term burden of sleep-related metabolic and cognitive disorders, benefiting both individuals and healthcare systems.

7.4.5.6 Conclusion: Implications for Future Research and Practice

The collective findings from SMART2D and related studies solidify sleep as a fundamental determinant of adolescent health. Experimental sleep manipulation studies, longitudinal research, and mechanistic investigations continue to strengthen the link between sleep duration and key health outcomes, including insulin sensitivity, energy balance, cognitive performance, and behavioural regulation.

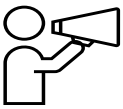
The collective findings from SMART2D and related studies solidify sleep as a fundamental determinant of adolescent health. Experimental sleep manipulation studies, longitudinal research, and mechanistic investigations continue to strengthen the link between sleep duration and key health outcomes, including insulin sensitivity, energy balance, cognitive performance, and behavioural regulation.

These results not only validate SMART2D's approach but also expand its scope, by demonstrating that sleep's impact extends across diverse populations, longer timeframes, and multiple health domains. The consistent evidence emerging from related studies supports making sleep health a priority in both public health and clinical interventions, especially for at-risk youth.

Moving forward, larger and longer-term trials, deeper mechanistic research, and integrated interventions will be essential in fully understanding how sleep can be leveraged as a powerful, accessible tool for disease prevention and cognitive well-being. As the scientific evidence base grows, the concept of "sleep as medicine" is gaining recognition, underscoring the need for sleep-centered strategies in both clinical practice and public health policy.

7.5 Key Message for Clinicians

For adolescents at high risk for T2D, adequate sleep should be recognized as an essential factor in disease prevention and management. Research, including findings from the SMART2D study, highlights that extending sleep duration by just one hour per night for a single week can significantly improve insulin sensitivity and cognitive functions. Given these benefits, incorporating sleep assessment and intervention into routine clinical practice may enhance the effectiveness of current obesity and diabetes prevention strategies.



To optimize patient outcomes, clinicians should:

- **Prioritize Sleep in Clinical Discussions:** Assess sleep duration, quality, and consistency as part of routine care for adolescents with obesity and metabolic risk factors.
- **Monitor Cognitive and Motor Function in High-Risk Youth:** Adolescents with severe obesity and insufficient sleep may experience impaired inhibitory control, slowed RTs, and poor postural stability, increasing their risk for falls, injuries, and academic difficulties. Clinicians should consider monitoring cognitive function and neuromotor performance, particularly in those struggling with daytime fatigue, balance issues, or behavioural concerns.
- **Educate on Sleep and Glucose Regulation:** Inform patients and caregivers that even one week of increased sleep can shift glucose profiles from unhealthy to healthier levels. Sleep should be emphasized alongside nutrition and exercise in diabetes prevention.
- **Address Barriers to Sleep:** Help adolescents and families identify common sleep disruptors, such as excessive screen time, irregular sleep schedules, and poor sleep hygiene, and provide evidence-based strategies to improve sleep habits.

- **Consider Sleep When Evaluating Metabolic Risk:** Given its strong impact on insulin sensitivity, sleep duration should be integrated into broader lifestyle interventions aimed at reducing T2D risk in youth.
- **Advocate for a Holistic, Multi-Disciplinary Approach:** Encourage collaboration among pediatric endocrinologists, family physicians, sleep specialists, dietitians, exercise physiologists, and psychologists to support comprehensive, sustainable health strategies for at-risk adolescents.

By recognizing sleep as a foundational component of adolescent health, clinicians can proactively identify risk factors, support preventive strategies, and improve overall metabolic, cognitive, and physical well-being in this vulnerable population.

