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The connection between mental and physical health:

Investigating the associations between psychosocial well-being, sleep and cardio-metabolic health in European children and adolescents

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Content

Summary

Background

The high prevalence of overweight and obesity and related cardio-metabolic disorders such as insulin resistance and hypertension in European children and adolescents is a matter of concern. Aspects of mental health have been suggested to be determinants of cardio-metabolic health and it has been hypothesised that lifestyle factors such as sleep may be part of the underlying mechanism. However, studies in young populations investigating the role of mental health for sleep or cardio-metabolic markers have mainly focussed on a psychopathological view of mental health. Further, studies on the association between sleep and specific cardio-metabolic markers are either limited or suffer from methodological limitations with respect to the measurement of sleep.

Aims

The present cumulative thesis consists of four original papers that aim to shed light on the associations between psychosocial well-being as one aspect of positive mental health and cardio-metabolic markers. A special focus was put on the role of sleep as a potential mediating factor.

Methods

Analyses were carried out based on data of children and adolescents from 8 European countries participating in the IDEFICS/I.Family study. The IDEFICS/I.Family study was set up to identify risk and protective factors for chronic non-communicable diseases and to develop and evaluate a community-based intervention for the prevention of childhood obesity. The data that were used for this thesis were collected during three examination waves with intervals of approximately 2 and 4 years in between them (Wave 1: 2007/2008, Wave 2: 2009/2010, Wave 3: 2013/2014). In 2015, these examination waves were complemented by an in-depth examination of a subsample in which children with overweight were overrepresented. The samples on which the analyses for the different papers were based varied in size between 559 and 6,519 subjects depending on the available data for the respective research question.

Psychosocial well-being comprised items on emotional well-being, self-esteem and social relationships. Sleep characteristics included questionnaire-based and objective measurements of sleep duration, sleep disturbances, sleep quality and sleep timing. Cardio-metabolic markers encompassed waist circumference, blood pressure, the homeostasis model assessment for insulin resistance (HOMA-IR), high-density lipoprotein cholesterol (HDL-C) and triglycerides.

Associations were examined applying a variety of statistical methods including multilevel regression analysis, quantile regression and path analysis.

Results

Higher psychosocial well-being was found to be cross-sectionally associated with longer sleep duration and fewer sleep disturbances (N=6,336). However, well-being at the second examination wave did not predict sleep characteristics 4 years later (N=3,379).

Using actigraphy- and sleep diary-derived sleep characteristics (sleep duration, sleep latency, sleep efficiency, bed- and wake time), the following distinct sleep subtypes were identified in a sample of 559 participants from whom detailed information on sleep was collected in 2015: (i) early birds, (ii) short sleep duration, (iii) optimal sleep and (iv) poor sleep quality. Neither sleep subtype nor the single sleep characteristics were found to be statistically significantly associated with body mass index.

In contrast, an analysis conducted in 3,900 children and adolescents participating in the second and third examination wave revealed a cross-sectional inverse association between parent- or self-reported sleep duration and waist circumference. Longer sleep duration was also found to be indirectly associated with lower HOMA-IR through lower waist circumference. This indirect pathway was also observed longitudinally, i.e. longer sleep duration at the second examination wave was indirectly associated with lower HOMA-IR four years later following the pathway through waist circumference at the second and waist circumference at the third examination wave.

After the associations (i) between psychosocial well-being and sleep and (ii) between sleep and cardio-metabolic markers were investigated in-depth, the associations between psychosocial well-being and cardio-metabolic markers considering sleep duration and other lifestyle factors as potential mediators were analysed in one cross-sectional (N=6,519) and one longitudinal path model (N=1,393). Cross-sectionally, higher psychosocial well-being was found to be indirectly associated with (i) lower waist circumference through a healthier lifestyle and with (ii) lower blood pressure, lower HOMA-IR, lower triglycerides and higher HDL-C through both a healthier lifestyle and lower waist circumference. These indirect effects were also shown in the longitudinal model where changes in psychosocial well-being over the 2- and 4-year-intervals, respectively, were investigated in relation to cardio-metabolic markers measured at the 6-year follow-up (third examination wave). Direct associations were observed between higher levels of psychosocial well-being and lower waist circumference, lower HOMA-IR and higher HDL-C independent of potential confounders and mediators. However, direct associations were less consistent across analyses, i.e. they were partially only observed in the cross-sectional or longitudinal analysis.

Discussion and conclusions

The results of the present thesis support the hypothesis that psychosocial well-being may be linked to cardio-metabolic health through sleep and other lifestyle factors in children and adolescents. One strategy to improve cardio-metabolic health of children and adolescents may therefore be to promote psychosocial well-being and a healthy sleep, e.g. through resilience training programs and mindfulness-based interventions. However, because of the scarcity of research more longitudinal studies designed for gaining further knowledge on the temporal relationships between positive mental health, lifestyle factors and cardio-metabolic health are needed.

Zusammenfassung

Hintergrund

Die hohe Prävalenz von Übergewicht und Adipositas und damit in Zusammenhang stehende kardiometabolische Störungen wie beispielsweise Insulinresistenz und Bluthochdruck in europäischen Kindern und Jugendlichen ist besorgniserregend. Es wird vermutet, dass Aspekte psychischer Gesundheit Determinanten von kardiometabolischer Gesundheit sein könnten und es wird angenommen, dass Lebensstilfaktoren wie z. B. Schlaf einen Teil des zugrundeliegenden Mechanismus ausmachen könnten. Studien in jungen Bevölkerungsgruppen, die die Rolle von psychischer Gesundheit für Schlaf oder kardiometabolische Marker untersucht haben, haben ihren Schwerpunkt auf eine psychopathologische Sicht von psychischer Gesundheit gelegt. Weiterhin sind Studien zum Zusammenhang zwischen Schlaf und bestimmten kardiometabolischen Markern entweder begrenzt oder haben methodische Limitationen im Hinblick auf die Messung von Schlaf.

Ziele

Die vorliegende kumulative Dissertation besteht aus vier Originalarbeiten, die das Ziel haben, Aufschluss über die Zusammenhänge zwischen psychosozialem Wohlbefinden, als einen Aspekt von positiver psychischer Gesundheit, und kardiometabolischen Markern zu geben. Ein besonderer Schwerpunkt liegt auf der Rolle von Schlaf als einen potenziellen verbindenden Faktor.

Methoden

Die Analysen wurden basierend auf Daten von Kindern und Jugendlichen aus 8 europäischen Ländern, welche an der IDEFICS/I.Family Studie teilgenommen haben, durchgeführt. Die IDEFICS/I.Family Studie wurde ins Leben gerufen, um Risikofaktoren und protektive Faktoren für chronische, nicht-übertragbare Krankheiten zu identifizieren sowie eine gemeindebasierte Intervention zur Prävention von kindlicher Adipositas zu entwickeln und zu evaluieren. Die Daten, welche für die vorliegende Dissertation genutzt wurden, wurden während drei Erhebungswellen mit einem zeitlichen Abstand von ungefähr zwei und vier Jahren gesammelt (Welle 1: 2007/2008, Welle 2: 2009/2010, Welle 3: 2013/2014). Diese Erhebungswellen wurden im Jahr 2015 durch eine eingehende Untersuchung einer Unterstichprobe, in welcher Kinder und Jugendliche mit Übergewicht überrepräsentiert waren, ergänzt. Die Stichproben, auf denen die Analysen für die verschiedenen Manuskripte basieren, variierten zwischen 559 und 6.519 Studienteilnehmenden in Abhängigkeit von den verfügbaren Daten für die jeweilige Forschungsfrage.

Psychosoziales Wohlbefinden umfasste Items zu emotionalem Wohlbefinden, Selbstwert und sozialen Beziehungen. Die Schlafcharakteristika schlossen fragebogenbasierte und objektive Messungen von Schlafdauer, Schlafstörungen, Schlafqualität und Schlafzeiten ein. Kardiometabolische Marker umfassten Taillenumfang, Blutdruck, das „Homeostasis Model Assessment" für Insulinresistenz (HOMA-IR), die Blutfette „High-Density Lipoprotein"-Cholesterin (HDL-C) und Triglyzeride.

Die Untersuchung der Zusammenhänge erfolgte unter Anwendung einer Vielzahl von statistischen Methoden wie beispielsweise Mehrebenenanalyse, Quantilsregression und Pfadanalyse.

Ergebnisse

In einer Querschnittsanalyse war höheres psychosoziales Wohlbefinden mit einer längeren Schlafdauer und weniger Schlafstörungen assoziiert (N=6.336). Im Längsschnitt jedoch war Wohlbefinden kein Prädiktor für Schlafcharakteristika vier Jahre später.

Auf Basis mehrerer Schlafcharakteristika (Schlafdauer, Schlaflatenz, Schlafeffizienz, Einschlaf- und Aufwachzeit), welche unter Nutzung von Aktigraphie und eines Schlaftagebuchs abgeleitet wurden, wurden die folgenden verschiedenen Schlaf-Subtypen in einer Stichprobe von 559 Teilnehmenden, von welchen im Jahr 2015 detaillierte Informationen zu Schlaf gesammelt wurden, identifiziert: (i) Frühaufsteher, (ii) kurze Schlafdauer, (iii) optimaler Schlaf und (iv) schlechte Schlafqualität. Weder Schlaf-Subtyp noch die einzelnen Schlafcharakteristika waren statistisch signifikant mit dem Body Mass Index assoziiert.

Im Gegensatz dazu zeigte eine Analyse auf Basis von 3.900 Kindern und Jugendlichen, welche an der zweiten und dritten Erhebungswelle teilgenommen hatten, im Querschnitt eine umgekehrte Assoziation zwischen elterlich oder selbst-berichteter Schlafdauer und Taillenumfang. In der Querschnittsanalyse war eine längere Schlafdauer außerdem indirekt durch einen niedrigeren Taillenumfang mit einem niedrigeren HOMA-IR assoziiert. Dieser indirekte Pfad wurde auch im Längsschnitt beobachtet, d.h. eine längere Schlafdauer während der zweiten Erhebungswelle war indirekt durch einen niedrigeren Taillenumfang während der zweiten und dritten Erhebungswelle mit einem niedrigeren HOMA-IR vier Jahre später assoziiert.

Nachdem die Zusammenhänge (i) zwischen psychosozialem Wohlbefinden und Schlaf und (ii) zwischen Schlaf und kardiometabolischen Markern untersucht worden waren, wurden die Zusammenhänge zwischen psychosozialem Wohlbefinden und kardiometabolischen Markern unter Berücksichtigung von Schlafdauer und anderen Lebensstilfaktoren als potenzielle Mediatoren in einem querschnittlichen (N=6.519) und einem längsschnittlichen Pfadmodell (N=1.393) analysiert. In der Querschnittsanalyse zeigte

sich ein indirekter Zusammenhang zwischen höherem psychosozialen Wohlbefinden und (i) einem niedrigeren Taillenumfang durch einen gesünderen Lebensstil und (ii) einem niedrigeren Blutdruck, niedrigeren HOMA-IR-Wert, niedrigeren Triglyzeriden und einem höheren HDL-Cholesterin durch sowohl einen gesünderen Lebensstil als auch einen niedrigeren Taillenumfang. Diese indirekten Effekte wurden auch im Längsschnittmodell sichtbar, in welchem Veränderungen im psychosozialen Wohlbefinden über Zeiträume von 2 bzw. 4 Jahren in Hinblick auf deren Zusammenhang mit kardiometabolischen Markern zum 6-Jahres Follow-up (dritte Erhebungswelle) untersucht wurden. Direkte Zusammenhänge wurden zwischen höheren Werten von psychosozialem Wohlbefinden und niedrigerem Taillenumfang, niedrigerem HOMA-IR Wert und höherem HDL-C unabhängig von potenziellen Confoundern und Mediatoren beobachtet. Diese direkten Zusammenhänge waren jedoch weniger konsistent über die Analysen hinweg, d.h. teilweise wurden sie nur in der Querschnitts- oder Längsschnittanalyse beobachtet.

Diskussion und Schlussfolgerungen

Die Ergebnisse der vorliegenden Dissertation stützen die Hypothese, dass Schlaf und andere Lebensstilfaktoren als zugrundeliegender Mechanismus fungieren könnten, der psychosoziales Wohlbefinden mit kardiometabolischer Gesundheit bei Kindern und Jugendlichen verbindet. Eine Strategie zur Verbesserung von kardiometabolischer Gesundheit bei Kindern und Jugendlichen könnte deshalb die Förderung psychosozialen Wohlbefindens und gesunden Schlafes sein, z. B. durch Trainingsprogramme zur Stärkung der Resilienz und durch achtsamkeitsbasierte Interventionen. Jedoch sind aufgrund des Mangels an Forschungsarbeiten weitere Längsschnittstudien nötig, die in ihrem Design so beschaffen sind, dass weitere Erkenntnisse über die zeitlichen Beziehungen zwischen positiver psychischer Gesundheit, Lebensstilfaktoren und kardiometabolischer Gesundheit gewonnen werden können.

Samenvatting

Achtergrond

De hoge prevalentie van overgewicht, obesitas en gerelateerd cardio-metabole ziektes zoals insuline resistentie en hypertensie bij Europese kinderen en adolescenten is zorgwekkend. Mentale gezondheid is een mogelijke determinant van cardio-metabole gezondheid en er wordt verondersteld dat leefstijl en slaap daarbij een onderliggend mechanisme vormen. Echter, studies rond de rol van mentale gezondheid bij slaap en cardio-metabole merkers in jonge populaties hanteren tot nu toe vooral een psychopathologische kijk op mentale gezondheid. Verder zijn de studies rond de associatie van slaap met specifieke cardio-metabole merkers beperkt en met vaak methodologische beperkingen in de slaapmeting.

Doelstelling

Het huidige cumulatieve proefschrift bestaat uit vier originele artikels die licht willen werpen op de associaties tussen psychosociaal welzijn als een aspect van positieve mentale gezondheid en cardio-metabole merkers. Speciale aandacht werd besteed aan de rol van slaap als mogelijke mediator.

Methoden

Analyses werden uitgevoerd op basis van gegevens van kinderen en adolescenten uit 8 Europese landen die deelnamen aan de IDEFICS / I.Family-studie. De IDEFICS / I.Family-studie werd opgezet om risico- en beschermende factoren voor chronische niet-overdraagbare ziekten te identificeren en om een gemeenschapsgerichte interventie te ontwikkelen en te evalueren voor de preventie van obesitas bij kinderen. De gegevens die voor dit proefschrift zijn gebruikt, zijn verzameld tijdens drie meetmomenten met een tijdsinterval van ongeveer 2 en 4 jaar (meting 1: 2007/2008, meting 2: 2009/2010, meting 3: 2013/2014). In 2015 zijn deze herhaalde metingen aangevuld met een verdiepend onderzoek binnen een deelsteekproef waarin kinderen met overgewicht oververtegenwoordigd waren. De steekproeven waarop de analyses voor de verschillende artikels waren gebaseerd, varieerden in grootte tussen 559 en 6519 proefpersonen, afhankelijk van de beschikbare gegevens voor de respectievelijke onderzoeksvraag.

Psychosociaal welzijn omvatte items over emotioneel welzijn, zelfrespect en sociale relaties. Slaapkenmerken omvatten vragenlijsten en objectieve metingen van slaapduur, slaapstoornissen, slaapkwaliteit en slaaptiming. Cardio-metabole merkers omvatten tailleomtrek, bloeddruk, insulineresistentie (HOMA-IR), hoge dichtheid lipoproteïne-cholesterol (HDL-C) en triglyceriden.

Associaties werden onderzocht met behulp van een verscheidenheid aan statistische methoden, waaronder multilevel regressieanalyse, kwantielregressie en padanalyse.

Resultaten

Een hoger psychosociaal welzijn bleek cross-sectioneel geassocieerd te zijn met een langere slaapduur en minder slaapstoornissen (n=6336). Echter, welzijn bij de tweede onderzoeksgolf voorspelde 4 jaar later geen slaapkenmerken (n=3379).

Aan de hand van slaapkenmerken afgeleid uit actigrafie en slaapdagboek (slaapduur, slaaplatentie, slaapefficiëntie, inslaaptijd en ontwaaktijd), werden de volgende slaapsubtypen geïdentificeerd in een steekproef van 559 deelnemers met gedetailleerde informatie over slaap in 2015: (i) vroege vogels, (ii) korte slaapduur, (iii) optimale slaap en (iv) slechte slaapkwaliteit. Noch het slaapsubtype, noch de aparte slaapkenmerken bleken statistisch significant geassocieerd te zijn met de BMI.

Een analyse uitgevoerd bij 3900 kinderen en adolescenten die deelnamen aan de tweede en derde onderzoeksgolf onthulde daarentegen een omgekeerde cross-sectionele associatie tussen slaapduur (door ouders of zichzelf gerapporteerd) en middelomtrek. Een langere slaapduur bleek ook indirect verband te houden met een lagere HOMA-IR door een lagere middelomtrek. Deze indirecte route werd tevens longitudinaal waargenomen, d.w.z. een langere slaapduur bij de tweede onderzoeksgolf was indirect geassocieerd met een lagere HOMA-IR vier jaar later via middelomtrek bij de tweede en derde golf.

Nadat de associaties (i) tussen psychosociaal welzijn en slaap en (ii) tussen slaap en cardio-metabole merkers diepgaand waren onderzocht, werden de associaties tussen psychosociaal welzijn en cardio-metabole merkers geanalyseerd, rekening houdend met de slaapduur en andere leefstijlfactoren als potentiële mediatoren in één cross-sectioneel (n=6519) en één longitudinaal padmodel (n=1393). Cross-sectioneel bleek hoger psychosociaal welzijn indirect geassocieerd te zijn met (i) een lagere tailleomtrek door een gezondere levensstijl en met (ii) een lagere bloeddruk, lagere HOMA-IR, lagere triglyceriden en hogere HDL-C via een gezondere levensstijl en lagere tailleomtrek. Deze indirecte effecten werden ook aangetoond in het longitudinale model waar veranderingen in psychosociaal welzijn over de intervallen van respectievelijk 2 en 4 jaar werden onderzocht in relatie tot cardio-metabole merkers gemeten tijdens de follow-up van 6 jaar (derde onderzoeksgolf). Directe associaties werden waargenomen tussen hogere niveaus van psychosociaal welzijn en lagere tailleomtrek, lagere HOMA-IR en hogere HDL-C onafhankelijk van mogelijke verstorende factoren en mediatoren. Directe associaties waren echter minder consistent tussen analyses, d.w.z. ze werden slechts gedeeltelijk waargenomen in de cross-sectionele of longitudinale analyse.

Discussie en conclusie

De resultaten van dit proefschrift ondersteunen de hypothese dat psychosociaal welzijn verband kan houden met cardio-metabole gezondheid door slaap en andere leefstijlfactoren bij kinderen en adolescenten. Een mogelijke strategie om de cardio-metabole gezondheid van kinderen en adolescenten te verbeteren is daarom het bevorderen van psychosociaal welzijn en een gezonde slaap, b.v. door middel van veerkrachttraining en op mindfulness gebaseerde interventies. Vanwege de schaarste aan onderzoek zijn echter meer longitudinale studies nodig om meer kennis te vergaren over de temporele relaties tussen positieve mentale gezondheid, leefstijlfactoren en cardio-metabole gezondheid.

Abbreviations

BMI	body mass index
CRP	C-reactive protein
IDEFICS	Identification and Prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS
IL-6	interleukin 6
HRQoL	Health-related Quality of Life
HOMA-IR	Homeostasis model assessment for insulin resistance
KINDL^R Questionnaire	Revidierter Fragebogen für KINDer und Jugendliche zur Erfassung der gesundheitsbezogenen Lebensqualität
USA	United States of America

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Outline of the thesis

The present thesis takes the form of a cumulative thesis consisting of four original papers published in, accepted by or ready to be submitted to peer-reviewed international journals (Appendix, page 61 ff). After important terms used in the thesis are introduced in a foreword, the overarching research context is described in five main chapters. *Chapter 1* provides insight into the motivation for the present thesis as well as background information on the main parameters of interest, i.e. on the epidemiology of psychosocial well-being, sleep and cardio-metabolic markers as well as possible assessment methods for psychosocial well-being and sleep. *Chapter 2* outlines the conceptual framework and aims of the thesis. Next, in *Chapter 3*, the study population, the methods used to assess parameters of interest and the statistical methods applied to analyse the data are presented. *Chapter 4* summarises the research results obtained and *Chapter 5* provides an interpretation of findings, a discussion of strengths and limitations and public health implications as well as suggestions for future research.

Foreword on terminology

To foster a correct understanding of the main parameters investigated in this thesis, this foreword explains how the terms psychosocial well-being and cardio-metabolic markers should be understood. Further, definitions of different sleep characteristics are provided.

The main exposure of interest of this thesis is *psychosocial well-being*. The term psychosocial well-being was chosen to describe a construct that covers two subdomains of *health-related quality of life (HRQoL)*, namely the *psychological* and *social* domain. The term psychosocial well-being may have a (slightly) different meaning in publications of other researchers. This is because there is – despite its widely use – no unique definition of *well-being* and also the word *psychosocial* may be interpreted differently. Generally, the concepts of well-being and HRQoL can be considered to belong to the overarching concept of *positive mental health*. Positive mental health and *mental ill-health* form the two dimensions of *mental health* [1]. Whereas positive mental health focusses on resources such as self-esteem, optimism and satisfying personal relationships, mental ill-health refers to mental disorders, symptoms and problems such as depressive symptoms and anxiety [1]. There has been debate whether (i) mental health is one continuum with mental ill-health on one end and positive mental health on the other end or whether (ii) mental health consists of two continua with one continuum going from low well-being ("languishing") to high well-being ("flourishing") and one continuum going from severe mental disorder to no mental disorder [2]. Figure 1 provides an overview of how psychosocial well-being can be contextualised in the mental health domain.

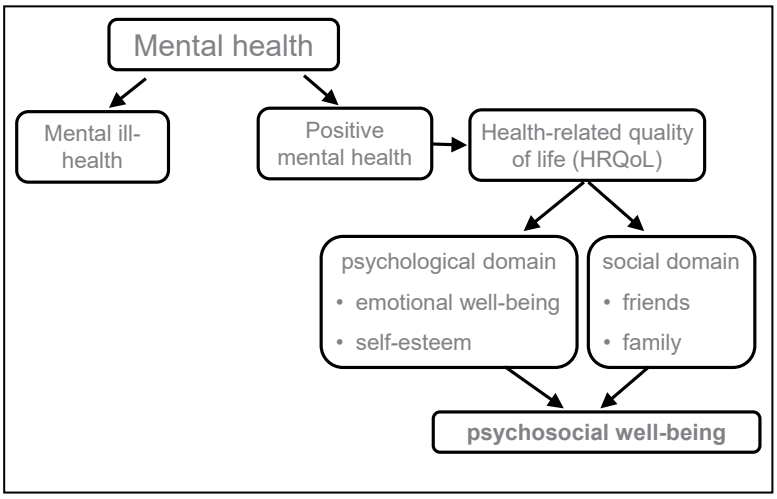

Figure 1: Concept of psychosocial well-being

Note. Psychosocial well-being comprises two domains of health-related quality of life. Health-related quality of life belongs to the "positive mental health"-dimension of mental health.

In line with common definitions, in the present thesis, the term *nocturnal sleep duration* refers to the time spent asleep at night while the term *napping* refers to a short period of sleep during the daytime and the term *sleep timing* refers to bed- and wake times. In contrast, there is no consensus about the definition of *sleep quality* [3,4]. For some researchers sleep quality contains both quantitative and qualitative aspects of sleep [5]. According to this definition, quantitative aspects of sleep quality are for instance sleep duration and sleep

latency, i.e. the time from turning the lights-off to sleep onset. A qualitative aspect of sleep is for example the subjective experience of sleep as deep and restful. Other researchers make a distinction between sleep quantity and sleep quality. In this view, sleep quantity comprises only sleep duration and sleep quality is described based on supposed underlying objective sleep features such as sleep latency [3]. In the present thesis, the latter definition is adopted. In epidemiological studies, the term *sleep disturbances* is often used to summarise symptoms of disturbed sleep such as frequent awakenings, prolonged sleep latency, sleep-disordered breathing and daytime sleepiness [6,7]. In the present thesis this term is also used to refer to such symptoms.

The term *cardio-metabolic marker* is widely used in the research literature. Generally, a biological marker can serve as an indicator for normal biological processes or pathogenic processes [8]. In this sense, a cardio-metabolic marker may be used as an indicator of normal functioning of the cardiovascular system and metabolism or indicate a cardio-metabolic disorder such as cardiovascular disease, stroke or diabetes or one of their precursors. Biomarkers can amongst others be obtained from biological samples such as blood and urine or by taking a recording from a person (e.g. by taking a blood pressure measurement) [8]. Cardio-metabolic markers commonly assessed in epidemiological studies and used in this thesis include for instance waist circumference as an indicator for abdominal obesity, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol and triglycerides as indicators for dyslipidaemia, blood pressure as an indicator for hypertension and insulin, glucose or their interplay in form of the homeostasis model assessment (HOMA-IR) [9] as indicators of insulin resistance.

1 INTRODUCTION

In the following, the relevance of psychosocial well-being and sleep for cardio-metabolic health and the potential underlying mechanisms will be outlined. Subsequently, the epidemiology of psychosocial well-being, sleep characteristics as well as obesity and cardio-metabolic disorders will be described. In addition, an overview of assessment methods for both psychosocial well-being and sleep characteristics will be provided.

1.1 Relevance of mental health and sleep for cardio-metabolic health

Research on the association between mental health and lifestyle-related disorders such as obesity and the metabolic syndrome in adults but also in youth has been growing over the last decades. However, existing research has often focussed on mental ill-health by concentrating on conditions such as depression and anxiety disorders. For example, several longitudinal studies have shown depression to be associated with obesity determined by a high body mass index (BMI) in children and adolescents [10-12]. Studies focussing on cardio-metabolic markers beyond BMI also reported mainly about detrimental effects of depressive symptoms on investigated parameters such as insulin resistance [13-15]. However, mental health is more than the absence of mental disorders [1]. So far, few studies have examined the association between aspects of positive mental health and obesity determined by a high BMI [16,17]. Even fewer studies exist with cardio-metabolic markers other than BMI as the outcome [18].

One pathway through which mental and physical health may influence each other is through lifestyle factors such as sleep [1].

Again, substantial research has been conducted on the association between psychopathological states and sleep [19]. In essence, they suggest that indicators of mental ill-health are associated with worse sleep outcomes. Few studies have, however, focussed on the role of indicators of positive mental health for sleep characteristics [20-23].

Research on the impact of sleep on cardio-metabolic markers in children is growing. In a review, Quist et al. [24] come to the conclusion that inadequate sleep is most likely associated with a higher cardio-metabolic risk. However, as the authors also point out, self-reported sleep is a limitation in many studies and longitudinal studies and randomised-controlled trials that would allow the assessment of causality are still scarce.

1.2 Potential underlying mechanisms

1.2.1 Pathways linking mental health with sleep

Aspects of mental health may be linked with sleep through physiological processes. For instance, it is well known that stress leads to the activation of the hypothalamic-pituitary-

adrenal axis with the release of hormones such as cortisol which affect sleep architecture [25]. Also the other direction of the association is biologically plausible: Poor sleep may lead to an additional cortisol release and may have an adverse effect on emotional brain networks [25,26]. Further, genetic influences on both well-being and sleep have been observed [27,28]. Hence, it may be possible that shared genetic factors underlie the association.

1.2.2 Pathways linking sleep with cardio-metabolic markers

There are different potential pathways linking sleep characteristics with cardio-metabolic markers.

First, it has been hypothesised that short sleep duration may lead to a dysregulation of appetite hormones (e.g. leptin and ghrelin) resulting in higher energy intake and weight gain [29,30]. Furthermore, poor sleep quality indicated by a reduced amount of restorative slow-wave sleep and sleep fragmentation (in the presence of unaltered total sleep duration) has been shown to increase cortisol release and sympathetic nervous system activity and decrease insulin sensitivity [31,32]. Again, these physiological and hormonal changes may contribute to a positive energy balance and weight gain [33]. A shorter sleep duration offers more time to eat due to longer waking hours and further might cause fatigue leading to less physical activity [34]. Also other aspects of sleep such as a later bedtime were found to be associated with a poorer diet quality, skipping breakfast and less physical activity [35-37]. Hence, these unhealthy behaviours may lead to obesity and especially gain in visceral fat which in turn are major risk factors for other cardio-metabolic disorders such as insulin resistance, hypertension and dyslipidaemia [38].

Sleep characteristics such as a short duration, poor quality and unfavourable timing might influence blood pressure, insulin resistance and blood lipids not only indirectly through obesity but also directly. For instance, it has been hypothesised that short sleep duration alters glucose metabolism which directly impacts on insulin resistance [29,30]. Blood pressure might be directly influenced by poor sleep by increasing sympathetic nervous system activity or by disrupting circadian rhythmicity [39].

1.2.3 Pathways linking mental health with cardio-metabolic markers

Both biological and behavioural mechanisms may explain the link between positive mental health and cardio-metabolic health. Literature discussing potential pathways has mainly focussed on studies in adults [40,41]. However, it seems possible that the same mechanisms also operate in young populations and first studies have already investigated related research questions [42,43].

First, positive mental health may have beneficial effects on the hypothalamic-pituitary-adrenal axis and the pattern of cortisol release which in turn can be advantageous for cardiovascular health [40-42]. For instance, studies in both adolescents and adults have

shown indicators of positive mental health to be associated with a steeper decline of cortisol across the day, a pattern that has been found to be associated with better health outcomes [40-42]. Another possibility may be that positive mental health reduces inflammation as indicated by lower levels of inflammatory markers such as C-reactive protein (CRP) and interleukin 6 (IL-6) which are known to play a role in cardiovascular disease [40,41,44]. Second, positive mental health may result in a healthier lifestyle such as increased physical activity, a healthier diet and better sleep and may thereby positively influence cardio-metabolic health [40,41]. For instance, a study in European children has shown higher self-esteem to be predictive of a healthier diet [43] which in turn is beneficial for cardio-metabolic health.

1.3 Mental health

1.3.1 Epidemiology

It has been estimated that mental health problems occur in 10-20% of children and adolescents worldwide [45]. This is in line with representative data from Europe which showed that 9.9% of 8-18 year old children and adolescents had borderline mental health problems and 5.2% had abnormal mental health problems based on an evaluation of the "Strengths and Difficulties Questionnaire", a brief behavioral screening questionnaire [46]. Of note, HRQoL was found to be lower in children being classified as having mental health problems (both borderline and abnormal) in comparison to those being classified as having normal levels of mental health problems [46].

A recent report based on nationally representative data of European and Canadian children aged 11, 13 and 15 years indicated that most adolescents are satisfied with their life with an overall score of 7.8 out of 10 [47]. However, the report revealed differences in life satisfaction between girls and boys with girls in most countries reporting lower life satisfaction than boys [47]. Further, age differences became apparent with older adolescents having lower life satisfaction in comparison to younger ones [47]. Albeit high levels of life satisfaction, approximately 25% of adolescents experienced symptoms of poor mental well-being such as nervousness or irritability every week [47].

The existence of important age and sex differences in positive mental health has also been indicated earlier by representative data from 7-17 year olds in Germany. These data showed that parentally reported HRQoL was lowest in 14-17 year olds and highest in 7-10 year olds [48]. Further, the trend of decreasing HRQoL with age was more pronounced in girls than in boys [48]. Self-reported HRQoL of adolescents aged 11-17 years showed similar patterns [48].

1.3.2 Assessment methods

To date, many generic and disease-specific instruments to assess HRQoL in children and adolescents have been developed. These include the "Pediatric Quality of Life Inventory" [49], the "KINDL^R Questionnaire" [50] and the "KIDSCREEN Questionnaire" [51]. An overview of instruments is provided in the reviews by Solans et al. [52] and Harding [53].

Apart from instruments assessing HRQoL, there are also other instruments that measure aspects of positive mental health. Amongst them are the following:

- "Positive and Negative Affect Schedule for Children" (consists of 12 items describing positive emotions and 15 items describing negative emotions) [54]
- "Rosenberg Self-Esteem Scale" (measures self-esteem based on 10 items) [55]
- "Life Orientation Test-Revised" (measures optimism with 6 items) [56]

1.4 Sleep duration, sleep quality, sleep disturbances and sleep timing

1.4.1 Epidemiology

There is evidence that sleep duration of children and adolescents has been decreasing over the last decades in many parts of the world [57-59]. For instance, the study by Matricciani et al. [58] indicates that sleep duration of 5-18 year olds decreased by more than 1 hour over the course of 103 years.

Further, studies using surveillance data from Western countries found that a considerable amount of children and adolescents can be categorised as sleeping less than recommended. For instance, 16.1% of Canadian pre-schoolers and 25.5% of Canadian children and adolescents do not meet the Canadian sleep duration recommendations [60,61]. Data from the "World Health Organization European Childhood Obesity Surveillance Initiative" showed that in 6-9 year old children the percentage of those with short sleep duration (defined as less than 9 hours) varies across European countries with 4% of Irish children and 26% of Bulgarian children having short sleep duration [62]. Of note, various societies such as the "National Sleep Foundation" (United States of America [USA]), the "American Society of Sleep Medicine" (USA) and the "Canadian Society for Exercise Physiology" provide sleep duration recommendations that are however quite similar (see Table 1) [63-66].

