# Sleep duration and its role in the aetiology of cardio-metabolic health outcomes

Dissertation

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1. **Gutachter: Prof. Dr. W. Ahrens**
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Hiermit erkläre ich, Sabrina Hense, geboren am 15. 01. 1981, dass für das Verfassen der vorliegenden Dissertation ‚Sleep duration and its role in the aetiology of cardio-metabolic health outcomes' folgende drei Aussagen zutreffen:

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2. Ich habe keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt.
3. Ich habe die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht.

Bremen, 15.09.2011

Sabrina Hense

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# Summary

The thesis consists of six main chapters. The introductory chapter (*Chapter 1*) is followed by four peer-reviewed scientific papers that form the *Chapters 2* to *5*. *Chapter 6* comprises a general discussion of the presented results.

An adequate amount of sleep is believed to be important for optimal health and functioning throughout life and changes in sleep duration were found to be associated with several – especially cardio-metabolic - health outcomes in adults as well as in children. The factors that influence sleep duration are multi-factorial and the interplay between sleep duration and other factors in the aetiology of cardio-metabolic outcomes is complex and not fully understood yet.

To promote an adequate amount of sleep already in childhood, the period of life where sleep patterns develop, it is necessary to enhance our knowledge about factors that influence the duration of sleep. Several determinants of sleep duration had been reported before, but no study had simultaneously investigated the effects of regional or country specific aspects (e.g. daylight duration) and individual factors (e.g. TV time, physical activity). Internationally comparable data from children ages 2 to 9 years participating in the IDEFICS study are presented in *Chapter 2*, outlining analyses of individual sleep determinants as well as regional differences, and their separate and joint impact on sleep duration. In the presented analysis nocturnal sleep duration differed significantly ($P < 0.001$) and up to 1.7 hours between countries in univariate as well as in multivariate analysis. Disparities between Northern, Southern and Eastern Europe were striking, with children from Northern countries sleeping the longest *(Chapter 2)*. The factor that was found to mainly affect children's sleep duration was country affiliation. Age also had a significant effect in all models, but accounted for less change in sleep duration than country. No association was found with environmental factors such as season or daylight duration. While other studies have reported a relationship between behavioral aspects, parental education level or lifestyle factors, no association with these characteristics were detected in the IDEFICS data after adjustment for country. These findings indicate that regional affiliation, including culture and environmental characteristics, seems to overlay individual determinants of sleep duration that have been reported to influence children's sleep in previous studies *(Chapter 2)*.

Another aspect that was in the focus of this thesis is the association between sleep duration and overweight. Data on this relationship has been published for different age groups from several countries; however, comparability of these results was limited by different study designs and methods. Moreover, it may also be suspected that sleep duration, weight status, and their relation are likely to be influenced by factors that

differ between regions. In *Chapter 3,* the association between sleep duration and overweight and a possible effect modification by geographic region are investigated in children from eight European populations based on the IDEFICS data. The analysis confirmed the observations from other research groups that sleep duration is associated with a higher probability of being overweight in childhood. The association between sleep and overweight was attenuated by an adjustment for geographic region, whereas no effect modification by region was found. Generally the association appeared to be much stronger in school children than in preschool children. The results suggest, that a major part of the relationship may be explained by biological processes rather than behavioral or environmental aspects that differ between regions.

*Chapter 4* gives a review of the literature on the relationship between sleep duration and weight status. It focuses on the biological mechanisms involved in the relationship on the one hand and on the epidemiological evidence from longitudinal studies in children and adults on the other hand. According to this review, a relationship between sleep duration and weight status can not only be seen in children but also in adults – even if the results are less consistent with increasing age. Different biological mechanisms have been discussed in this context, and a special influence has been attributed to hormonal changes including mainly the adipose tissue derived Leptin, the 'hunger hormone' Ghrelin and the carbohydrate and fat metabolism regulating Insulin as potential mediators.

A further aspect of cardio-metabolic health that was under investigation in this thesis is cardiovascular mortality. Recently, epidemiologic evidence has been accumulated which showed that short as well as long sleep duration increased the risk of cardiovascular mortality. However, the dichotomization of sleep duration into short versus normal, or long versus normal sleep duration leads to a loss of information which might underestimate or obscure a dose-effect relation of sleep duration with cardiovascular mortality. *Chapter 5* comprises a systematic review of the epidemiological evidence on sleep duration and cardiovascular mortality. It includes a meta-analysis that attempts to quantify the dose dependency of the association between sleep duration and cardiovascular mortality. The presented results show a clear non linear dose-effect relationship in this context. Furthermore they indicate, that the suggested U-shape in the relationship is mainly explained by the effect of sleep duration on CHD. For stroke and CVD the association could mainly be seen with sleep durations of more than 7.5 hours. The pattern of the relationship seemed to be similar in men and in women, while for CHD the effects of sleep duration were generally stronger, but differed between sexes, with short sleep duration being associated with CHD to a higher extent in men than in women. In contrast, long sleep duration seemed to increase the risk in women, while no significant effect was seen in men. To get a more specific

insight in this relationship, confirmatory studies that draw a distinction between types of cardiovascular events as well as between sexes need to be conducted.

In Chapter 6 the findings are discussed in light of methodological aspects, coherence with previous findings and potential impact for public health. Previous findings generally support the presented results and plausible mechanisms for the associations and suggested pathways exist. In conclusion we suggested a twofold effect of sleep duration on cardiovascular outcomes: directly and indirectly via the effect of overweight. Furthermore, investigation on sleep duration as a tracking risk factor for cardio-metabolic outcomes as well as internationally comparable studies to give insight in regional aspects of sleep duration was proposed. Such research might create the basis for specific and appropriate public health actions with regard to sleep induced cardio-metabolic conditions.

# Contents

# Abbreviations

REM: Rapid Eye Movement

IDEFICS: Identification and prevention of dietary and lifestyle induced health effects in children and infants

BMI: Body mass index

ISCED: International standard classification of education

CI / CL: Confidence interval / Confidence limit

OR: Odds ratio

RR: Risk ratio

MVPA: Moderate to vigorous physical activity

BZgA: Bundeszentrale für gesundheitliche Aufklärung

STH: Somatotropin

KIGGS: Kinder- und Jugendgesundheitssurvey

HOMA: Homeostatic model assessment

CVD: Cardiovascular disease

CHD: Coronary heart disease

NOS: Newcastle-Ottawa quality assessment scale

GH: Growth hormone

hs-CRP: high sensitive C-reactive protein

IOTF: International obesity task force

DXA: Dual energy x-ray absorptiometry

BIA: Bioelectrical impedance

ICD: International classification of diseases

PSG: Polysomnography

OSA: Obstructive sleep apnea

# Figures

# Tables

# 1 Introduction

Sleep is something we have in common not only with all humans but with nearly all organisms living on earth. In humans, ideas about sleep but also sleep patterns have changed. For example, US-American surveys have shown a reduction of 1.5 to 2.0 hours in self-reported sleep-duration during the last 50 years [1] - even though the physiological need for sleep has probably not changed significantly during that time. Many of our ideas about sleep have varied, and still vary between cultures but also in response to the growing scientific understanding of what determines healthy sleep [2]. The following sections give an overview on theories about why we sleep, physiological mechanisms involved in the process of sleeping, the relation between sleep and human health, and on the development of sleeping patterns throughout the life span.

## 1.1 Why do we sleep?

From the days of the past, people have always aimed at making their sleep more comfortable or safer, thus trying to incorporate sleep into their everyday lives to a greater or lesser extent. Already Aristotle concluded that sleep is necessary for physical renewal, and accordingly he wrote: 'Sleep is […] a seizure of the primary sense-organ, rendering it unable to actualize its powers; arising of necessity […] for the sake of its conservation.' [3]. But even today, after many decades of research and investigation, the question of why we sleep has not been answered definitively. The following theories have been developed which try to help explain why we spend a third of our lives sleeping [2].

***Inactivity theory***

One of the oldest theories is the evolutionary theory, which suggests that certain animals that were able to stay still (inactive) during periods of vulnerability (night) had an advantage over other animals. Through natural selection, this behavioural strategy presumably evolved to become what we now recognize as sleep.

***Energy conservation theory***

Another theory, which is related to the inactivity theory above, is the energy conservation theory. It is based on the consideration that one of the strongest factors in natural selection is competition for and effective use of energy resources - although this may be less apparent nowadays with many people living in societies with plentiful food sources. Due to this theory, the primary function of sleep was to reduce energy demand and expenditure, especially at times when it is least efficient to search for food, and thereby conserve energy resources .

***Restorative theory***

A further explanation of why we (have to) sleep is predicated on the belief that sleep serves to 'restore' what is lost in the body while we are awake, and that sleep thus provides an opportunity for the body to repair and rejuvenate itself. This theory is supported by studies which found that major restorative functions, like muscle growth, tissue repair, protein synthesis and growth hormone release, occur mostly or only during sleep.