7.6 Testimonials from SMART2D Participants and Parting Words

7.6.1 Testimonials from SMART2D Participants

At the conclusion of the study, we conducted a final check-in with participants to express our gratitude for their involvement and to gather feedback on their experiences. Each participant was invited to share their thoughts through the following open-ended request:

> *"When you have a chance, could you let me know what you liked, disliked, or learned from your experience in the SMART2D study? If something made you happy and/or mad, we'd love to hear about it. You don't have to answer every question, but your thoughts matter to us. Thank you!* 😊*"*

This feedback provided valuable insight into the participant experience, highlighting the challenges, positive moments, and personal takeaways from their time in the study. Here are some of the feedback that we have gathered:

> *"Being part of the SMART2D study was really fun, the leader Caroline was an amazing researcher and had an awesome sense of humour and gave me some amazing advice for my future. The other interns Irina, Amelia, and Keashan were awesome they had a good sense of humour too. We had a lot of the same interests. It was really fun coming each week because you didn't expect what would happen it was so much fun and brought a smile each time I walked in through the doors at CHEO. They all really know their stuff and do their job very well. And also, Sandra the phlebotomist was an amazing blood drawer, you could not even feel when she poked you and your done in seconds. Overall this*

was an awesome experience and I would definitely want to be part of another [study].”

“The thing I liked the most about the study was the people. They were so nice and fun to work with throughout the month. I also enjoyed being able to learn about all the fancy stuff in the lab. One thing I disliked was going to bed at 10PM during the increased sleep, it was very hard. But I learned that when I went to bed early I had lots of energy the next day and I learned that I should go to bed at a better time now. I wanted to thank everyone who helped with this study and thank you for the opportunity.”

“I really liked working with you guys and want to say thanks for making it so simple. Who knew contributing to science could be so easy? And with that thanks to all of you and goodbye, I’ll miss you!”

“I really liked the entirety of the experience. Sure it hurt a little but it has a reason so I wasn’t mad at anything. Overall it was really cool and interesting study and I did learn from it. God bless you and your team with whatever projects you guys do next”

“Thank you so much I really enjoyed participating in this study and meeting all of you guys, it was a lot of fun this past month.
I found it so cool today that parts of my brain could actually be asleep even while I’m performing tasks and activities.
This past month was such a cool and wonderful experience, if you guys ever

have another study that needs participants I would definitely be willing.
Thank you so much for this opportunity and I hope your study is successful"

"I liked everything about it and especially the vibe 😃. Also there's not many things I could say that I disliked 😉. And I learned quite a few things like how to organize my lifestyle according to a specific bedtime."

"I personally had a great time doing the study, you guys were all super kind and nice and made a very accepting environment.
I couldn't really think of anything better or different. I just has a blast.
I'm doing good, it was just an exciting last day. Thank you so much."

"I liked about the study having a lot of people around, it was nice and made sure I could never be bored. I liked the catheter even though it was a little tough to take off, so I wasn't poked a bunch.
I obviously did not enjoy the glucose drink but having it cold did make it much more bearable.
I liked the week of break in the middle.
The only thing I could really think to change was taking a longer break between the catheter out and starting the task since my arm was a little numb and tired but that cuts into the time so it's hard to avoid that. Also, maybe nametags for everyone since new people were there every week, and I did feel bad not remembering everyone's names!
It is obviously a study that requires a lot of time and energy but I am glad that I did it as you guys were very nice and the compensation is well worth it,

especially as the study lasts a month while others are much much longer. In the end I am glad that I participated and I feel that you guys were professional, nice, encouraging and understanding about more demanding tasks. Thank you again, I hope you will remember your favorite girl#[X] 😃."

"I think the study was interesting, the whole cap thing. I didn't like the standing task but the food image one was pretty fun and I'm happy to have done this research. Thank you very much."

"J'ai beaucoup aimé mon expérience. C'est définitivement quelque chose que je croyais jamais faire. J'ai eu beaucoup de plaisir à faire ce projet. Le repas que tu as cuisiner était hyper bon. Y'a beaucoup de chose que j'ai appris. Aussi, la technologie dans le labo est vraiment cool. J'ai aussi eu beaucoup de fun, passer ces trois jours avec vous. Ce sont des moments que je ne vais jamais oublier. Surtout, Ryan essayer de parler en français. J'ai bien rigolée. Je suis, aussi, contente de vous aider dans ce projet. "

"I really liked how I got to see what researchers do, there was really nothing to dislike except for the loud pop sound and I loved how I learned a lot about the equipment you used and other medical stuff.
It was a great pleasure to be there and I'd like to thank you and everyone else for helping me have such a great time whenever I came to see you guys. And the beefaroni you guys gave me was just so good (my compliments to the chef)"

“Thank you so much. It makes me happy that I am able to help others with this study. This study has shown me how important my sleep is to my health. Once again thanks to you and Ryan for everything!”