Apart from a comparison of sleep duration with the recommendations, comparison of sleep duration with self-defined sleep need might be an indicator of insufficient sleep duration. A study in Norwegian adolescents found that subjective sleep need during weekdays was on average 2 hours and 9 minutes higher than reported sleep duration [67]. In another study in adolescents from the USA a substantial proportion reported that they get less sleep than they should [57].

In general, research and data on sleep characteristics other than sleep duration is scarce. Research studies reported that difficulties in initiating and maintaining sleep are common in young populations [67-69]. Also surveillance data from Germany suggest that sleep problems are not rare. For instance, it was found that 13% of 0-17 year old children and adolescents have difficulties falling asleep and 8.8% have difficulties to sleep through the night [70].

Table 1: Sleep duration recommendations by different societies

National Sleep Foundation [64]		**American Society of Sleep Medicine [63]**		**Canadian Society for Exercise Physiology (Canadian 24-hour movement guidelines) [65,66]**	
Age group	Hours recommended	Age group	Hours recommended	Age group	Hours recommended
Newborns 0-3 months	14-17	Newborns 0-3 months	---	Newborns 0-3 months	14-17
Infants 4-11 months	12-15	Infants 4-11 months	12-16	Infants 4-11 months	12-16
Toddlers 1-2 years	11-14	Toddlers 1-2 years	11-14	Toddlers 1-2 years	11-14
Preschoolers 3-5 years	10-13	Preschoolers 3-5 years	10-13	Preschoolers 3-4 years	10-13
School-aged children 6-13 years	9-11	School-aged children 6-12 years	9-12	School-aged children 5-13 years	9-11
Teenagers 14-17 years	8-10	Teenagers 13-18 years	8-10	Teenagers 14-18 years	8-10

1.4.2 Assessment methods

Sleep characteristics can be assessed both objectively and subjectively. The respective methods are described in the following. A summary of advantages and disadvantages of the methods is further provided in Table 2.

Objective methods

Polysomnography can be regarded as the current gold standard for sleep assessment and describes the recording of numerous physiological signals from the brain, heart, eyes and muscles during sleep [71]. Polysomnography includes amongst others an electroencephalogram for assessing the electrical activity of the brain and an electrocardiogram for recording the heart rhythm [72]. The evaluation of these recordings allows the identification of wakefulness and sleep including different sleep stages [71]. Polysomnography is typically carried out in a laboratory setting although there are also ambulatory polygraphic devices that can be used at home [71,73]. Polysomnography is time-

consuming and expensive and therefore not suitable for the assessment of sleep in large population-based epidemiological studies.

Another objective assessment method for sleep is actigraphy. Actigraphs are small devices that – for the purpose of sleep assessment - are typically worn by participants on the non-dominant wrist during the night over a period of one week. The device records movements from which sleep and wake periods can be derived [74]. Certain measures such as sleep latency can only be calculated when the actigraphy measurement is complemented by a sleep diary in which participants are asked for the time the lights were turned off [75]. Actigraphy has the advantage that it can objectively measure sleep in the natural environment over extended periods of time [74]. In comparison to subjective methods, actigraphy is not prone to multiple biases such as social desirability bias and recall bias [76]. Further, validation studies of actigraphy against polysomnography have shown high sensitivity, i.e. Actigraphs are able to correctly identify sleep periods [77,78]. However, specificity was found to be low, i.e. periods of wakefulness were often not detected as such by the device [77,78].

Subjective methods

Sleep diaries have also been used as standalone instruments [79]. It has been found that for adolescents at least five weekday diary entries are needed to reliably estimate sleep timing, sleep latency and sleep duration [79]. Average sleep duration across one week has shown good agreement with sleep duration obtained with Actigraphs [76]. Sleep diaries are therefore considered as a cost-effective method in comparison to actigraphy although compliance might drop and data might become incomplete in cases of extended measurement periods [74,76].

In large population-based epidemiological studies, sleep is often subjectively assessed by questionnaires because they are easy to administer [80]. For sleep duration, this is often done by one or a few questions, for instance to cover nocturnal sleep duration and daytime napping separately for weekdays and weekend days. For nocturnal sleep duration, researchers typically either (i) ask for the amount of time spent asleep during the night or (ii) ask for bed- and wake times in order to calculate sleep duration. The first approach has the advantages that the participant is more likely to exclude time spent reading or watching TV in bed or longer times of wakefulness during the night. However, it has the disadvantage that participants have to calculate their sleep duration by themselves which might be error-prone. The second approach counteracts this disadvantage as the calculation is done by the researchers. However, it may be less accurate because the time difference may include activities other than sleep or periods of wakefulness. Generally, sleep duration is overestimated when being assessed by questionnaires as compared to actigraphy [76,81,82].

Further, sleep duration is overestimated by parents in comparison to self-reports by adolescents [83]. Questionnaires can also be used to assess sleep quality. Sometimes this is done with just one single question inquiring a subjective rating of sleep quality overall. However, there are also validated sleep questionnaires for children for the assessment of sleep quality such as the "Pittsburgh Sleep Quality Index" [5], the "Children's Sleep Habits Questionnaire" [84], the "Pediatric Sleep Questionnaire" [85] and the "Sleep Disturbance Scale for Children" [86].

Table 2: Overview of advantages and disadvantages of different sleep assessment methods

		Advantages	Disadvantages
Objective methods	**Polysomno-graphy**	• Accurate ("gold standard"-measure) • Detailed information about sleep duration, sleep quality indicators, etc.	• Time-consuming • Expensive • Typically conducted in a clinical setting and therefore results may not be fully transferable to natural environment
	Actigraphy	• Measurement of sleep in natural environment over extended periods of time	• Relatively expensive • Periods of wakefulness are not detected by the device if participant does not move
Subjective methods	**Sleep diary**	• Good agreement with actigraphy-derived sleep duration • Cost-effective	• Burdensome for participants if implemented over longer time periods
	Questionnaire	• Easy to administer • Minimal time and costs	• Poor agreement with actigraphy-derived sleep duration

Note: The advantages and disadvantages of the different methods have to be outweighed depending on the specific research question. Some information can only be gained with subjective methods (e.g. subjective rating of sleep quality) and some only with objective methods (e.g. information on sleep stages is only provided by polysomnography). Further, to obtain the intended information some methods may need to be combined (e.g. to calculate sleep latency actigraphy needs to be combined with a sleep diary).

1.5 Epidemiology of obesity and related cardio-metabolic disorders

In Europe, the prevalence of overweight and obesity in children and adolescents is at a high level although the rising trend over the last decades has levelled off in many countries [87,88]. Based on studies conducted in 28 European countries between 2011 and 2016, the prevalence of overweight and obesity among 2-13 year old children has been estimated to be 22.9% (95% confidence interval [CI]: 20.1-25.9) [87]. Overweight and obesity are associated with a higher risk for cardio-metabolic disorders such as hypertension, type 2 diabetes and dyslipidaemia. However, nationally representative data from European countries on such disorders are scarce.

Surveillance data from Germany showed that 7.9% (95% CI: 6.7-9.1) of children aged 3-10 years and 11.2% (95% CI: 8.6-14.0) of children and adolescents aged 11-17 years had

hypertensive blood pressure defined by a systolic or diastolic blood pressure at or above the 95th age-, sex- and height-specific percentile [89]. A similarly high prevalence of borderline high or high blood pressure was also observed in a nationally representative sample of children and adolescents from the USA [90].

Although the prevalence of type 2 diabetes in European children and adolescents is presumably low [91,92], the prevalence of insulin resistance as its precursor is likely to be higher. Data from the non-representative European IDEFICS (Identification and Prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS) study suggests an overall prevalence of insulin resistance of 17.8% in 3-10 year old children [93]. The prevalence showed a strong trend with weight status ranging from 2.2% in thin/underweight children to 66.7% in obese children [93]. These results are in line with representative data from the USA that revealed a similarly high prevalence of insulin resistance [94].

According to single European studies, dyslipidaemia is present in quite a substantial proportion of children. For instance, a Danish study reported a prevalence of 6.4% in a population-based cohort [95]. Similar to the prevalence observed in children and adolescents from the USA [90], a German study reported percentages of 0-16 year old children with abnormal lipid levels varying between 6.1% and 22.1% depending on the specific blood lipid investigated [96].

2 AIMS OF THE THESIS

In the following two chapters the conceptual framework depicting the hypothesised associations between psychosocial well-being, sleep characteristics and cardio-metabolic markers is displayed and the overall research aim and objectives are outlined.

2.1 Conceptual framework

Considering previous research results (see section 1.1) as well as the potential underlying mechanisms described above (see section 1.2), I developed a conceptual framework depicting the hypothesised associations between (i) psychosocial well-being, (ii) sleep and other lifestyle factors such as dietary intake, physical activity and electronic media use as well as (iii) cardio-metabolic markers (Figure 2).

Higher psychosocial well-being was hypothesised to be associated with longer sleep duration and fewer sleep disturbances. This association was investigated in Paper 1 (Appendix, page 63). Second, longer sleep duration, better sleep quality and better sleep timing were hypothesised to be associated with a healthier weight status determined by a lower body mass index (Appendix, Paper 2, page 99). Longer sleep duration was assumed to be associated with lower insulin resistance, partially mediated through lower waist circumference (Appendix, Paper 3, page 127). Lastly, higher psychosocial well-being was hypothesised to be directly associated with lower waist circumference, lower blood pressure, lower HOMA-IR, lower triglycerides and higher HDL-C. Further, higher psychosocial well-being was assumed to be indirectly associated with (i) lower waist circumference through a healthier lifestyle and with (ii) lower blood pressure, lower HOMA-IR, lower triglycerides and higher HDL-C through both a healthier lifestyle and lower waist circumference These associations were investigated in Paper 4 (Appendix, page 171). It is possible that some of the depicted associations in Figure 2 are bidirectional. However, only the hypothesised associations that were actually investigated in the present thesis are displayed.

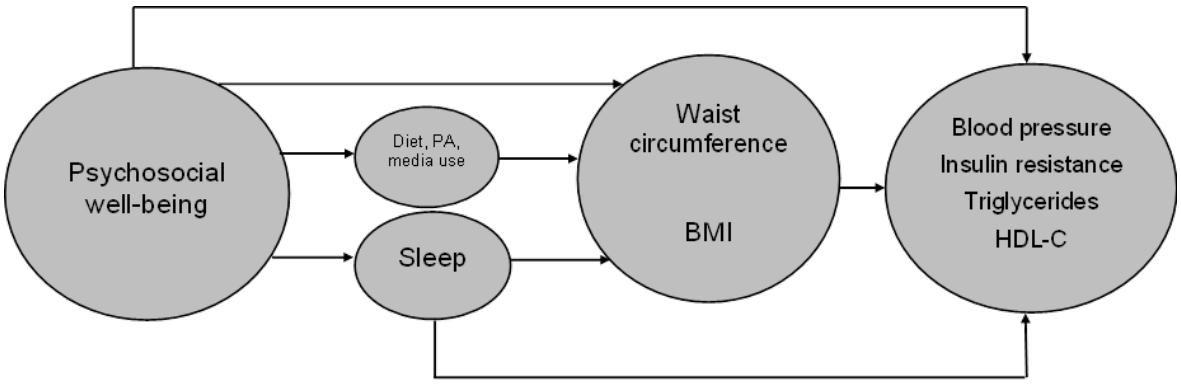

Figure 2: Conceptual framework
Note. Framework depicts the hypothesised associations between psychosocial well-being, sleep and other lifestyle factors as well as cardio-metabolic markers; PA – physical activity; BMI – body mass index; HDL-C - high-density lipoprotein cholesterol

2.2 Overall aim and research objectives

The overall aim of this PhD thesis was to investigate potential pathways from positive mental health to cardio-metabolic health in children and adolescents. A special focus was put on the role of sleep as a potential mediator in this association. To achieve the overall aim of the thesis, the following specific objectives were pursued:

- To investigate the associations between psychosocial well-being and sleep characteristics, i.e. both sleep duration and sleep disturbances (Appendix, Paper 1, page 63)
- To study the association between objectively measured sleep duration and weight status (Appendix, Paper 2, page 99)
- To examine the association between sleep duration and insulin resistance (Appendix, Paper 3, page 127)
- To study the associations between psychosocial well-being and biological markers of abdominal obesity, insulin resistance, hypertension and dyslipidaemia under consideration of potential behavioural pathways (Appendix, Paper 4, page 171)

3 SUBJECTS AND METHODS

In the following, the study population under investigation is presented and details with respect to the data collection are given. In addition, information on the methods used for assessing psychosocial well-being, sleep characteristics, cardio-metabolic markers and potential confounding or mediating variables is provided. The last part of this chapter provides an overview of the statistical methods applied in this thesis including an overview of their advantages.

3.1 Study population

For this thesis, data collected in the framework of the IDEFICS/I.Family cohort study were used [97]. The IDEFICS/I.Family study was conducted in eight European countries, namely Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden. The baseline examination (in the following referred to as the first examination wave) was carried out as part of the IDEFICS study in 2007/2008 [98]. Children aged 2 to 9.9 years old were recruited through a setting-based approach in two regions in each country (N=16,228). In each country, one of the two regions was defined as the intervention region, where a childhood obesity prevention program was implemented in schools and communities [99]. The other region served as the control region with no intervention. During the second examination wave in 2009/2010, 11,041 children who already participated in the first examination wave and also 2,555 newcomers were examined [97]. The intervention was evaluated with a postal survey in autumn 2010. A third examination wave occurred in 2013/2014 as part of the I.Family study, the successor of the IDEFICS study, during which 7,105 children who already participated in IDEFICS as well as 2,512 newly recruited siblings were examined [97]. In 2015, an in-depth investigation of sleep and other health parameters was conducted in the so-called contrasting groups, i.e. a subsample of participants with divergent weight trajectories from either the first or second examination wave to the third examination wave. Based on their weight trajectories, children were either classified as “stable normal weight”, “stable overweight/obesity” or “excessive weight gain” [97]. An overview of the time points of all examinations/surveys in the IDEFICS/I.Family cohort is depicted in Figure 3.

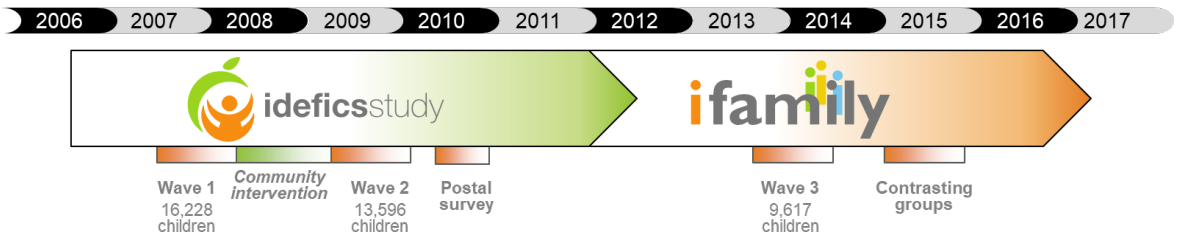

Figure 3: Timeline of examination waves in the IDEFICS/I.Family study

Further, an overview of the sample size for the single papers of this thesis is provided in Table 3. The sample sizes varied between 559 and 6,519 subjects because relevant information to answer the respective research question was not collected at all examination waves.

Table 3: Sample sizes of the four papers included in this thesis

	Data cross-sectional analysis	$N_{cross\text{-}sectional}$	Data longitudinal analysis	$N_{longitudinal}$
Paper 1	Wave 3	6,336	Wave 2, Wave 3	3,379
Paper 2	Contrasting groups	559	N/A	N/A
Paper 3	Wave 2	3,900	Wave 2, Wave 3	3,900
Paper 4	Wave 3	6,519	Wave 1, Wave 2, Wave 3	1,393

N/A – not applicable

3.2 Data collection and procedures

For the IDEFICS/I.Family study, data on weight status and related health outcomes such as blood pressure and insulin resistance as well as their potential determinants (e.g. socio-demographic status and lifestyle factors) were collected [97]. This was done by using a variety of methods including interviews, self-completion questionnaires, physical examinations, biological samples and accelerometry [97]. All instruments implemented and their development are described in detail in Bammann et al. [100]. As a general procedure, parents filled in all questionnaires if their children were younger than 12 years old while older children reported for themselves. Before children entered the study, parents provided informed written consent. Moreover, children 12 years and older provided simplified written consent. Younger children gave oral consent for examinations and sample collection on site. Ethical approval was obtained by the appropriate Ethics Committees by each of the eight study centres conducting fieldwork.

The following chapters (chapter 3.3 to chapter 3.6) describe measures and methods relevant for this PhD thesis.

3.3 Assessment of psychosocial well-being

Psychosocial well-being was measured with four subscales of the "KINDL^R Questionnaire" [50,101]. Each subscale, i.e. "emotional well-being", "self-esteem", "family" and "friends", comprised four items and referred to the past week. Ten items were positively worded (for instance "My child had fun and laughed a lot") and six items were negatively worded (for instance "My child felt different from other children"). In questionnaires of the first and

second examination wave, a 4-point response scale (never, seldom, sometimes, often/all the time) was used. In the third examination wave, however, a 5-point response scale (never, seldom, sometimes, often, all the time) was implemented. As data on well-being from all three examination waves were used in Paper 1 and Paper 4, I applied a scoring suitable for both response scales and assigned points as follows:

- "never" = 0 points
- "seldom" = 1 point
- "sometimes" = 2 points
- "often/all the time", "often", "all the time"= 3 points

Six negatively worded items were coded inversely. The points of all items were summed which resulted in a well-being score with a theoretical range from 0-48 points.

3.4 Assessment of sleep

3.4.1 Subjective assessment of sleep duration and sleep disturbances

Information on habitual sleep duration in hours and minutes on weekdays and weekend days/vacations (in the following referred to as weekend days) was collected by self-completion questionnaires. The instructions read as follows: "What is the amount of time the child sleeps during a 24 hour period on weekdays? Give separate information for night time sleep and naps in the daytime." Information was collected for weekend days in the same way. The following formula was used to calculate the weighted average of nocturnal sleep duration for each child:

*(nocturnal sleep duration on weekdays*5 + nocturnal sleep duration on weekend days*2) / 7*

The weighted average of daily napping time (minutes) was calculated in the same manner:

*(napping on weekdays*5 + napping on weekend days*2) / 7*

Sleep disturbances were assessed by asking whether the child/adolescent generally has "trouble getting up in the morning" (yes/no) and "difficulties falling asleep" (yes/no).

3.4.2 Objective assessment of sleep duration and sleep quality

In the contrasting groups (in-depth examination of a subsample in 2015), sleep was assessed using wrist-worn accelerometers (GT3X+, Actigraph LLC, Pensacola, FL, USA) in combination with a sleep diary. Participants were asked to wear the Actigraph on the non-dominant wrist for up to seven consecutive days and nights over the study period. In case participants refused to wear the device during the daytime, night wear only was also acceptable. Furthermore, participants recorded the type of day (school day, day off, sick day, etc.), the time the lights were turned off (lights-off time) and their wake-up time for each day of the measurement period in a sleep diary. After the raw data were downloaded from the Actigraphs at the end of the measurement period, they were complemented by information

on lights-off and wake-up times. Subsequently, the Sadeh algorithm was used to distinguish sleep times from non-sleep times [102]. The following sleep variables are of interest for this thesis:

- sleep duration: hours and minutes slept per night as detected by the algorithm
- sleep latency: minutes between reported lights-off time and sleep onset (as detected by the algorithm)
- sleep efficiency: percentage of time spent asleep while in bed calculated as sleep duration/(reported wake-up time – reported lights-off time)*100
- reported wake-up time
- reported lights-off time

First, the average across all available weekdays and the average across all available weekend days were calculated. Second, the weighted average of weekdays and weekend days was calculated such as:

*(average sleep duration on weekdays*5 + average sleep duration on weekend days*2)/7*

3.5 Assessment of cardio-metabolic markers

Cardio-metabolic markers considered in this thesis and their assessment methods are summarised in Table 4.

Table 4: Overview of cardio-metabolic markers, measurement methods and instruments

	1st and 2nd examination wave		*3rd examination wave*	
Cardio-metabolic marker	**Measurement method**	**Instrument and manufacturer**	**Measurement method**	**Instrument and manufacturer**
Waist circumference (cm)	Inelastic tape	Seca 200, seca GmbH & Co. KG, Hamburg, Germany	Inelastic tape	Seca 200, seca GmbH & Co. KG, Hamburg, Germany
HOMA-IR calculated from insulin and glucose (fasting blood samples)	Insulin			
	Luminescence immunoassay	AUTO-GA Immulite 2000, Siemens, Eschborn, Germany	Electrochemi-luminescence technology	MULTI-SPOT® Assay System - Human Leptin, Insulin Assay Kit, Meso Scale Diagnostics, LLC., Rockville, MD, USA
	Glucose			
	Point-of-care analyser	Cholestech LDX, Cholestech Corp., Hayward, CA, USA	Enzymatic UV test	Cobas c701, Roche Diagnostics GmbH, Mannheim, Germany
Blood pressure (mean of systolic and diastolic blood pressure)	Automated oscillometric device	Welch Allyn 4200B-E2, Welch Allyn Inc., Skaneateles Falls, NY, USA	Automated oscillometric device	Welch Allyn 4200B-E2, Welch Allyn Inc., Skaneateles Falls, NY, USA
Triglycerides and HDL-C	Point-of-care analyser	Cholestech LDX, Cholestech Corp., Hayward, CA, USA	Enzymatic colorimetric test	Cobas c701, Roche Diagnostics GmbH, Mannheim, Germany

Waist circumference was measured in upright standing position with relaxed abdomen and feet together, midway between the lowest rib margin and the iliac crest to the nearest 0.1 cm.

For obtaining insulin, glucose, triglycerides and HDL-C, venous fasting blood was collected. In the first and second examination wave, capillary blood by finger-prick was also acceptable in case venipuncture was refused.

Blood pressure measurement was undertaken using the appropriate cuff length according to the child's arm circumference and after participants had rested for at least 5 minutes. Generally, two measurements were taken with 2 minutes interval in between them. A third one was only taken in case the first and second measurement differed by more than 5%. Subsequently, the average of the two measurements (in case of three measurements: the two measurements most closely together) of systolic and diastolic blood pressure, respectively, was calculated to obtain one value for systolic and one value for diastolic blood pressure. To obtain one value for blood pressure, the average of these two values was calculated.

3.6 Assessment of further potential mediating and confounding variables

Information on potential mediating and confounding variables was collected by questionnaires. Age in years (rounded to one decimal place) was calculated from date of birth and date of examination. Further, the sex of the child was recorded and the highest level of parental education was queried and categorised according to the International Standard Classification of Education (levels 0-2=low, 4-5=medium, 6-8=high) [103]. Information on diet was collected with a food frequency questionnaire. Frequency of fruit and vegetable consumption (times/week) was used as an indicator for healthy dietary intake. Frequency of intake of snacks and salty foods such as hamburger, kebab and fritters (times/week) was used as an indicator for unhealthy dietary intake. Information on participation in sports club physical activity (hours/week) was also obtained by questionnaires. Further, the weighted average of the time spent in front of the TV and in front of the computer across weekdays and weekend days was calculated (hours/week). Lastly, menarche (girls) and voice mutation stages (boys) were inquired by self-completion questionnaires using questions adapted from Carskadon and Acebo [104] and used as an indicator for pubertal status.

3.7 Statistical methods

The following statistical methods were used to answer the research questions of this thesis:

In Paper 1 and Paper 2, *linear and logistic mixed effects regression models* were used. These models provide a flexible tool for modelling clustered data (e.g. siblings in the present sample) accounting for non-independence of data.

Furthermore, in Paper 1 *quantile regression* was applied. Quantile regression allows to model any quantile of the outcome distribution and not just the mean as it is done in linear regression [105]. Thereby, it can be investigated whether the association between the exposure variable and the outcome variables is heterogeneous across the distribution of the outcome variable [106]. For instance, associations may be stronger or weaker at the extreme ends of the distribution of the outcome variable.

Another statistical method applied in Paper 2 is *latent class analysis*. This statistical method is used to identify underlying subgroups of individuals who respond similarly to categorical variables [107]. Unlike traditional cluster analysis techniques, latent class analysis is a model-based approach and therefore regarded as a more objective method [107].

In Paper 3 and Paper 4 associations of interest were investigated using *path models*. Path analysis is a special case of structural equation modelling where all variables are observed (and not latent) variables [108]. With a path model so-called direct, indirect and total effects can be estimated. A direct effect is defined as the influence of one variable on another, unmediated by any other variable, and an indirect effect as the influence of one variable on another, mediated by at least one intervening variable [109]. The total effect is the sum of direct and indirect effect(s) of one variable on another [109]. It should be noted that the terms "direct effect", "indirect effect" and "total effect" are standard terminology in path analysis but this does not necessarily imply causality of associations.

In contrast to path analysis, where all regressions of a mediation model are modelled simultaneously, mediation has traditionally been assessed by fitting the regressions between the single variables of a mediation model separately. The causal steps approach by Baron and Kenny, for instance, is one of the most widely used methods [110,111]. According to this approach, in a simple mediation model with one independent, one mediating and one dependent variable (see Figure 4), four criteria need to be fulfilled for mediation to be established:

1) The independent variable needs to be statistically significantly associated with the dependent variable in a regression model without the potential mediator.
2) The independent variable needs to be statistically significantly associated with the mediating variable.
3) The mediating variable needs to be statistically significantly associated with the dependent variable in a model also including the independent variable.
4) The effect size of the association between the independent variable and the dependent variable needs to be reduced after inclusion of the mediating variable.

Another approach is the product of coefficients method whereby the indirect effect is calculated as the product of (i) the regression coefficient of the association between the independent variable and the mediating variable and (ii) the regression coefficient of the

association between the mediating and the dependent variable controlling for the independent variable. Statistical significance of this indirect effect can be assessed either by the so-called delta method/Sobel test or by bootstrapped confidence intervals [111,112]. Helpful computational tools such as the PROCESS macro have been developed to calculate indirect effects and to assess statistical significance [113,114].

However, in case of more complex mediation situations these approaches have their limitations [115]. A path model has the following advantages over the traditional approaches:

- A path model is much more flexible in terms of model specification because it is in principle not limited in the number of independent, mediating and dependent variables and the dependent variables can be of any type (continuous, dichotomous, ordered categorical, count, etc.) [115].
- In case of clustered data, path analysis allows for correction of standard errors or conducting multilevel mediation analysis.
- A path model can easily handle missing values in mediating and dependent variables in the model because parameter estimation is typically based on maximum likelihood estimation.

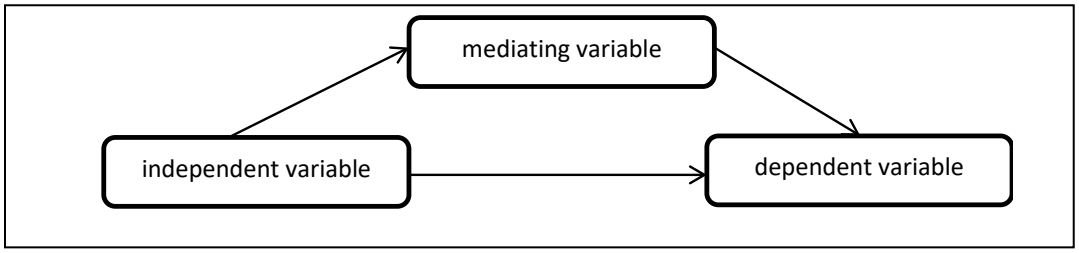

Figure 4: Simple mediation model

4 MAIN FINDINGS

In this chapter the main results of the four papers included in this thesis are summarised.

4.1 Associations between psychosocial well-being and sleep characteristics

The cross-sectional and longitudinal associations between psychosocial well-being and sleep characteristics are presented in Paper 1 (Appendix, page 63).

Cross-sectionally, higher psychosocial well-being was found to be associated with longer sleep duration. The association was found to be particularly strong at the lower tail of the sleep duration distribution suggesting that children with very short sleep duration might benefit the most from an increase in their well-being. Furthermore, higher psychosocial well-being was found to be cross-sectionally associated with lower odds of "difficulties falling asleep" and lower odds of "trouble getting up in the morning".

Longitudinally, an increase in well-being between the second and third examination wave was found to be associated with longer sleep duration and fewer sleep disturbance at the third examination wave. However, well-being at the second examination wave did not predict sleep parameters four years later except for adolescents in whom higher well-being was associated with lower odds of "trouble getting up in the morning" at the third examination wave.

4.2 Associations between sleep characteristics and body mass index

The associations between objectively measured sleep characteristics and body mass index are described in Paper 2 (Appendix, page 99).

There was a weak inverse association between sleep duration and BMI that was statistically non-significant. Also none of the other sleep characteristics under investigation, i.e. sleep efficiency, sleep latency, lights-off time and wake-up time, were statistically significantly associated with BMI in the whole sample. Only in an age-stratified analysis longer sleep latency was associated with higher BMI in adolescents (13-16 years old) but the 95% confidence interval included the null after adjustment for sleep duration.

Sleep subtypes were identified by conducting a latent class analysis using the five dichotomised sleep variables (sleep duration, sleep efficiency, sleep latency, lights-off time and wake-up time). Four different sleep subtypes were identified and children were assigned to the different subgroups based on their highest probability for belonging to a specific subtype: (i) early birds (17.5% of the sample), (ii) short sleep duration (14.7%), (iii) optimal sleep (47.6%) and (iv) poor sleep quality (20.2%). Early birds were characterised by a high probability for having an early wake-up time. Children belonging to the "short sleep duration" subtype had a high probability of having short sleep duration. Those children characterised

as having “optimal sleep” had a high probability of being allocated to the most favourable category of each sleep characteristic. The subtype “poor sleep quality” incorporated those children with a high probability of having poor sleep efficiency and long sleep latency. Sleep subtype was not found to be associated with BMI.

4.3 Associations between sleep duration and insulin resistance

Cross-sectional and longitudinal associations between sleep duration and HOMA-IR were investigated within one path model considering waist circumference as a mediator in Paper 3 (Appendix, page 127).

Cross-sectionally, longer sleep duration was associated with a lower waist circumference. No direct association between sleep duration and HOMA-IR was found. However, an inverse indirect association between longer sleep duration and lower HOMA-IR through waist circumference was observed.

Also longitudinally, no direct association between sleep duration at the second examination wave and HOMA-IR at the third examination wave was found. However, sleep duration at the second examination wave was indirectly associated with HOMA-IR at the third examination wave through waist circumference at the second and waist circumference at the third examination wave.

4.4 Associations between psychosocial well-being and cardio-metabolic markers

Lastly, the cross-sectional and longitudinal associations between psychosocial well-being and cardio-metabolic markers were investigated based on path models in Paper 4 (Appendix, page 171).

The cross-sectional path model showed a negative direct effect of psychosocial well-being on waist circumference and HOMA-IR, respectively. Longitudinally, an increase in well-being score between the second and third examination wave exerted an inverse direct effect on waist circumference and a positive direct effect on HDL-C at the third examination wave. An increase in well-being score further in the past, i.e. between the first and the second examination wave, did not directly predict cardio-metabolic markers at the third examination wave.

In both the cross-sectional and longitudinal analysis indirect effects of well-being on cardio-metabolic markers were observed. Specifically, all three exposures, i.e

(1) higher psychosocial well-being at the third examination wave,

(2) increase in well-being between the second and third examination wave and

(3) increase in well-being between the first and the second examination wave

were indirectly associated with

- a lower waist circumference at the third examination wave through lifestyle factors at the third examination wave and
- lower blood pressure, lower HOMA-IR, lower triglycerides and higher HDL-C at the third examination wave through both lifestyle factors and waist circumference at the third examination wave.

5 GENERAL DISCUSSION

In the following, the main results obtained will be interpreted and integrated into the overall research context. Further, overall strengths and limitations of the thesis will be acknowledged followed by an outline of public health implications. The chapter closes with suggestions for future research.

5.1 Discussion of results

Overall, the results of this thesis provide support for most of the hypothesised associations depicted in the conceptual framework (see section 2.1), i.e. they suggest a link between (i) psychosocial well-being and sleep duration/sleep disturbances, (ii) sleep duration and abdominal obesity, (iii) sleep duration and insulin resistance mediated through waist circumference, (iv) psychosocial well-being and waist circumference, insulin resistance and HDL-C as well as (v) psychosocial well-being and all cardio-metabolic markers mediated through lifestyle factors. The identified associations are also displayed in Figure 5. In the following, the results from the single papers are discussed in detail.