***Brain plasticity theory***

One of the more recent theories is based on findings that sleep is correlated to structural and organizational changes of the brain. This phenomenon is called brain plasticity and its connection with sleep has several implications. Thus, it has become clear that sleep plays a critical role in the brain development of infants and young children; but an association between sleep and brain plasticity was suggested in adults as well. This is shown by the impact which sleep and sleep deprivation have on the ability to learn and perform various tasks. It has been suggested that sleep may be particularly important for the learning of children, as it is involved in fundamental aspects of brain plasticity and important for the process of embedding new information into developing neuronal systems. Hence, the effects of insufficient sleep in childhood may have important long-term effects on learning, especially if sleep curtailment occurs chronically and in key-periods during development [4].

## 1.2 Sleep patterns throughout the lifespan

Nocturnal sleep duration is influenced by several factors and is subject to high variability between individuals. In contrast, it is rather stable on an intra-individual level [5]. The sleep need is different in diverse phases of life and usually decreases with age. Accordingly, toddlers need between 12 to 16 hours of sleep over the day (polyphasic sleep pattern) [6,7], of which they spend about half in the REM-phase (Rapid Eye Movement) sleep. This stage of sleep is also called 'dream sleep', since in adults it is the stage with the most intensive dreaming. In pre-school children the proportion of REM-sleep decreases to less than 35% and sleep is concentrated mainly on the nights, where the recommendation is to sleep between 11 and 13 hours per night, while school age children should sleep 10-11 hours [6,7]. For adolescents a sleep need of about 9 hours has been reported [5]. With higher age humans return to the polyphasic sleep pattern, whereas the cumulative sleep duration of about 8 hours usually does not change [5].

While sleep needs vary considerably from person to person and are thus individually determined, sleep patterns are influenced not only by personal factors and preferences but also by cultural, environmental and behavioural aspects. It is, therefore, of interest to identify and quantify the influence of different determinants of sleep duration,

especially in childhood, where sleep patterns develop. A better understanding of these determinants should help to assess the potential impact that changing sleep patterns in the population might have.

## 1.3 Physiological mechanisms of sleep

Although the above presented theories on the ultimate causes of sleep remain mostly unproven and partly speculative, science has made enormous progress especially in the past fifty years to explain the functions of sleep for the human body, and research on the effects of sleep curtailment and deprivation is growing rapidly [2].

Sleep – in contrast to a state of wakefulness – is characterized by a nearly non-existent motor activity and an extremely low disposition to react on internal as well as external stimuli. On the other hand it is a highly active state, as suggested by the regulated order of REM and Non-REM sleep with its partly high neuronal activity [5].

The multiple physiological changes during sleep affect basically all bodily functions. Thus, in the cardiovascular system, heart rate, conduction velocities, stroke volume and cardiac output, systemic arterial blood pressure, including the cerebral blood flow, all decrease significantly during sleep, while the pulmonary arterial pressure increases. Another affected body compartment is the gastrointestinal tract, where the frequency of swallowing, the gastrointestinal motility, and the saliva secretion are reduced while we are asleep; or the urogenital system, where the production of urine and the urinosmolality are lower during sleep than in the state of wakefulness [5]. Furthermore an effect of sleep on the endocrine system has been reported [8]. Therefore, it appears plausible that the physiological effects of sleep may also contribute to the occurrence of health related outcomes. Their role with regard to cardio-metabolic health is depicted in the following chapter.

## 1.4 Sleep and cardio-metabolic health

Already more than a century ago, the psychologist G. Stanley Hall [9] suggested that ‘everything possible should be done to favour sleep as deep and sound in quality and usually as long in quantity as possible, and everything that seriously interferes with this end should be sedulously avoided’. According to current knowledge, the aspect of sleeping that seems to have the most relevant impact on health is sleep duration and an adequate amount of sleep is believed to be important for optimal health and functioning throughout life [10]. To that effect, this thesis investigates the role sleep duration rather than the complex construct of sleep quality. A detailed and critical description of the assessment of sleep duration is given in Chapter 6.3.1. Changes in sleep duration were found to be associated with several physiological as well as psychological health outcomes in adults as well as in children [11-15]. However, the strongest evidence for an

association between sleep duration and health has been reported for overweight and cardiovascular events, which additionally are two of the health conditions that present the most relevant burden of disease worldwide [16,17].

The following paragraphs give an overview of the current state of research concerning the relationship between sleep duration and overweight as well as sleep duration and cardiovascular events separately in children and adults.

### 1.4.1 Sleep and cardio-metabolic health in adults

The association between sleep duration and overweight or obesity has been in the focus of sleep epidemiology in the past years and in fact, epidemiologic evidence has been increasing on the relation between short sleep duration and weight status [1,10,18-23]. However, a systematic review of more than 20 studies revealed that findings for this association are still rather inconsistent in adults [22]. Several cross-sectional as well as longitudinal studies reported a clear inverse association between duration of sleep and body weight, while other results indicated rather a U-shaped curve and some studies found no association at all.

A relationship between sleep duration and metabolic dysfunction has also been suggested [8,24,25]. Thus, some studies found an influence of sleep duration on the activity of hormones like leptin, ghrelin, insulin, cortisol and growth hormones, and it was hypothesized that sleep deficits may potentially result in hormonal imbalances [26]. Recent studies showing an association between sleep duration and an increased risk of insulin resistance and the development of diabetes type 2 [25,27] seem to support such considerations.

In addition, several publications have presented findings on the association of sleep duration with cardiovascular morbidity and mortality [28-31]. As yet, based on the existing literature, no clear direction of this association could be identified. A recent review concluded that short as well as long sleep duration raise the risk for cardiovascular related outcomes [32]. However, no analysis has been published to date that could provide a detailed insight into the dose-effect relationship of sleep and cardiovascular outcomes.

### 1.4.2 Sleep and cardio-metabolic health in childhood

Like in adults, the effect of sleep duration on the weight status has been in the focus of recent research in children. Interestingly, results for this association were found to be more consistent in children than in adult populations. Accordingly, a systematic review from 2008 showed that several cross-sectional as well as longitudinal studies confirmed significant effects of short sleep duration on overweight and obesity in children [22].

By contrast, no data on the relationship between metabolic dysfunctions and sleep duration in children are available to date. The same applies for studies on the

association between sleep duration and cardiovascular events, which is presumably most likely due to the low prevalence of this outcome in young age. However, a study in Japanese children showed an association between sleep duration and blood pressure, an established risk factor for cardiovascular disease that tracks from adolescence into adulthood [33].

### 1.4.3 Biological plausibility

The biological mechanisms underlying the association between sleep duration and cardio-metabolic health are not completely understood yet. However, some potential pathways have been identified based on laboratory studies.

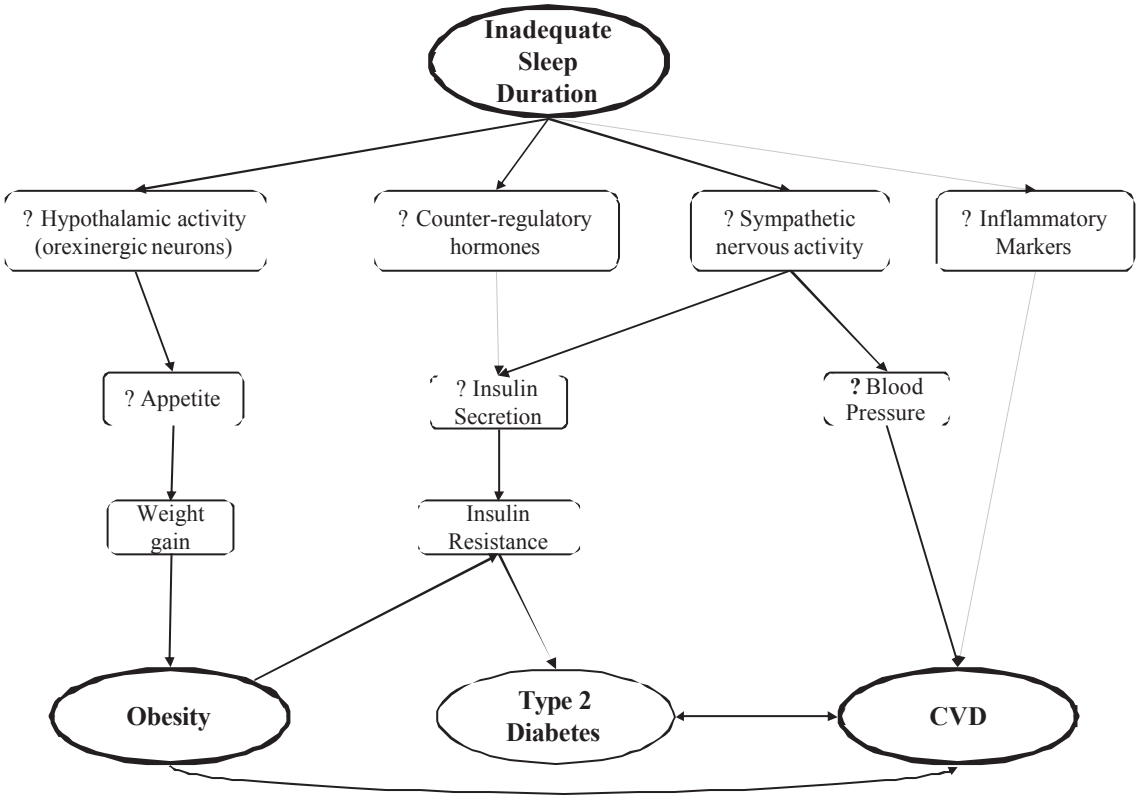


**Figure 1.1: Schematic representation of possible pathways between inadequate sleep duration and CVD (based on Knutson 2010 [34])**

It is unlikely that there is one single pathway that fully explains the relationship: rather, a combination of several mechanisms is involved that eventually lead to an increased cardio-metabolic risk. A comprehensive concept was recently presented by Knutson [34] and an adapted version is graphically depicted in Figure 1.1.