“I think the part I enjoyed the most was chatting with you guys during the blood tests. Thank you for letting me participate”

“*I thought the study was a big learning experience there wasn’t anything I disliked and it was interesting to find out how much your metabolism speeds up when you get proper sleep! I will be sleeping more from now on. Thank you!”*

“Thanks for the opportunity, it was really nice getting to know you and everyone else at the study. I personally had a lot of fun and will miss it.”

“There are no complaints from me. Everything was as easy as you guys could put it. It was a little confusing at first but I got used to it. Sometimes it was hard to remember to click the watch and do everything but I got used to it. The study was fun. The lab was really cold you should heat up the place lol.”

“Who knew participating in research was as easy as following a sleep schedule? I loved coming to CHEO and seeing you guys. The beefaroni thing was so good. I will miss this. Thank you!”

7.6.2 Closing Remarks: Reflections from SMART2D and Looking Ahead

The SMART2D study was more than just a research project; it was a shared journey between researchers, participants, and families, united by a commitment to advancing knowledge about sleep and metabolic health. As I close this chapter, the voices of our participants remind me that research is not only about data and findings; it is much more about the experiences, relationships, and impact we create along the way.

Their testimonials speak to the warmth, professionalism, and enthusiasm of the SMART2D team. From the laughter shared in the lab to the friendships formed, from the challenges of adjusting to an earlier bedtime to the realization of how much sleep truly matters, their feedback highlights the human side of research. Participants walked away not only having contributed to science but also having gained valuable insights about their own health, sleep habits, and the research process itself.

Many reflected on the fun and welcoming environment we strived to create, where they felt safe, supported, encouraged, and valued. Others expressed newfound appreciation for the role of sleep in their daily energy levels, cognitive function, and overall well-being. Some even left with a greater sense of agency over their health, recognizing that small changes, like prioritizing sleep, can make a meaningful difference. Importantly, this study could not have been possible without the dedication of our participants. Their willingness to step outside their comfort zones, endure early bedtimes, wear sleep monitors, complete cognitive tasks (that included the loud pop), withstand all of my puns, and even tolerate glucose drinks and blood draws made SMART2D a success. Each of them played an essential role in helping me answer critical questions that could shape future diabetes prevention strategies for adolescents at risk.

As I move forward, the insights gained from SMART2D will, I hope, continue to inform and inspire new research. My deepest desire for this work is to have an impact that extend beyond the walls of our lab, influencing clinical practice, public health initiatives, and the broader understanding of how sleep affects metabolic and cognitive health in youth.

To our participants, I thank you for your time, your energy, your patience, and your curiosity. You made this study what it is for me. I hope that, in return, this experience left a positive mark on you as well. And to the future researchers and clinicians who will build on these findings, I encourage you to keep asking questions, challenging assumptions, and pushing the boundaries of what we know about sleep, health, and human potential.

This is not just the end of a study, it is also the beginning of what comes next.



7.6.3 Figure 14. The test meal, affectionately known as the beefaroni, a favourite among SMART2D participants.

Note. A little-known fact: the famous beefaroni was made with care by my husband, who followed my instructions to the letter. This simple meal became a cherished part of the study, embodying the warmth and connection that made SMART2D a unique experience and not just for data collection, but for the shared moments that made it special.

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Appendix A

CHEO Ethics Approval



Research Ethics Board

Approval Letter

Principal Investigator: Dr. Jean-Philippe Chaput

REB Protocol No: 17/63X

Romeo File No: 20170184

Project Title: CHEOREB# 17/63X - Effect of Increasing Sleep Duration on Insulin Sensitivity in Adolescents having Risk Factors for Type 2 Diabetes

Primary Affiliation: HALO\HALO

Protocol Status: Active

Approval Date: March 18, 2018

Approval Expiry Date: April 15, 2019

This is to notify you that the CHEO REB has granted approval to the renewal for the above named research study for a period of one year. The renewal was reviewed in the delegated stream and approved by the Chair or a delegate of the Chair. Decisions made by the Chair under delegated review are ratified by the full Board at its subsequent meeting.