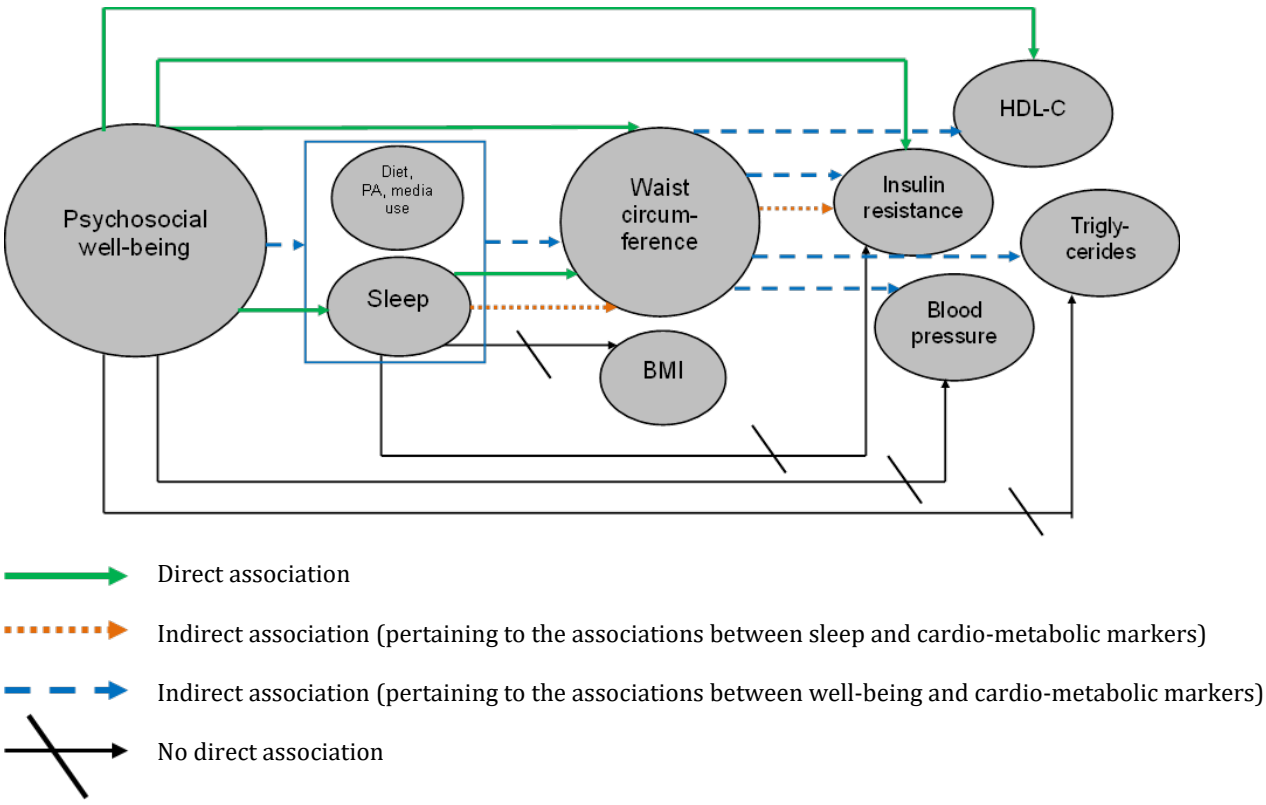

Figure 5: Graphical display of identified associations in the PhD thesis
Note. PA – physical activity, BMI – body mass index, HDL-C – high-density lipoprotein cholesterol

5.1.1 Psychosocial well-being and sleep characteristics

In agreement with my hypotheses and previous research [20-23], higher psychosocial well-being was found to be cross-sectionally associated with longer sleep duration and lower odds of sleep disturbances. However, higher psychosocial well-being did in general not predict sleep characteristics several years later. As a sensitivity analysis, the reverse direction was investigated, i.e. whether sleep characteristics at baseline predict psychosocial well-being after 4 years of follow-up. Although effect estimates all pointed to the expected direction, i.e. longer sleep duration and absence of sleep disturbances at baseline were associated with higher psychosocial well-being after 4 years of follow-up, no statistically significant association was found. To summarise, although psychosocial well-being and sleep were found to be cross-sectionally associated with each other, there was no evidence that psychosocial well-being predicted sleep characteristics or that sleep characteristics predicted psychosocial well-being over several years. One of the reasons for this observation could be that effects of psychosocial well-being on sleep (or effects of sleep on well-being) are acting mainly in the short term (only days, weeks or few months), especially in growing children and adolescents. In other words, short-term effects may have faded out over the follow-up period of 4 years. Hence, longitudinal studies with a shorter time interval between measurements or with repeated assessments of psychosocial well-being and sleep over longer time periods may be able to shed light on the direction of the association.

5.1.2 Sleep characteristics and body mass index

In the study investigating the association between objectively measured sleep characteristics and BMI no associations between the single sleep variables (sleep latency, sleep efficiency, etc.) and BMI were found. Other studies using objectively measured sleep duration as the exposure are comparably scarce and findings are inconsistent with some studies showing an inverse association [116,117] and others reporting null findings [118,119]. In contrast, studies investigating the association between subjectively measured sleep duration and BMI are numerous with the majority reporting a negative association [120-122]. Also a previous study based on cross-sectional data of 2 to 9 year old children (N=7,867) collected during the first examination wave of the IDEFICS/I.Family study found parentally reported short sleep duration to be associated with higher odds of overweight (10 hours or less vs. more than 11 hours) with larger effect sizes in primary school-aged children in comparison to pre-school aged children [123]. Hence, one reason for the null finding might be that the association between sleep duration and BMI differs across age groups. Miller et al. [124] reported in a meta-analysis of longitudinal studies that associations between longer sleep duration and changes in BMI were statistically significant in infants and children but not in adolescents [124]. Nevertheless, associations between short sleep duration and incidence of

overweight/obesity became apparent across all age groups (infants, children and adolescents) [124]. Also another meta-analysis reported associations between short sleep duration and risk of overweight/obesity across all age groups [120].

To gain more insight into potential differential associations across age groups within our cohort, I also investigated associations between self-reported sleep duration and BMI in 5,397 children (9-16 years old) participating in the third examination wave of the IDEFICS/I.Family study (unpublished data). The effect size of the association between sleep duration and BMI adjusted for relevant covariates was only slightly larger than the effect size obtained for the association between objectively measured sleep duration and BMI but statistically significant. Hence, once reason for the null finding could be that our sample providing objective sleep data (N=559) was not large enough to detect small effects.

5.1.3 Sleep duration and insulin resistance

In the study investigating the association between sleep duration and HOMA-IR, the hypothesis of an association between longer sleep duration and lower waist circumference was confirmed as well as the hypothesis of an indirect association between longer sleep duration and lower HOMA-IR mediated through waist circumference. However, no evidence was found for an association between sleep duration and HOMA-IR independent of waist circumference. Generally, in young populations the evidence for an association between longer sleep duration and lower insulin resistance independent of adiposity markers is not convincing [24]. In many studies the association between longer sleep duration and lower insulin resistance was markedly attenuated after adjustment for weight status [125-127]. In contrast, adult laboratory and epidemiological studies provide more consistent results with respect to an association between longer sleep duration and lower diabetes risk independent of weight status [128]. Whereas the laboratory studies may only reflect the short-term effects of sleep deprivation on glucose metabolism it is also conceivable that the association between longer sleep duration and lower insulin resistance becomes apparent at a later age.

5.1.4 Psychosocial well-being and cardio-metabolic markers

Consistently, in both the cross-sectional and longitudinal analysis, indirect effects of well-being on waist circumference through lifestyle factors as well as indirect effects of well-being on blood pressure, HOMA-IR and blood lipids through both lifestyle factors and waist circumference were found. Effect sizes of these indirect effects were of small size and may be considered not clinically relevant. From a preventive perspective, however, even a small effect may be considered as meaningful as it suggests a pathway [129], i.e. it indicates that higher well-being may lead to a healthier lifestyle and subsequently to fewer cardio-metabolic disorders.

I also found direct effects of higher levels of well-being on lower waist circumference, lower HOMA-IR and higher HDL-C although results were less consistent across analyses, i.e. some of these direct associations were only observed in the cross-sectional or longitudinal analysis. Unexpectedly, in sensitivity analyses stratified by sex, higher well-being was directly associated with higher blood pressure in boys. Likewise, counterintuitive associations between indicators of mental ill-health such as depression and lower blood pressure have been observed in studies in adolescent boys and in adults [13,130,131]. Hence, the direct (and thus potentially psychobiological) pathway from well-being to cardio-metabolic markers requires further investigation.

5.2 Strengths and limitations of the thesis

One of the strengths of the thesis is the use of data from a large sample of European children and adolescents that were collected following standardised procedures at multiple time points. Nevertheless, it has to be kept in mind that the sample was not representative of the populations in the eight participating countries, i.e. observed levels of well-being, duration and quality of sleep, etc. may not be generalisable to the whole childhood/adolescent populations in these European countries. However, observed associations are less likely to be influenced by this non-representativeness of participants. Furthermore, not all children participated in all three examination waves and both overweight and poor well-being were amongst others found to be determinants of attrition [132,133]. For instance, if those children experiencing both constant poor well-being and constant overweight were more likely to drop out, this would have led to an underestimation of the protective effect increases in well-being can have for an unfavourable development of abdominal obesity.

The use of objective methods such as anthropometric measurements, biological samples and accelerometers in a comparably large and young population is a further strength. However, some variables were obtained by questionnaires which may introduce measurement error. For instance, previous research has found that sleep duration is overestimated in questionnaires answered by adolescents and parents (as proxies for pre-school aged children) in comparison to actigraphy [76,81]. Furthermore, questionnaires were answered by parents for children below 12 years of age and it has been found that parents rate their children's HRQoL higher than the children do themselves [134]. With respect to the assessment of well-being it also needs to be mentioned that only four subscales of the KINDL^R Questionnaire were implemented and that the response scale varied across waves. Hence, the psychometric properties reported for the original KINDL^R Questionnaire may not be directly transferable to our measure. However, for both Paper 1 and Paper 4 internal consistency of the 16 psychosocial well-being items was assessed and satisfactory results were obtained.

A major strength of the thesis is that for most research questions longitudinal associations could be investigated. Nevertheless, the time spans between the single waves were large, i.e. two years between the first and the second examination wave and four years between the second and third examination wave. Some studies indicate that well-being in childhood has poor stability over time [135]. Therefore, well-being measured at one point in time might be a poor predictor of health outcomes several years later, i.e. effects may have dissipated in the meantime. This hampered investigating directionality of associations in longitudinal analyses.

A further strength of the thesis is the use of sophisticated statistical analysis methods to investigate associations of interest. For instance, path analysis is suitable for investigating mediation and overcomes many of the disadvantages of simple mediation models (see 3.7 Statistical methods).

5.3 Public health implications

The results of this thesis suggest higher psychosocial well-being and longer sleep duration to be associated with fewer cardio-metabolic disorders. Hence, both psychosocial well-being and sleep may be promising targets for interventions as they could influence cardio-metabolic health. Below, aspects that need to be considered in interventions aiming to improve psychosocial well-being and sleep are described and evidence on existing intervention strategies is summarised. However, it should be kept in mind that in the present thesis the direction of many associations could not be determined for certain. More longitudinal studies designed for gaining further knowledge on the temporal relationships between positive mental health, lifestyle factors and cardio-metabolic health are needed to support these intervention recommendations.

5.3.1 Psychosocial well-being

Considering the multidimensional nature of psychosocial well-being as defined in the present thesis, it is conceivable that any potential intervention to improve well-being may address either single domains of well-being (e.g. self-esteem) or multiple domains. However, in some cases the improvement in one domain may also foster improvement in another, e.g. an improvement in social relationships may also positively impact on emotional well-being. Furthermore, well-being may be improved through intervening at different levels relevant for children and adolescents, i.e. at the individual, family, kindergarten/school and community level.

Generally, with the increasingly recognized importance of well-being, also interest in effective interventions to improve well-being is growing. “Public Health England”, an executive agency of the United Kingdom’s national “Department of Health and Social Care”, has recently conducted a synthesis of systematic reviews dealing with the effectiveness of

interventions to promote amongst others resilience, i.e. the ability to overcome serious hardship [136], and subjective well-being in 4-18 year olds [137]. With respect to resilience, the report concludes that among the many interventions identified, a few programs (one at the individual level, two at the family level and two at the school level) seem to be effective in improving resilience [137]. However, the effectiveness of most programs identified was either not maintained in the long-term or maintenance was not investigated. With respect to subjective well-being, the authors concluded that mindfulness-based interventions may have some potential to be effective [137]. Mindfulness-based interventions aim to improve amongst others emotion regulation. The acquisition or enhancement of effective/adaptive emotion regulation skills such as awareness of emotions and understanding emotions has also been suggested by other authors to be a potentially useful new approach for combating and treating childhood obesity. This is because a healthy emotion regulation may have a positive effect on both psychophysiological responses to stress (such as cortisol) and health behaviours (such as diet and physical activity) [138].

5.3.2 Sleep

Interventions for improving sleep duration and quality in children and adolescents can be delivered by several means and in various settings.

A healthy sleep hygiene that may be initiated by parents for younger children and by adolescents themselves has been shown to be associated with better sleep outcomes. The term "sleep hygiene" refers to practices during the day and adjacent to bedtime that support a healthy sleep, i.e. amongst others sufficient duration and good quality [139,140]. For instance, for younger children calming bedtime routines such as storytelling have been found to be associated with better sleep outcomes [139,141]. Further, in school-aged children and adolescents restricting electronic media use before sleeping may foster longer sleep duration [139,140].

The effectiveness of sleep education programs delivered in the school-setting has been tested in several studies [142]. Although these programs improved knowledge about sleep, evidence for their influence on sleep parameters such as sleep duration was mixed [142]. The IDEFICS study is one of very few that aimed to improve sleep duration through a community-oriented setting-based intervention program [143]. It has been found that the intervention did not lead to clinically relevant changes in sleep duration, possibly because the intervention did not last long enough, was not intense enough or sleep assessment was not accurate enough [143]. Other interventions may build on these experiences thereby enhancing the likelihood to design effective intervention programs.

As early school start times are considered to be a strong determinant of short sleep duration in adolescents [80], there has been much debate whether delaying school start time

could increase adolescents sleep duration. The "American Academy for Pediatrics", for instance, stated that school start times before 8:30 a.m. are a key modifiable contributor to insufficient sleep and recommends that schools should aim for school start times that allow adolescents to get sufficient sleep [144]. In agreement with previous studies suggesting a beneficial effect of later school start times, a recent study conducted in the USA reported that sleep duration of adolescents increased in schools that delayed their school start times in comparison to schools that maintained early school start times [145]. Barriers for implementing later school start times are amongst others limited time for after-school activities, the need for adapting transportation schedules, disruption of family routines and alignment of school start and end times with that of younger children [80,146].

5.4 Future research

This thesis sheds light on the interplay between psychosocial well-being, sleep and cardio-metabolic markers. Nevertheless, some questions remained unanswered and new questions arose. In the following, suggestions for future research are made.

5.4.1 Aspects of sleep timing and cardio-metabolic health

Apart from sleep duration and sleep disturbances, interest in the role of aspects of sleep timing for weight status and cardio-metabolic markers is growing [147]. I touched upon this topic in Paper 2 where I investigated amongst others associations between bed- and wake times and BMI. Other aspects related to sleep timing include for instance:

- Chronotype: This is a trait that constitutes at which time of the day someone prefers to go to bed and to rise, to work or to be physically active, etc. [148]. For example, morning-types prefer the "early to bed, early to rise"-schedule whereas evening-types prefer to go to bed late and get up late. Chronotype can be assessed by specific questionnaires or midpoint of sleep on free days can also serve as an indicator [149].
- Social jetlag: This is a phenomenon that occurs when biological preferences for sleep and wake times are not aligned with social schedules such as those for school and work. It is calculated as midpoint of sleep on free days minus midpoint of sleep on school/work days [149].

Potential mechanisms through which aspects of sleep timing may influence cardio-metabolic health are their potential effect on health behaviours and on other sleep characteristics such as sleep duration and sleep quality. For instance, studies in adolescents have shown that evening types are more likely to have an unhealthier dietary pattern and to have shorter weekday sleep duration in comparison to morning types [150,151].

Because of the scarcity of research in young populations, other researchers have called for longitudinal studies to investigate the role of aspects of sleep timing for cardio-metabolic

markers in children [152,153]. It would be important that such studies also consider the role of lifestyle factors and other sleep characteristics such as sleep duration.

5.4.2 Psychosocial well-being and inflammatory markers

It has been hypothesised that positive mental health may reduce levels of inflammatory markers such as CRP and IL-6 which subsequently may have a beneficial effect on cardio-metabolic health [40,41,44]. To date, some studies exist in young populations investigating the association between aspects of mental ill-health and inflammation. For instance, Slopen et al. [154] found internalising and externalising problems to be associated with higher IL-6 and/or higher CRP in childhood and Copeland et al. [155] reported multiple depressive episodes during childhood as a predictor of higher levels of CRP. In contrast, research focussing on the association between positive mental health and inflammatory markers in young populations is scarce. Hence, in order to elucidate the potential direct psychophysiological pathway from positive mental health to cardio-metabolic markers more studies that consider the role of inflammatory markers are needed.

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Appendix

Paper 1

Cross-sectional and longitudinal associations between psychosocial well-being and sleep in European children and adolescents

Thumann BF, Börnhorst C, Michels N, Veidebaum T, Solea A, Reisch LA, Moreno LA, Lauria F, Kaprio J, Hunsberger M, Heidinger-Felsö R, Gwozdz W, De Henauw S, Ahrens W, on behalf of the IDEFICS and I.Family consortia

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Cross-sectional and longitudinal associations between psychosocial well-being and sleep in European children and adolescents

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Short Title:
Associations between well-being and sleep

Author Contributions:
BFT conceptualized and designed the study and carried out the initial analyses. CB, WA and JK assisted with conceptualization and/or interpretation of data analyses. LR and WG contributed to the design of the data collection instruments. TV, AS, LAM, NM, FL, MH, RF and SDH contributed to the acquisition of data. BFT drafted the initial manuscript and all other authors reviewed and revised it. All authors approved the final manuscript as submitted.

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Conflicts of Interest:
All authors have no conflicts of interest to disclose.

Supporting Information:
Table S1: Item list KINDL^{R} Health-Related Quality of Life Questionnaire
Table S2: Cross-sectional associations between well-being (exposure) and weekday nocturnal sleep duration and weekend nocturnal sleep duration (outcomes) in 2013/14 in the whole group and stratified by age
Table S3: Longitudinal associations between change in well-being between baseline (2009/10) and follow-up (2013/14) and weekday nocturnal sleep duration and weekend nocturnal sleep duration at follow-up (2013/14) in the whole group and stratified by age
Table S4: Longitudinal associations between well-being at baseline (2009/10) and weekday nocturnal sleep duration and weekend nocturnal sleep duration at follow-up (2013/14) in the whole group and stratified by age
Table S5: Longitudinal associations between well-being at baseline (2009/10) and sleep characteristics at follow-up (2013/14) stratified by nocturnal sleep duration at follow up in the whole group and stratified by age
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SUMMARY

Research on associations of positive mental health, in contrast to mental ill-health, with sleep duration and sleep disturbances in young populations is scarce. In particular, longitudinal studies focussing on the influence of positive mental health on sleep characteristics are lacking. Therefore, we investigated cross-sectional and longitudinal associations of psychosocial well-being with sleep duration and sleep disturbances. For the cross-sectional analysis, we used data of 3-15 year old children and adolescents participating in the 2013/14 examination of the European IDEFICS/I.Family cohort study (N=6,336). The longitudinal analysis was restricted to children who also participated in the 2009/10 examination (N=3,379). Associations between a psychosocial well-being score created from 16 items of the KINDL^{R} Health-Related Quality of Life Questionnaire covering emotional well-being, self-esteem and social relationships, an age-standardized nocturnal sleep duration z-score and two sleep disturbance indicators ("trouble getting up in the morning", "difficulties falling asleep") were estimated using linear and logistic mixed-effects models. Cross-sectionally, a higher well-being score was associated with longer sleep duration and lower odds of sleep disturbances. A positive change in the well-being score over the 4-year period was associated with longer sleep duration and lower odds of sleep disturbances at follow-up. However, there was only weak evidence that higher psychosocial well-being at baseline was associated with better sleep 4 years later. Thus, our results suggest that increases in well-being are associated with improvements in both, sleep duration and sleep disturbances, but that well-being measured at one point in time does not predict sleep characteristics several years later.

Keywords: sleep quality, longitudinal studies, multi-country, sleep wake disorders

INTRODUCTION

Sleep duration of children and adolescents decreased over the last decades (Matricciani et al., 2012, Keyes et al., 2015) and especially adolescents often do not get enough sleep according to their individual need (Hysing et al., 2013, Keyes et al., 2015). One factor contributing to insufficient sleep can be an evening circadian phase preference ("eveningness"). This trait occurs more frequently in adolescents in comparison to children and includes amongst others a preference for late bedtimes and late get up times (Carskadon et al., 1993, Owens, 2014, Randler et al., 2017). Further, difficulties in initiating and maintaining sleep are common in both children and adolescents (Fricke-Oerkermann et al., 2007, Spruyt et al., 2005, Hysing et al., 2013). This is alarming because poor sleep, i.e. short sleep duration and sleep disturbances, and eveningness have previously been shown to be associated with obesity (Cappuccio et al., 2008, Jarrin et al., 2013), cardio-metabolic disorders (Quist et al., 2016), poor academic achievement (Dewald et al., 2010) and/or poor mental health (Gregory and Sadeh, 2012, Lovato and Gradisar, 2014, Randler, 2011). With regard to the latter, previous studies typically focussed on mental ill-health such as depressive symptoms and anxiety (Gregory and Sadeh, 2012, Lovato and Gradisar, 2014). Aspects of positive mental health, the second dimension of mental health next to mental ill-health (World Health Organization, 2005), have less often been investigated in relation to sleep. The concept of positive mental health is closely related to quality of life and subjective well-being (Diener, 1984) and characterised by positive emotions and resources such as self-esteem, optimism and satisfying personal relationships (World Health Organization, 2005).

Aspects of mental health and sleep are most likely bidirectionally linked through physiological processes. On the one hand, research has shown that stress – which in childhood can emerge from various sources like problems with the family and peers (Ryan-Wenger et al., 2005) – leads to the activation of the hypothalamic-pituitary-adrenal axis with the release of hormones such as cortisol which affect sleep architecture (Buckley and Schatzberg, 2005). On the other hand, poor sleep has been shown to lead to an additional cortisol release (Buckley and

Schatzberg, 2005) and to adversely affect emotional brain networks (Kahn et al., 2013). Further, genetic influences on both well-being and sleep have been observed, so there may be shared genetic factors underlying the association (Okbay et al., 2016).

Cross-sectional studies observed good sleep, i.e. amongst others adequate sleep duration and absence of sleep disturbances, and morningness to be associated with higher levels of optimism and self-esteem (Lemola et al., 2011, Randler, 2011), health-related quality of life (HRQoL) (Roeser et al., 2012, Hiscock et al., 2007, Quach et al., 2009, Magee et al., 2017, Delgado Prieto et al., 2012), life satisfaction (Segura-Jimenez et al., 2015) and good family relationships (Randler, 2011, Segura-Jimenez et al., 2015). Further, some longitudinal studies reported indicators of good sleep to be predictive of higher self-esteem (Fredriksen et al., 2004) and HRQoL (Quach et al., 2009, Magee et al., 2017). Although it seems biologically plausible that positive mental health also influences sleep, longitudinal studies focussing on this direction of the association are scarce. Further, only few studies focussed on multiple sleep characteristics such as sleep duration, difficulties falling asleep and sleep efficiency although they are all interrelated. For example, some researchers have shown longer sleep latency to be associated with shorter sleep duration (Nixon et al., 2009, Lemola et al., 2011). However, intervention studies revealed that sleep latency went down after sleep restriction (Jenni et al., 2005, Sadeh et al., 2003), possibly as a result of increasing homeostatic sleep drive. This was confirmed by an observational study that has found shorter sleep duration to be associated with shorter sleep latency and better sleep efficiency (Michels et al., 2014).

Therefore, the aims of the present study were (1) to investigate whether psychosocial well-being, as one domain of HRQoL covering emotional well-being, self-esteem, family life and relations to friends, is associated with nocturnal sleep duration and sleep disturbances ("trouble getting up in the morning", "difficulties falling asleep") in 3-15 year old European children and adolescents, (2) to examine the potential influence of psychosocial well-being on sleep in

longitudinal analyses and (3) to explore whether associations between psychosocial well-being and each single sleep characteristic exist independent of the effect of other sleep characteristics.

METHODS

Study Population

For the IDEFICS study, 2-9 year old children from Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden were first examined in 2007/08 (N=16,228) and again in 2009/10 after an intervention aiming to prevent childhood overweight (N=11,041 plus 2,555 newcomers) (Ahrens et al., 2011). In 2013/14, children participating in IDEFICS (N=7,105) and some newly recruited siblings (N=2,512) were (re-)examined in the framework of the I.Family study (Ahrens et al., 2017).

The cross-sectional analysis for this study was based on 2013/14 data to enable the investigation of associations in both children and adolescents. The analysis comprised only participants aged 3-15 years with complete and plausible information on all variables used in the analysis (N=6,336). The longitudinal analysis included children with complete information in 2009/10 (in the following referred to as baseline) and 2013/14 (in the following referred to as follow-up) because only in these waves all sleep variables of interest were assessed (N=3,379). The selection process of the analysis groups is shown in Figure 1.

- Figure 1 approximately here -

Procedures

All measures used in the present investigation were obtained by questionnaires. Questionnaires were developed in English, translated into local languages and then back-translated to check for translation errors. Parents answered on behalf of children younger than 12 years old. Before children entered the study, parents provided informed written consent. Additionally, children 12 years and older gave simplified written consent. The Ethics Committees of all study centres gave ethical approval.

Sleep duration

Participants reported nocturnal sleep duration and napping time (hours and minutes) separately for kindergarten/school days, i.e. weekdays, and weekend days/vacations. A weighted average of nocturnal sleep duration was calculated for each child as follows: (nocturnal sleep duration on weekdays*5 + nocturnal sleep duration on weekend days/vacations*2) / 7 and transformed to an age-specific z-score. Analogously, the weighted average of daily napping time (minutes) was calculated.

Sleep disturbances

We inquired whether the child/adolescent in general has "trouble getting up in the morning" (yes/no) and "difficulties falling asleep" (yes/no). Similar items were used previously in other large population-based studies (Magee et al., 2017).

Psychosocial well-being

Psychosocial well-being was measured with 16 items of four subscales of the "KINDL^R Questionnaire for Measuring Health-Related Quality of Life (HRQoL) in Children and Adolescents" (emotional well-being, self-esteem, family life and relations to friends; see supporting information, Table S1) (Ravens-Sieberer and Bullinger, 2000, Bullinger et al., 2008). The KINDL^R Questionnaire was originally developed in German but was translated to English and other languages. Survey centres were advised to use already existing language versions, if available. At follow-up, response categories corresponded to the original 5-point Likert scale (never, seldom, sometimes, often, all the time). At baseline the two highest response categories were combined into one category. Therefore, we deviated from the original scoring (1-5 points per item) and assigned 0 points for "Never" and 3 points for both "Often" and "All the time" (at follow-up) or "Often/All the time" (at baseline), respectively (six negatively worded items were coded reversely). Consequently, the score ranged from 0-48 with a higher score indicating a

higher well-being. In our cross-sectional sample, Cronbach's alpha for this set of items was 0.75. For the longitudinal analysis we created a variable for annual change in well-being to account for the variation of follow-up times between study subjects: Δ well-being score = (follow-up well-being score – baseline well-being score) / (follow-up age – baseline age).

Covariates

We considered age in years, sex, highest educational level of parents defined according to the "International Standard Classification of Education (ISCED)" (UNESCO Institute for Statistics, 2012) (levels 0-2=low, 3-5=medium and 6-8=high), pubertal status (yes/no; yes if menarche has occurred in girls or if voice alterations have started or were completed in boys), duration of electronic media use (weighted average of hours of PC and TV consumption on kindergarten/school days and weekend days/vacations), country of recruitment and an indicator variable for self- vs. proxy-reported data.

Statistical Analysis

Cross-sectional analysis

Associations between the well-being score and the three outcomes (nocturnal sleep duration z-score and the two sleep disturbances) measured at follow-up were investigated using linear and logistic mixed-effects models (Hox, 2010), where a random effect for family affiliation was added to account for the inclusion of siblings in the sample. First, for each outcome a model adjusting for age, sex, country, highest educational level of parents, duration of electronic media use, pubertal status, napping time (only in models with nocturnal sleep duration as the outcome) and an indicator for self- vs. proxy reports was fitted (Model 1). With Model 2 we explored whether the inclusion of the respective other sleep characteristics in addition to the covariates already included in Model 1 would amend associations (e.g. inclusion of both sleep disturbances

in the model investigating the association between well-being and nocturnal sleep duration z-score).

Well-being may exert differential effects on nocturnal sleep duration across the sleep duration distribution. For instance, well-being could have a greater effect on sleep duration among those with short sleep duration compared to those with long sleep duration. Thus, we also estimated a quantile regression model (regarding the 0.05, 0.20, 0.35, 0.50, 0.65, 0.80 and 0.95 quantiles) to investigate the potential heterogeneous effect of well-being on different levels of nocturnal sleep duration (same covariates as for Model 1). Quantile regression allows to model any quantile of the outcome distribution and not just the mean as it is done in linear regression (Beyerlein, 2014). In our study, the quantile regression coefficients express how much each specific quantile of the nocturnal sleep duration distribution changes by a 1-unit change (≙ 4 points) in well-being score.

All models were fitted both for the whole analysis group and stratified by age: preschool children (aged 3-5 years); primary school-aged children (aged 6-11 years) and adolescents (aged 12-15 years).

Longitudinal analysis

Longitudinal associations between well-being and sleep characteristics were again investigated using linear and logistic mixed-effects models including a random effect for family affiliation. We used the following two analytical approaches:

Approach A: Regression of sleep characteristics at follow-up on change in well-being between baseline and follow-up

Approach B: Regression of sleep characteristics at follow-up on well-being at baseline

Comparable to the cross-sectional analysis, for both analytical approaches two models with different adjustments were estimated. Model 1 was adjusted for age, sex, country, highest educational level of parents, duration of electronic media use (all at baseline), pubertal status (at

follow-up), napping time (at follow-up, only in models with nocturnal sleep duration as the outcome), self- versus proxy-report and the baseline value of the respective outcome. Model 2 included covariates from Model 1 plus the respective other sleep characteristics. Further, all models following analytical approach A were also adjusted for baseline well-being score and those following analytical approach B were also adjusted for follow-up time (follow-up age – baseline age).

All models were fitted for the whole analysis group and stratified by age: primary school-aged children (aged 6-11 years at follow-up) and adolescents (aged 12-15 years at follow-up).

Additional analyses

Instead of using average nocturnal sleep duration, cross-sectional and longitudinal models were fitted separately for weekday and weekend nocturnal sleep duration. Further, in order to assess the reverse direction, well-being at follow-up was regressed on sleep characteristics at baseline.

All analyses were conducted using SAS (Statistical Analysis System, SAS Institute Inc., Cary, USA), Version 9.3. We report 95% confidence intervals and corresponding p-values. A footnote indicates p-values exceeding 0.05 after adjustment for multiple testing according to Holm's sequential Bonferroni procedure (Holm, 1979).

RESULTS

Descriptive characteristics of the cross-sectional sample are displayed in Table 1. Older participants tended to sleep shorter and to have a lower well-being score. Prevalence of having "trouble getting up in the morning" and "difficulties falling asleep" was highest in adolescents. The distributions of key variables such as sleep characteristics and well-being score were similar in both the larger cross-sectional and the smaller longitudinal analysis group.

- Table 1 approximately here -

Cross-sectional analysis

For every 4-point increase in the well-being score there was a 0.041 (95% confidence interval (CI) [0.022; 0.060]) unit increase in nocturnal sleep duration z-score (Model 1, Table 2). For example, a child with a well-being score of 46 slept on average 5-7 minutes longer than a child with a score of 34 (exact duration depends on age group). The age-stratified analysis showed that this association was strongest in adolescents. When sleep disturbances were included (Model 2), the association was slightly attenuated and no longer statistically significant in the whole group. Furthermore, higher well-being was associated with lower odds of having "trouble getting up in the morning" and "difficulties falling asleep" in both Model 1 and Model 2. Effect sizes were similar in the three age groups although not statistically significant in preschoolers. Quantile regression revealed increasingly stronger associations between well-being and nocturnal sleep duration for the lower tail of the nocturnal sleep duration distribution (Figure 2).

- Table 2 approximately here –

- Figure 2 approximately here -

Longitudinal analysis

Approach A: Change in well-being score was positively associated with nocturnal sleep duration z-score at follow-up (Model 1, β for 1-point annual increase: 0.052 [0.028; 0.077]) (Table 3). For instance, a child with a well-being score of 34 at baseline and a well-being score of 46 after 4 years of follow-up slept on average 6-11 minutes longer at follow-up compared to a child with no improvement in well-being. The effect was marginally stronger in adolescents compared to primary school-aged children. Change in well-being score was negatively associated with "trouble getting up in the morning" and "difficulties falling asleep" at follow-up.