The first pathway involves hormone-induced alterations in hypothalamic activity as a result of inadequate sleep duration. This implies an increase of hypothalamic activity in appetite centres and a loss of inhibition of the activity of orexigenic neurons, leading to

increased hunger, which results in increased food intake thereby leading to overweight or obesity [35,36].

The second pathway may involve increases in evening cortisol release as well as in daytime release of growth hormone (GH) and Ghrelin [37]. These are so-called counter-regulatory hormones that have insulin-antagonistic effects and are able to increase blood glucose concentrations by stimulating hepatic glucose production and / or inhibiting tissue glucose uptake. The daily secretion of cortisol and GH follows a complex pattern of temporal organization. Changes in the circadian rhythm or insufficient sleep might therefore result in decreased insulin sensitivity in tissues and an altered glucose metabolism, eventually resulting in insulin resistance [34].

Another hypothesis implies that acute sleep curtailment may cause a chronic over-activity of the sympathetic nervous system and hence result in increased blood pressure [38,39], a well-established risk factor for cardiovascular events, and impaired insulin secretion [34]. In addition, studies on short-term sleep deprivation have shown elevated inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), in sleep-deprived individuals. Since inflammatory mechanisms are important factors in the development of atherosclerosis and cardiovascular disease, this association may also play a role in the cardiovascular risk associated with short sleep [40].

Unfortunately, studies of the biological mechanisms involved in this context are commonly experimental studies that generally define inadequate sleep as short term forced sleep deprivation. The biological effects of this type of short sleep will probably differ from those associated with chronic sleep deprivation.

As for the association between long sleep duration and cardiovascular events, the underlying neurobiology and mechanistic mediators linking habitual long sleep with increased risk are even less well defined than those of short sleep. However, there is some suggestion that people who self-report long sleep may actually be spending more time in bed, but not sleeping longer. Furthermore, long sleep duration might be an indicator of underlying disease [41]. Analyses of the Nurses Health Study suggested that depression, antidepressant use and unemployment were associated with reported long sleep duration and these are factors which may also play a role with regard to cardiovascular mortality [42].

### 1.4.4 Determinants of sleep and cardio-metabolic health

The factors that influence sleep duration are multi-factorial and the interplay between sleep duration and other factors in the aetiology of overweight and cardiovascular events is complex and not fully understood yet. To disentangle the distinct contribution of sleep duration in this context, its interference with other health related aspects such as, for example, diet or physical activity needs to be taken into account. These factors

are also influenced by or have an impact on sleep duration [10,43,44]. Observational studies can be used to track some of these determinants and to identify the interrelationship of these factors with sleep. Figure 1.2 depicts the characteristics which are in the focus of the present thesis.

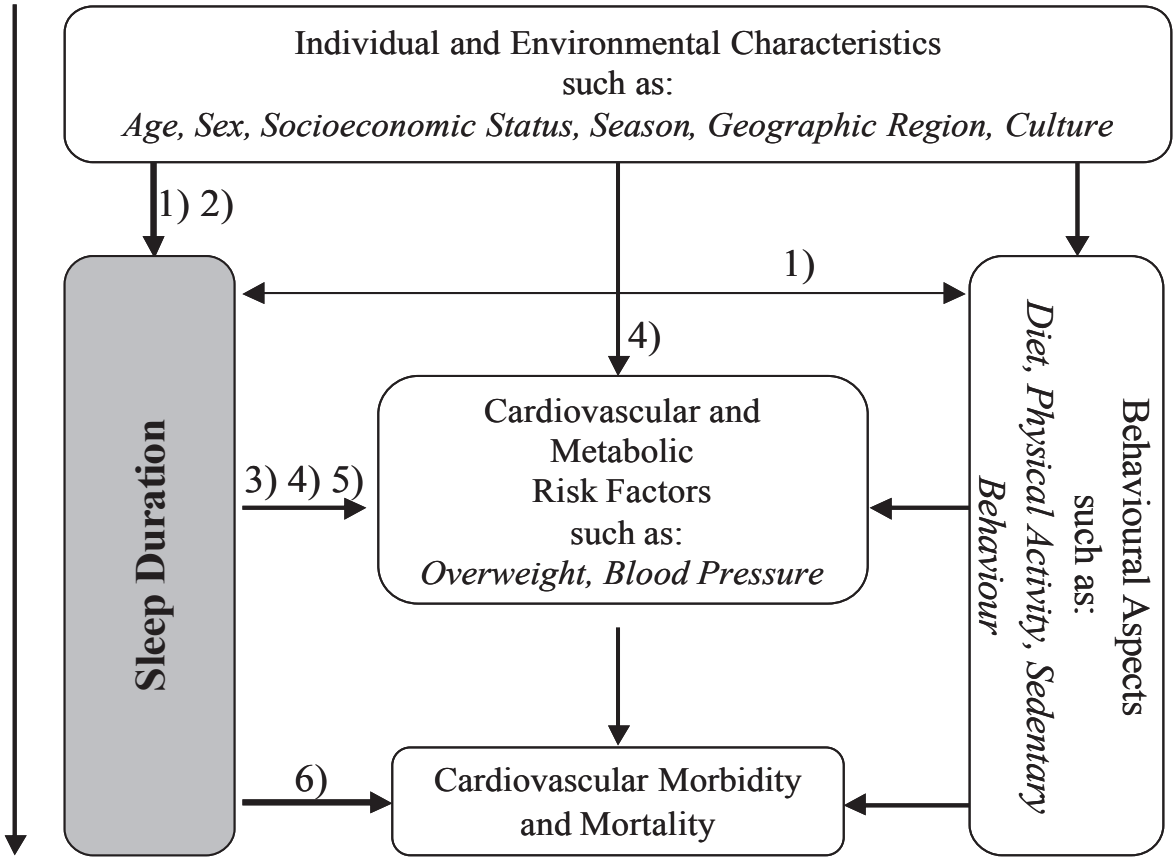


**Figure 1.2: Interrelationship between sleep duration and other health related characteristics**

## 1.5 Research questions

Obviously, the presumed effects of sleep duration on health suggest sleep as an issue of potential public health relevance and as an emerging risk factor for several cardio-metabolic health outcomes. Sleep plays a central role in every human being's life from the very first days. Its basic patterns are defined already in early childhood by a combination of various individual as well as environmental factors [45]. It appears therefore appropriate to investigate which relevant elements in the aetiological chain leading to cardio-metabolic health outcomes are related to sleep duration and how different stages of life impact on this relationship.

To elucidate some features of this complex issue, the following study questions will be addressed in this thesis (question numbers are indicated in Figure 1):

1) What are the main factors that determine children's sleep duration? *(Chapter 2)*

2) Does sleep duration vary between children in populations from different geographic regions? *(Chapter 2)*

3) Is there a cross sectional association between sleep duration and overweight in children? *(Chapter 3)*

4) Is the association between sleep duration and overweight in children modified by geographic region? *(Chapter 3)*

5) Is inadequate sleep duration longitudinally associated with overweight in different stages of life? *(Chapter 4)*

6) Is there a dose-effect relationship in the association between sleep duration and cardiovascular mortality? *(Chapter 5)*

## 1.6 Outline of the thesis

The thesis consists of six main chapters. The introductory chapter (*Chapter 1*) is followed by four peer-reviewed scientific papers that form Chapters 2 to 5 (*Chapter 2, Chapter 3, Chapter 4: Accepted; Chapter 5: Submitted*). *Chapter 6* comprises a general discussion of the presented results. A list of the respective literature can be found at the end of each chapter.

The first two research questions are addressed in the first article, which forms *Chapter 2* of this thesis. The analyses presented in this chapter were performed using data from the IDEFICS (Identification and Prevention of dietary- and lifestyle-induced health effects in children and infants) study. IDEFICS is a population based multi-centre study, including more than 16,000 children from eight European countries. A detailed description of the study design and its main objectives has been presented elsewhere [46-48]. To promote an adequate amount of sleep already in childhood, the period of life during which sleep patterns develop, it is necessary to enhance our knowledge about factors that influence the duration of sleep. Several determinants of sleep duration had been reported before, but no study had simultaneously investigated the effects of regional or country specific aspects (e.g. daylight duration) and individual factors (e.g. TV time, physical activity). Internationally comparable data from the IDEFICS study are presented in *Chapter 2*, outlining analyses of individual sleep determinants as well as regional differences, and their separate and joint impact on sleep duration.