Approval is granted with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. The investigator is responsible for complying with all applicable guidelines and regulations regarding the ethical conduct of research with humans, as applicable to the research project.
3. Investigators must obtain annual renewal approval prior to the expiry date stated above.

4. The investigator must not implement any deviation from, or changes to, the protocol without the approval of the REB except where necessary to eliminate an immediate hazard to the research subject, or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number or research staff). As soon as possible, however, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment(s) should be submitted to the Board for review and approval.
5. The investigator must, prior to use, obtain approval from the Board for changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
6. Investigators must obtain approval from the Board of French version(s) of the consent/assent form(s), unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.
7. For clinical drug or device trials, investigators must promptly report to the REB all adverse events that are both serious and unexpected (SAEs) or unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches.
8. For SAE reports on clinical drug trials, the investigator must also comply with the hospital-wide Policy regarding, Procedures for Considering Medical Error in the Differential Diagnosis of Severe Adverse Events (SAE) Associated with the Drugs Administered in a Clinical Trial.
9. Investigators must promptly report to the REB any new information regarding the safety of research subjects (e.g., changes to the product monograph or investigator's brochure of drug trials). Where available, any reports produced by the Data Safety Monitoring Board should also be promptly submitted to the REB for acknowledgement.
10. Investigators must notify the REB of any study closures (closed to accrual, temporary, premature or permanent).
11. Investigators must submit a study closure event form at the conclusion of the study.

If you have any questions, pertaining to this letter, please contact the Research Ethics Board Office.

Regards,

Richard Carpentier, PhD

Chair, Research Ethics Board

Président, Comité d’éthique de la recherche

Approval - Minor Modification

Principal Investigator: Dr. Jean-Philippe Chaput

REB Protocol No: 17/63X

Romeo File No: 20170184

Project Title: CHEOREB# 17/63X - Effect of Increasing Sleep Duration on Insulin Sensitivity in Adolescents having Risk Factors for Type 2 Diabetes

Primary Affiliation: HALO\HALO

Protocol Status: Active

Date Modifications Approved: October 26, 2018

Documents Reviewed & Approved:

Document Name	Comments	Version Date
Protocol	Protocol - SLEEP Study - Version 4 - CLEAN	9/15/2018
Questionnaire/Survey	Brunell Mood Scale	9/17/2018
Questionnaire/Survey	Epworth Sleepiness Scale	9/17/2018
Questionnaire/Survey	PANAS	9/17/2018
Questionnaire/Survey	PedsQL	9/17/2018
Questionnaire/Survey	PHQ-A	9/17/2018
Questionnaire/Survey	Sedentary Behaviour Questionnaire	9/17/2018
Questionnaire/Survey	SDQ	9/17/2018
Questionnaire/Survey	Three Factor Eating Questionnaire	9/17/2018
Assent Form	Assent Form CLEAN	10/25/2018
Consent Form	Consent Form CLEAN	10/25/2018
Investigator Response	Response Letter	10/25/2018

The CHEO REB has reviewed and granted approval of the study documents listed above; which is to be conducted under the auspices of CHEO and/or CHEO Research Institute by the investigator noted above. The minor modification was reviewed in the delegated stream and approved by the Chair,

and will be ratified by the full Board at its subsequent meeting.

Approval is granted with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. The investigator is responsible for complying with all applicable guidelines and regulations regarding the ethical conduct of research with humans, as applicable to the research project.
3. Investigators must obtain annual renewal approval prior to the expiry date stated on the final approval letter.
4. The investigator must not implement any deviation from, or changes to, the protocol without the approval of the REB except where necessary to eliminate an immediate hazard to the research subject, or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number or research staff). As soon as possible, however, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the Board for review and approval.
5. The investigator must, prior to use, obtain approval from the Board for changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
6. Investigators must obtain approval from the Board for French version(s) of the consent/assent form(s), unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.
7. For clinical drug or device trials, investigators must promptly report to the REB all adverse events that are both serious and unexpected (SAEs) or unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
8. For SAE reports on clinical drug or device trials, the investigator must also comply with the hospital-wide Policy regarding, Procedures for Considering Medical Error in the Differential Diagnosis of Severe Adverse Events (SAE) Associated with the Drugs Administered in a Clinical Trial
9. Investigators must promptly report to the REB any new information regarding the safety of research participants (e.g., changes to the product monograph or investigator's brochure for drug trials). Where available, any reports produced by the Data Safety Monitoring Board should also be promptly submitted to the REB for acknowledgement.
10. Investigators must notify the REB of any study closures (closed to accrual, temporary, premature or permanent).
11. Investigators must submit a study closure event form at the conclusion of the study.