- Table 3 approximately here –

Approach B: There was a negative association between well-being score at baseline and sleep duration z-score at follow-up (Model 1, β for 4-point increase: -0.030; [-0.058; -0.002], Table 4) that was no longer statistically significant after adjustment for multiple testing. On the contrary, associations between well-being score at baseline and the two indicators of sleep disturbances at follow-up both showed the expected direction where only the association between well-being score at baseline and "trouble getting up in the morning" at follow-up in primary school-aged children (Model 1) reached statistical significance.

In general, further adjustment for sleep characteristics other than the respective outcome of interest (Model 2) did not markedly change the results in any of the longitudinal models.

- Table 4 approximately here –

Additional analyses

Estimates of the models using weekday nocturnal sleep duration z-score were similar to those obtained with the average nocturnal sleep duration z-score. In contrast, models using weekend sleep duration z-score generated smaller effect estimates (see Tables S2 – S4).

Sleep duration z-score at baseline was not associated with well-being score at follow-up (see Table S6). With respect to the two indicators for sleep disturbances, especially "trouble getting up in the morning" at baseline predicted lower well-being at follow-up. The association appeared to be specifically strong in primary school-aged children.

The slightly negative association between well-being score at baseline and nocturnal sleep duration z-score approximately 4 years later was an unexpected finding. As our cross-sectional quantile regression analysis showed stronger associations at the lower tail of the nocturnal sleep duration distribution, we suspected that the longitudinal association might also be non-linear and estimated the model stratified by nocturnal sleep duration quartiles at follow-up (see Table S5): A positive association between well-being and nocturnal sleep duration was found in children having short sleep at follow-up (1st quartile of nocturnal sleep duration z-score), no association in those with medium sleep duration (2nd and 3rd quartile) and a negative association, though not being statistically significant, in those with long sleep duration (4th quartile). The same analysis was conducted stratified by age group revealing that this negative association was mainly present in adolescents with long sleep duration.

DISCUSSION

This study demonstrated that higher psychosocial well-being was associated with longer nocturnal sleep duration and lower levels of sleep disturbances in European children and adolescents. Further, positive changes in psychosocial well-being were associated with improvements in these sleep characteristics over a 4-year period. In contrast, higher baseline psychosocial well-being was predominantly not associated with the considered sleep characteristics after 4 years. In general, associations between well-being and sleep disturbances appeared to be more consistent across the different analytical approaches and age groups. Further, associations persisted in most cases after adjustment for nocturnal sleep duration. In contrast, associations between well-being and nocturnal sleep duration were less robust. Effect sizes for the latter were generally small. However, our cross-sectional quantile regression showed that the association was much stronger at the lower quantiles of the nocturnal sleep duration distribution compared to the higher ones. For instance, the effect estimate at the 5th nocturnal sleep duration quantile was twice as high as the effect estimate obtained from the linear regression. These results indicate that in children/adolescents with very short nocturnal sleep duration the association between well-being and nocturnal sleep duration appears to be particularly strong. In this cross-sectional quantile regression we considered well-being as the exposure and sleep duration as the outcome. If this assumption holds true, these children may benefit most from an improvement of their wellbeing.

The negative association between higher well-being at baseline and shorter sleep duration at follow-up was unexpected. However, our additional analysis suggested that the association was not consistently negative across the different strata of nocturnal sleep duration at follow-up. Especially in participants with short sleep duration the association was positive and therefore agrees with our cross-sectional findings. Hence, interpreting the effect estimate obtained from the non-stratified model might be misleading. The tendency for a negative association observed in adolescents who sleep comparably long at follow-up might be plausible. It has been claimed

previously that sleep duration self-reported by adolescents might be biased such that they report time in bed rather than actual sleep duration (Arora et al., 2013). High well-being comprises amongst others feeling active and doing things with friends. Thus, we may speculate that in adolescents spending a lot of time in bed, increased well-being results in lower reported sleep duration. This subgroup effect may not fully account for the negative association observed for the whole group in our main analysis. However, it has to be considered that the longitudinal analysis is complicated by change in reporting mode from proxy- to self-report and further by the long follow-up time covering important developmental periods such as the transition from pre-school to primary school and the transition from childhood to adolescence during which sleep habits may change considerably (decrease in nocturnal sleep duration, changes in daytime napping and chronotype, etc.).

With regard to the additional analysis it is noteworthy that children's well-being was more strongly associated with weekday nocturnal sleep duration compared to weekend nocturnal sleep duration, i.e. those with higher well-being tended to sleep longer especially during the week.

Comparison with previous research results

Sleep problems, morning tiredness and difficulties going to sleep were found to be cross-sectionally associated with poorer psychosocial HRQoL measured with the Pediatric Quality of Life Inventory (PedsQL) in preschoolers participating in the Longitudinal Study of Australian Children (LSAC) (Hiscock et al., 2007). We also observed an association between well-being and sleep disturbances in this young age group. However, the effect estimate was statistically non-significant due to the small sample size although effect estimates were similar to those for the two older age groups. Also in agreement with our findings, Roeser et al. (2012) reported lower scores on the Sleep Disturbance Scale for Children to be cross-sectionally associated with higher HRQoL measured with the KINDL^{R} questionnaire in a small sample of German adolescents (N=92). Comparable to our findings, children's mild and moderate/severe sleep

problems were cross-sectionally associated with lower HRQoL measured with the PedsQL in 6-7 year old participants of the LSAC (Quach et al., 2009). Consistently, a further study based on another wave of the LSAC data with in-depth sleep assessment showed that 10-11 year old children categorised as having disordered sleep, i.e. amongst others experiencing difficulties falling asleep, morning tiredness and/or frequent nocturnal awakenings, had concurrently lower scores on all four subscales of the PedsQL compared to those categorised as having good sleep, i.e. sufficient sleep duration and good sleep quality according to self-reports (Magee et al., 2017).

As it becomes clear from the description of these cross-sectional results, most researchers assumed sleep to influence HRQoL and not the other way round. Although some longitudinal studies reported aspects of mental ill-health such as depression and anxiety to predict sleep (Roberts and Duong, 2014, Johnson et al., 2006, Kelly and El-Sheikh, 2014), we are not aware of any longitudinal study that investigated the influence of HRQoL or a measure spanning several subdomains of HRQoL as done in our study on sleep.

Strengths and limitations

One of the major strengths of our study is the detailed longitudinal analysis. With models such as those according to analytical approach B the direction of the association can be examined. However, as mentioned earlier, 4 years is a very long follow-up time – especially in growing children and adolescents – and hence it might be that there are effects of psychosocial well-being on sleep that are acting over shorter time periods. Models as those according to analytical approach A take this into account by calculating change in the exposure rather than only using the baseline value of the exposure. Making a statement regarding the direction of the association from such models in which change in the exposure is modelled against change in the outcome is not possible. We focussed on the potential influence of well-being on sleep duration and indicators of sleep disturbances because this has rarely been investigated so far.

Nevertheless, it is possible that the association is bidirectional and that sleep characteristics may also affect well-being. Thus, reverse causality cannot be excluded in the cross-sectional analysis and the longitudinal analysis following analytical approach A. Reversing the models according to analytical approach B in an additional analysis, i.e. using sleep characteristics at baseline as the exposure and well-being at follow-up as the outcome, only revealed weak associations. Hence, our longitudinal results did not suggest one direction of the association to be more pronounced than the other.

Further strengths of our study are the standardised data collection from a large sample of European children and adolescents and consideration of multiple sleep characteristics. Nevertheless, our study had the limitation that sleep and well-being were subjectively and not objectively measured. In general, sleep duration is overestimated when obtained from questionnaires compared to accelerometry (Arora et al., 2013) and both sleep duration and HRQoL reported by parents are overestimated compared to self-reports (Jozefiak et al., 2008, Short et al., 2013). However, we assume these measurement errors most likely to be non-differential. It is likely that such misclassification would have resulted in an underestimation of the effect sizes rather than introducing spurious associations. Further, to control for potential differences in reporting of well-being, sleep measures and potential confounders, we included an indicator for proxy- vs. self-report in our analyses. Lastly, our assessment of sleep disturbances was rather simple (disturbances present yes vs. no). A more detailed assessment, e.g. inquiring about the frequency of the occurrence and severity of the disturbances, would have allowed us to investigate the association between well-being and sleep disturbances in more depth.

Conclusions

Our study confirms findings of previous studies by showing higher psychosocial well-being, covering aspects of emotional well-being, self-esteem and social relationships, to be cross-sectionally associated with longer sleep duration and especially fewer sleep disturbances in

European children and adolescents. We add further evidence for this by demonstrating that associations between higher psychosocial well-being and fewer sleep disturbances were consistent across three age groups (preschool children, primary school-aged children and adolescents). Further, our study is one of very few studying the longitudinal association between well-being and sleep characteristics. We showed that an improvement in well-being over time was longitudinally associated with improvements in sleep characteristics. However, our study provides only weak evidence that well-being measured at one point in time has an effect on sleep characteristics several years later. Hence, well-being and sleep may influence each other mainly over short time periods.

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Table 1: Description of the study population

	Cross-sectional analysis group (2013/14)				Longitudinal analysis group (2013/14)
	Whole group N=6,336	**Preschool children (3-5 years) N=347**	**Primary school-aged children (6-11 years) N=3,417**	**Adolescents (12-15 years) N=2,572**	**Whole group N=3,379**
Well-being score, median (interquartile range)	40 (37; 43)	43 (40; 45)	41 (38; 44)	39 (35; 42)	40 (37; 43)
Nocturnal sleep duration (weekly average, hours), mean (SD)	9.21 (0.94)	9.88 (0.84)	9.50 (0.76)	8.74 (0.98)	9.14 (0.92)
Weekday nocturnal sleep duration (hours), mean (SD)	8.94 (1.06)	9.76 (0.89)	9.32 (0.83)	8.32 (1.05)	8.86 (1.03)
Weekend nocturnal sleep duration (hours), mean (SD)	9.90 (1.26)	10.17 (1.04)	9.94 (1.01)	9.80 (1.54)	9.86 (1.25)
Napping (yes), n (%)	1,227 (19.4)	195 (56.2)	339 (9.9)	693 (26.9)	571 (16.9)
Napping time (weekly average, minutes per day), median (interquartile range)*	43 (17; 86)	86 (60; 111)	39 (17; 69)	39 (17; 77)	34 (17; 64)
Trouble getting up in the morning (yes), n (%)	2,407 (38.0)	84 (24.2)	989 (28.9)	1,334 (51.9)	1,332 (39.4)
Difficulties falling asleep (yes), n (%)	988 (15.6)	45 (13.0)	388 (11.4)	555 (21.6)	536 (15.9)
Age (years), mean (SD)	10.9 (2.7)	4.6 (0.8)	9.6 (1.5)	13.5 (0.9)	11.5 (1.9)
Girls, n (%)	3,236 (51.1)	188 (54.2)	1,692 (49.5)	1,356 (52.7)	1,726 (51.1)
Proxy-report (yes), n (%)	3,770 (59.5)	347 (100.0)	3,381 (99.0)	42 (1.6)	1,854 (54.9)
Country, n (%)					
Italy	1,085 (17.1)	61 (17.6)	565 (16.5)	459 (17.9)	656 (19.4)
Estonia	1,083 (17.1)	76 (21.9)	568 (16.6)	439 (17.1)	714 (21.1)
Cyprus	1,238 (19.5)	94 (27.1)	563 (16.5)	581 (22.6)	367 (10.9)
Belgium	266 (4.2)	6 (1.7)	200 (5.9)	60 (2.3)	82 (2.4)
Sweden	611 (9.6)	23 (6.6)	388 (11.4)	200 (7.8)	465 (13.8)
Germany	766 (12.1)	36 (10.4)	412 (12.1)	318 (12.4)	345 (10.2)
Hungary	931 (14.7)	36 (10.4)	497 (14.5)	398 (15.5)	501 (14.8)
Spain	356 (5.6)	15 (4.3)	224 (6.6)	117 (4.6)	249 (7.4)
Highest educational level of parents, n (%)					
Low	269 (4.3)	13 (3.8)	128 (3.8)	128 (5.0)	143 (4.2)
Medium	2,746 (43.3)	136 (39.2)	1,464 (42.8)	1,146 (44.6)	1,433 (42.4)
High	3,321 (52.4)	198 (57.1)	1,825 (53.4)	1,298 (50.5)	1,803 (53.4)
Duration of electronic media use (TV + PC) (hours per day), median (interquartile range)	2.0 (1.3; 3.0)	1.5 (1.0; 2.2)	1.9 (1.2; 2.8)	2.5 (1.5; 3.6)	2.1 (1.3; 3.2)
Pubertal status (pubertal), n (%)	2,217 (35.0)	0	337 (9.9)	1,880 (73.1)	1,280 (37.9)

* Calculated only for those who napped
SD: standard deviation

Table 2: Cross-sectional associations between well-being (exposure) and sleep characteristics (outcomes) in 2013/14 in the whole group and stratified by age

	Nocturnal sleep duration z-score											
	Whole group N=6,336			Preschool children N=347			Primary school-aged children N=3,417			Adolescents N=2,572		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score[§]												
Model 1[°]	0.041	0.022; 0.060	<0.001	-0.023	-0.121; 0.075	0.64	0.036	0.010; 0.061	0.006[*]	0.054	0.026; 0.082	<0.001
Model 2[†]	0.031	0.011; 0.050	0.002[*]	-0.019	-0.119; 0.082	0.72	0.026	0.000; 0.052	0.05	0.045	0.016; 0.074	0.003[*]
	Trouble getting up in the morning											
	Whole group N=6,336			Preschool children N=347			Primary school-aged children N=3,417			Adolescents N=2,572		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Well-being score[§]												
Model 1	0.73	0.69; 0.77	<0.001	0.67	0.51; 0.89	0.006[*]	0.69	0.63; 0.74	<0.001	0.78	0.74; 0.83	<0.001
Model 2[§]	0.76	0.72; 0.80	<0.001	0.72	0.54; 0.96	0.03[*]	0.71	0.66; 0.77	<0.001	0.81	0.76; 0.86	<0.001
	Difficulties falling asleep											
	Whole group N=6,336			Preschool children N=347			Primary school-aged children N=3,417			Adolescents N=2,572		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Well-being score[§]												
Model 1	0.70	0.65; 0.74	<0.001	0.65	0.46; 0.91	0.01[*]	0.68	0.62; 0.75	<0.001	0.72	0.66; 0.79	<0.001
Model 2[‡]	0.73	0.69; 0.78	<0.001	0.70	0.50; 0.99	0.04[*]	0.73	0.66; 0.80	<0.001	0.75	0.68; 0.82	<0.001

All models were adjusted for age, sex, country, highest educational level of parents and duration of electronic media use. All models conducted with the whole group were further adjusted for self- vs. proxy-report, pubertal status and included a random effect for family affiliation. All models conducted in primary school-aged children and adolescents were also adjusted for pubertal status and included a random effect for family affiliation. If applicable, additional adjustment variables are given in the footnotes.

[§] 1 unit ≙ 4 points

[°] additionally adjusted for napping time

[†] additionally adjusted for napping time, trouble getting up in the morning, difficulties falling asleep

[§] additionally adjusted for nocturnal sleep duration z-score, difficulties falling asleep

[‡] additionally adjusted for nocturnal sleep duration z-score, trouble getting up in the morning

[*] p-value>=0.05 after correction for multiple testing according to Holm's sequential Bonferroni procedure (Holm, 1979)

CI: confidence interval; OR: odds ratio

Table 3: Longitudinal associations between change in well-being between baseline (2009/10) and follow-up (2013/14) and sleep characteristics at follow-up (2013/14) in the whole group and stratified by age

	Nocturnal sleep duration z-score at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Δ Well-being score[§]									
Model 1[°]	0.052	0.028; 0.077	<0.001	0.045	0.011; 0.079	0.01[*]	0.051	0.016; 0.086	0.005[*]
Model 2[†]	0.042	0.017; 0.067	0.001	0.038	0.004; 0.073	0.03[*]	0.042	0.005; 0.078	0.03[*]
	Trouble getting up in the morning at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Δ Well-being score[§]									
Model 1[‡]	0.72	0.66; 0.77	<0.001	0.73	0.64; 0.83	<0.001	0.73	0.63; 0.83	<0.001
Model 2[¶]	0.74	0.69; 0.80	<0.001	0.75	0.67; 0.85	<0.001	0.75	0.66; 0.86	<0.001
	Difficulties falling asleep at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Δ Well-being score[§]									
Model 1[£]	0.71	0.65; 0.78	<0.001	0.71	0.61; 0.83	<0.001	0.74	0.68; 0.81	<0.001
Model 2[§]	0.75	0.68; 0.82	<0.001	0.76	0.65; 0.88	<0.001	0.77	0.70; 0.85	<0.001

All models were adjusted for well-being score, age, sex, country, highest educational level of parents, duration of electronic media use (all at baseline), pubertal status (at follow-up) and included a random effect for family affiliation. All models conducted with the whole group were further adjusted for self- vs. proxy-report. If applicable, additional adjustment variables are given in the footnotes.

[§] 1 unit ≙ 1 point per year

[°] additionally adjusted for nocturnal sleep duration z-score (at baseline), napping time (at follow-up)

[†] additionally adjusted for nocturnal sleep duration z-score (at baseline), napping time (at follow-up), trouble getting up in the morning (at follow-up), difficulties falling asleep (at follow-up)

[‡] additionally adjusted for trouble getting up in the morning (at baseline)

[¶] additionally adjusted for trouble getting up in the morning (at baseline), nocturnal sleep duration z-score (at follow-up), difficulties falling asleep (at follow-up)

[£] additionally adjusted for difficulties falling asleep (at baseline)

[§] additionally adjusted for difficulties falling asleep (at baseline), nocturnal sleep duration z-score (at follow-up), trouble getting up in the morning (at follow-up)

[*] p-value>=0.05 after correction for multiple testing according to Holm's sequential Bonferroni procedure (Holm, 1979)

CI: confidence interval; OR: odds ratio

Table 4: Longitudinal associations between well-being at baseline (2009/10) and sleep characteristics at follow-up (2013/14) in the whole group and stratified by age

	Nocturnal sleep duration z-score at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score at baseline[§]									
Model 1[°]	-0.030	-0.058; -0.002	0.04[*]	-0.015	-0.053; 0.023	0.44	-0.032	-0.074; 0.011	0.14
Model 2[†]	-0.035	-0.063; -0.006	0.02[*]	-0.020	-0.059; 0.018	0.29	-0.034	-0.077; 0.008	0.11
	Trouble getting up in the morning at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Well-being score at baseline[§]									
Model 1[‡]	0.90	0.83; 0.97	0.008[*]	0.80	0.70; 0.91	0.001	0.98	0.88; 1.08	0.62
Model 2[¶]	0.91	0.84; 0.98	0.02[*]	0.82	0.72; 0.93	0.002[*]	0.98	0.89; 1.09	0.72
	Difficulties falling asleep at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Well-being score at baseline[§]									
Model 1[£]	0.89	0.81; 0.98	0.02[*]	0.81	0.68,0.97	0.02[*]	0.95	0.85; 1.07	0.37
Model 2[§]	0.90	0.82; 0.99	0.04[*]	0.85	0.71; 1.01	0.06	0.95	0.85; 1.07	0.40

All models were adjusted for age, sex, country, highest educational level of parents, duration of electronic media use (all at baseline), pubertal status (at follow-up), follow-up time and included a random effect for family affiliation. All models conducted with the whole group were further adjusted for self- vs. proxy-report. If applicable, additional adjustment variables are given in the footnotes.

[§] 1 unit ≙ 4 points

[°] additionally adjusted for nocturnal sleep duration z-score (at baseline), napping time (at follow-up)

[†] additionally adjusted for nocturnal sleep duration z-score (at baseline), napping time (at follow-up), trouble getting up in the morning (at follow-up), difficulties falling asleep (at follow-up)

[‡] additionally adjusted for trouble getting up in the morning (at baseline)

[¶] additionally adjusted for trouble getting up in the morning (at baseline), nocturnal sleep duration z-score (at follow-up), difficulties falling asleep (at follow-up)

[£] additionally adjusted for difficulties falling asleep (at baseline)

[§] additionally adjusted for difficulties falling asleep (at baseline), nocturnal sleep duration z-score (at follow-up), trouble getting up in the morning (at follow-up)

[*] p-value>=0.05 after correction for multiple testing according to Holm's sequential Bonferroni procedure (Holm, 1979)

CI: confidence interval; OR: odds ratio

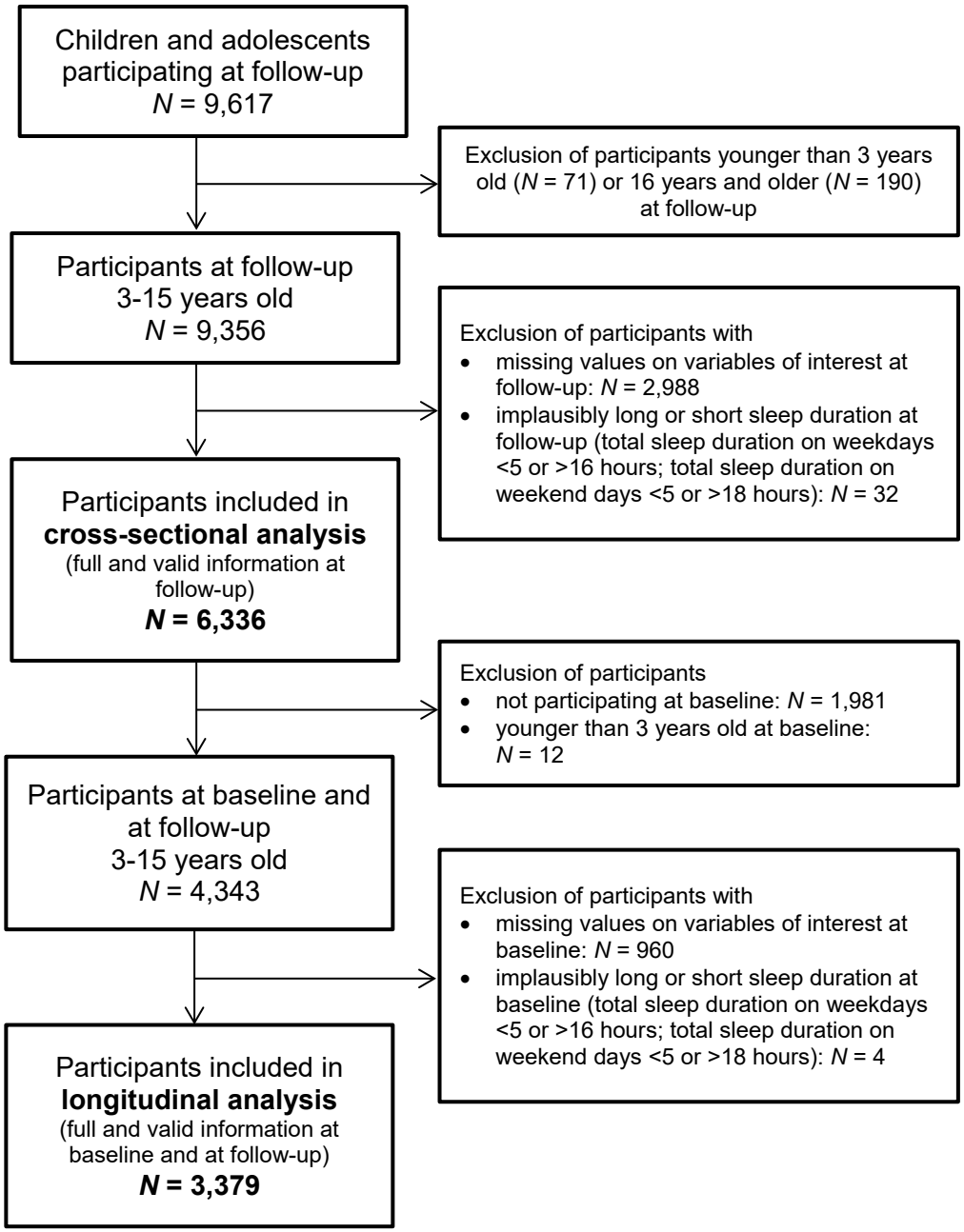

Figure 1: Flow chart of children (N) included in final analysis groups (cross-sectional and longitudinal analysis), follow-up examination: 2013/14, baseline examination: 2009/10

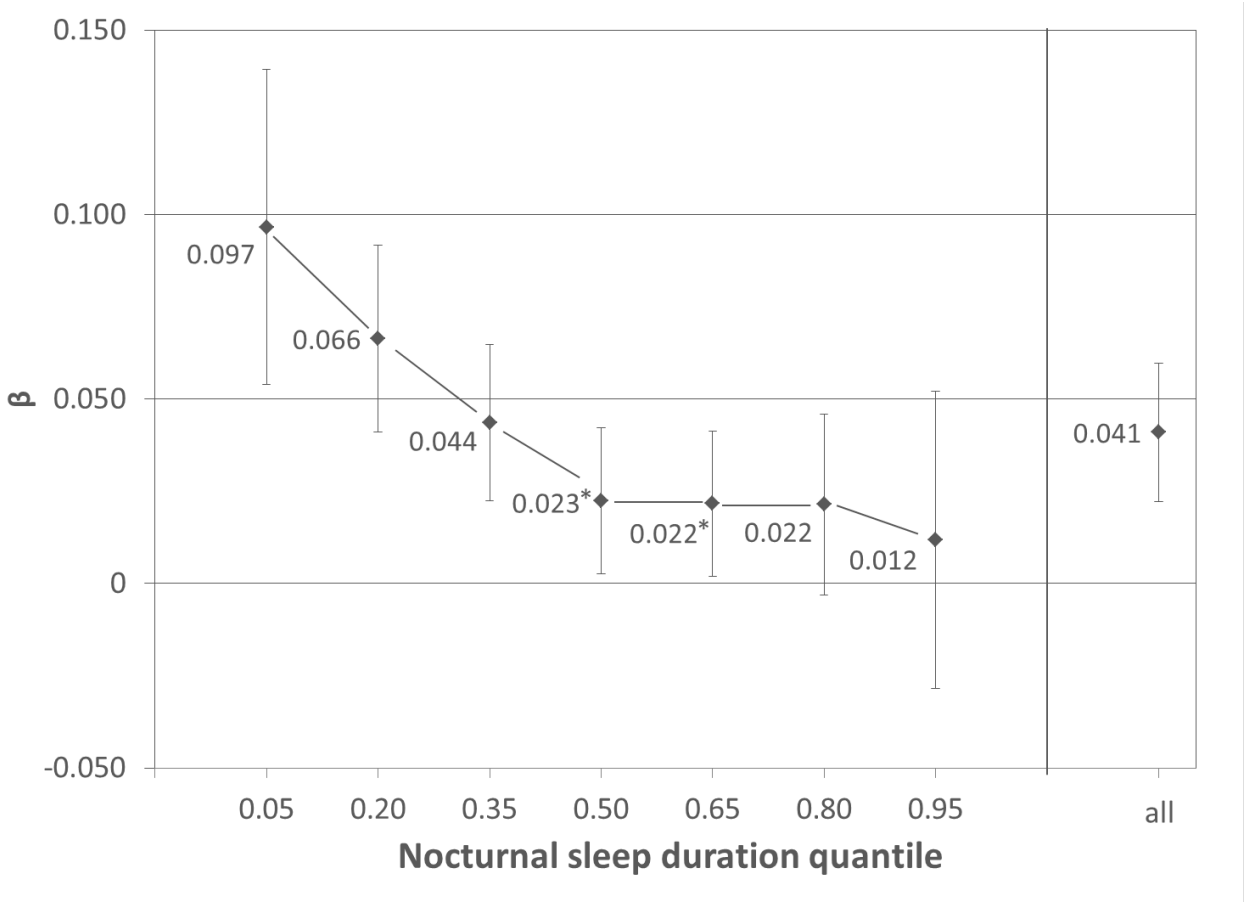

Figure 2: Effect estimates for well-being (β with 95% confidence interval) on different nocturnal sleep duration quantiles obtained from quantile regression adjusting for age, sex, country, highest educational level of parents, duration of electronic media use, self- vs. proxy-report, pubertal status and napping time (N=6,336). The corresponding estimate from the linear regression is given for comparison (see also Table 2). P-values >=0.05 after correction for multiple testing according to Holm's sequential Bonferroni procedure (Holm, 1979) are denoted with *

SUPPLEMENTARY MATERIAL

Paper 1

SUPPORTING INFORMATION

Table S1: Item list KINDL^R Health-Related Quality of Life Questionnaire

Kid- & Kiddo-KINDL^R parents version for 7-17 year old children/adolescents / Kiddy KINDL^R parents version for 3-6 year old children	**Kiddo-KINDL^R self-report version for 14-17 year old adolescents**
During the past week…	During the past week…
Emotional well-being	**Emotional well-being**
…my child had fun and laughed a lot	... I had fun and laughed a lot
... my child didn't feel much like doing anything	... I was bored
... my child felt alone	... I felt alone
... my child felt scared or unsure of him-/herself	... I felt scared or unsure of myself
Self-esteem	**Self-esteem**
... my child was proud of him-/herself	... I was proud of myself
... my child felt on top of the world	... I felt on top of the world
... my child felt pleased with him-/herself	... I felt pleased with myself
... my child had lots of good ideas	... I had lots of good ideas
Family	**Family**
... my child got on well with us as parents	... I got on well with my parents
... my child felt fine at home	... I felt fine at home
... we quarrelled at home	... we quarrelled at home
... my child felt that I was bossing him/her around	... I felt restricted by my parents
Friends	**Friends**
... my child did things together/played with friends	... I did things together with my friends
... my child was liked by other kids	... I was a "success" with my friends
... my child got along well with his/her friends	... I got along well with my friends
... my child felt different from other children	... I felt different from other people
Response categories and scoring:	
Never (0 points), seldom (1 point), sometimes (2 points), often (3 points)*, all the time (3 points)*	

* for both categories 3 points as in the 2009/10 wave "often" and "all the time" were combined into one category

Source: Ravens-Sieberer U, Bullinger M. KINDL-R. Questionnaire for Measuring Health-Related Quality of Life in Children and Adolescents - Revised Version - Manual. 2000; http://www.kindl.org/english/manual/. Accessed 11th January 2016.

Table S2: Cross-sectional associations between well-being (exposure) and weekday nocturnal sleep duration and weekend nocturnal sleep duration (outcomes) in 2013/14 in the whole group and stratified by age

	Weekday nocturnal sleep duration z-score											
	Whole group N=6,336			Preschool children N=347			Primary school-aged children N=3,417			Adolescents N=2,572		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score[§]												
Model 1[°]	0.043	0.024; 0.061	<0.001	-0.026	-0.121; 0.069	0.59	0.036	0.011; 0.061	0.005	0.058	0.030; 0.086	<0.001
	Weekend nocturnal sleep duration z-score											
	Whole group N=6,336			Preschool children N=347			Primary school-aged children N=3,417			Adolescents N=2,572		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score[§]												
Model 1[†]	0.020	0.001; 0.040	0.04	-0.015	-0.127; 0.097	0.79	0.020	-0.007; 0.048	0.15	0.021	-0.008; 0.049	0.16

All models were adjusted for age, sex, country, highest educational level of parents and duration of electronic media use. All models conducted with the whole group were further adjusted for self- vs. proxy-report, pubertal status and included a random effect for family affiliation. All models conducted in primary school-aged children and adolescents were also adjusted for pubertal status and included a random effect for family affiliation. If applicable, additional adjustment variables are given in the footnotes.

[§] 1 unit ≙ 4 points

[°] additionally adjusted for weekday napping time

[†] additionally adjusted for weekend napping time

CI: confidence interval

Table S3: Longitudinal associations between change in well-being between baseline (2009/10) and follow-up (2013/14) and weekday nocturnal sleep duration and weekend nocturnal sleep duration at follow-up (2013/14) in the whole group and stratified by age

	Weekday nocturnal sleep duration z-score at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Δ Well-being score[§]									
Model 1[°]	0.053	0.029; 0.077	<0.001	0.048	0.014; 0.082	0.006	0.052	0.017; 0.087	0.004
	Weekend nocturnal sleep duration z-score at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Δ Well-being score[§]									
Model 1[†]	0.025	0; 0.051	0.05	0.019	-0.017; 0.056	0.30	0.024	-0.013; 0.060	0.20

All models were adjusted for well-being score, age, sex, country, highest educational level of parents, duration of electronic media use (all at baseline), pubertal status (at follow-up) and included a random effect for family affiliation. All models conducted with the whole group were further adjusted for self- vs. proxy-report. If applicable, additional adjustment variables are given in the footnotes.