Data on sleep duration and its relation to overweight were published for different age groups from several countries; however, comparability of these results was limited by different study designs and methods. Moreover, it may also be suspected that sleep duration, weight status, and their relation are likely to be influenced by factors that differ between regions. In the second publication, which forms *Chapter 3,* the association between sleep duration and overweight and a possible effect modification by

geographic region are investigated in children from eight European populations based on the IDEFICS data.

The third publication, forming *Chapter 4* gives a review of the literature on the effect of sleep duration and weight status. It focuses on the biological mechanisms involved in the relationship on the one hand and on the epidemiological evidence from longitudinal studies in children and adults on the other hand.

Recently, epidemiologic evidence has been accumulated which showed that short as well as long sleep duration had an impact on cardiovascular mortality. However, the dichotomization of sleep duration into short versus normal, or long versus normal leads to a loss of information which might underestimate or obscure a dose-effect relation of sleep duration with cardiovascular mortality. The fourth publication (*Chapter 5*) comprises a systematic review of the epidemiological evidence on sleep duration and cardiovascular mortality. It includes a meta-analysis that attempts to quantify the dose dependency of the association between sleep duration, measured as a continuous variable, and cardiovascular mortality.

Finally, a general discussion reviews the results from the formerly presented analyses and evaluates them critically against the background of methodological limitations and with a perspective on possible implications for further research, including preventive aspects of cardio-metabolic health and lifestyle-related diseases.

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# 2 Factors that influence weekdays sleep duration in European children

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On behalf of the European Consortium of the IDEFICS Project (www.idefics.eu)

**Study Objectives:** To compare nocturnal sleep duration in children from 8 European countries and identify its determinants.

**Design:** Cross-sectional

**Setting:** Primary schools and preschools participating in the IDEFICS study.

**Participants:** 8542 children aged 2 to 9 years from 8 European countries with complete information on nocturnal sleep duration.

**Interventions:** Not applicable.

**Measurements:** Nocturnal sleep duration was assessed by means of a computer based parental 24-h recall. Data on personal, social, environmental, and behavioral factors were collected by means of standardized parental questionnaire. Physical activity was surveyed with accelerometers.

**Results:** Nocturnal sleep duration in the participating countries ranged from 9.5 h (SD 0.8) in Estonia to 11.2 h (SD 0.7) in Belgium and differed significantly between countries ($P < 0.001$) in univariate as well as in multivariate analyses, with children from northern countries sleeping the longest. Sleep duration decreased by about 6 min with each year of age over all countries. No effect of season, daylight duration, overweight, parental education level, or lifestyle factors could be seen.

**Conclusion:** Sleep duration differs significantly between countries. Our findings allow for the conclusion that regional affiliation, including culture and environmental characteristics, seems to overlay individual determinants of sleep duration.

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## INTRODUCTION

The effect of sleep duration on diverse health outcomes seems undisputable, and an adequate amount of sleep is believed to be important for optimal health and functioning throughout life.[1] National US surveys have shown a reduction of 1.5 to 2 hours in self-reported sleep duration over the last 50 years.[2] Moreover, associations between reduced sleep duration and cognitive deficits or mood disturbances have been found in adults, and evidence for similar effects in children is increasing.[1,3] For example, behavioral problems of attention deficit hyperactivity disorder appear to be associated with sleep curtailment in the young.[4] Concurrent with the decrease in sleep duration, a worldwide increase of overweight and obesity has been reported and mounting evidence in the recent past has identified sleep duration as a new risk factor for overweight and obesity already in childhood.[1,2,5-11] Likewise, an association between reduced sleep duration and metabolic dysfunction has been discussed.[12-14] Therefore, sleep appears to be an issue of public health interest as a potential new risk factor that needs to be further examined, especially in children.

Information on average sleep duration has been published for different age groups from several countries[1,15-17] but comparability of those results is limited by reasons of different study designs and methods. In particular, sleep assessment methods differed. For example, some studies assessed sleep duration by means of structured interviews, asking parents questions on habitual bedtime and wake up time of their children, while other studies applied diaries to assess nocturnal sleep duration. Against the background of a previous study that has reported unsatisfactory agreement rates between questionnaires and diaries to assess sleep duration in children,[18] this heterogeneity hampers comparability of study results from different studies, while uniform methods and the high degree of standardization of data collection in a multicenter study allows for comparability of data.

Previous studies have reported several determinants of sleep duration in children. One of the main factors in this context is age, which has been shown to be negatively associated with sleep duration.[17,19] Physical activity has also been suggested to influence sleep duration, but no significant correlation between physical activity and sleep in children has been found.[1] A slightly different picture can be drawn for sociodemographic factors. For example, a study from New Zealand did not find any effect of gender, socioeconomic status, or maternal education on children's sleep duration,[1] while others observed associations between sociodemographic variables and sleep.[19,20] Another aspect that has been discussed to influence sleep duration in children is the time spent in front of the TV. Studies have shown adverse effects of TV time on sleep duration, though the findings were not always statistically significant.[1,21] It has also been suggested that season may play a role on sleep duration: a previous survey

reported longer sleep duration in fall, winter, and spring than in summer.[1] Another factor that has been discussed intensely in the past years in association with sleep duration is overweight. The association is well known in adults, and evidence for the relationship is growing also in children.[2,10] The respective research has mainly focused on overweight as the outcome variable, but the direction of this association is not yet entirely clear, and the published data allow only limited conclusions on causality, especially in children. Furthermore, studies have shown that sleep duration is probably influenced by cultural and environmental factors and differs between countries.[16,22] To the authors' knowledge, no study that has simultaneously investigated the effect of regional or country-specific aspects and individual determinants of sleep duration has been done. Against this background it is of interest if regional aspects, for example, geographic (e.g., daylight duration) or other differences between European countries affect sleep duration in children, and how their impact on sleep duration relates to the above-mentioned individual determinants of sleep duration. To answer this question, internationally comparable data from a population based study of sufficient sample size are necessary.

We present here data from diverse European countries and multiple age groups which were collected within the "identification and prevention of dietary- and lifestyle-induced health effect in children and infants" (IDEFICS) project, an international collaborative study involving 8 European countries.[23,24] The present study compared nocturnal sleep duration assessed in a consistent and standardized manner in the participating countries to find out whether sleep duration differs between European countries independent of individual determinants of sleep duration. This study offered a unique opportunity to describe the distribution of sleep duration by age in European children based on epidemiological data.

## METHODS

The IDEFICS project is a population based multicenter study which includes children aged 2 to 9 years from 8 European countries. Between September 2007 and June 2008, a total of 31,543 children from primary schools and preschools in selected regions in Italy, Estonia, Cyprus, Belgium, Sweden, Hungary, Germany, and Spain were invited to participate in the baseline survey (T0), with an adhesion rate of 53.4%. Examination period was the same in all countries. A total of 16,223 (96.2%) fulfilled the inclusion criteria and gave full information on sex, height, and weight. Sample size across countries ranged from 1507 children in Spain to 2567 in Hungary. In each country, the participating centers obtained ethical approval by their responsible authority. Parents or legal guardians provided written informed consent for all examinations and/or the collection of samples, subsequent analysis, and storage of personal data and collected samples. Before the start of the study, all instruments were pre-tested. The final

instruments were introduced through a central training by the coordinating center and by subsequent local trainings of the field staff in each recruitment center. All data were collected according to standard operating procedures and adherence to the protocol was assured by quality control site visits in all study centers conducted by the coordinating center (Bremen Institute for Prevention Research and Social Medicine). Questionnaires were translated in the national languages and then retranslated into English by the respective study centers to ensure compatibility of translations with the English original. More detailed information on the study procedures can be obtained from previous reports.[23-25]

**Sleep Duration**

Information on sleep duration was collected in the context of a standardized 24-h recall (SACINA) that was developed to be used in children, based on an instrument previously used in adolescents.[26] The SACINA is a computer-based instrument filled out by parents or guardian of each participating child and contained questions on the time at which the child got up in the morning and went to bed on the previous day. Nocturnal sleep duration was calculated as the difference between bedtime and get-up time in the SACINA interview. Data were collected on all days of the week, including weekends. However, preliminary analyses of variance showed no significant sleep duration differences from Monday to Thursday, while there were significant differences ($P < 0.001$) between Fridays, Saturdays, and Sundays. This may be due to the fact, that in some countries only very few or no data were available for weekend days. Therefore, we decided to include only nocturnal sleep duration data from Monday to Thursday for the present analysis. Parents had the possibility to fill out the 24-h recall on more than one day, if they wanted to. However, if information on sleep duration was given for more than one night, the first weekday night was included in the analysis to avoid differences in variability of the data.

**Anthropometry**

Anthropometric measurements were done according to a standardized manual in all centers. Body height was measured without shoes by trained staff using a portable stadiometer (SECA 225). Weight was measured by means of an adapted version of electronic scale (TANITA BC 420 SMA), with subjects wearing only underwear. Body mass index (BMI) was calculated and then categorized referring to cutoff points according to the criteria of International Obesity Task Force.[27] Our category "overweight" included overweight and obese children, while the reference category included normal and underweight children.