The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.

The CHEO REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonization Good Clinical Practice Consolidated Guideline (ICH GCP) ; Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; And Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The CHEO REB is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

If you have any questions, pertaining to this letter, please contact the Research Ethics Board office.

Regards,

Richard Carpentier, PhD

Chair, Research Ethics Board

Président, Comité d'éthique de la recherche

Appendix B

uOttawa Ethics Approval

26/08/2019

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Lettre d'approbation administrative | Letter of administrative approval

Numéro de dossier / Ethics File Number	H-08-19-4893
Titre du projet / Project Title	Effect of increasing sleep duration on insulin sensitivity in adolescents having risk factors for type 2 diabetes
Type de projet / Project Type	Thèse de doctorat / Doctoral thesis
CÉR primaire / Primary REB	CHEO / CHEO
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	26/08/2019
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	15/04/2020

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Caroline DUTIL	École des sciences de l'activité physique / School of Human Kinetics	Chercheur Principal / Principal Investigator
Jean-Philippe CHAPUT	Département de pédiatrie / Department of Paediatrics	Superviseur / Supervisor
Denis PRUD'HOMME		Co-superviseur / Co-supervisor
Anastasia HADJIYANNAKIS		Co-chercheur / Co-investigator
Mark TREMBLAY	CHEO Research Institute	Co-chercheur / Co-investigator
Anthony CARLSEN	École des sciences de l'activité physique / School of Human Kinetics	Co-superviseur / Co-supervisor

Conditions spéciales ou commentaires / Special conditions or comments:

CHEO REB # 17/63X

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Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

L'Université d'Ottawa a signé une Entente, conforme aux exigences de la plus récente version de l'EPTC et tout autre règlement ou législation applicable, permettant au CÉR ci-haut nommé d'être désigné comme CÉR primaire pour les projets de recherche où

1) les activités principales de recherche sont menées sous l'autorité ou sous les auspices de l'établissement lié au CÉR primaire et

2) Une partie du projet est également réalisé sous l'autorité ou sous les auspices de l'Université d'Ottawa.

Cette lettre confirme que l'Université d'Ottawa a autorisé que le CÉR primaire soit le CÉR officiel pour l'évaluation et la supervision de ce projet de recherche. Ceci n'est pas une approbation éthique.

Afin de nous aider à garder votre dossier à jour, veuillez soumettre une copie de toutes demandes de modification, renouvellement d'approbation éthique etc. soumis à et approuvé par le CÉR primaire dès qu'elles sont disponibles.

Cette approbation administrative est valide pour la durée indiquée ci-haut et est sujette aux conditions énumérées dans la section intitulée « Conditions spéciales ou commentaires ».

The University of Ottawa has signed an Agreement, compliant with current TCPS guidelines and any other applicable guidelines or legislation regarding multisite review, allowing the REB named above to serve as Board of Record (BoR) for research projects where

1) the main research activities are conducted within the auspices or jurisdiction of the BoR's institution and

2) parts of the project are also conducted under the jurisdiction or auspices of the University of Ottawa.

This letter confirms that the University of Ottawa has authorized the REB named above to serve as Board of Record for the review and oversight of this research project. This is not an REB approval.

In order to help us keep your file up to date, please submit a copy of all amendment requests, project renewals or any other changes submitted to and approved by the BoR, as they become available.

Administrative approval is valid for the period indicated above and is subject to the conditions listed in the section entitled «Special conditions or comments».

Catherine PAQUET
Directeur / Director
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences sociales et humanités / Social Sciences and Humanities Research Ethics Board**

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