[§] 1 unit ≙ 1 point per year

[°] additionally adjusted for weekday nocturnal sleep duration z-score (at baseline), weekday napping time (at follow-up)

[†] additionally adjusted for weekend nocturnal sleep duration z-score (at baseline), weekend napping time (at follow-up)

CI: confidence interval

Table S4: Longitudinal associations between well-being at baseline (2009/10) and weekday nocturnal sleep duration and weekend nocturnal sleep duration at follow-up (2013/14) in the whole group and stratified by age

	Weekday nocturnal sleep duration z-score at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score at baseline[§]									
Model 1[°]	-0.029	-0.057; -0.001	0.04	-0.020	-0.058; 0.017	0.29	-0.026	-0.067; 0.016	0.23
	Weekend nocturnal sleep duration z-score at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score at baseline[§]									
Model 1[†]	-0.017	-0.047; 0.012	0.25	0.003	-0.038; 0.044	0.90	-0.029	-0.072; 0.014	0.18

All models were adjusted for age, sex, country, highest educational level of parents, duration of electronic media use (all at baseline), pubertal status (at follow-up), follow-up time and included a random effect for family affiliation. All models conducted with the whole group were further adjusted for self- vs. proxy-report. If applicable, additional adjustment variables are given in the footnotes.

[§] 1 unit ≙ 4 points

[°] additionally adjusted for weekday nocturnal sleep duration z-score (at baseline), weekday napping time (at follow-up)

[†] additionally adjusted for weekend nocturnal sleep duration z-score (at baseline), weekend napping time (at follow-up)

CI: confidence interval

Table S5: Longitudinal associations between well-being at baseline (2009/10) and sleep characteristics at follow-up (2013/14) stratified by nocturnal sleep duration at follow up in the whole group and stratified by age

Short nocturnal sleep duration at follow-up (lowest quartile of nocturnal sleep duration z-score)

	Nocturnal sleep duration z-score at follow-up								
	Whole group N=841			Primary school-aged children N=450			Adolescents† N=391		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score at baseline§									
Model 1°	0.040	0.005; 0.074	0.03	0.056	0.004; 0.108	0.04	0.022	-0.026; 0.070	0.37

Medium nocturnal sleep duration at follow-up (two middle quartiles of nocturnal sleep duration z-score)

	Nocturnal sleep duration z-score at follow-up								
	Whole group N=1,712			Primary school-aged children N=918			Adolescents N=794		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score at baseline§									
Model 1°	-0.002	-0.017; 0.013	0.78	-0.010	-0.31; 0.011	0.33	0.007	-0.018; 0.032	0.54

Long nocturnal sleep duration at follow-up (highest quartile of nocturnal sleep duration z-score)

	Nocturnal sleep duration z-score at follow-up								
	Whole group N=826			Primary school-aged children N=479			Adolescents† N=347		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Well-being score at baseline§									
Model 1°	-0.013	-0.050; 0.023	0.46	0.006	-0.046; 0.058	0.80	-0.028	-0.081; 0.024	0.29

All models were adjusted for age, sex, country, highest educational level of parents, duration of electronic media use (all at baseline), pubertal status (at follow-up), follow-up time and included a random effect for family affiliation. All models conducted with the whole group were further adjusted for self- vs. proxy-report. If applicable, additional adjustment variables are given in the footnotes.

§ 1 unit ≙ 4 points

° nocturnal sleep duration z-score (at baseline), napping time (at follow-up)

† no random effect for family affiliation due to low number of siblings in strata

CI: confidence interval; OR: odds ratio

Table S6: Longitudinal associations between sleep characteristics at baseline (2009/10) and well-being at follow-up (2013/14) in the whole group and stratified by age

	Well-being score at follow-up								
	Whole group N=3,379			Primary school-aged children N=1,847			Adolescents N=1,532		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
Nocturnal sleep duration z-score (1 unit ≙ 1 SD) at baseline									
Model 1*	-0.02	-0.21; 0.17	0.86	0.21	-0.03; 0.46	0.09	-0.23	-0.54; 0.07	0.13
Model 2°	-0.03	-0.22; 0.17	0.78	0.21	-0.03; 0.46	0.09	-0.26	0.57; 0.05	0.09
Trouble getting up in the morning at baseline									
Model 1									
Yes	-0.60	-1.00; -0.20	0.004	-0.81	-1.30; -0.32	0.001	-0.26	-0.94; 0.41	0.44
No	0			0			0		
Model 2‡									
Yes	-0.55	-0.96; -0.14	0.009	-0.79	-1.29; -0.29	0.002	-0.18	-0.86; 0.50	0.60
No	0			0			0		
Difficulties falling asleep at baseline									
Model 1									
Yes	-0.55	-1.15; 0.05	0.07	-0.44	-1.13; 0.24	0.21	-0.80	-1.19; 0.31	0.15
No	0			0			0		
Model 2§									
Yes	-0.42	-1.03; 0.20	0.18	-0.20	-0.90; 0.50	0.58	-0.87	-2.00; 0.27	0.13
No	0			0			0		

All models were adjusted for age, sex, country, highest educational level of parents, duration of electronic media use, well-being score (all at baseline), pubertal status (at follow-up), follow-up time and included a random effect for family affiliation. All models conducted with the whole group were further adjusted for self- vs. proxy-report. If applicable, additional adjustment variables are given in the footnotes.

* napping (at baseline)

° additionally adjusted for napping, trouble getting up in the morning, difficulties falling asleep (all at baseline)

‡ additionally adjusted for nocturnal sleep duration z-score, difficulties falling asleep (all at baseline)

§ additionally adjusted for nocturnal sleep duration z-score, trouble getting up in the morning (all at baseline)

CI: confidence interval

Paper 2

Cross-sectional associations between objectively measured sleep characteristics and body mass index in European children and adolescents

Thumann BF, Buck C, Cooper A, De Henauw S, Hadjigeorgiou C, Hebestreit A, Lauria F, Lissner L, Molnár D, Moreno LA, Page A, Veidebaum T, Ahrens W, Hunsberger M, on behalf of the I.Family Consortium

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Cross-sectional associations between objectively measured sleep characteristics and body mass index in European children and adolescents

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ABSTRACT

Background: Short sleep duration has been found to be associated with a higher risk for overweight and obesity. However, previous studies have mainly relied on subjective measures of sleep duration and other sleep characteristics such as sleep quality and timing have often been neglected. Therefore, we aimed to investigate associations between several, mainly objectively measured sleep characteristics and BMI. Further, we aimed to identify distinct sleep subtypes based on these sleep characteristics and to study their association with BMI.

Methods: Children aged 9-16 year old participating in the European I.Family study (N=559, 32.9% overweight/obese) wore an accelerometer for one week on their wrist and recorded their daily wake-up and lights-off times in a sleep diary. Information on sleep duration, sleep efficiency and sleep latency was derived. To identify distinct sleep subtypes, we conducted a latent class analysis using all five sleep variables. Associations between the single sleep variables, sleep subtype and age- and sex-specific BMI z-score were investigated using linear mixed-effects regression models.

Results: We found only weak associations between sleep duration (β=-0.056, 95% Confidence Interval [-0.138; 0.027]), sleep efficiency, sleep latency, wake-up and lights-off times, respectively, and BMI z-score that were statistically non-significant. Four sleep subtypes were identified and children were assigned to the different groups based on their highest probability for latent group membership: “early birds” (17.5% of the sample), “short sleep duration” (14.7%), “optimal sleep” (47.6%) and “poor sleep quality” (20.2%). Sleep subtype was not associated with BMI z-score.

Conclusions: Using objective sleep data, we did not find convincing evidence for associations between the sleep variables under investigation and BMI.

INTRODUCTION

The prevalence of overweight and obesity in European children is still at a high level, even though the rising trend over the last decades has levelled off in some countries.[1] This parallels with the trend of decreasing sleep duration among European children and adolescents over the last decades, as reported by a systematic literature review.[2] To date there exist many cross-sectional and longitudinal studies that found an association between short sleep duration and higher odds of overweight and obesity in young populations.[3-6] Some studies also indicate that poor sleep quality and unfavourable sleep timing are associated with higher odds of overweight and obesity.[7,8]

Although the mechanisms explaining these associations are still not fully understood, it has been hypothesised that short sleep duration might be associated with overweight and obesity through a dysregulation of appetite hormones such as leptin and ghrelin.[9,10] These hormonal changes along with the increased opportunities to eat during longer waking hours and the consequent increased energy intake may increase the risk for weight gain.[11] Furthermore, studies have shown that indicators of poor sleep quality such as a reduced amount of restorative slow-wave sleep and sleep fragmentation (in the presence of unaltered total sleep duration) increase cortisol release, sympathetic nervous system activity and feelings of appetite and decrease insulin sensitivity.[12,13] It has been proposed that these physiological and hormonal changes contribute to a positive energy balance through stimulating food intake resulting in storage of excessive energy in body fat and ultimately weight gain.[14] Sleep timing may also be related to weight status through a behavioural pathway. For instance, later bedtime was found to be associated with risk factors for overweight and obesity such as a poorer diet quality, skipping breakfast and less physical activity.[15-17]

The vast majority of studies investigating associations between sleep and weight status in pediatric populations relies on self-reports. However, it has been shown that adolescents overestimate their sleep duration in questionnaires in comparison to accelerometers such as Actigraphs used to measure sleep objectively.[18] A review identified 23 studies that investigated the association between objectively measured sleep duration and obesity indices.[19] Most of these studies found longer sleep duration to be associated with a more favourable weight status. According to a meta-analysis,[7] only three studies used Actigraphs to study the association between sleep quality indicators and weight status in pediatric populations.[20-22] These three and other recent studies reported mixed findings. For instance, whereas some studies reported a negative association between sleep efficiency, i.e. the percentage of time asleep while in bed, and body mass index (BMI),[23-25] other studies did not find an association.[20-22,26] In addition, evidence for an association between aspects of sleep

timing and weight status from studies using objective methods or sleep diaries is weak.[23,25-27] Lastly, most previous studies have investigated aspects of sleep with BMI separately although sleep duration, sleep quality and sleep timing are associated with each other.

Therefore, the first aim of this study was to investigate the associations between sleep duration, sleep quality indicators and sleep timing and BMI, separately. The second aim was to classify children into distinct sleep subtypes by integrating information on sleep duration, sleep quality and sleep timing and to study the association between sleep subtype and BMI.

MATERIALS AND METHODS

Study Population

Children from eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden) participating in the IDEFICS/I.Family cohort, contributed data. For the IDEFICS study, children were first examined in 2007/2008 when they were 2-9 years old (N=16,229) and again two years later after an intervention for the prevention of childhood obesity was completed (N=13,586).[28] For the I.Family study, 7,117 children who already participated in IDEFICS and 2,501 newly recruited siblings were examined in 2013/2014 with the aim to investigate the determinants of eating behaviour in European families.[29] Once the I.Family follow-up examination was concluded, a subsample of participants with divergent weight trajectories over a six-year observation period ("stable normal weight", "stable overweight/obesity", "excessive weight gain") were selected for further measurements of sleep and other factors in 2015. Hence, participants with overweight and obesity were overrepresented in these so-called contrasting groups. The present investigation uses data from the contrasting groups.

Procedures

Data were collected by physical examinations, accelerometers and questionnaires. Questionnaires were developed in English, translated into local languages and then back-translated to maintain comparability across languages. Parents filled in all questionnaires if their children were younger than 12 years old while older children reported for themselves. Before children entered the study, parents provided informed written consent. Moreover, children 12 years and older provided simplified written consent. Younger children gave oral consent for examinations. Ethical approval was obtained by the appropriate Ethics Committees by each of the eight study centres conducting fieldwork.

Anthropometry

Participants' weight and height were measured in a fasting state according to a standardised manual in all centres. Body height was measured to the nearest 0.1 cm without shoes with a calibrated stadiometer (SECA 225, seca GmbH & Co. KG, Hamburg, Germany). Weight was measured with subjects wearing only light underwear by means of a segmental scale accurate to 0.1 kg (TANITA BC 418 MA, Tanita Europe GmbH, Sindelfingen, Germany). BMI was calculated as weight divided by height squared and converted to age- and sex-specific z-scores according to Cole and Lobstein[30].

Sleep assessment and sleep variables

Sleep was assessed using wrist-worn accelerometers in combination with a sleep diary. Accelerometers (GT3X+, Actigraph LLC, Pensacola, FL, USA) were set to record data at 30HZ and participants were asked to wear the accelerometer on the non-dominant wrist for up to seven consecutive days and nights (night wear only was also acceptable). Using a sleep diary, participants recorded the type of day (school day, day off, sick day, etc.), the time the lights were turned off (lights-off time) and their wake-up time for each day. After seven days, data were downloaded from the accelerometer in raw format (gt3x file) and then converted to a 60 second epoch for further analysis using ActiLife 6 software (Actigraph LLC, Pensacola, FL, USA). To generate sleep variables, the lights-off and wake-up times for each night reported in the sleep diary were manually entered. Files were then processed using the Sadeh algorithm to score individual epochs as either sleep or non-sleep and thus to generate sleep variables for each night.[31] The main variables of interest were (i) sleep duration: hours and minutes actually slept per night, subtracting periods of wakefulness, (ii) sleep latency: minutes between reported lights-off time and sleep onset (as detected by the algorithm), (iii) sleep efficiency: percentage of time spent asleep between lights-off and wake-up time calculated as sleep duration/(reported wake-up time – reported lights-off time)*100, (iv) reported wake-up time and (v) reported lights-off time. For all sleep variables, first, the average across all available weekdays and the average across all available weekend days were calculated. Second, the weighted average of weekdays and weekend days was calculated such as: (average sleep duration on weekdays*5 + average sleep duration on weekend days*2)/7. In addition, for sleep duration, wake-up time and lights-off time age-specific z-scores were calculated to account for the age-dependency of these measures. Children were further categorised as having long sleep latency and late lights-off time (scoring above the respective 75th percentile) and short sleep duration, early wake-up time and poor sleep efficiency (scoring below the respective 25th percentile).

Covariates

Covariates assessed by questionnaires included age (years and one decimal place), sex and pubertal status using questions adapted from Carskadon and Acebo[32]. Pubertal status was defined by menarche in girls and voice mutation in boys. Highest level of parental education was defined according to the "International Standard Classification of Education" (levels 0-2=low, 3-5=medium and 6-8=high).[33]

For a sensitivity analysis, we used information on lifestyle factors collected by questionnaires which included consumption frequencies of fruit and vegetables (times/week), time spent being physically active in a sports club (hours/week) and the weighted average of hours of computer and TV time during weekdays and weekend days.

Analysis dataset

Sleep measures were initially obtained from 800 children providing a total of 4,946 nights of sleep measurements. We excluded measurements obtained from sick days and restricted our sample to participants who provided at least 4 nights of sleep measurements (minimum 1 weekend night and minimum 2 weekday nights) (N=605). After exclusion of a participant with extreme underweight and participants younger than 9 years and older than 16 years as well as those with incomplete information on any variable used in the analysis, our final analysis sample comprised 559 children of whom the vast majority (87%) provided 6 or 7 nights of measurements (Figure 1).

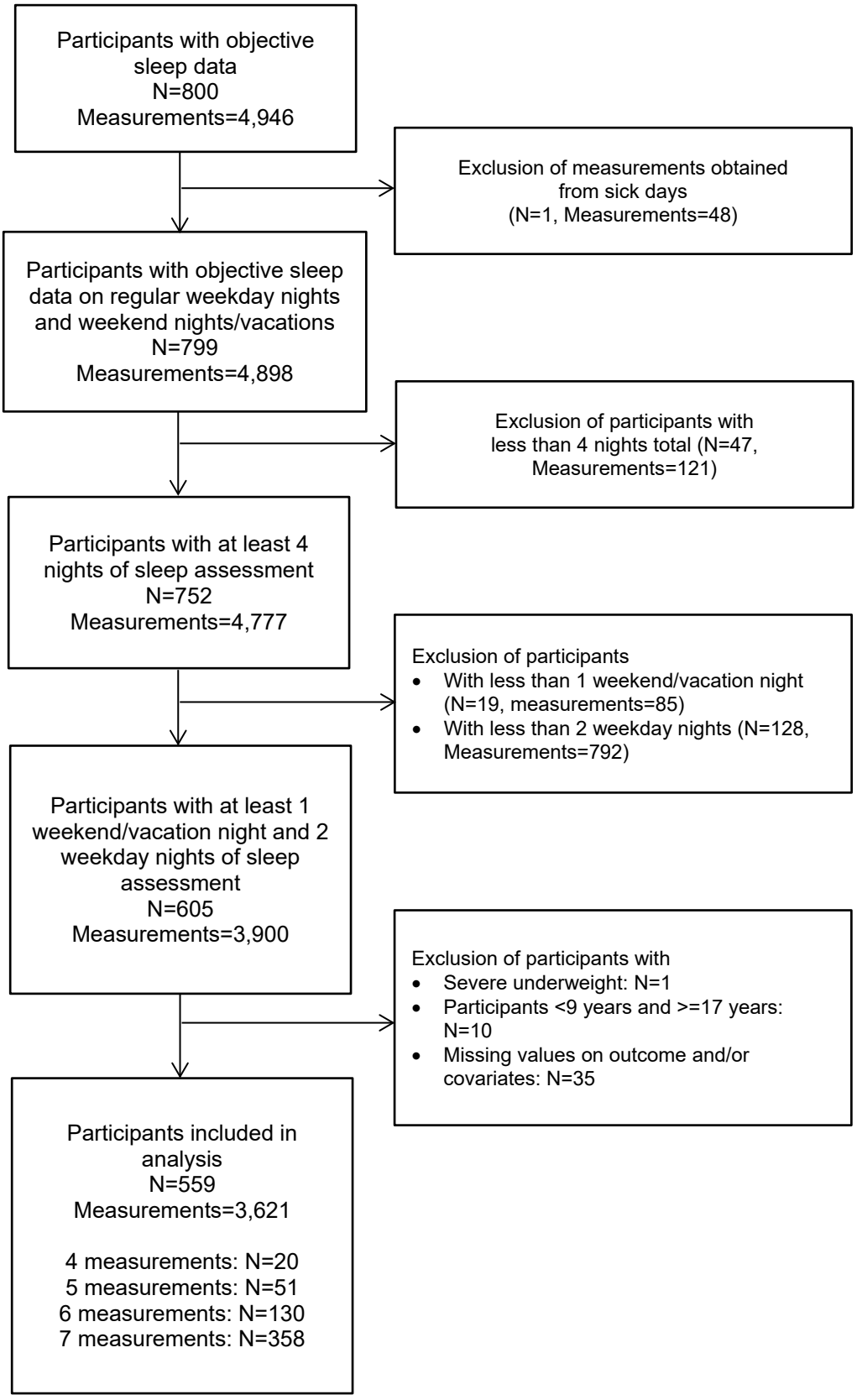

Figure 1: Flowchart of participants

Statistical analysis

Correlations among the five continuous sleep variables were examined by calculating Pearson and Spearman correlation coefficients. Next, associations between the continuous sleep variables and BMI z-score were investigated using linear mixed-effects models,[34] where a random effect for family affiliation was added to account for the inclusion of siblings in the sample. In Model 1 the association between each sleep variable and BMI z-score adjusting for age, sex, highest educational level of parents, pubertal status and country was investigated. Using a second model, we investigated the association between the single sleep quality (sleep latency, sleep efficiency) and sleep timing indicators (wake-up time z-score, lights-off time z-score), respectively, and BMI z-score independent of sleep duration z-score. Hence, Model 2 was adjusted for the same covariates as Model 1 plus sleep duration z-score.

In a sensitivity analysis we adjusted all models for lifestyle factors (consumption frequencies of fruit and vegetables, time spent being physically active in a sports club and computer/TV time). Second, we ran all models stratified by age (children: 9-12 years old, adolescents: 13-16 years old). Further, we (i) estimated the models using either weekday or weekend sleep values as the exposure in the model instead of weighted average sleep values. We also investigated the association between weekend "catch-up sleep" (calculated as average sleep duration on weekends minus average sleep duration on weekdays) and BMI z-score and examined whether this association depends on the amount of weekday sleep duration, i.e. whether weekday sleep duration acts as an effect modifier in the association between "catch-up sleep" and BMI.

For the identification of sleep subtypes we conducted a latent class analysis (LCA) using the five dichotomous sleep variables.[35,36] Models with one to five latent classes were estimated. For the decision on the number of classes, i.e. subtypes, the following statistical criteria were considered: (i) the sample-size adjusted Bayesian Information Criterion [aBIC]) as a model fit index, (ii) entropy as an index of classification accuracy and (iii) the result of the parametric bootstrapped likelihood ratio test (BLRT). Models with smaller aBIC and entropy values approaching 1.0 indicate better fit. P-values below 0.05 of the BLRT indicate that the current model fits better than a model with one class less. In addition, the decision on the number of subtypes was also guided by theoretical considerations, i.e. that subtypes are interpretable and clearly distinguishable from each other as indicated by different patterns of item-response probabilities. Subsequently, the association between sleep subtype and BMI z-score was investigated in terms of a linear mixed-effects model. The LCA was conducted with Mplus 7.[37] For all other data analyses we used the Statistical Analysis System (SAS) software package (Version 9.3; SAS Institute, Cary, NC, USA). Statistical significance level was set to α=0.05.

RESULTS

Participant characteristics are shown in Table 1. The majority of children were categorised as having normal weight (65.1%). Two percent of children were categorised as thin, 21.8% as overweight and 11.1% as obese. Values of sleep variables did not differ substantially between underweight/normal weight children as compared to overweight/obese children. Correlations between sleep variables themselves were mostly weak to moderate, i.e. most correlation coefficients ranged between 0.20 and 0.59 (Table 2).[38]

Results of the linear mixed regression models are displayed in Table 3. Associations between sleep variables and BMI z-score adjusted for covariates were generally weak (Model 1, Table 3). For instance, sleep duration z-score and sleep efficiency were (not statistically significantly) inversely associated with BMI z-score ($\beta_{Model\ 1}$=-0.056, 95% confidence interval [CI] [-0.138; 0.027] and $\beta_{Model\ 1}$=-0.032, 95% CI [-0.105; 0.040], respectively). Associations of sleep latency, sleep efficiency, wake-up time z-score and lights-off time z-score with BMI z-score remained statistically non-significant after adjustment for sleep duration z-score (Model 2, Table 3).

Results of the sensitivity analyses are displayed in Supplementary Tables S1-S6. Adjustment for lifestyle factors of associations between the single sleep variables and BMI z-score did not remarkably alter results (Supplementary Table S1). The age-stratified analysis revealed a positive association between sleep latency and BMI z-score in adolescents ($\beta_{Model\ 1}$=0.076, 95% CI [0.007; 0.144] (Supplementary Table S3) but the 95% confidence interval included the null after adjustment for sleep duration. Other sensitivity analyses by age group and weekday/weekend day did not reveal any marked differences (Supplementary Tables S2-S5). Also weekend "catch-up" sleep was not associated with BMI z-score (Supplementary Table S6) and there was no indication of effect modification of this association by weekday sleep duration z-score.

Table 1: Characteristics of study participants included in the analysis stratified by weight status

	Whole analysis group N=559	**Underweight/ normal weight‡ N=375**	**Overweight/obese‡ N=184**
Sleep latency (minutes), median (interquartile range)*	10.4 (5.5-16.7)	10.8 (5.5-18.3)	9.0 (5.4-14.6)
Sleep efficiency (%), mean (SD)†	83.5 (5.8)	83.4 (5.8)	83.8 (5.9)
Sleep duration (hours), mean (SD)	7.2 (0.7)	7.3 (0.7)	7.2 (0.7)
Wake-up time (hour:minute), mean (SD)	7:26 (0:38)	7:28 (0:38)	7:22 (0:38)
Lights-off time (hour:minute), mean (SD)	22:44 (0:56)	22:43 (0:58)	22:46 (0:52)
Age, mean (SD)	12.8 (1.8)	12.9 (1.8)	12.7 (1.7)
Girls, n (%)	286 (51.2)	197 (52.5)	89 (48.4)
Highest educational level of parents, n (%)§			
Low	23 (4.1)	7 (1.9)	16 (8.7)
Medium	252 (45.1)	162 (43.2)	90 (48.9)
High	284 (50.8)	206 (54.9)	78 (42.4)
Country, n (%)			
Italy	141 (25.2)	67 (17.9)	74 (40.2)
Estonia	111 (19.9)	71 (18.9)	40 (21.7)
Cyprus	15 (2.7)	8 (2.1)	7 (3.8)
Belgium	14 (2.5)	12 (3.2)	2 (1.1)
Sweden	52 (9.3)	51 (13.6)	1 (0.5)
Germany	81 (14.5)	53 (14.1)	28 (15.2)
Hungary	67 (12.0)	47 (12.5)	20 (10.9)
Spain	78 (14.0)	66 (17.6)	12 (6.5)
Pubertal status, n (%)			
Non-pubertal	259 (46.3)	176 (46.9)	83 (45.1)
Pubertal	300 (53.7)	199 (53.1)	101 (54.9)

SD: standard deviation

‡ categorisation according to the IOTF cut-off points[30]

* calculated as minutes between reported lights-off time and sleep onset (as detected by the algorithm)

† calculated as percentage of time spent asleep while in bed: sleep duration/(reported wake-up time – reported lights-off time)*100

§ categorisation according to the "International Standard Classification of Education" (levels 0-2=low, 3-5=medium and 6-8=high)[33]

Table 2: Mutual correlation coefficients and p-values between sleep latency, sleep efficiency, sleep duration z-score, wake-up time z-score and lights-off time z-score (N=559)

	Sleep latency	**Sleep efficiency**	**Sleep duration z-score**	**Wake-up time z-score**	**Lights-off time z-score**
Sleep latency	1.00				
Sleep efficiency	**-0.393*** **<0.001**	1.00			
Sleep duration z-score	-0.033* 0.44	**0.439** **<0.001**	1.00		
Wake-up time z-score	-0.014* 0.75	**-0.102** **0.02**	**0.164** **<0.001**	1.00	
Lights-off time z-score	**-0.252*** **<0.001**	**0.257** **<0.001**	**-0.452** **<0.001**	**0.518** **<0.001**	1.00

All correlation coefficients are Pearson correlation coefficients except those labelled with a * which are Spearman correlation coefficients; figures in bold indicate statistically significant correlations

Table 3: Cross-sectional associations of sleep latency, sleep efficiency, sleep duration z-score, wake-up time z-score and lights-off time z-score with BMI z-score (N=559)

	Model 1 **BMI z-score**			**Model 2** **BMI z-score**		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Sleep latency§	-0.013	-0.056; 0.030	0.55	-0.015	-0.057; 0.028	0.50
Sleep efficiency‡	-0.032	-0.105; 0.040	0.38	-0.012	-0.095; 0.070	0.76
Sleep duration z-score	-0.056	-0.138; 0.027	0.18	---	---	---
Wake-up time z-score	-0.040	-0.135; 0.054	0.40	-0.027	-0.124; 0.070	0.58
Lights-off time z-score	0.009	-0.089; 0.107	0.86	-0.029	-0.141; 0.082	0.60

§ 1 unit ≙ 5 minutes
‡ 1 unit ≙ 5%
Model 1 is adjusted for age, sex, highest level of parental education, pubertal status and country and includes a random effect for family affiliation
Model 2 is adjusted for the same variables as Model 1 plus sleep duration z-score and includes a random effect for family affiliation
CI: confidence interval

Among the five latent class models estimated, the 4-class model was considered as the best solution based on statistical criteria (aBIC, entropy and BLRT) and theoretical considerations (Table 4). Children having a 100% probability for an early wake-up time (17.5% of the sample) were assigned to the subtype labelled as "early birds" (Table 5). Children having a 100% probability of having short sleep duration were assigned to the subtype labelled "short sleep duration" (14.7% of the sample). The third subtype was labelled "optimal sleep" (47.6% of the sample) including children with a high probability (at least 75%) to belong to the most favourable category of each sleep variable. Lastly, the fourth subtype was labelled "poor sleep quality" (20.2% of the children). It comprises children who showed a high probability of having long sleep latency (56.9%) and poor sleep efficiency (100%). In comparison to belonging to the "optimal sleep" subtype, belonging to the "poor sleep quality"-subtype was associated with a lower BMI z-score (Table 6). However, the confidence interval was wide and included the null. The two other sleep subtypes did not show relevant associations with BMI z-score.

Table 4: Fit indices of latent class solutions

	Sample-size adjusted BIC	**BLRT p-value**	**Entropy**
1 Class Model	3153.15	---	---
2 Class Model	3087.37	<0.001	1.00
3 Class Model	3039.33	<0.001	1.00
4 Class Model	3029.57	<0.001	0.92
5 Class Model	3038.62	0.16	0.78

BIC: Bayesian information criterion; BLRT: Parametric Bootstrapped Likelihood Ratio Test

Table 5: Item-response probabilities of participants assigned to one of the four sleep subtypes. Numbers indicate the probabilities of children to belong to either of the two categories for every sleep variable (N=559)

	Sleep subtype			
	Early birds N=98	**Short sleep duration** N=82	**Optimal sleep** N=266	**Poor sleep quality** N=113
	Prob (%)	Prob (%)	Prob (%)	Prob (%)
Lights-off time early	97.4	30.7	75.0	100.0
Lights-off time late§	2.6	69.3	25.0	0.0
Wake-up time late	0.0	85.5	100.0	64.8
Wake-up time early‡	100.0	14.5	0.0	35.2
Sleep duration long	84.6	0.0	100.0	66.0
Sleep duration short*	15.4	100.0	0.0	34.0
Sleep latency short	87.7	79.7	78.8	43.1
Sleep latency long†	12.3	20.3	21.2	56.9
Sleep efficiency good	100.0	68.0	91.2	0.0
Sleep efficiency poor¶	0.0	32.0	8.8	100.0

Prob: probability
§ Late: lights-off time later than 22:42 (9 year olds), 22:43 (10 year olds), 23:00 (11 year olds), 23:04 (12 year olds), 23:22 (13 year olds), 23:43 (14 year olds), 00:05 (15 year olds), 00:13 (16 year olds)
‡ Early: wake-up time earlier than 7:03 (9 year olds), 6:57 (10 year olds), 7:05 (11 year olds), 7:01 (12 year olds), 7:06 (13 year olds), 6:54 (14 year olds), 7:07 (15 year olds), 6:42 (16 year olds)
* Short: sleep duration shorter than 7.1 hours (9 year olds), 7.2 hours (10 year olds), 7.1 hours (11 year olds), 7.0 hours (12 year olds), 6.8 hours (13 year olds), 6.5 hours (14 year olds), 6.4 hours (15 year olds), 5.8 hours (16 year olds)
† Long: sleep latency longer than 17 minutes
¶ Poor: sleep efficiency less than 80%

Table 6: Association between sleep subtype and BMI z-score (N=559)

	BMI z-score	**95% CI**	**p-value**
Subtype "Early birds"	-0.010	-0.243; 0.223	0.93
Subtype "Short sleep duration"	-0.001	-0.244; 0.241	0.99
Subtype "Poor sleep quality"	-0.138	-0.359; 0.083	0.22
Subtype "Optimal sleep" (reference)	0		

Model is adjusted for age, sex, highest level of parental education, pubertal status and country and includes a random effect for family affiliation

DISCUSSION

Our study is one of very few investigating the association between multiple objectively measured sleep characteristics combined with diary entries and BMI. Further, to our knowledge it is the first study that classified study subjects into distinct sleep subtypes ("early birds", "short sleep duration", "optimal sleep" and "poor sleep quality") to investigate their association with BMI. Neither the single sleep variables nor sleep subtypes were markedly associated with BMI in our study.

In general, mean values obtained for sleep duration, sleep efficiency and sleep latency were similar to those observed in other studies in young populations using Actigraphs for sleep assessment.[39] Likewise, mean lights-off and wake-up times were largely consistent with Actigraphy-recorded sleep onset and offset times in other studies.[39]

We observed a weak inverse association between sleep duration and BMI that was statistically non-significant. This result is in line with the observations made by McNeil et al.[23] and Gomes et al.[40] who investigated the association between objectively measured sleep duration and BMI in 9-11 year old Canadian (N=514) and Portuguese (N=686) children participating in the "International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE)". Likewise, null results were reported by small studies conducted in US American (8-17 years old, N=125),[27] Belgian (6-12 years old, N=193)[22] and Icelandic (15-16 years old, N=281)[26] children and adolescents. However, other studies have reported an inverse association between objectively measured sleep duration and BMI. In the whole ISCOLE population (N=6,025)[41] and in Canadian 8-10 year old children (N=550)[42] longer objectively measured sleep duration was cross-sectionally associated with lower odds of obesity. Likewise, Cespedes Feliciano et al.[24] also found an inverse association between objectively measured sleep duration and BMI in 827 US American adolescents (11-16 years old) as did Taylor et al.[25] in 823 New Zealand children (6-10 years old). Inverse associations were also reported by smaller studies (less than 400 participants) conducted in the United Kingdom and the USA.[20,21,43] Furthermore, a previous study based on cross-sectional IDEFICS data of 2 to 9 year old children (N=7,867) found parentally reported short sleep duration to be associated with higher odds of overweight.[6] As the children were much younger then, we investigated for comparison the association between self-reported sleep duration and BMI in 5,397 children (9-16 years old) participating in the third examination wave of the IDEFICS/I.Family cohort (unpublished data). The effect size of the association between sleep duration z-score and BMI z-score adjusted for relevant covariates was only slightly larger than in the present study but statistically significant (β=-0.080; 95% confidence interval [-0.109; -0.051]; $p<0.001$). Therefore, rather than suggesting a differential effect by age group,

these results indicate that the sample in the present study was possibly not large enough to detect small effects.