### Personal and Environmental Factors

Sex, age, country, season, daylight duration, parental education level, overweight, time spent in front of a TV or PC, weekly hours spent in a sports club, time playing outside, and physical activity according to accelerometer measurements were considered potential determinants of sleep duration. Data on personal, social, environmental and behavioral factors were collected by means of a standardized parental questionnaire, while children's physical activity was surveyed with accelerometers (Actigraph GT1M and ActiTrainer) with cutoffs for moderate to vigorous activity according to Sirard et al.,[28] resulting in a continuous variable of daily minutes spent in moderate to vigorous physical activity. Accelerometers were worn around the waist for 3 consecutive days and had to be taken off for swimming, showering or bathing, and during sleep. The parents were asked to keep records of each time the device was taken off in an accelerometer diary. Education level categorized according to the International Standard Classification of Education (ISCED)[29] was used as a surrogate measurement for socioeconomic status. Three levels of education (low, medium, high) of the 6 ISCED levels were created, with ISCED levels 0, 1, and 2 indicating low education; 3 and 4 indicating medium education, and =5 indicating high education. Information on daylight duration was obtained from astronomical tables available at www.timeanddate.com. Daylight duration is given in decimal hours.

### Non-Responder Analysis

Non-responder analysis by sex, age, and parental education level was performed in each country for children whose parents did not answer the SACINA interview and for those providing sleep data only for weekend days. These analyses showed no differences for sex, while there were some significant differences for age and parental education level in some countries. In Estonia, Belgium, Germany, and Spain, nonparticipants were slightly older than participants, while in Cyprus and Hungary nonparticipants were younger. In Hungary nonparticipants had a slightly lower education than participants.

### Statistical Analysis

Preliminary analyses revealed that sleep duration was normally distributed in all countries. Therefore, we applied parametric tests in our statistical analyses. Differences in continuously distributed variables were compared using the Student *t*-statistics while the $?^2$ statistic was used for the comparison of categorical variables. Percentile curves of sleep duration based on cubic interpolation of age-specific percentiles have been developed to model the distribution of sleep duration by age. For some analysis 2 age groups were created, with one group including children aged 2 to <6 years (pre-school children) and the other group including children aged 6 to 9 years (primary school children).

Analysis of variance was used to compare means of unadjusted values by categorical variables. To estimate the mean sleep duration in each country sample, controlling for confounding factors, we fit multivariate linear regression models and calculated adjusted mean values using minutes of sleep as the effect measure. Model 1 included only non-modifiable factors such as country, season, daylight duration, age, and parental education level. Model 2 included the same variables as Model 1 plus modifiable variables such as overweight, time spent playing outside, weekly time spent in a sports club, and daily time spent in front of a TV or PC screen. A test for interaction between age group and country was conducted. Models were constructed using the SAS procedure PROC GLM and including only variables that were found to be significantly related to sleep duration in univariate analysis. Because of the large sample size, a more stringent criterion for statistical significance was chosen, with a = 0.01. Statistical analyses were done with SAS Version 8.2 (SAS Institute, Cary, NC, USA).

## RESULTS

Data on nocturnal sleep duration were available for 10,613 (65.4%) of 16,223 children. After exclusion of children reporting only sleep duration for weekend days, data from 8,542 (52.6%) children were used for the present analysis.

**Table 2.1: Characteristics of study samples and distribution of covariates, by country**

| Variable | EST | ITA | HUN | CYP | ESP | SWE | GER | BEL | All |
|---|---|---|---|---|---|---|---|---|---|
| | (n=1331) | (n=1643) | (n=902) | (n=953) | (n=504) | (n=1215) | (n=1586) | (n=408) | (n=8542) |
| Age (Mean) | 5.8 | 6.2 | 6.7 | 6.3 | 5.5 | 5.7 | 6.1 | 5.5 | 6.0 |
| Boys (%) | 48.9 | 52.0 | 49.2 | 49.4 | 42.4 | 51.7 | 51.5 | 52.5 | 50.8 |
| Fall/Winter (%) | 37.0 | 79.1 | 75.8 | 78.9 | 95.4 | 66.9 | 72.6 | 61.5 | 64.0 |
| Overweight (%) | 13.8 | 40.8 | 17.3 | 24.0 | 17.9 | 9.8 | 15.8 | 6.6 | 20.2 |
| Education level | | | | | | | | | |
| High (%) | 9.6 | 13.2 | 38.4 | 34.1 | 48.6 | 56.6 | 9.7 | 53.4 | 14.5 |
| Medium (%) | 83.1 | 57.0 | 55.0 | 43.4 | 25.4 | 35.8 | 54.5 | 38.2 | 53.1 |
| Low (%) | 3.9 | 27.4 | 4.2 | 5.5 | 16.3 | 4.9 | 30.6 | 4.4 | 27.2 |
| Screen time | | | | | | | | | |
| Not at all (%) | 0.6 | 2.1 | 3.6 | 1.6 | 5.6 | 0.9 | 4.0 | 1.7 | 2.3 |
| ≤0.5 h (%) | 5.5 | 8.2 | 15.3 | 7.5 | 22.2 | 7.4 | 12.2 | 13.0 | 10.1 |
| ≥0.5 h to <1 h (%) | 18.6 | 19.8 | 26.8 | 19.9 | 28.0 | 22.2 | 26.4 | 32.1 | 23.0 |
| ≥1 h to <2 h (%) | 23.5 | 27.1 | 24.8 | 32.0 | 25.6 | 32.3 | 26.4 | 27.5 | 27.4 |
| ≥2 h to <3 h (%) | 17.7 | 19.0 | 15.0 | 16.7 | 11.5 | 19.5 | 14.1 | 14.5 | 16.6 |
| ≥3 h (%) | 32.1 | 23.6 | 12.1 | 12.0 | 6.2 | 15.4 | 12.9 | 11.0 | 17.6 |
| Play outside (%) | 94.1 | 85.6 | 95.0 | 81.0 | 95.8 | 93.2 | 85.2 | 91.7 | 98.0 |
| Time in sports club | | | | | | | | | |
| <1 h (%) | 1.7 | 0.2 | 0.4 | 5.1 | 2.4 | 1.2 | 0.5 | 0.3 | 0.8 |
| ≥1 h to <4 h (%) | 29.7 | 24.5 | 16.3 | 0.9 | 24.4 | 14.7 | 25.5 | 24.0 | 21.1 |
| ≥4 h (%) | 14.3 | 4.7 | 4.3 | - | 6.0 | 0.9 | 2.5 | 2.5 | 4.8 |

The mean age ranged from 5.5 in Spain (SD 1.9) and Belgium (SD 1.5) to 6.7 (SD 1.8) in Hungary. The frequency of boys and girls was very similar in each of the country samples. A more detailed description of the study sample can be found in Table 2.1, which also gives an overview of the distribution of possible determinants of sleep duration within the sample.Sleep duration showed a significant decline with age ($P < 0.001$). Comparing sleep duration between age groups, significant differences between preschool and school children could be seen in all countries except for Hungary and Cyprus (data not shown). To give an impression of the distribution of sleep duration by age in the overall sample, we present percentile curves of sleep duration based on cubic interpolation of age-specific percentiles in Figure 2.1.

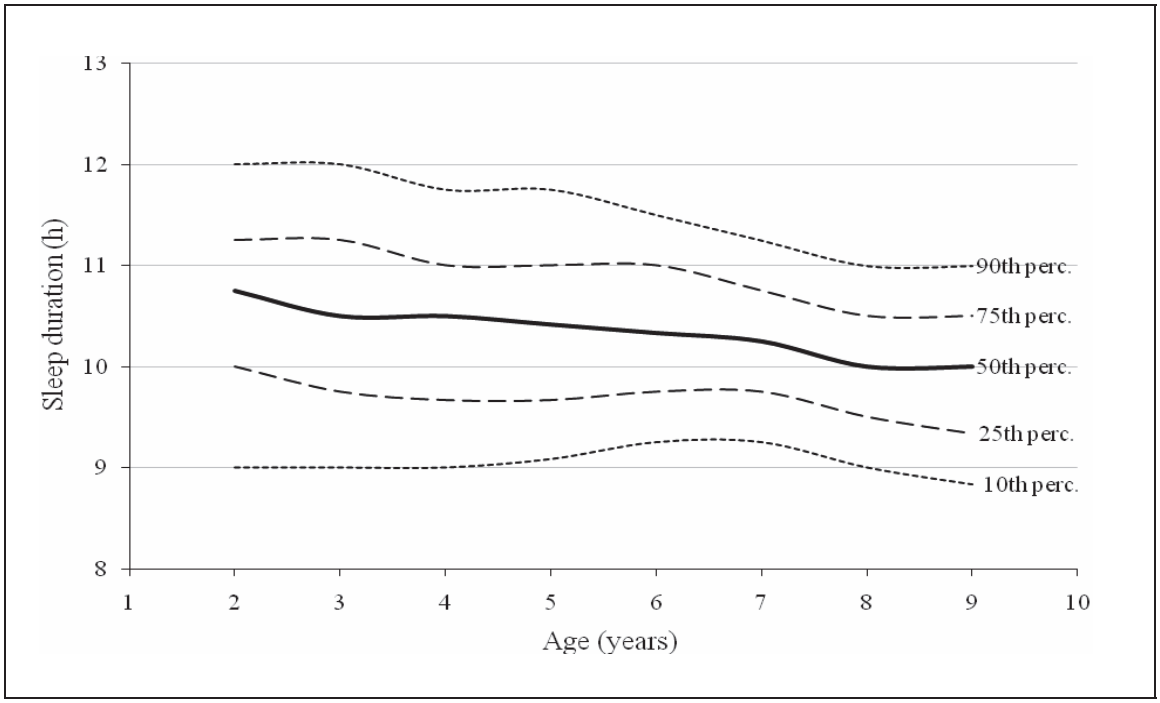


**Figure 2.1: Percentile curves of sleep duration by age in all countries**

Unadjusted nocturnal sleep duration differed significantly between countries ($P < 0.001$), with children from northern Europe (Sweden, Germany, Belgium) showing longer sleep duration than children in southern (Italy, Spain, Cyprus) or eastern (Estonia, Hungary) Europe.