In agreement with our results, many previous studies did not find an association between sleep efficiency and BMI.[20-22,26] Nevertheless, McNeil et al.[23], Cespedes Feliciano et al.[24] and Taylor et al.[25] observed an inverse association between sleep efficiency and BMI z-score. However, in the study by Cespedes Feliciano et al.[24] this association disappeared in models with either additional adjustment for obesity-related behaviours (physical activity, etc.) or additional adjustment for sleep duration. The number of studies investigating the association between objectively measured sleep latency and BMI is very limited. Similar to our study, Michels et al.[22] and Rognvaldsdottir et al.[26] did not observe an association between sleep latency and BMI. Further, the apparent absence of associations between lights-off and wake-up time, respectively, and BMI seems to be in agreement with the results of previous studies.[23,25-27]

As already mentioned, no study has yet grouped children/adolescents into sleep subtypes using objectively measured sleep variables to study their association with BMI. There are, however, studies in young populations that applied LCA using subjectively measured sleep variables and investigated the association between sleep subtype and BMI[44] and other outcomes.[45,46] However, sleep variables used in these studies are different to the ones used in our study hampering comparison of the identified sleep subtypes.

Strengths of our study are the inclusion of children and adolescents from eight European countries and the standardised data collection including objective sleep assessment with accelerometers. Further, respondents entered "lights-off time" in their sleep diary which allowed us to calculate sleep latency,[47] a measure rarely investigated in previous studies with BMI as the outcome. Accelerometers overcome some of the major limitations of self-reports as they are not prone to multiple biases such as recall and social desirability biases.[18] They have been validated against polysomnography, the gold standard in sleep research, and it has been found that accelerometers are able to correctly identify sleep periods although it has to be mentioned that their ability to detect periods of wakefulness is more limited.[48-49] Hence, sleep duration and sleep efficiency might have been overestimated in our study. For the latent class analysis, cut-offs for the single sleep variables were subjectively chosen based on values of our own sample (25^{th} and 75^{th} percentiles, respectively). However, existing sleep duration recommendations may not be appropriate to define cut-offs for short sleep duration measured by Actigraphs as the recommendations are mainly derived from studies that used self- or parent-reported sleep duration.[50] Although sleep quality recommendations for children and adolescents provided by the National Sleep Foundation were derived by experts under consideration of studies using objective methods,

there are still uncertainties about which values are optimal[51] and to our knowledge no recommendations with respect to optimal sleep timing exist.

In conclusion, we did not find convincing evidence for an association between objectively measured sleep duration, sleep quality and sleep timing, respectively, and BMI in European children and adolescents. Previous studies that are comparable to ours have either reported inverse or no associations. In addition, we did not observe statistically significant differences in BMI between four distinct sleep subtypes. Nevertheless, our approach of integrating various aspects of sleep by creating sleep subtypes might inspire future studies.

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SUPPLEMENTARY MATERIAL

Paper 2

Table S1: Cross-sectional associations between sleep latency, sleep efficiency, sleep duration z-score, wake-up time z-score, lights-off time z-score and BMI z-score adjusting for lifestyle factors (N=499)

	Model 1 BMI z-score			Model 2 BMI z-score		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Sleep latency§	-0.015	-0.060; 0.030	0.50	-0.016	-0.062; 0.087	0.47
Sleep efficiency‡	-0.024	-0.101; 0.053	0.53	0.003	-0.085; 0.091	0.95
Sleep duration z-score	-0.063	-0.150; 0.024	0.15	---		
Wake-up time z-score	-0.055	-0.153; 0.044	0.27	-0.040	-0.142; 0.062	0.43
Lights-off time z-score	0.012	-0.093; 0.118	0.81	-0.029	-0.148; 0.090	0.63

§ 1 unit ≙ 5 minutes
‡ 1 unit ≙ 5%
Model 1 is adjusted for age, sex, highest level of parental education, pubertal status, country, consumption frequencies of fruit and vegetables (times/week), time spent doing physical activity in a sports club (hours/week) and computer and TV time (hours/day) and includes a random effect for family affiliation
Model 2 is adjusted for the same variables as Model 1 plus sleep duration z-score and includes a random effect for family affiliation
CI: confidence interval

Table S2: Cross-sectional associations between sleep latency, sleep efficiency, sleep duration z-score, wake-up time z-score, lights-off time z-score and BMI z-score in children (9-12 years old) (N=299)

	Model 1 BMI z-score			Model 2 BMI z-score		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Sleep latency§	-0.042	-0.101; 0.017	0.15	-0.042	-0.102; 0.018	0.16
Sleep efficiency‡	0.007	-0.105; 0.118	0.90	-0.002	-0.133; 0.129	0.98
Sleep duration z-score	0.017	-0.102; 0.136	0.76	---		
Wake-up time z-score	-0.031	-0.171; 0.109	0.64	-0.040	-0.186; 0.107	0.57
Lights-off time z-score	-0.051	-0.200; 0.098	0.47	-0.051	-0.219; 0.116	0.52

§ 1 unit ≙ 5 minutes
‡ 1 unit ≙ 5%
Model 1 is adjusted for age, sex, highest level of parental education, pubertal status and country and includes a random effect for family affiliation
Model 2 is adjusted for the same variables as Model 1 plus sleep duration z-score and includes a random effect for family affiliation
CI: confidence interval

Table S3: Cross-sectional associations between sleep latency, sleep efficiency, sleep duration z-score, wake-up time z-score, lights-off time z-score and BMI z-score in adolescents (13-16 years old) (N=260)

	Model 1 BMI z-score			Model 2 BMI z-score		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Sleep latency§	0.076	0.007; 0.144	0.04	0.067	-0.008; 0.143	0.07
Sleep efficiency‡	-0.072	-0.199; 0.055	0.21	-0.045	-0.194; 0.103	0.47
Sleep duration z-score	-0.098	-0.253; 0.057	0.17	---		
Wake-up time z-score	-0.040	-0.215; 0.135	0.60	-0.015	-0.204; 0.175	0.85
Lights-off time z-score	0.020	-0.160; 0.200	0.80	-0.048	-0.265; 0.168	0.59

§ 1 unit ≙ 5 minutes
‡ 1 unit ≙ 5%
Model 1 is adjusted for age, sex, highest level of parental education, pubertal status and country and includes a random effect for family affiliation
Model 2 is adjusted for the same variables as Model 1 plus sleep duration z-score and includes a random effect for family affiliation
CI: confidence interval

Table S4: Cross-sectional associations between weekday sleep latency, sleep efficiency, sleep duration z-score, wake-up time z-score, lights-off time z-score and BMI z-score (N=559)

	Model 1 BMI z-score			Model 2 BMI z-score		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Sleep latency§	0.002	-0.036; 0.039	0.92	0.000	-0.037; 0.038	0.98
Sleep efficiency‡	-0.015	-0.084; 0.054	0.66	0.010	-0.070; 0.089	0.81
Sleep duration z-score	-0.055	-0.138; 0.028	0.19	---	---	---
Wake-up time z-score	-0.075	-0.172; 0.021	0.12	-0.065	-0.164; 0.035	0.20
Lights-off time z-score	0.015	-0.085; 0.115	0.76	-0.028	-0.147; 0.090	0.63

§ 1 unit ≙ 5 minutes
‡ 1 unit ≙ 5%
Model 1 is adjusted for age, sex, highest level of parental education, pubertal status and country and includes a random effect for family affiliation
Model 2 is adjusted for the same variables as Model 1 plus sleep duration z-score and includes a random effect for family affiliation
CI: confidence interval

Table S5: Cross-sectional associations between weekend sleep latency, sleep efficiency, sleep duration z-score, wake-up time z-score, lights-off time z-score and BMI z-score (N=559)

	Model 1 BMI z-score			Model 2 BMI z-score		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Sleep latency§	-0.031	-0.064; 0.002	0.06	-0.033	-0.066; 0.001	0.06
Sleep efficiency‡	-0.052	-0.113; 0.010	0.10	-0.049	-0.115; 0.017	0.14
Sleep duration z-score	-0.032	-0.115; 0.050	0.44	---	---	---
Wake-up time z-score	0.012	-0.077; 0.101	0.78	0.042	-0.063; 0.147	0.43
Lights-off time z-score	0.003	-0.087; 0.094	0.94	-0.008	-0.104; 0.087	0.86

§ 1 unit ≙ 5 minutes
‡ 1 unit ≙ 5%
Model 1 is adjusted for age, sex, highest level of parental education, pubertal status and country and includes a random effect for family affiliation
Model 2 is adjusted for the same variables as Model 1 plus sleep duration z-score and includes a random effect for family affiliation
CI: confidence interval

Table S6: Cross-sectional associations between weekend catch-up sleep and BMI z-score (N=559)

	Model 1 BMI z-score			Model 2 BMI z-score		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Weekend catch up sleep§	0.007	-0.073; 0.087	0.86	0.008	-0.072; 0.088	0.84

§ 1 unit ≙ 1 hour
Model 1 is adjusted for age, sex, highest level of parental education, pubertal status and country and includes a random effect for family affiliation
Model 2 is adjusted for the same variables as Model 1 plus sleep duration z-score and includes a random effect for family affiliation
CI: confidence interval

Paper 3

Associations between sleep duration and insulin resistance in European children and adolescents considering the mediating role of abdominal obesity

Thumann BF, Michels N, Felsö R, Hunsberger M, Kaprio J, Moreno LA, Siani A, Tornaritis M, Veidebaum T, De Henauw S, Ahrens W, Börnhorst C, on behalf of the IDEFICS and I.Family consortia

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RESEARCH ARTICLE

Associations between sleep duration and insulin resistance in European children and adolescents considering the mediating role of abdominal obesity

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Data Availability Statement: Ethical restrictions prohibit the authors from making the minimal data set publicly available because this study is based on highly sensitive data collected in young children.

Abstract

Background

Short sleep duration has been suggested to lead to insulin resistance both directly by altering glucose metabolism and indirectly through obesity. This study aims to investigate associations between nocturnal sleep duration and insulin resistance considering abdominal obesity as a mediator.

Methods

We analysed data of 3 900 children aged 2–15 years participating in the second (2009/10) and third (2013/14) examination wave of the European IDEFICS/I.Family study (hereafter referred to as baseline and follow-up). Information on nocturnal sleep duration was collected by questionnaires and age-standardised (SLEEP z-score). The homeostasis model assessment (HOMA) was calculated from fasting insulin and fasting glucose obtained from blood samples; waist circumference (WAIST) was measured with an inelastic tape. HOMA and WAIST were used as indicators for insulin resistance and abdominal obesity, respectively, and transformed to age- and sex-specific z-scores. Cross-sectional and longitudinal associations between SLEEP z-score and HOMA z-score were investigated based on a path model considering WAIST z-score as a mediator adjusting for relevant confounders.

Data can only be accessed by registered scientists who are authorised to access the data with an individual account and an individual password. Statistical analyses are done on a secured central data server (CDS). It is strictly forbidden to copy or download any data from the CDS. Data are available on request and all requests need approval by the study's Steering Committee. Interested researchers can contact the IDEFICS or I.Family consortium (http://www.ideficsstudy.eu and http://www.ifamilystudy.eu) or the study coordinator (ahrens@leibniz-bips.de) to request data access. All requests for accessing data of the IDEFICS/I. Family cohort are discussed on a case-by-case basis by the Steering Committee. For this, interested parties are asked to provide details (e.g. for testing reproducibility of results) on the purpose of their request.

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Competing interests: The authors declare no competing interests.

Results

Cross-sectionally, baseline SLEEP z-score was negatively associated with baseline WAIST z-score (unstandardised effect estimate -0.120, 95% confidence interval [-0.167; -0.073]). We observed no direct effect of baseline SLEEP z-score on baseline HOMA z-score but a negative indirect effect through baseline WAIST z-score (-0.042 [-0.058; -0.025]). Longitudinally, there was no direct effect of baseline SLEEP z-score on HOMA z-score at follow-up but a negative indirect effect through both baseline WAIST z-score and WAIST z-score at follow-up (-0.028 [-0.040; -0.016]).

Conclusions

Our results do not support the hypothesis of an association between short sleep duration and insulin resistance independent of abdominal obesity. However, longer sleep duration may exert short and long term beneficial effects on insulin resistance through its beneficial effects on abdominal obesity.

Introduction

Prevalence rates of overweight and obesity in European children are at a high level although the rising trend over the last decades has been stopped in some countries [1, 2]. Obesity is associated with a higher risk for insulin resistance which is considered to be a central component of the metabolic syndrome and a risk factor for type 2 diabetes mellitus [3, 4]. Short sleep duration has been suggested as a potential risk factor for both obesity and insulin resistance [5]. Various mechanisms have been proposed to explain the links between sleep duration, obesity and insulin resistance. One hypothesis is that sleep deprivation leads to a dysregulation of appetite hormones such as leptin and ghrelin resulting in higher energy intake and weight gain [5, 6]. Apart from hormonal changes, short sleep duration might also negatively influence weight status through a behavioural pathway. For instance, more time being awake implies more time to eat [7]. Further, short sleep might cause fatigue resulting in less physical activity [7]. However, in general there is more evidence supporting the hypothesis that short sleep leads to an increase in energy intake than to a decrease in energy expenditure [7, 8]. Subsequent obesity and especially gain in visceral fat are major risk factors for insulin resistance [3]. However, short sleep duration might influence insulin resistance not only indirectly through obesity but also directly by altering glucose metabolism [5, 6].

To date, most cross-sectional and longitudinal studies conducted in young populations have found an association between short sleep duration and obesity determined by a high body mass index (BMI) [9–12]. As revealed by a review by Quist et al. [13] on sleep and cardio-metabolic risk in children and adolescents, there exists also a wealth of cross-sectional studies that investigated the association between sleep duration and waist circumference. Waist circumference has been found to be a better predictor of visceral adipose tissue than BMI [14] and is widely used as a marker of abdominal obesity. The majority of studies found longer sleep duration to be associated with lower waist circumference [13]. However, the respective longitudinal studies included in this review [13] and also one recent publication [15] showed inconsistent associations.

Both laboratory and epidemiological studies in adults have suggested short sleep duration to be a risk factor for type 2 diabetes independent of weight status [16, 17]. Also in a study in

21 adolescent boys sleep restriction over three nights was found to be associated with biological markers of insulin resistance including the homeostasis model assessment (HOMA-IR) which is calculated from fasting insulin and fasting glucose [18]. However, there are only few population-based studies that investigated the association between sleep duration and markers of insulin resistance in children and adolescents [13]. Cross-sectional studies provided only weak evidence for an association [13, 19], although two longitudinal studies reported a beneficial effect of longer sleep duration on insulin resistance [20, 21]. However, this association was independent of obesity in only one study [21]. Generally, the majority of studies in pediatric populations that investigated the association between sleep duration and insulin resistance adjusted for waist circumference or another measure of obesity, often explicitly mentioning the potential mediating role of obesity [22, 23]. However, according to our knowledge, no study to date used appropriate statistical methods to quantify this potentially mediating effect.

To close this gap, the present study aimed to investigate the potential mediating role of abdominal obesity in the cross-sectional and longitudinal associations between nocturnal sleep duration and insulin resistance.

Subjects and methods

Study population and procedures

The data used in this study were collected in eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden) in the framework of the IDEFICS/I.Family cohort study [24, 25]. Participants were recruited via a setting-based community-oriented approach in kindergartens and primary schools in two regions in each country; one region was defined as the intervention region, where an intervention for the prevention of childhood obesity was implemented, and the other served as the control region with no intervention [26]. The regions were selected by convenience, i.e. it was not feasible to obtain nationally representative samples [24]. However, the study followed a population-based approach and study regions were similar to the surrounding regions with respect to their socio-demographic profiles [27]. Generally, all children attending the kindergartens/primary schools in the selected regions who were between 2 and 9.9 years old were eligible to participate in the study. Further details about the study can also be inferred from the ISRCTN trial registry (http://www.isrctn.com/ISRCTN62310987).

Children were first examined between September 2007 and May 2008 (N = 16 229). Subsequently, the intervention was implemented and after its completion, 11 043 children were examined again between September 2009 and June 2010. In addition, 2 543 newly recruited children joined the IDEFICS study at this time point. For the I.Family study, children participating in IDEFICS (N = 7 117) and some of their siblings (N = 2 501) were examined again between January 2013 and June 2014. Information was collected by physical examinations, biological samples and questionnaires [25]. Usually, examinations took place on site at the kindergartens/primary schools. In addition, in some cases an examination site on the premises of the research centre, a public building or a hospital was established where examinations at kindergartens/schools were not feasible [24]. As a general procedure, questionnaires were developed in English, translated into local languages and then back-translated to maintain comparability across languages. In general, parents answered on behalf of children younger than 12 years old; older children reported for themselves. Before children entered the study, parents provided informed written consent. Moreover, children 12 years and older provided simplified written consent. Younger children gave oral consent for examinations and sample collection. Ethical approval was obtained by the appropriate Ethics Committees by each of the eight study centres conducting fieldwork, namely from the Ethics Committee of the University

Hospital Ghent (Belgium), the National Bioethics Committee of Cyprus (Cyprus), the Tallinn Medical Research Ethics Committee of the National Institutes for Health Development (Estonia), the Ethics Committee of the University of Bremen (Germany), the Scientific and Research Ethics Committee of the Medical Research Council Budapest (Hungary), the Ethics Committee of the Health Office Avellino (Italy), the Ethics Committee for Clinical Research of Aragon (Spain) and the Regional Ethical Review Board of Gothenburg (Sweden). The present study is based on the data of children and adolescents who participated in the second (2009/10) and third (2013/14) examination wave of the IDEFICS/I.Family cohort study (hereafter referred to as baseline and follow-up, respectively). This is because habitual nocturnal sleep duration was assessed for both weekdays and weekend days only during these waves.

Waist circumference

We used waist circumference as a measure of abdominal obesity. Both at baseline and at follow-up, participants' waist circumference (cm) was measured with an inelastic tape (Seca 200, seca GmbH & Co. KG, Hamburg, Germany) in an upright position with relaxed abdomen and feet together, midway between the lowest rib margin and the iliac crest to the nearest 0.1 cm. To account for differences in waist circumference by age and sex, we calculated age- and sex-specific z-scores (WAIST z-score). For this purpose, we used percentile curves of waist circumference derived from both the IDEFICS and I.Family populations that were calculated as a function of age stratified by sex using the General Additive Model for Location Scale and Shape (GAMLSS) method [28]. Further details on the application of this method to our data can be found elsewhere [29, 30].

Insulin resistance

Venous blood was collected from children after an overnight fast. At baseline, children who refused venepuncture were offered the alternative of giving fasting capillary blood by finger-prick. At this wave, insulin was analysed using a luminescence immunoassay (AUTO-GA Immulite 2000, Siemens, Eschborn, Germany) and blood glucose was assessed with a point-of-care analyser (Cholestech LDX, Cholestech Corp., Hayward, California, USA). At follow-up, insulin was determined by electrochemiluminescence technology (MULTI-SPOT® Assay System—Human Leptin, Insulin Assay Kit, Meso Scale Diagnostics, LLC., Rockville, Maryland, USA) and glucose with an enzymatic UV test (Cobas c701, Roche Diagnostics GmbH, Mannheim, Germany). HOMA-IR was used as a measure of insulin resistance [31] and calculated as insulin[μU/ml]*glucose[mg/dl]/405. HOMA-IR was standardised according to age and sex (HOMA z-score) using reference values derived from both the IDEFICS and I.Family populations according to previously described methods [30, 32]. As a different assessment method for insulin and glucose was used in the third examination wave, two separate reference curves were estimated for HOMA-IR depending on the assessment method used to account for the lower variation of insulin/glucose measurements in the third examination wave.

Sleep duration

At both baseline and at follow-up, participants reported sleep duration in hours and minutes in self-completion questionnaires, i.e. the instructions read as follows: "What is the amount of time the child sleeps during a 24 hour period on weekdays? Give separate information for night time sleep and naps in the daytime." Analogously, information was collected for weekend days/vacations (in the following referred to as weekend days). We used the following formula to obtain the weighted average of nocturnal sleep duration for each child: (nocturnal sleep duration on weekdays*5 + nocturnal sleep duration on weekend days*2) / 7. The

weighted average of daily napping time (minutes) was calculated in the same manner. To account for the strong age-dependency of nocturnal sleep duration, i.e. the fact that sleep duration naturally decreases during childhood [33], we calculated an age-specific z-score (SLEEP z-score) based on the final analysis sample.

Covariates

Covariates assessed at baseline by questionnaires included age (years), sex and highest level of parental education defined according to the "International Standard Classification of Education" (levels 0–2 = low, 3–5 = medium and 6–8 = high) [34]. A psychosocial well-being score (0–48 points with a higher score indicating higher well-being) was calculated using four subscales of the "KINDL^R Questionnaire for Measuring Health-Related Quality of Life in Children and Adolescents" (emotional well-being, self-esteem, family life and relations to friends) [35]. Pubertal status was self-reported by children 8 years and older at follow-up using questions adapted from Carskadon and Acebo [36]. Girls were classified as pubertal when they reported that their menarche had already occurred and boys when they reported that their voice mutation had already started or was completed. Further, information on country of recruitment was recorded. For a sensitivity analysis, we used information on lifestyle factors collected by questionnaires at baseline. These included consumption frequencies of fruit and vegetables (times/week) as an indicator for dietary quality, time spent doing physical activity (PA) in a sports club (hours/week) as a measure of PA and the weighted average of hours of computer and TV time on weekdays and weekend days as an approximate measure of the weekly duration of electronic media use. Covariates were selected *a priori* according to pre-existing knowledge.

Analysis dataset

As displayed in Fig 1, from the initial sample participating at both baseline and follow-up (N = 6 162), we excluded children with missing information on sleep duration and waist circumference as well as covariates (at baseline and/or follow-up) (N = 2 232). Of the remaining 3 930 participants, we excluded those with implausible values on any variable used in the analysis (N = 30), resulting in an analysis sample of 3 900 children (see Fig 1 for definitions of implausible values).

Statistical analysis

For data preparation and descriptive analysis we used SAS 9.3 (Statistical Analysis System, SAS Institute Inc., Cary, North Carolina, USA). In order to investigate associations of interest, we conducted a path analysis in Mplus 7 [37]. With a path model, the hypothesised interrelationships among a set of variables can be investigated by modelling several related regression relationships simultaneously [37, 38]. Mediating variables in a path model are those that are a dependent variable in one relationship and an independent variable in another [37]. Hence, it is hypothesised that through a mediating variable some of the causal effects of prior variables are passed onto subsequent variables [38]. A direct effect is defined as the influence of one variable on another, unmediated by any other variable, and an indirect effect as the influence of one variable on another, mediated by at least one intervening variable [39]. The total effect is the sum of direct and indirect effect(s) of one variable on another [39]. It should be noted that the terms "direct effect", "indirect effect" and "total effect" are standard terminology in path analysis but this does not necessarily imply causality of associations. To account for non-independence of data (siblings in the sample) we used maximum likelihood estimation with robust standard errors together with the "TYPE = COMPLEX" command and the "CLUSTER"

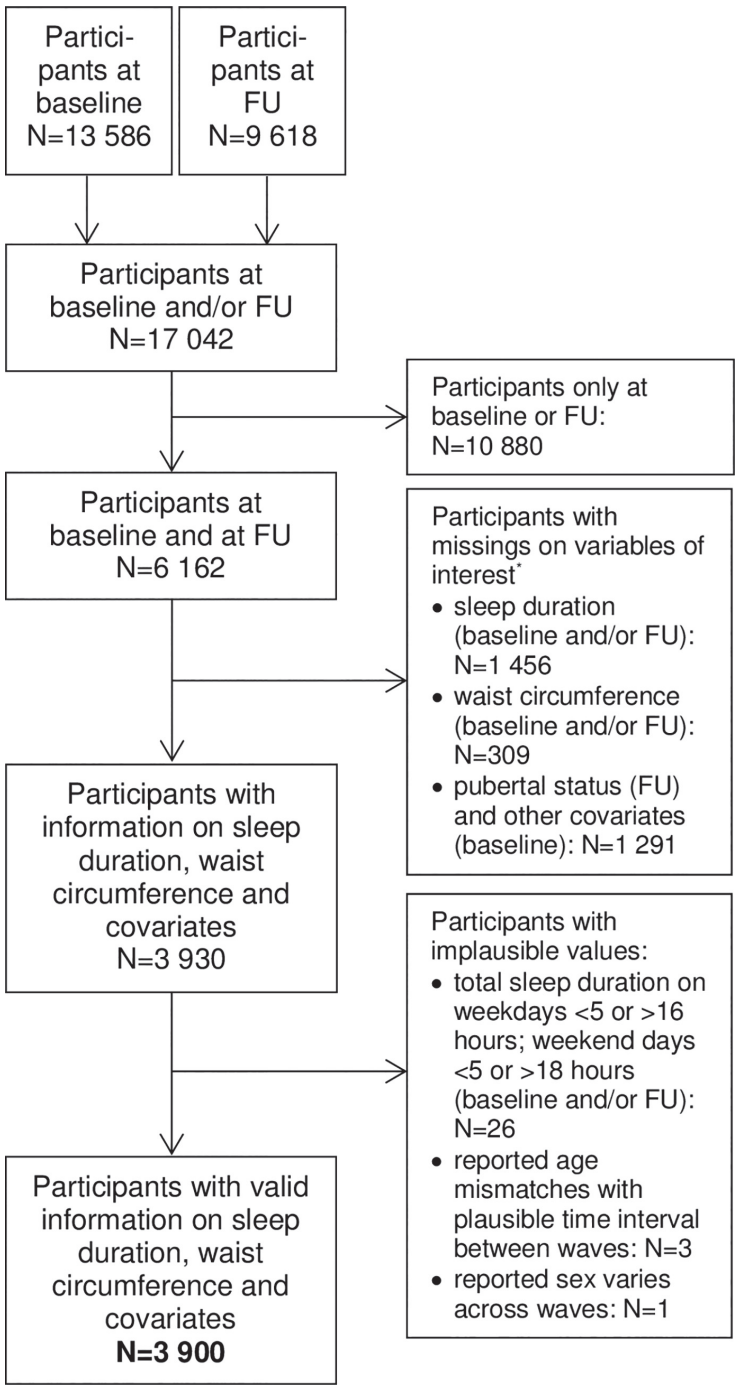
Partici-pants at baseline N=13 586
Partici-pants at FU N=9 618
Participants at baseline and/or FU N=17 042
Participants only at baseline or FU: N=10 880
Participants at baseline and at FU N=6 162
Participants with missings on variables of interest*
• sleep duration (baseline and/or FU): N=1 456
• waist circumference (baseline and/or FU): N=309
• pubertal status (FU) and other covariates (baseline): N=1 291
Participants with information on sleep duration, waist circumference and covariates N=3 930
Participants with implausible values:
• total sleep duration on weekdays <5 or >16 hours; weekend days <5 or >18 hours (baseline and/or FU): N=26
• reported age mismatches with plausible time interval between waves: N=3
• reported sex varies across waves: N=1
Participants with valid information on sleep duration, waist circumference and covariates
N=3 900

Fig 1. Flow chart of participants, baseline examination: 2009/10; follow-up (FU) examination: 2013/14, * missings on multiple variables possible.

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option [37]. Maximum likelihood estimation with robust standard errors can further handle missing values in dependent variables in the model under a missing at random assumption [37]. Thus, with this technique even those participants with missing information on HOMA-IR at baseline and/or at follow-up could be included.

Guided by our conceptual framework (Fig 2), we set up a path model to investigate both cross-sectional and longitudinal associations between nocturnal sleep duration, abdominal obesity and insulin resistance within one model. Specifically, we estimated the direct effects of baseline SLEEP z-score on baseline WAIST z-score, baseline HOMA z-score, WAIST z-score at follow-up and HOMA z-score at follow-up. Further, we estimated the indirect effects of baseline SLEEP z-score on (i) baseline HOMA z-score (through baseline WAIST z-score) (ii) WAIST z-score at follow-up (through baseline WAIST z-score and SLEEP z-score at follow-up) and (iii) HOMA z-score at follow-up (through baseline WAIST z-score, baseline HOMA z-score, WAIST z-score at follow-up and SLEEP z-score at follow-up). Socio-demographic variables (baseline age, sex, country, highest educational level of parents), pubertal status at follow-up and follow-up time were included as covariates in all regressions of the path model. Furthermore, psychosocial well-being was included as a covariate because of its association with sleep duration [40] and the potential role of psychosocial stressors in the development of abdominal obesity and insulin resistance [41, 42]. Lastly, models were also adjusted for napping time because napping has been found to be associated with shorter nocturnal sleep duration [43]. The path model was also estimated stratified by age (pre-school children 2–5 years old at baseline vs. school children 6–11 years old at baseline) to examine whether there are differences between age groups.

Adequate model fit was achieved as indicated by values close to 0.95 for the Comparative Fit Index and the Tucker-Lewis Index and a value close to 0.06 for the Root Mean Square Error of Approximation (specific values see S1 Table) [44]. Multiple testing was accounted for

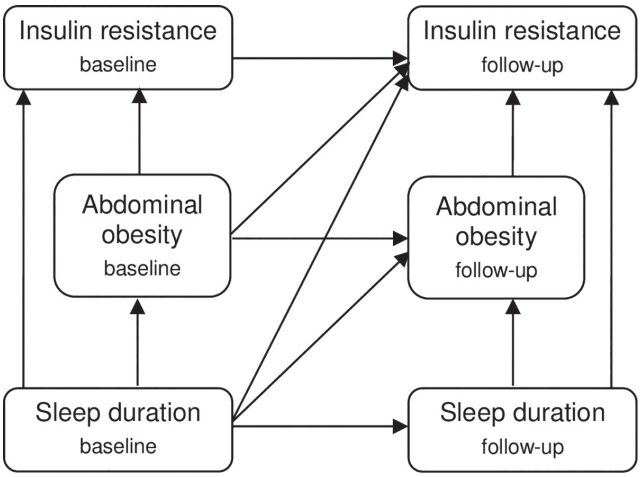

Fig 2. Conceptual framework displaying associations assumed between sleep duration, abdominal obesity and insulin resistance at baseline and follow-up.

https://doi.org/10.1371/journal.pone.0235049.g002

by using the adjustment method of Benjamini and Hochberg [45] to control for the false discovery rate at the 0.05 level of significance resulting in an adjusted alpha level of 0.019.

Several sensitivity analyses were conducted: As it has been suggested that short sleep duration might just be a marker of an unfavourable lifestyle [10], we ran the analysis additionally adjusting all regressions of the path model for baseline consumption frequencies of fruit and vegetables, sports club physical activity and duration of electronic media use (N = 3 239). Further, as some studies indicate that children may sleep shorter during weekday nights in comparison to weekend nights [46, 47], we estimated the path model using either weekday or weekend nocturnal sleep duration as the exposure in the model (WD SLEEP z-score and WE SLEEP z-score, respectively) instead of average nocturnal sleep duration. Lastly, as the number of participants with missing values on HOMA-IR was quite high (missing only at baseline: N = 831 [21.3%], missing only at follow-up: N = 902 [23.1%], missing at both baseline and follow-up: N = 848 [21.7%]), we ran the model again with participants providing HOMA-IR at least at one time point (N = 3 052) and with participants providing complete information on all variables used in the analysis (N = 1 319).

Results

The characteristics of the analysis group are displayed in Table 1. At baseline, the percentages of participants with a waist circumference and/or HOMA-IR value at or above the 90th age- and sex-specific reference percentile were 26.5% and 17.2%, respectively [29, 32]. Children above the 90th percentile of waist circumference and/or HOMA-IR were on average older, slept shorter at night and had less educated parents (S2 Table).

In an unadjusted analysis, baseline SLEEP z-score was negatively correlated with baseline WAIST z-score, baseline HOMA z-score and WAIST z-score at follow-up but not with HOMA z-score at follow-up (S3 Table).

Cross-sectional and longitudinal results of the path model on the association of nocturnal sleep duration with waist circumference and insulin resistance for the whole group and stratified by age are displayed in Fig 3 (direct effects) and Table 2 (indirect and total effects).

Cross-sectionally, baseline SLEEP z-score showed a negative direct effect on baseline WAIST z-score (unstandardised effect estimate -0.120; 95% confidence interval [-0.167; -0.073]) but no direct effect on baseline HOMA z-score (Fig 3). However, baseline SLEEP z-score exerted a negative indirect effect on baseline HOMA z-score through baseline WAIST z-score (-0.042 [-0.058; -0.025]), i.e. baseline HOMA z-score is expected to decrease on average by 0.042 units for every unit increase in baseline SLEEP z-score mediated through baseline WAIST z-score (Table 2). The total effect of baseline SLEEP z-score on baseline HOMA z-score was negative but did not reach statistical significance.