Mean sleep duration ranged from 9.5 (SD 0.8) h in Estonia to 11.2 (SD 0.7) h in Belgium. There were also some differences of within-sample variability of sleep duration, which was highest in the German and lowest in the Cypriote sample (Fig. 2.2).

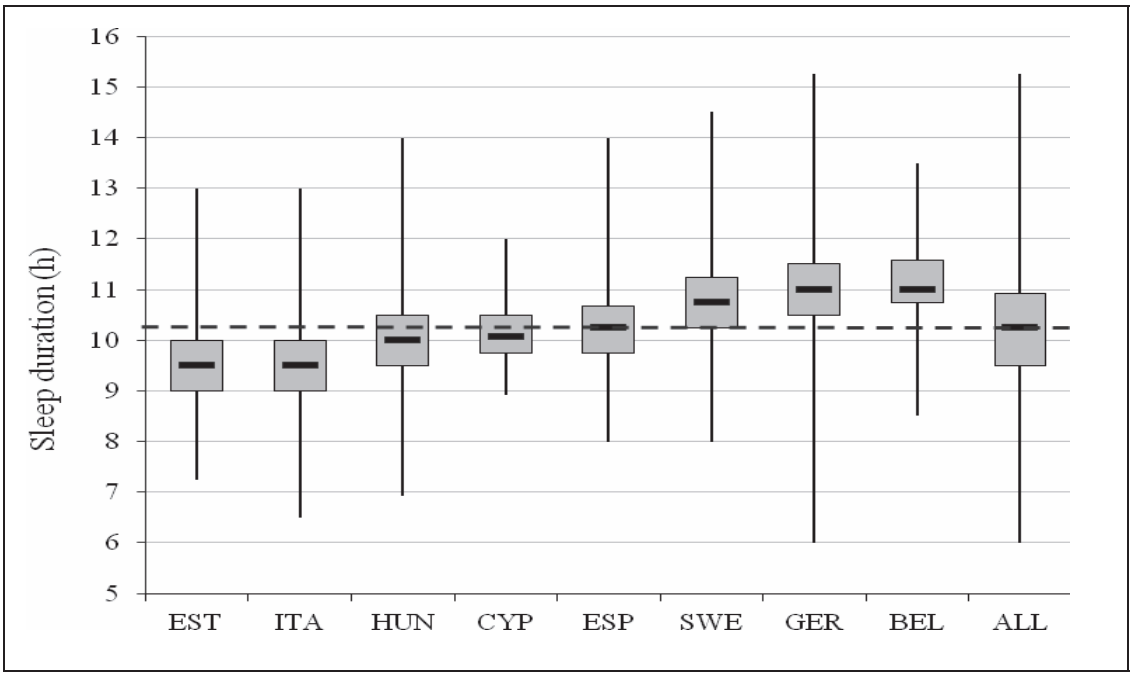


**Figure 2.2: Distribution of crude sleep duration by country. Box plots indicate median, 25th and 75th percentile and min / max.**

Results of univariate and multivariate analyses are shown in Table 2.2. Based on Model 1, sleep duration generally decreases by about 5.5 min per year of age increase. Adjusted (Model 1) sleep duration differed significantly between countries ($P < 0.001$), largely confirming the differences already observed in the unadjusted analysis. Thus, Swedish children (reference group) slept >1 h more than children in Estonia and Italy. Shorter sleep durations in Hungary, Cyprus, and Spain were less pronounced but still significant, while children in Germany and Belgium slept even longer than the Swedish reference group. With regard to seasonal influences and daylight duration, no effect on sleep duration could be found. Parental education level showed no association with sleep duration. Unexpectedly, none of the additionally included variables in Model 2 accounted for significant changes in sleep duration. Since inclusion of the variable "weekly time spent in a sports club" led to a substantial reduction in sample size (n = 2,269) and the variable showed no effect on sleep duration ($P = 0.442$) in the multivariate analysis, we conducted sensitivity analyses excluding this variable. Exclusion did not account for relevant changes in the estimates of the remaining variables and therefore we decided to drop the variable in Model 2. Also in this model, main effects were revealed in association with age and country. These results remained strongly significant, although to a lower extent than in the first model. Generally, the biggest effect was observed for country, with an $r^2 = 0.36$ already in the univariate analysis. The multivariate analyses showed that most of the univariate associations did not persist after controlling for covariates, indicating independent effects on sleep duration only for a few factors.

**Table 2.2: Associations between various factors and nocturnal sleep duration. Results are expressed as effect size in minutes (99% CI)**

| Variable | Univariate analysis | | Model 1* ($r^2$=0.39) | | Model 2** ($r^2$=0.47) | |
|---|---|---|---|---|---|---|
| | ß (99%CI) | P † | ß (99%CI) | P † | ß (99%CI) | P † |
| Male sex | -0.9 (-4.1; 2.4) | 0.493 | | | | |
| Age | -6.0 (-6.9; -5.1) | <0.001 | -5.5 (-6.2; -4.8) | <0.001 | -6.0 (-7.7; -4.2) | <0.001 |
| Education level | | <0.001 | | 0.453 | | 0.247 |
| High | ref. | | ref. | | ref. | |
| Medium | -14.9 (-18.7; 11.0) | | 0.7 (-2.6; 4.0) | | -4.6 (-11.0; 1.7) | |
| Low | -7.5 (-12.8; 2.2) | | -2.8 (-7.4; 1.7) | | -3.3 (-13.2; 6.5) | |
| Country | | <0.001 | | <0.001 | | <0.001 |
| Estonia | -74.9 (-79.7; -70.1) | | -72.5 (-78.0; -67.9) | | -59.5 (-70.4; -48.6) | |
| Italy | -66.5 (-71.1; -62.0) | | -64.5 (-69.6; -60.0) | | -49.7 (-60.5; -38.9) | |
| Hungary | -44.8 (-50.1; -39.6) | | -39.9 (-45.4; -34.8) | | -30.6 (-42.5; -18.8) | |
| Cyprus | -35.6 (-40.8; -30.4) | | -35.5 (-41.4; -30.5) | | -21.3 (-39.9; -2.8) | |
| Spain | -31.7 (-38.1; -25.4) | | -29.8 (-36.4; -22.9) | | -23.7 (-37.0; -10.3) | |
| Sweden | ref. | | ref. | | ref. | |
| Germany | 14.8 (10.3; 19.4) | | 17.5 (12.5; 22.2) | | 28.6 (18.2; 38.9) | |
| Belgium | 24.9 (18.0; 31.7) | | 24.6 (17.6; 31.3) | | 30.0 (15.6; 44.5) | |
| Fall/winter vs. Spring/summer | 10.5 (7.1; 13.9) | <0.001 | 4.0 (-1.0; 9.0) | <0.041 | 3.8 (-6.3; 13.8) | 0.331 |
| Daylight hours | -3.1 (-3.7; -2.5) | <0.001 | -0.4 (-1.3; 0.5) | <0.232 | -0.3 (-2.0; 1.4) | 0.655 |
| Normal weight vs. overweight | 20.6 (17.6; 23.7) | <0.001 | | | 5.4 (-1.1; 11.7) | 0.034 |
| Screen time | | <0.001 | | | | 0.043 |
| Not at all | ref. | | | | ref. | |
| <30 min | 0.5 (-8.3; 9.4) | | | | -3.5 (-22.3; 15.3) | |
| <1 h | -6.5 (-14.9; 1.9) | | | | -9.8 (-27.8; 8.1) | |
| >1 h and <2 h | -14.3 (-22.6; -5.9) | | | | -10.8 (-28.7; 7.1) | |
| >2 h and <3 h | -21.7 (-30.2; -13.1) | | | | -14.6 (-32.8; 3.6) | |
| >3 h | -34.6 (-43.1; -26.1) | | | | -13.2 (-31.5; 5.0) | |
| Play outdoors | 4.4 (3.6; 5.5) | <0.001 | | | 0.9 (-1.3; 3.1) | 0.301 |
| Time spent in sports club | | <0.001 | | | | |
| < 1 h | 21.1 (6.0; 36.3) | | | | | |
| ≥1 h and <4 h | 23.0 (16.8; 29.3) | | | | | |
| ≥4 h | ref. | | | | | |
| Mean (min) of moderate to vigorous activity | -0.1 (-0.3; 0.1) | 0.134 | | | | |
| *including age, parental education level, country, season, daylight hours; n = 8093 | | | | | | |
| ** Model 1 + modifiable variables (overweight, screen time, and time playing outside); n=8093 | | | | | | |
| † P-values of multivariate analyses of variance | | | | | | |

To account for the striking differences between age groups, we present adjusted mean values of sleep duration from Model 2, for preschool and primary school children by country (Figure 2.3).