Longitudinally, there was no direct effect of baseline SLEEP z-score on WAIST z-score at follow-up (Fig 3) but a negative indirect effect through baseline WAIST z-score (-0.095 [-0.131; -0.058]) (Table 2). This indirect effect was the main driver of the strong total effect of baseline SLEEP z-score on WAIST z-score at follow-up (-0.108 [-0.158; -0.057]) (Table 2). Further, baseline SLEEP z-score exerted no direct effect on HOMA z-score at follow-up. However, we observed a negative indirect effect of baseline SLEEP z-score through both baseline WAIST z-score and WAIST z-score at follow-up on HOMA z-score at follow-up (-0.028 [-0.040; -0.016]) (Table 2). The total effect of baseline SLEEP z-score on HOMA z-score at follow-up was negative although not statistically significant. All other indirect effects investigated within the model were small in magnitude and mostly not statistically significant.

The age-stratified analysis (Fig 3, Table 2) showed that in both pre-school and school children effect estimates of baseline SLEEP z-score on baseline WAIST z-score and WAIST z-

Table 1. Descriptive characteristics of the study population (N = 3 900).

Sociodemographic information and covariates[a]	
Age, mean (SD)	7.7 (1.9)
Girls, N (%)	1 980 (50.8)
Country, N (%)	
Italy	772 (19.8)
Estonia	805 (20.6)
Cyprus	475 (12.2)
Belgium	97 (2.5)
Sweden	509 (13.1)
Germany	422 (10.8)
Hungary	534 (13.7)
Spain	286 (7.3)
Highest level of parental education, N (%)[b]	
Low	181 (4.6)
Medium	1 639 (42.0)
High	2 080 (53.3)
Pubertal status (pubertal), N (%)	1 484 (38.1)
Well-being score, median (IQR)	40 (36.5–43)
Napping (yes), N (%)	828 (21.2)
Average napping time (minutes per day), median (IQR)[c]	83 (43–103)
Sleep duration, waist circumference and HOMA-IR at baseline (2009/10)	
Nocturnal sleep duration (hours), mean (SD)	
Weekly average	9.80 (0.78)
Weekday	9.67 (0.86)
Weekend day	10.12 (0.98)
Waist circumference (cm), median (IQR)	56.2 (52.2–62.0)
Waist circumference $\geq 90^{th}$ percentile, N (%)[d]	1 032 (26.5)
HOMA-IR, median (IQR)[e]	1.11 (0.71–1.63)
HOMA-IR $\geq 90^{th}$ percentile, N (%)[d,e]	382 (17.2)
Sleep duration, waist circumference and HOMA-IR at follow-up (2013/14)	
Nocturnal sleep duration (hours), mean (SD)	
Weekly average	9.14 (0.93)
Weekday	8.86 (1.04)
Weekend day	9.86 (1.27)
Waist circumference (cm), median (IQR)	64.6 (59.0–72.0)
Waist circumference $\geq 90^{th}$ percentile, N (%)[d]	1 157 (29.7)
HOMA-IR, median (IQR)[f]	1.24 (0.81–1.88)
HOMA-IR $\geq 90^{th}$ percentile, N (%)[d,f]	368 (17.1)

HOMA-IR homeostasis model assessment for insulin resistance, *IQR* interquartile range, *SD* standard deviation

[a] all measured at baseline (2009/10) except pubertal status which was measured at follow-up (2013/14)

[b] categorisation according to the "International Standard Classification of Education" (levels 0–2 = low, 3–5 = medium and 6–8 = high) [34]

[c] children not having a nap were not considered in this statistic (N = 3 072)

[d] based on reference values derived from data of normal weight children participating in the IDEFICS/I.Family studies according to previously described methods [29, 30, 32]

[e] missing: 1 679

[f] missing: 1 750

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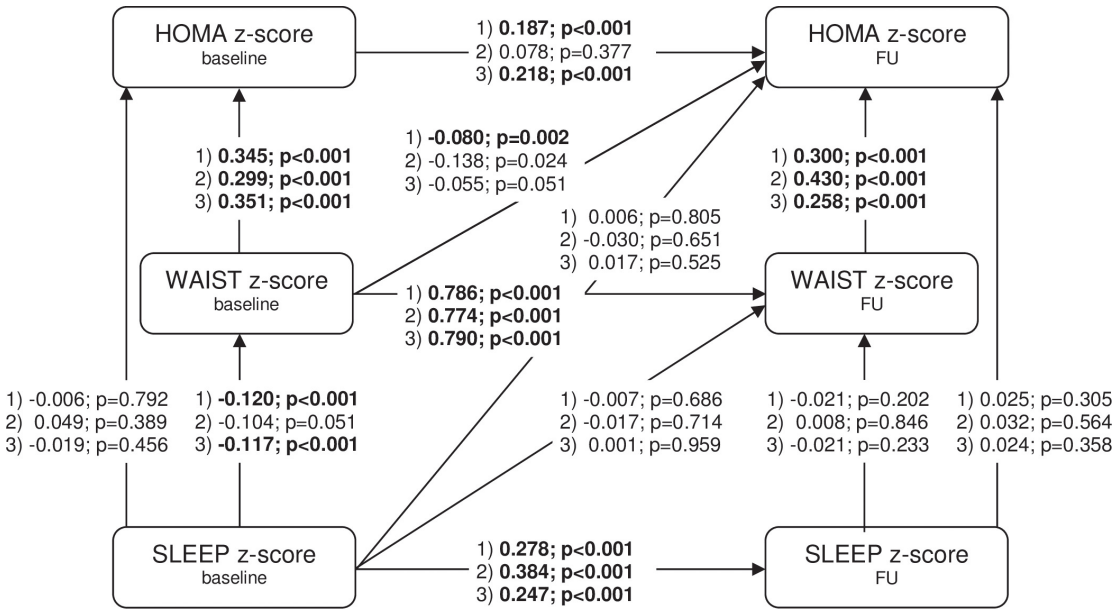

Fig 3. Path model for the association of nocturnal sleep duration (SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment (HOMA) for insulin resistance z-score adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status (at follow-up [FU]) and follow-up time: Unstandardised direct effect estimates and p-values; 1) = Whole group (N = 3 900), 2) = Pre-school children (N = 863), 3) = School children (N = 3 037); baseline: 2009/10, FU: 2013/14; bold figures indicate a false discovery rate (FDR) <0.05, an FDR adjusted significance value corresponds to $\alpha_{adj} = 0.019$.

https://doi.org/10.1371/journal.pone.0235049.g003

score at follow-up generally pointed to the same direction though failing to reach statistical significance in the smaller sample of pre-school children. In school children, effect sizes of baseline SLEEP z-score on baseline HOMA z-score and HOMA z-score at follow-up were similar to those of the whole group. Overall, also the age-stratified models suggested a predominantly indirect effect of baseline SLEEP z-score on baseline HOMA z-score and HOMA z-score at follow-up through the WAIST z-score(s).

In the sensitivity analysis with additional adjustment for lifestyle factors results remained almost unchanged (S1 Fig and S4 Table). There were no major differences when distinguishing between weekday and weekend nocturnal sleep duration with the exception that there was a strong negative total effect of baseline WD SLEEP z-score on baseline HOMA z-score that was not observed for baseline WE SLEEP z-score (S2 and S3 Figs, S5 and S6 Tables). Models based on samples with varying percentages of missing values on HOMA-IR yielded similar results and did not lead to different conclusions (S4 and S5 Figs, S7 and S8 Tables).

Discussion

To our knowledge, this is the first study quantifying the potential mediating effect of abdominal obesity in the association between nocturnal sleep duration and insulin resistance. Cross-sectionally, we found longer sleep duration to be associated with lower waist circumference and further showed sleep duration to be indirectly associated with HOMA-IR through waist circumference. In other words, our results suggest that some of the direct effect of baseline sleep duration on baseline waist circumference is transmitted onto HOMA-IR. Longer

Table 2. Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score.

	Whole group (N = 3 900)		*Pre-school children (N = 863)*		*School children (N = 3 037)*	
	Unst. estimate	*p-value*	*Unst. estimate*	*p-value*	*Unst. estimate*	*p-value*
Indirect effects						
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	**-0.042**	**<0.001**	-0.031	0.053	**-0.041**	**<0.001**
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	**-0.095**	**<0.001**	-0.081	0.051	**-0.092**	**<0.001**
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	-0.006	0.204	0.003	0.846	-0.005	0.237
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.687	-0.008	0.715	0.000	0.959
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	**0.010**	**0.010**	0.014	0.142	0.006	0.079
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.001	0.793	0.004	0.538	-0.004	0.460
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.007	0.308	0.012	0.566	0.006	0.360
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	**-0.028**	**<0.001**	-0.035	0.060	**-0.024**	**<0.001**
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.204	0.001	0.847	-0.001	0.239
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	**-0.008**	**0.001**	-0.002	0.431	**-0.009**	**<0.001**
Total effects						
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.048	0.052	0.018	0.756	-0.060	0.027
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	**-0.108**	**<0.001**	-0.095	0.130	**-0.097**	**0.001**
SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.018	0.469	-0.043	0.547	-0.008	0.753

Unst. unstandardised; *SLEEP* nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status (at FU) and follow-up time; bold figures indicate a false discovery rate (FDR) <0.05, an FDR adjusted significance value corresponds to $\alpha_{adj} = 0.019$

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baseline sleep duration was also indirectly associated with lower HOMA-IR at follow-up through both baseline waist circumference and waist circumference at follow-up. This mediating role of waist circumference agrees with the well-documented link between sleep duration and abdominal obesity and the predicting role of obesity in the development of insulin resistance in childhood [4, 13, 48]. In our young study population, we did not find evidence for an association between sleep duration and HOMA-IR independent of waist circumference.

Effect sizes of the associations between nocturnal sleep duration and waist circumference and HOMA-IR, respectively, are similar to other studies using subjective measures of sleep duration [49, 50]. For instance, our cross-sectional results suggest that in comparison to a 9-year old girl who sleeps 8.5 hours/night with a waist circumference of 58.0 cm and a HOMA-IR value of 1.32, we would expect a girl of the same age who sleeps 10.2 hours/night to have a waist circumference of 56.8 cm and a HOMA-IR value of 1.23, the lower HOMA-IR value assumed to be primarily induced indirectly through the lower waist circumference. These effect sizes appear small. However, it has to be considered that sleep duration is only one among several factors potentially influencing abdominal obesity and insulin resistance in children.

Most cross-sectional studies observed similar associations between average and/or weekday sleep duration and both waist circumference and HOMA-IR as we did. A Danish study in 8–11 year old children (N = 473) found average nocturnal sleep duration to be negatively associated with both waist circumference and HOMA-IR adjusting for physical activity and sedentary time [21]. The association with HOMA-IR became non-significant after additional adjustment for fat mass index, indicating an indirect effect through fat mass [21]. A German study found total weekday sleep duration (nocturnal sleep duration and napping time

combined) to be negatively associated with waist circumference and also HOMA-IR in girls [23]. Comparably to the study by Hjorth et al. [21] and to our results, the latter association was dependent on waist circumference [23]. An association between short weekday nocturnal sleep duration and higher HOMA-IR dependent on abdominal obesity was also observed in an ethnically diverse sample of US American adolescents; the association between long weekday nocturnal sleep duration and higher HOMA-IR remained after adjustment for abdominal obesity [22]. In another study in 829 US American adolescents, objectively measured sleep duration was negatively associated with waist circumference [19]. In that study, the association of sleep duration with HOMA-IR was also negative, although not statistically significant, and was further attenuated after adjustment for BMI [19]. Contrary to our findings, in a study in 14–19 year old US American adolescents (N = 245), both average and weekday nocturnal sleep duration were found to be associated with HOMA-IR, independent of obesity indices [51]. The use of an objective method for the assessment of sleep duration but also differences in participant characteristics (e.g. inclusion of both black and white adolescents, higher proportion of overweight participants) may explain these differing results. Lastly, in contrast to our results and those of the majority of previous studies, no association between total weekday sleep duration and HOMA-IR (unadjusted for weight status) was observed in 12–17 year old adolescents participating in the European HELENA study [52].

Longitudinal studies on the associations of sleep duration with waist circumference and HOMA-IR are scarce and yielded inconsistent results. In US American children, chronic insufficient average sleep duration, determined by repeated measurements of total sleep duration from the age of 6 months to 7 years, was found to be associated with both a higher waist circumference and higher HOMA-IR at the age of 7 years (N = 652) [20]. The association with HOMA-IR became statistically non-significant after adjustment for BMI being in line with the predominantly indirect effect of baseline nocturnal sleep duration on HOMA-IR at follow-up that we observed [20]. The higher number of repeated measurements in the same subjects in that study may have resulted in a more accurate measure of habitual sleep duration enhancing the likelihood to detect also small effects. The study by Hjorth et al. [21] also included a longitudinal analysis (N = 486) showing that change in average nocturnal sleep duration over a 200-day period was not associated with change in waist circumference but with change in HOMA-IR [21]. The use of an objective method for sleep assessment, the shorter follow-up time and the different statistical analysis approach might be accountable for this discrepancy with our finding.

Strengths of our study include the large European sample and the standardised collection of questionnaire data, anthropometric measurements and biological samples in all study centres. In addition, as waist circumference and HOMA-IR are strongly dependent on age and sex, we standardised these parameters using recently developed reference values provided by the IDEFICS/I.Family cohort study based on a huge sample of normal weight children and adolescents from all over Europe. Furthermore, the use of path analysis allowed us to explore potential short and long term effects of nocturnal sleep duration on insulin resistance in one model. However, any causal interpretation of our results relies on strong structural assumptions. For instance, we assumed baseline sleep duration to influence baseline waist circumference, although the direction of the association cannot be determined given the cross-sectional data. Further, in agreement with the literature [5, 6] and existing epidemiological studies [22, 23] we assumed abdominal obesity to mediate the association between nocturnal sleep duration and insulin resistance. Because insulin may support the onset and development of obesity [53], some researchers suggested the opposite direction, i.e. insulin resistance to mediate the association between nocturnal sleep duration and obesity [8, 9, 54]. We did not follow this hypothesis because population-based studies in children on the role of insulin resistance as a risk

factor for obesity have yielded inconsistent results [55]. Moreover, we assumed associations between sleep duration and waist circumference and HOMA-IR, respectively, to be linear. Although a few studies reported u-shaped associations [22, 56], the majority of previous studies in pediatric populations indicates that associations are more likely to be linear [13, 57]. Besides, we conducted additional analyses and did not find evidence for u-shaped associations between sleep duration and both waist circumference and HOMA-IR (S9 Table). Approximately 44% of the children in our study sample lived in the intervention regions. The intervention for the prevention of childhood obesity was implemented between 2007/08 and 2009/10. The present analysis comprised only data collected after the intervention was completed and included children from both regions. The intervention did not reveal any relevant effects on sleep duration, waist circumference and HOMA-IR [58, 59]. However, to preclude any potential effect of the intervention on our results, we conducted additional analyses adjusting the path model for residence in the intervention vs. control region as well as stratifying the model by residence in the intervention vs. control region. This did not markedly change our results (S6 and S7 Figs, S10 and S11 Tables). Another limitation of our study is that sleep duration was measured subjectively by questionnaires. Actigraphy has been described as the gold standard for sleep research under natural conditions but was not feasible in our large study for logistical and cost reasons [60]. It has been shown that sleep duration is usually overestimated when obtained by questionnaires in comparison to Actigraphs [61, 62]. Resulting non-differential measurement error of sleep duration may have led to an underestimation of effect sizes. Pubertal status was self-reported based on menarche and voice mutation. Information on breast (girls) and pubic hair (boys) development based on Tanner stages, which may be considered more accurate, was only available for a subsample (N = 2 999). However, adjustment for Tanner stage instead of menarche/voice mutation in this subsample did not alter results (S8 Fig and S12 Table). We used waist circumference as a surrogate marker for abdominal obesity that has been found to be highly correlated with visceral adipose tissue measured by magnetic resonance imaging, which is considered a gold standard measure [14]. Further, we used HOMA-IR as a surrogate marker for insulin resistance that has been validated against the hyperinsulinemic-euglycemic clamp, the gold standard measure for determining insulin resistance, and the frequently sampled intravenous glucose tolerance test, which is also considered a valid measure, with good results [63, 64]. The use of waist circumference and HOMA-IR in large-scale epidemiological studies is common and accepted because the superior gold standard measures are time consuming and burdensome for participants and hence not feasible in large population-based studies like ours, particularly not in children [4]. This choice of assessment instruments may introduce random measurement error that may attenuate the strength of any association, but this would hardly reverse the direction of any association observed. Lastly, a high proportion of children did not participate at follow-up. However, in an earlier analysis of data from the IDEFICS study overweight status, but not short nocturnal sleep duration, appeared to be a determinant of attrition [65]. Therefore, our estimates would not be biased by such a selection effect. Furthermore, the analysis method we applied allowed us to make efficient use of the existing data as even participants with missing values on some variables could be included.

Conclusions

In conclusion, our study confirms findings of previous studies showing a cross-sectional association between longer sleep duration and lower waist circumference in a young population. The hypothesis of an association between short sleep duration and insulin resistance independent of abdominal obesity was not confirmed. However, longer sleep duration was found to be

indirectly associated with lower HOMA-IR through lower waist circumference in both cross-sectional and longitudinal analyses. Hence, our results suggest that longer nocturnal sleep duration may contribute to lower levels of insulin resistance by exerting beneficial effects on abdominal obesity.

Supporting information

S1 Table. Model fit indices.
(DOCX)

S2 Table. Descriptive characteristics of the study population at baseline by abdominal obesity and insulin resistance status at baseline.
(DOCX)

S3 Table. Pearson correlation coefficients and p-values among baseline SLEEP z-score, baseline WAIST z-score, baseline HOMA z-score, WAIST z-score at follow-up and HOMA z-score at follow-up.
(DOCX)

S4 Table. Sensitivity analysis (additional adjustment for lifestyle factors).
(DOCX)

S5 Table. Sensitivity analysis (weekday nocturnal sleep duration).
(DOCX)

S6 Table. Sensitivity analysis (weekend nocturnal sleep duration).
(DOCX)

S7 Table. Sensitivity analysis (complete case analysis).
(DOCX)

S8 Table. Sensitivity analysis (HOMA at baseline and/or follow-up).
(DOCX)

S9 Table. Additional analysis for investigating potential u-shaped associations.
(DOCX)

S10 Table. Sensitivity analysis (additional adjustment for residence in the intervention vs. control region).
(DOCX)

S11 Table. Sensitivity analysis (stratified by residence in the intervention vs. control region).
(DOCX)

S12 Table. Sensitivity analysis (adjustment for either Tanner stage or menarche/voice mutation).
(DOCX)

S1 Fig. Sensitivity analysis (additional adjustment for lifestyle factors).
(DOCX)

S2 Fig. Sensitivity analysis (weekday nocturnal sleep duration).
(DOCX)

S3 Fig. Sensitivity analysis (weekend nocturnal sleep duration).
(DOCX)

S4 Fig. Sensitivity analysis (complete case analysis).
(DOCX)

S5 Fig. Sensitivity analysis (HOMA at baseline and/or follow-up [FU]).
(DOCX)

S6 Fig. Sensitivity analysis (additional adjustment for residence in the intervention vs. control region).
(DOCX)

S7 Fig. Sensitivity analysis (stratified by residence in the intervention vs. control region).
(DOCX)

S8 Fig. Sensitivity analysis (adjustment for either Tanner stage or menarche/voice mutation).
(DOCX)

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SUPPLEMENTARY MATERIAL

Paper 3

S1 Table: Model fit indices

	Main model - whole group N=3 900	**Main model - pre-school children** N=863	**Main model - school children** N=3 037	**Sensitivity analysis - additional adjustment for lifestyle factors** N=3 239	**Sensitivity analysis - weekday nocturnal sleep duration** N=3 900	**Sensitivity analysis - weekend nocturnal sleep duration** N=3 900
Chi-Square Test of Model Fit						
Degrees of freedom	3	3	3	3	3	3
P-Value	0.17	0.08	0.68	0.09	0.17	0.13
Comparative Fit Index	1.00	1.00	1.00	1.00	1.00	1.00
Tucker-Lewis Index	0.99	0.91	1.01	0.97	0.99	0.99
Root Mean Square Error of Approximation	0.013	0.038	<0.001	0.019	0.013	0.015

	Sensitivity analysis - complete case analysis - whole group N=1 319	**Sensitivity analysis - complete case analysis - pre-school children** N=234	**Sensitivity analysis - complete case analysis - school children** N=1 085	**Sensitivity analysis - HOMA-IR at baseline and/or follow-up - whole group** N=3 052	**Sensitivity analysis - HOMA-IR at baseline and/ or follow-up - pre-school children** N=594	**Sensitivity analysis - HOMA-IR at baseline and/or follow-up - school children** N=2 458
Chi-Square Test of Model Fit						
Degrees of freedom	3	3	3	3	3	3
P-Value	0.27	0.21	0.36	0.14	0.07	0.29
Comparative Fit Index	1.00	1.00	1.00	1.00	1.00	1.00
Tucker-Lewis Index	0.99	0.88	1.00	0.99	0.86	1.00
Root Mean Square Error of Approximation	0.015	0.046	0.009	0.016	0.048	0.010

HOMA-IR homeostasis model assessment for insulin resistance

S2 Table: Descriptive characteristics of the study population at baseline by abdominal obesity and insulin resistance status at baseline

	Waist circumference <90th percentile[a]	**Waist circumference ≥90th percentile[a]**	**HOMA-IR <90th percentile[a]**	**HOMA-IR ≥90th percentile[a]**
	N=2 868	**N=1 032**	**N=1 839**	**N=382**
Age, mean (SD)	7.5 (1.9)	8.2 (1.7)	7.8 (1.9)	8.1 (1.8)
Girls, N (%)	1 454 (50.7)	526 (51.0)	911 (49.5)	206 (53.9)
Country, N (%)				
Italy	392 (13.7)	380 (36.8)	334 (18.2)	143 (37.4)
Estonia	656 (22.9)	149 (14.4)	432 (23.5)	78 (20.4)
Cyprus	313 (10.9)	162 (15.7)	83 (4.5)	17 (4.5)
Belgium	88 (3.1)	9 (0.9)	79 (4.3)	4 (1.1)
Sweden	426 (14.9)	83 (8.0)	255 (13.9)	24 (6.3)
Germany	358 (12.5)	64 (6.2)	140 (7.6)	12 (3.1)
Hungary	403 (14.1)	131 (12.7)	306 (16.6)	84 (22.0)
Spain	232 (8.1)	54 (5.2)	210 (11.4)	20 (5.2)
Highest level of parental education, N (%)[b]				
Low	84 (2.9)	97 (9.4)	71 (3.9)	35 (9.2)
Medium	1 119 (39.0)	520 (50.4)	743 (40.4)	189 (49.5)
High	1 665 (58.1)	415 (40.2)	1 025 (55.7)	158 (41.4)
Well-being score, median (IQR)	40 (37-43)	39 (36-42)	40 (37-43)	39.5 (36-42)
Napping (yes), N (%)	655 (22.8)	173 (16.8)	370 (20.1)	81 (21.2)
Average napping time (minutes per day), median (IQR)[c]	86 (43-103)	64 (34-90)	86 (43-99)	86 (43-90)
Nocturnal sleep duration (hours), mean (SD)				
Weekly average	9.86 (0.80)	9.61 (0.71)	9.82 (0.76)	9.65 (0.70)
Weekday	9.74 (0.87)	9.48 (0.77)	9.69 (0.83)	9.47 (0.75)
Weekend day	10.18 (0.98)	9.96 (0.96)	10.14 (0.95)	10.08 (0.99)

HOMA-IR homeostasis model assessment for insulin resistance, *IQR* interquartile range, *SD* standard deviation

[a] based on reference values derived from data of normal weight children participating in the IDEFICS/I.Family studies according to previously described methods [1-3]

[b] categorisation according to the "International Standard Classification of Education" (levels 0-2=low, 3-5=medium and 6-8=high) [4]

[c] children not having a nap were not considered in this statistic (N=3 072)

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S3 Table: Pearson correlation coefficients and p-values among baseline SLEEP z-score, baseline WAIST z-score, baseline HOMA z-score, WAIST z-score at follow-up and HOMA z-score at follow-up

	SLEEP $\mathbf{z\text{-}score_{baseline}}$	**WAIST** $\mathbf{z\text{-}score_{baseline}}$	**HOMA** $\mathbf{z\text{-}score_{baseline}}$	**WAIST** $\mathbf{z\text{-}score_{FU}}$	**HOMA** $\mathbf{z\text{-}score_{FU}}$
SLEEP $\mathbf{z\text{-}score_{baseline}}$	1.00				
WAIST $\mathbf{z\text{-}score_{baseline}}$	-0.141	1.00			
	<0.001				
	N=3 900				
HOMA $\mathbf{z\text{-}score_{baseline}}$	-0.129	0.501	1.00		
	<0.001	<0.001			
	N=2 221	N=2 221			
WAIST $\mathbf{z\text{-}score_{FU}}$	-0.137	0.778	0.430	1.00	
	<0.001	<0.001	<0.001		
	N=3 900	N=3 900	N=2 221		
HOMA $\mathbf{z\text{-}score_{FU}}$	-0.027	0.313	0.325	0.410	1.00
	0.219	<0.001	<0.001	<0.001	
	N=2 150	N=2 150	N=1 319	N=2 150	

SLEEP nocturnal sleep duration, *HOMA* homeostasis model assessment for insulin resistance, *WAIST* waist circumference, *FU* follow-up

S4 Table: Sensitivity analysis (additional adjustment for lifestyle factors) - Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score

	Whole group (N=3 239)	
	Unst. estimate	*p-value*
Indirect effects		
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.035	<0.001
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.081	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	-0.007	0.125
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.685
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.007	0.039
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.001	0.815
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.007	0.368
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.023	0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.126
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.007	0.001
Total effects		
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.041	0.137
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.096	0.001
SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.006	0.829

Unst. unstandardised; *SLEEP* nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment for insulin resistance; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time, fruit and vegetable consumption (times/week), sports club physical activity (hours/week), duration of electronic media use (hours/week) (all at baseline), pubertal status (at FU) and follow-up time

S5 Table: Sensitivity analysis (weekday nocturnal sleep duration) - Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of weekday nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score

	Whole group (N=3 900)	
	Unst. estimate	*p-value*
Indirect effects		
WD SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.034	<0.001
WD SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.078	<0.001
WD SLEEP z-score$_{baseline}$ → WD SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	-0.007	0.129
WD SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	0.000	0.932
WD SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.008	0.015
WD SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.005	0.246
WD SLEEP z-score$_{baseline}$ → WD SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.005	0.442
WD SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.023	<0.001
WD SLEEP z-score$_{baseline}$ → WD SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.130
WD SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.006	0.001
Total effects		
WD SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.062	0.013
WD SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.084	0.001
WD SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.017	0.512

Unst. unstandardised; *WD SLEEP* weekday nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment for insulin resistance; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country, highest educational level of parents, well-being score, weekday napping time (all at baseline), pubertal status (at FU) and follow-up time

S6 Table: Sensitivity analysis (weekend nocturnal sleep duration) - Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of weekend nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score

	Whole group (N=3 900)	
	Unst. estimate	*p-value*
Indirect effects		
WE SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.035	<0.001
WE SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.080	<0.001
WE SLEEP z-score$_{baseline}$ → WE SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	-0.001	0.763
WE SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.006	0.194
WE SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.008	0.011
WE SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.006	0.127
WE SLEEP z-score$_{baseline}$ → WE SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.005	0.305
WE SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.024	<0.001
WE SLEEP z-score$_{baseline}$ → WE SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	0.000	0.763
WE SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.007	0.001
Total effects		
WE SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.003	0.908
WE SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.101	<0.001
WE SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.012	0.606

Unst unstandardised; *WE SLEEP* weekend nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment for insulin resistance; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country, highest educational level of parents, well-being score, weekend napping time (all at baseline), pubertal status (at FU) and follow-up time

S7 Table: Sensitivity analysis (complete case analysis) - Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score

	Whole group (N=1 319)		*Pre-school children (N=234)*		*School children (N=1 085)*	
	Unst. estimate	*p-value*	*Unst. estimate*	*p-value*	*Unst. estimate*	*p-value*
Indirect effects						
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.060	<0.001	-0.077	0.036	-0.057	0.001
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.126	<0.001	-0.182	0.035	-0.119	0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	-0.006	0.411	0.017	0.634	-0.007	0.324
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	0.001	0.921	-0.008	0.801	0.003	0.695
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.009	0.121	0.005	0.782	0.008	0.177
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.003	0.639	0.008	0.468	-0.007	0.323
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.003	0.766	0.030	0.319	0.000	0.979
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.033	<0.001	-0.055	0.053	-0.029	0.002
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.409	0.005	0.642	-0.002	0.325
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.011	0.002	-0.006	0.381	-0.012	0.003
Total effects						
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.074	0.026	0.014	0.872	-0.088	0.014
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.129	0.003	-0.191	0.120	-0.113	0.016
SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.022	0.502	-0.085	0.389	-0.010	0.767

Unst. unstandardised; *SLEEP* nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment for insulin resistance; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status (at FU) and follow-up time

S8 Table: Sensitivity analysis (HOMA at baseline and/or follow-up) - Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score

	Whole group (N=3 052)		*Pre-school children (N=594)*		*School children (N=2 458)*	
	Unst. estimate	*p-value*	*Unst. estimate*	*p-value*	*Unst. estimate*	*p-value*
Indirect effects						
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.042	<0.001	-0.030	0.107	-0.043	<0.001
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.096	<0.001	-0.080	0.106	-0.096	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	-0.003	0.586	0.013	0.468	-0.003	0.478
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.789	0.002	0.931	0.000	0.937
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.010	0.013	0.014	0.191	0.007	0.085
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.001	0.793	0.004	0.538	-0.004	0.460
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.007	0.309	0.012	0.567	0.006	0.361
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.029	<0.001	-0.035	0.116	-0.025	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.001	0.585	0.006	0.474	-0.001	0.478
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.008	0.001	-0.002	0.450	-0.009	0.001
Total effects						
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.048	0.054	0.019	0.745	-0.061	0.027
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.104	<0.001	-0.062	0.414	-0.101	0.002
SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.017	0.501	-0.030	0.691	-0.009	0.727

Unst. unstandardised; *SLEEP* nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment for insulin resistance; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status (at FU) and follow-up time

S9 Table: Additional analysis for investigating potential u-shaped associations - Multilevel regression models investigating the cross-sectional associations between baseline sleep duration categories (sleep duration z-score according to quartiles), baseline waist circumference z-score and baseline homeostasis model assessment for insulin resistance z-score

	WAIST z-score$_{baseline}$ (N=3 900)			HOMA z-score$_{baseline}$ (N=2 221)*		
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*
SLEEP z-score$_{baseline}$						
1st quartile (N=959)	0.206	0.077; 0.335	0.002	0.103	-0.029; 0.235	0.117
2nd quartile (N=992)	0.174	0.050; 0.299	0.007	0.037	-0.090; 0.163	0.546
3rd quartile (ref) (N=963)	0			0		
4th quartile (N=986)	-0.059	-0.191; 0.072	0.371	-0.025	-0.160; 0.110	0.702

SLEEP sleep duration*; WAIST* waist circumference; *HOMA* homeostasis model assessment; *CI* confidence interval; Both models were adjusted for age, sex, country, highest educational level of parents, napping time and well-being score (all at baseline) and pubertal status (at follow-up) and included a random effect for family affiliation; *missing: 1 679 (1st quartile SLEEP z-score$_{baseline}$: 428, 2nd quartile: 434, 3rd quartile: 356, 4th quartile: 461)

S10 Table: Sensitivity analysis (additional adjustment for residence in the intervention vs. control region) - Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score

	*Whole group (N=3 900)**	
	Unst. estimate	*p-value*
Indirect effects		
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.042	<0.001
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.094	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	-0.006	0.242
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	0.001	0.885
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.008	0.030
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.001	0.769
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.006	0.417
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.028	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.242
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.008	0.001
Total effects		
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.050	0.061
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.096	<0.001
SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.023	0.403

Unst. unstandardised; *SLEEP* nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment for insulin resistance; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time, indicator for residence in the intervention vs. control region (all at baseline), pubertal status (at FU) and follow-up time; *children not participating in 2007/08 (N=570) were excluded from this analysis

S11 Table: Sensitivity analysis (stratified by residence in the intervention vs. control region) - Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score