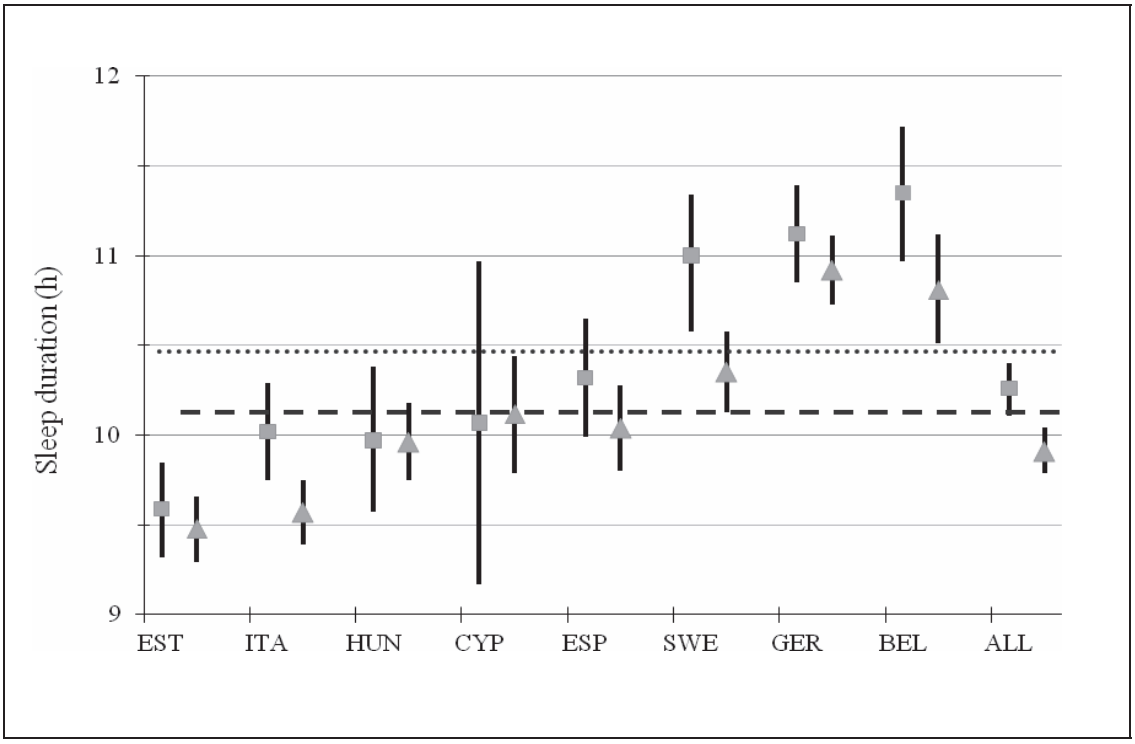


**Figure 2.3: Adjusted (model 2) mean sleep duration in pre-school (squares) and school (triangles) children, by country (99% CI)**

As expected, the adjusted sleep duration confirmed the trend observed for unadjusted sleep duration shown in Figure 2.2. However, tests for an interaction between country and age group showed no significant results. Of note, sex of the child and physical activity measured by means of accelerometry were not associated with sleep duration in the univariate analysis and were therefore not included in any of the models.

## DISCUSSION

The present study investigated nocturnal sleep duration in children aged 2 to 9 years from 8 European countries participating in the IDEFICS project. Adjusted as well as unadjusted mean sleep duration differed up to 1.7 hours in the participating countries, and disparities between northern, southern, and eastern Europe were striking. Age accounted for less difference, but still had a significant effect in all models. Season, daylight duration, overweight, behavioral factors, and parental education level were not found to be associated with sleep duration in the multivariate analysis.

Mean values and percentiles of sleep duration in children have been reported in studies from different countries.[17,30,31] Additionally, attempts to define a "normal" sleep duration and develop reference values have been made.[6,17] Our study demonstrates that

sleep duration differs significantly between countries within Europe. This is in line with previous reports that have compared sleep duration between countries and cultures. However, no other study has presented data that has been collected within large-scale studies including several countries to systematically compare results and test effects within and between European countries.

In our study children from southern and eastern European countries sleep less than children in northern countries. In fact, differences in bedtime routines have been shown in a study that compared infant care practices in the Boston area and a small town close to Rome, Italy.[32] Italian parents were less concerned about their children's sleep habits than parents of American children. In Italy, the integration of children in the adults' evening social activities and letting them fall asleep before going to bed is a common feature. Such unstructured and flexible bedtime habits escape our observation since they were not assessed in the present study and seem to result in later bedtimes in comparison to children from other industrialized countries. These results from Italy are paralleled by similar patterns reported from other southern European countries such as Spain and Greece.[32] Such cultural diversity needs to be kept in mind when developing recommendations or reference values of "normal" sleep duration in children. Another factor that should be taken into account is the season in which the survey takes place. Our data did not confirm the findings of another study[1] that showed differences in sleep duration due to seasonality. Another aspect that we hypothesized to have an effect on sleep duration, and which may partly explain the effect of season that has been found previously, was daylight duration. However, we could not support this hypothesis with our data. Since daylight duration is determined by season, we conducted sensitivity analysis excluding daylight duration from the multivariate model to avoid over-adjustment, but this did not result in relevant changes in the estimate for season.

Sleep needs change with age, especially in childhood. Our data were in line with other studies reporting significant changes in sleep duration in children of different age groups.[16,17] Due to the elevated sample size and the multicenter study design, our data offered the unique possibility to develop percentile curves for sleep duration of European children. A previous study presenting such curves was based on a much smaller sample size drawn from only one country (Switzerland).[17] However, our data show a more moderate decline of sleep duration by age in the European sample than the report from Switzerland. It can be assumed that the transition from preschool to primary school involves a change in sleep duration, if only due the modified daily routine.[33] To account for this difference, we conducted an age-stratified analysis with our final model and presented adjusted mean values for each country by age group.

Several studies have indicated an effect of sleep duration on overweight in children.[1,2,5-11] However, the direction and causality of this association is not yet clear, since very

few longitudinal studies are available, and to the authors' knowledge, no data have been published on the effect that overweight may have on sleep duration in healthy children. Anyway, our results do not support the hypothesis that overweight influences sleep duration, and further studies are necessary in order to investigate on this aspect.

Previous studies have shown variable results concerning the influence of sex and socioeconomic status on sleep duration. US studies have documented an association between sleep and those variables,[20] while our results are similar to those from a study in New Zealand, showing no such association.[1]

Concerning time spent in front of a television or computer screen, our results were not clearly in line with other studies showing an adverse effect of TV time on sleep duration.[1] However, the estimates for screen time suggest that there might be an inverse trend in the association between screen time and sleep duration in our data, even if a test for trend was statistically not significant at a = 0.01. A different categorization of screen time might have led to significant results in this context. It could be assumed that parents who have stricter rules concerning screen time are also more likely to have rules regarding bedtime routines, with the child going to bed earlier, resulting in longer sleep duration. We found that in the southern countries, 14.7% of the children watched TV more than 2 hours each day, while in eastern and northern Europe, these percentages were 9.8% and 6.7%, respectively. Against the background of the before-mentioned more flexible bedtime rules in southern families, this result could lead to the consideration that in those countries leisure time in general is less structured and rules concerning this matter are less strict than in other countries.

The effect of physical activity on sleep duration has also been discussed in other papers. A meta-analysis from the US has shown a weak impact of physical exercise,[34] whereas other studies could not report an association between moderate or vigorous physical activity and sleep duration.[1,35] Our data confirmed these findings, since we could not find the weekly hours spent in a sports club and the time spent playing outside being associated with sleep in the multivariate analysis.

Generally, our findings suggest that the effect of country-specific factors, such as culture—as it has already been discussed by Owens[22]—or environmental factors may overlay the individual determinants of sleep duration that have been found in previous studies.

The strengths of our study include a large dataset of international data—collected under strongly standardized procedures—with a population-based sample including children from different age groups, which allows for stratified analyses without losing much power. Weaknesses such as differences between participants and nonparticipants concerning age have been mentioned above. However, the age difference between

countries was less than six months and is not expected to lead to bias. Sleep duration in large-scale studies can be most objectively measured by means of accelerometry. Parental report seems to overestimate objectively measured sleep duration.[1] This possible bias is expected to be non-differential and hence should not distort the trends shown in our study. Another aspect that should be discussed is sleep duration on weekends. It may be expected that sleep duration differs between weekend and weekday nights and that different factors may influence these parameters. Since our data on sleep duration on weekend days were very limited in some countries and variability was very high between weekend days, we excluded weekend days from the analysis. The aspect of napping should be considered when interpreting differences between countries. Recent studies have reported an influence of daytime napping on nighttime sleep duration in children and cultural differences in napping patterns have been shown.[32] However, only data on nocturnal sleep duration were available in our study.