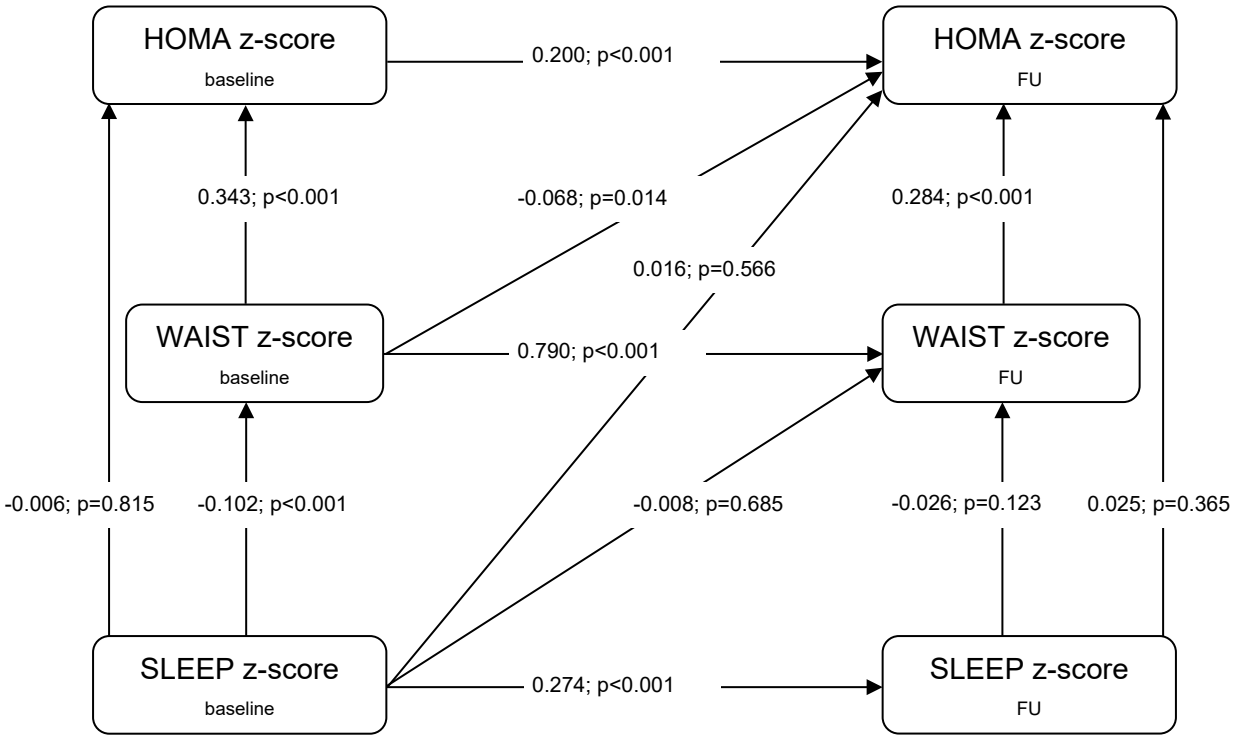
	*Whole group (N=3 330)**		*Children living in intervention region (N=1 703)**		*Children living in control region (N=1 627)**	
	Unst. estimate	*p-value*	*Unst. estimate*	*p-value*	*Unst. estimate*	*p-value*
Indirect effects						
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.043	<0.001	-0.038	0.008	-0.048	<0.001
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.094	<0.001	-0.080	0.008	-0.109	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	-0.006	0.243	-0.005	0.484	-0.008	0.239
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	0.001	0.904	-0.003	0.722	0.002	0.859
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.009	0.029	0.000	0.955	0.022	0.005
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.001	0.763	-0.003	0.510	0.001	0.946
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.007	0.365	0.019	0.121	-0.005	0.516
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.028	<0.001	-0.021	0.012	-0.039	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.002	0.243	-0.001	0.483	-0.003	0.240
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.008	0.001	-0.006	0.062	-0.011	0.002
Total effects						
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.050	0.059	-0.061	0.094	-0.045	0.227
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.097	<0.001	-0.096	0.018	-0.112	0.003
SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.021	0.449	-0.037	0.399	-0.003	0.923

Unst. unstandardised; *SLEEP* nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment for insulin resistance; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country (in the model using data of children living in the intervention region Hungary and Germany were collapsed into one category because of estimation problems), highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status (at FU) and follow-up time; *children not participating in 2007/08 (N=570) were excluded from this analysis

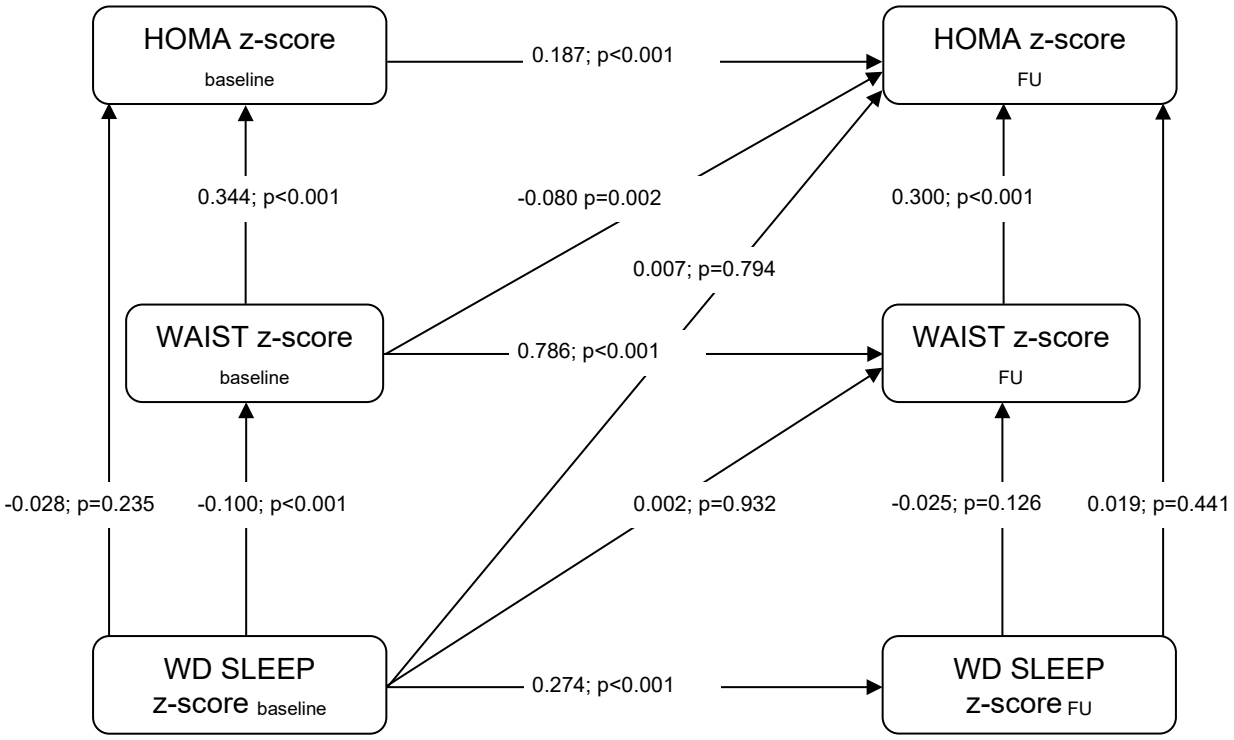
S12 Table: Sensitivity analysis (adjustment for either Tanner stage or menarche/voice mutation) - Indirect and total effects and corresponding p-values obtained from path analysis of cross-sectional and longitudinal associations of nocturnal sleep duration z-score with waist circumference z-score and homeostasis model assessment for insulin resistance z-score

	Adjustment for Tanner stages (N=2 999)		*Adjustment for menarche/voice mutation (N=2 999)*	
	Unst. estimate	*p-value*	*Unst. estimate*	*p-value*
Indirect effects				
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.042	<0.001	-0.043	<0.001
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.098	<0.001	-0.099	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$	0.001	0.915	0.000	0.924
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.001	0.806	-0.002	0.766
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.008	0.053	0.008	0.047
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	0.000	0.941	0.000	0.952
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → HOMA z-score$_{FU}$	0.006	0.443	0.005	0.488
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	-0.025	<0.001	-0.027	<0.001
SLEEP z-score$_{baseline}$ → SLEEP z-score$_{FU}$ → WAIST z-score$_{FU}$ → HOMA z-score$_{FU}$	0.000	0.915	0.000	0.924
SLEEP z-score$_{baseline}$ → WAIST z-score$_{baseline}$ → HOMA z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.007	0.002	-0.007	0.002
Total effects				
SLEEP z-score$_{baseline}$ → HOMA z-score$_{baseline}$	-0.044	0.132	-0.044	0.130
SLEEP z-score$_{baseline}$ → WAIST z-score$_{FU}$	-0.102	<0.001	-0.105	<0.001
SLEEP z-score$_{baseline}$ → HOMA z-score$_{FU}$	-0.004	0.880	-0.007	0.817

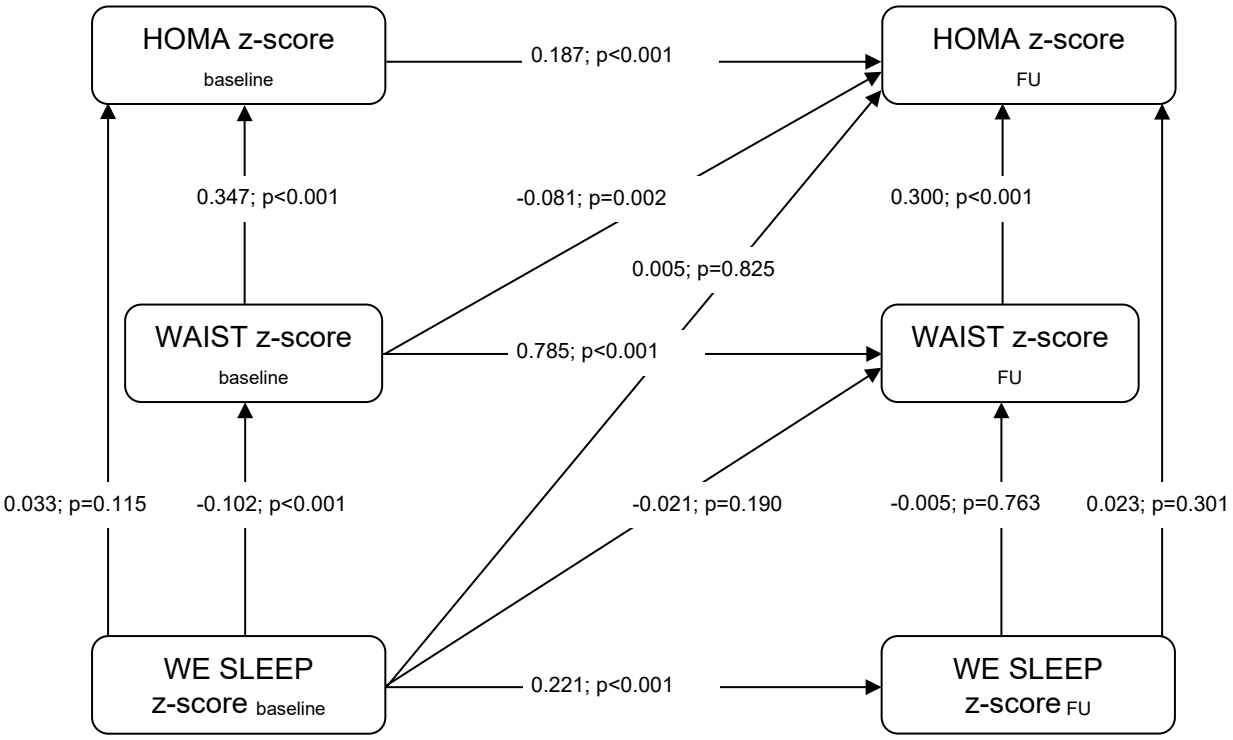
Unst. unstandardised; *SLEEP* nocturnal sleep duration; *WAIST* waist circumference; *HOMA* homeostasis model assessment for insulin resistance; baseline: 2009/10, follow-up (FU): 2013/14; Path model was adjusted for age, sex, country (in the model using data of children living in the intervention region Hungary and Germany were collapsed into one category because of estimation problems), highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status based on Tanner stages or menarche/voice mutation (at FU) and follow-up time



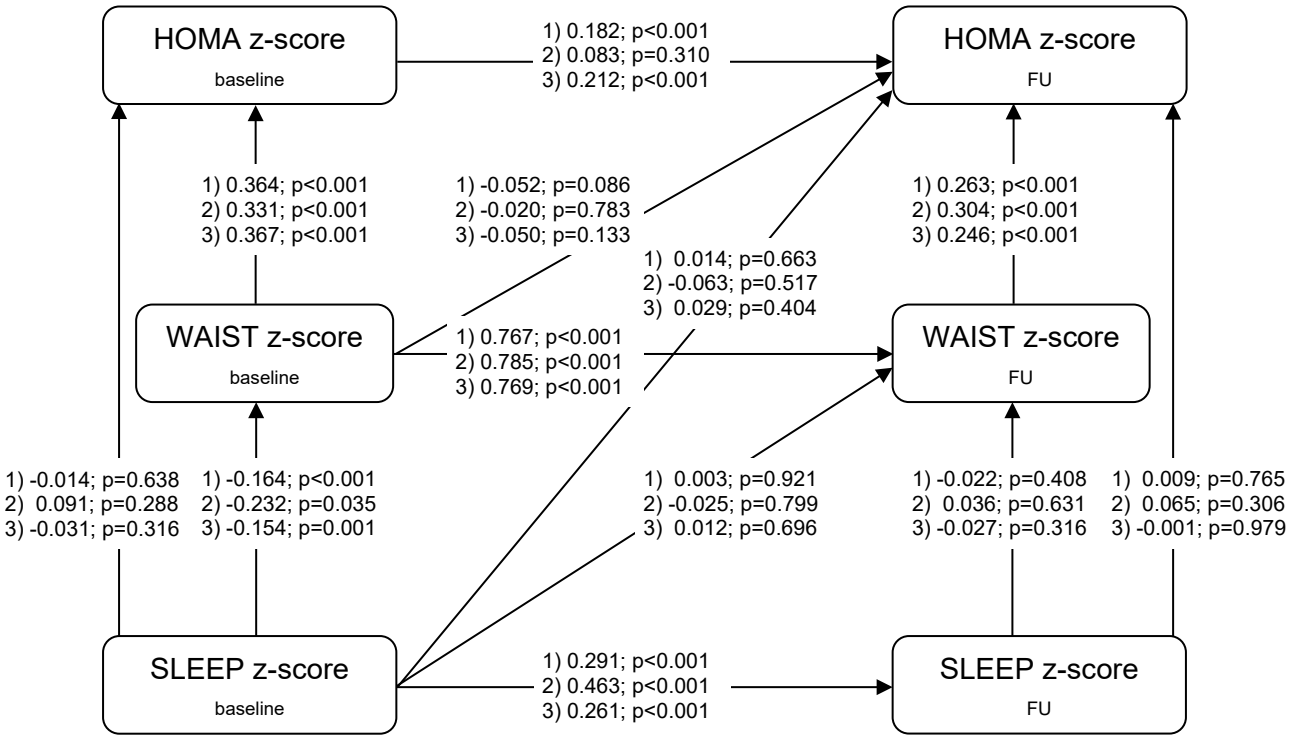
S1 Figure: Sensitivity analysis (additional adjustment for lifestyle factors) – Path model for the associations of nocturnal sleep duration (SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment for insulin resistance (HOMA) z-score adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time, fruit and vegetable consumption frequencies (times/week), sports club physical activity (hours/week), duration of electronic media use (hours/week) (all at baseline), pubertal status (at follow-up [FU]) and follow-up time: Unstandardised direct effect estimates and p-values (N=3 239); baseline: 2009/10, FU: 2013/14



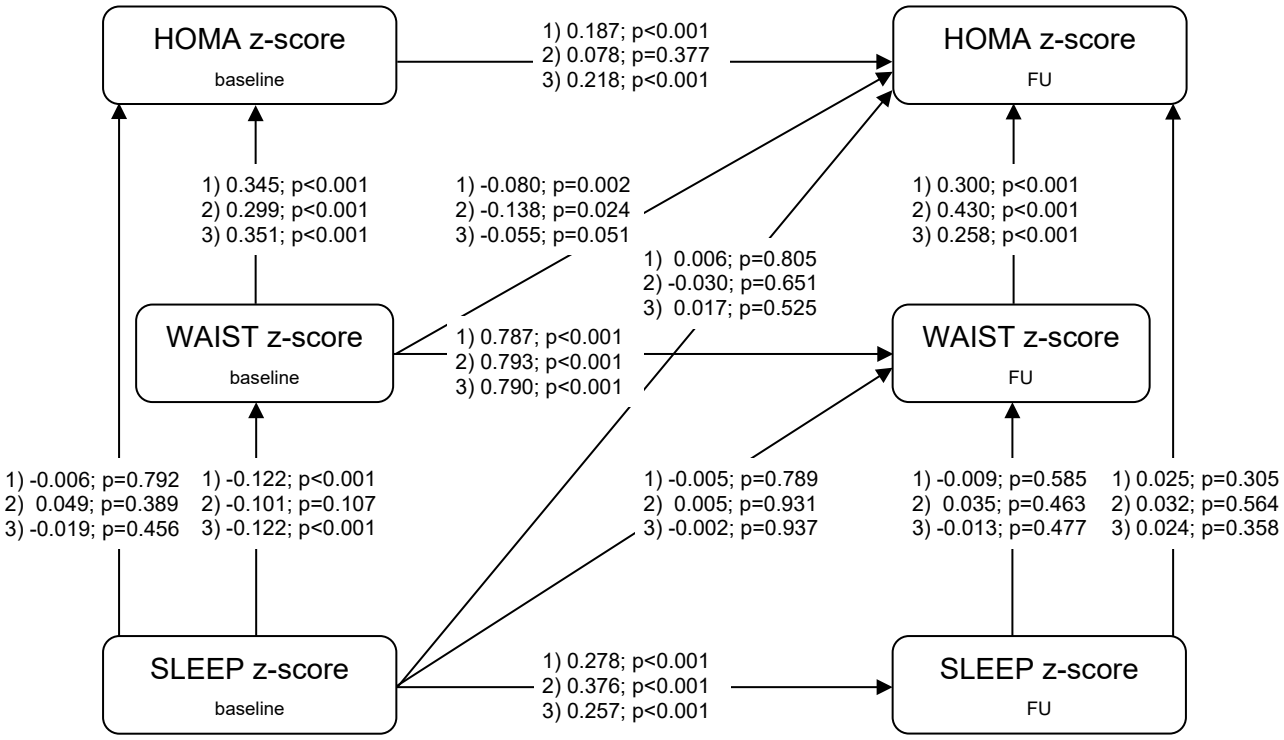
S2 Figure: Sensitivity analysis (weekday nocturnal sleep duration) - Path model for the association of weekday nocturnal sleep duration (WD SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment for insulin resistance (HOMA) z-score adjusted for age, sex, country, highest educational level of parents, well-being score, weekday napping time (all at baseline), pubertal status (at follow-up [FU]) and follow-up time: Unstandardised direct effect estimates and p-values (N=3 900); baseline: 2009/10, FU: 2013/14



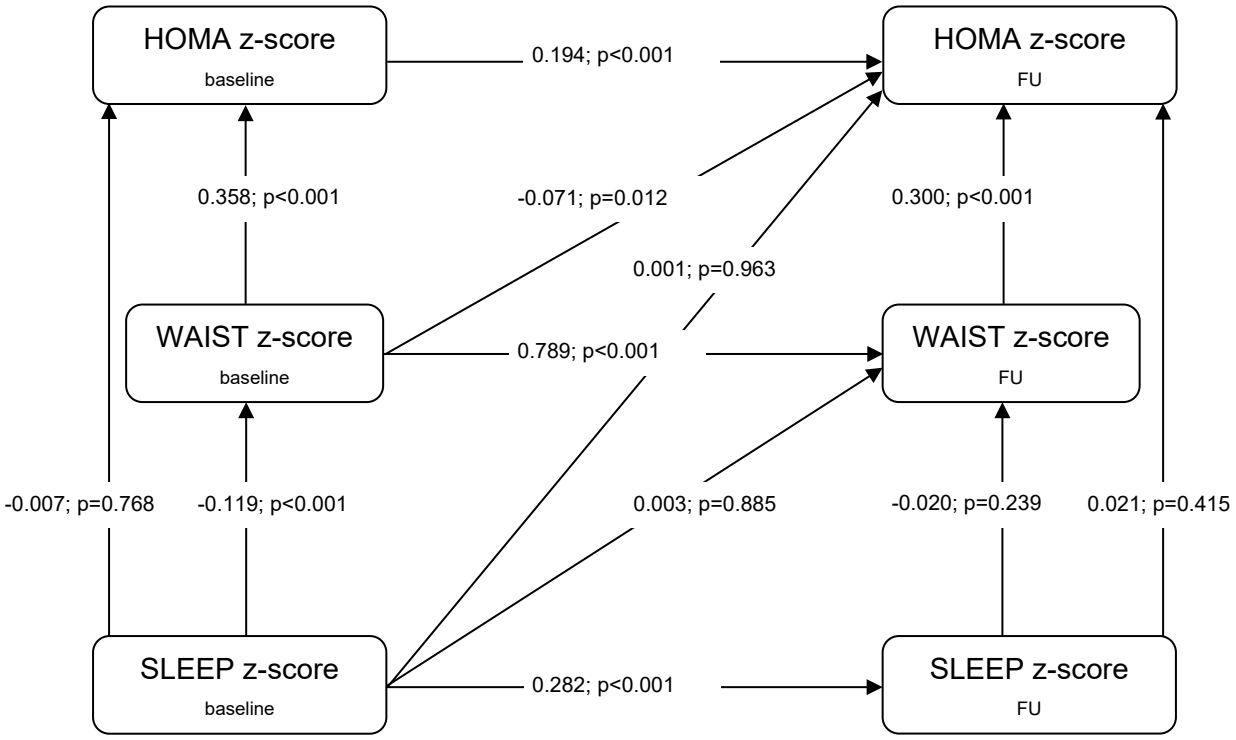
S3 Figure: Sensitivity analysis (weekend nocturnal sleep duration) - Path model for the association of weekend nocturnal sleep duration (WE SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment for insulin resistance (HOMA) z-score adjusted for age, sex, country, highest educational level of parents, well-being score, weekend napping time (all at baseline), pubertal status (at follow-up [FU]) and follow-up time: Unstandardised direct effect estimates and p-values (N=3 900); baseline: 2009/10, FU: 2013/14



S4 Figure: Sensitivity analysis (complete case analysis) - Path model for the association of nocturnal sleep duration (SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment for insulin resistance (HOMA) z-score adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status (at follow-up [FU]) and follow-up time: Unstandardised direct effect estimates and p-values; 1) = Whole group (N=1 319), 2) = Pre-school children (N=234), 3) = School children (N=1 085); baseline: 2009/10, FU: 2013/14

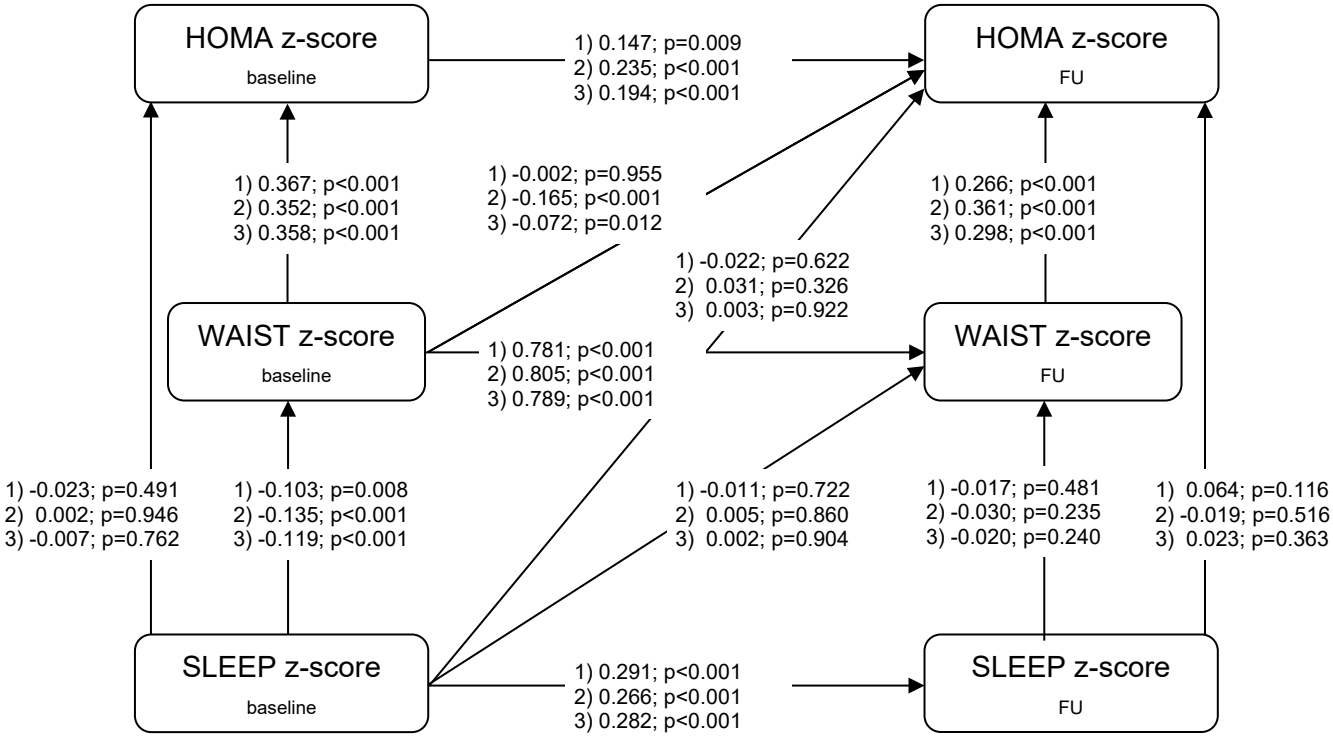


S5 Figure: Sensitivity analysis (HOMA at baseline and/or follow-up [FU]) - Path model for the association of nocturnal sleep duration (SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment for insulin resistance (HOMA) z-score adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status (at FU) and follow-up time: Unstandardised direct effect estimates and p-values; 1) = Whole group (N=3 052), 2) = Pre-school children (N=594), 3) = School children (N=2 458); baseline: 2009/10, FU: 2013/14

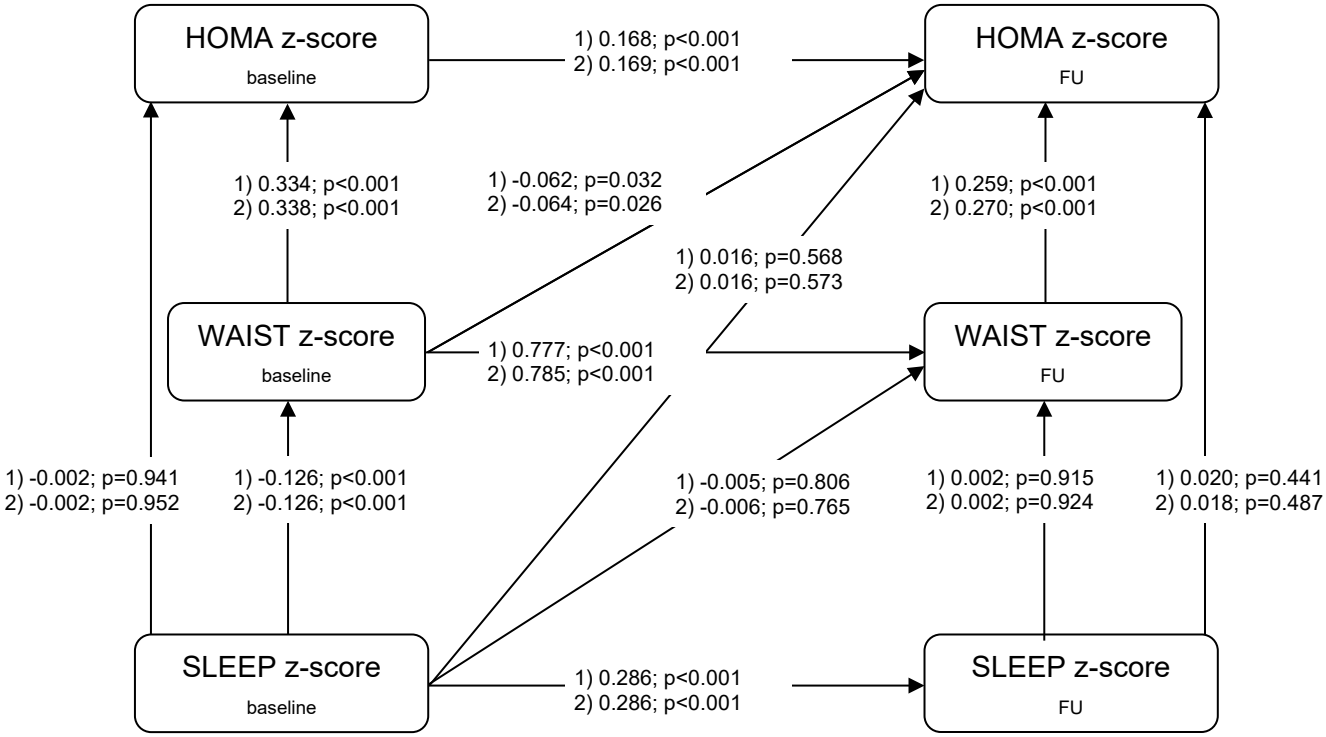


S6 Figure: Sensitivity analysis (additional adjustment for residence in the intervention vs. control region) – Path model for the associations of nocturnal sleep duration (SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment for insulin resistance (HOMA) z-score adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time, indicator for residence in the intervention vs. control region (all at baseline), pubertal status (at follow-up [FU]) and follow-up time: Unstandardised direct effect estimates and p-values (N=3 330)*; baseline: 2009/10, FU: 2013/14

*children not participating in 2007/08 (N=570) were excluded from this analysis



S7 Figure: Sensitivity analysis (stratified by residence in the intervention vs. control region) – Path model for the associations of nocturnal sleep duration (SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment for insulin resistance (HOMA) z-score adjusted for age, sex, country, highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status (at follow-up [FU]) and follow-up time: Unstandardised direct effect estimates and p-values (N=3 330)*; 1) = Children living in the intervention region (N=1 703); 2) = Children living in the control region (N=1 627); 3) = Whole group (N=3 330); baseline: 2009/10, FU: 2013/14
*children not participating in 2007/08 (N=570) were excluded from this analysis



S8 Figure: Sensitivity analysis (adjustment for either Tanner stage or menarche/voice mutation) – Path model for the associations of nocturnal sleep duration (SLEEP) z-score with waist circumference (WAIST) z-score and homeostasis model assessment for insulin resistance (HOMA) z-score adjusted for age, sex, country , highest educational level of parents, well-being score, average napping time (all at baseline), pubertal status based on Tanner stages or menarche/voice mutation (at follow-up [FU]) and follow-up time: Unstandardised direct effect estimates and p-values; 1) = Adjustment for Tanner stages (N=2 999); 2) = Adjustment for menarche/voice mutation (N=2 999); baseline: 2009/10, FU: 2013/14

Paper 4

Cross-sectional and longitudinal associations between psychosocial well-being and cardio-metabolic markers in European children and adolescents

Thumann BF, Börnhorst C, Ahrens W, Arvidsson L, Gwozdz W, Iguacel I, Mårild S, Molnár D, Rach S, Russo P, Tornaritis M, Veidebaum T, De Henauw S, Michels N

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Cross-sectional and longitudinal associations between psychosocial well-being and cardio-metabolic markers in European children and adolescents

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ABSTRACT

Objective: Research examining aspects of positive mental health as potential determinants of cardio-metabolic health in young populations is scarce. We investigated associations between psychosocial well-being and waist circumference (WAIST), blood pressure (BP), the homeostasis model assessment (HOMA) for insulin resistance, triglycerides (TRG) and high-density lipoprotein cholesterol (HDL-C) considering lifestyle factors as mediators.

Methods: Data of European children and adolescents participating in the baseline (2007/2008), first follow-up (FU1, 2009/2010) and second follow-up (FU2, 2013/2014) examinations of the IDEFICS/I.Family study were used ($N_{cross\text{-}sectional}$=6,519; $N_{longitudinal}$=1,393). A psychosocial well-being score was calculated from 16 items on emotional well-being, self-esteem and social relationships (0-48 points). Cardio-metabolic markers were transformed to age- and sex-specific and in case of BP also height-specific z-scores. Lifestyle factors included diet, physical activity, sleep and electronic media use. Applying path analysis, unstandardized estimates of direct and indirect effects of well-being on cardio-metabolic markers were obtained.

Results: Cross-sectionally, well-being score showed a negative direct and a negative indirect effect through lifestyle factors on WAIST z-score (estimate per 4-point increase -0.051 p=0.001 and -0.014, p<0.001, respectively). Longitudinally, positive changes in well-being score between baseline and FU1 and between FU1 and FU2, respectively, demonstrated negative indirect effects through lifestyle $factors_{FU2}$ on WAIST $z\text{-}score_{FU2}$. Both cross-sectionally and longitudinally, higher levels of well-being showed lowering indirect effects on HOMA, BP and TRG z-scores and an increasing indirect effect on HDL-C z-score through both lifestyle factors and WAIST z-score.

Conclusions: Our results supported our hypothesis that a healthier lifestyle may be one mechanism through which higher well-being is linked with lower abdominal obesity and fewer other cardio-metabolic disorders in young populations.