To the best of the authors' knowledge, this study is the first of its type to provide a large number of comparable data from several European countries on sleep duration. Based on this data, percentile curves for sleep duration in European children were developed to give an overview of the distribution of sleep duration in this population. Furthermore the present study found, that individual determinants such as overweight and behavioral factors, which have been found to influence sleep duration in children in other studies, did not show any effect after adjustment for age and country. These findings allow for the conclusion that country affiliation, which includes culture (e.g., parenting practices, culturally determined values) and environmental characteristics seems to be one (if not the main) factor that influences sleep duration in children—overlaying the effects of individual factors such as age, parental education, overweight, and behavioral habits. Further internationally comparable studies including napping behavior and more precise measurements of sleep characteristics will be needed to give a more comprehensive picture of factors determining sleeping behavior in different countries and cultures. This may offer further evidence for country-specific recommendations on adequate sleeping behavior of children.

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# 3 Sleep duration and overweight in European children Is the association modified by geographic region?

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**Study Objectives:** To investigate differences and a possible effect modification by geographical region in the association between sleep duration and overweight.

**Design:** Cross-sectional

**Setting:** Primary schools and preschools in 8 European countries.

**Participants:** 7867 children aged 2 to 9 years.

**Interventions:** Not applicable.

**Measurements**: Nocturnal sleep duration was assessed as part of a parental 24-h recall. Height and weight were measured by standardized procedures across centers. Data on personal, social, environmental and behavioral factors were collected using a standardized parental questionnaire.

**Results:** Sleep duration differed ($P < 0.001$) between European regions and normal vs. overweight children. A dose-dependent inverse association between sleep duration and overweight could be seen, with crude odds ratios ranging from 1.73 (99% CI 1.33; 2.25) for sleeping between 10 and 11 h to 3.81 (99% CI 2.85; 5.09) for sleeping less than 9 h (reference category >11 h). This persisted after adjustment, but remained significant only for sleeping less than 9 h per night (north: OR = 1.70; 99% CI 1.13; 2.58 vs. south: OR = 2.84; 99% CI 1.57; 5.12) if stratified by region. No effect modification by region could be found, but adjustment for region accounted for changes in the effect estimate for sleeping less than 9 h (OR = 2.22; 99% CI 1.64; 3.02). The association was stronger in school children than in preschool children.

**Conclusion:** Geographic region and related aspects—even if they do not seem to modify the association between sleep and overweight—should in any case be taken in consideration as a confounding factor on this association.

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## INTRODUCTION

An adequate amount of sleep is believed to be important for optimal health and functioning throughout life, and the effect of sleep duration on diverse health outcomes seems undisputable.[1] Concurrent with the worldwide increase of overweight and obesity, a decrease in sleep duration has been observed and mounting evidence in the recent years has identified sleep duration as a potentially new risk factor for overweight and obesity already in childhood.[1-8] Also an association between short sleep duration and metabolic dysfunction has been discussed.[9-11] Several studies suggest an influence of sleep on hormones including leptin, ghrelin, insulin, cortisol, and growth hormones. These hormonal changes potentially result in hormonal imbalances accounting for overweight and obesity.[12] Since overweight children often become overweight or obese adults, which increases the risk for secondary diseases including type 2 diabetes or cardiovascular diseases,[2,3,5,13] this risk factor may have a relevant impact on public health and needs to be further examined with special focus on children.

Data on sleep duration and its relation to overweight have been published for different age groups from several countries[1,12,14-18] but comparability of those results is limited by reasons of different study designs and methods. Moreover, it can be assumed that sleep duration as well as body mass index (BMI) are likely to be influenced by several cultural and environmental factors.[15,19-21] The present study reports data from an epidemiological survey conducted in children from 8 European countries. Data were collected within the framework of an international collaboration, according to a standardized protocol[22-24] and therefore allow for comparability and internal consistency of data. The study aims to investigate if there are significant differences in the association between sleep duration and overweight in diverse culture areas such as northern and southern Europe, where children are exposed to a broad range of different sleep durations[25] and if regional affiliations may even act as an effect modifier for this association. The possibility to statistically test for regional differences in the association is only possible, if a large data set and internationally comparable data is available. The present study gives an opportunity to appropriately investigate on these regional effects. Moreover the high degree of standardization of data collection in a multicenter study allows for comparability of the data, while the comparison of different studies is hampered by methodological heterogeneity. Thus the present study leaves less room for the occurrence of differences that can be attributed to methodological differences than a comparison of different studies from different countries would do.

## METHODS

The “identification and prevention of dietary- and lifestyle-induced health effects in children and infants” (IDEFICS) project is a population-based multicenter study which includes children aged 2 to 9 years from 8 European countries. Between September

2007 and May 2008, 31,543 children from schools and preschools in selected regions in Italy, Estonia, Cyprus, Belgium, Sweden, Hungary, Germany and Spain were asked to participate in the baseline survey (T0), and 16,864 (53.4%) accepted the invitation. Of those children 16,223 (51.4%) gave full information on sex, height, and weight and thus fulfilled the inclusion criteria. Data on BMI and sleep duration were available for 10,613 (65.4%) of 16,223 children. After exclusion of children reporting only sleep duration for weekend days and those without full information on all covariates, 7,867 (48.5%) children were eligible for the present analysis (more information on sleep data and the covariates is given in the respective paragraphs). Children with information on sleep duration did not differ from children without sleep information in terms of sex, while there were some significant differences concerning age in southern Europe, where children with sleep information were older than those without sleep data (mean difference 0.2 years, $p < 0.001$). No significant differences in age were seen in northern countries.

Two age groups were created with one group including children aged 2 to <6 years (preschool children) and the other group including children aged 6 to 9 years (school children). Additionally, age was included in the analysis as a continuous variable with increments of one decimal. Since previous studies,[19,26] as well as our own data[25] suggest that sleep habits and bedtime routines differ between southern and northern European countries, we decided to create two regional groups with southern Europe including Italy, Spain, Hungary and Cyprus and northern Europe including Sweden, Belgium, Estonia and Germany. In each country, the participating centers obtained ethical approval by their responsible authority. All children and their parents provided oral and written informed consent respectively for all examinations and/or the collection of samples, subsequent analysis and storage of personal data and collected samples. More detailed information on the study procedures are published elsewhere.[22,24]

**Anthropometry**

Anthropometric measurements were done according to a standardized manual in all centers. Body height was measured without shoes by trained staff using a portable stadiometer (SECA 225). Weight was measured by means of an adapted version of electronic scale (TANITA BC 420 SMA), with subjects wearing only underwear. Body mass index (BMI) was calculated and then categorized referring to cutoff points according to the criteria of International Obesity Task Force.[27] Our category "overweight" included overweight and obese children, while the reference category included normal and underweight children.

### Sleep Duration

Information on sleep duration was collected in the context of a standardized 24-h dietary recall (SACINA). SACINA is a computer-based instrument filled out by parents or guardian of each participating child and contained questions on the time at which the child got up in the morning and went to bed on the previous day. Data were collected on all days of the week, including weekends. However, weekday sleep is likely to be more representative of usual sleep duration, because children in the relevant age group are expected to have a more regular bedtime and get-up routine on weekdays than during the weekend. In fact, analysis of variance confirmed no significant differences in sleep duration from Monday to Thursday while there were significant differences between Fridays, Saturdays, and Sundays ($P < 0.001$). Therefore, only sleep duration data for the nights from Monday to Thursday were included in the analysis. If data on sleep duration was given for more than one night, the first weekday night was included in the analysis to ensure homogeneity of the variability within the data.

Nocturnal sleep duration was calculated as the difference between bed- and get-up time in the SACINA interview resulting in a continuous variable. For our multivariate analysis we created 4 sleep categories (=9 h, >9 h to =10 h, >10 h to =11 h, >11 h). The smallest number of subjects per category was 1,441 (sleeping more than 11 h).

### Confounding Variables

Data on personal, social, environmental, and behavioral factors of each child, such as time spent in front of a television or computer screen (screen time) and parental education level was collected by means of a standardized parental self-completion questionnaire. Education level was categorized according to the International Standard Classification of Education (ISCED). Two levels of education (low vs. medium / high) were created out of the 6 ISCED levels, with ISCED levels 0-2 being defined as low education, and =3 being defined as medium or high education. Information on dietary habits was obtained from a standardized Food Frequency Questionnaire. Since recent research suggests an association between fat consumption and sleep duration,[28] a fatty food variable was included in the present analysis. Consumption of fatty foods was calculated by summing consumption frequencies of fried potatoes, whole fat milk, whole fat yoghurt, fried fish, fried meat, butter/margarine, savory pastries and fritters and fried eggs and dividing it by consumption frequency of all food items. The derived propensity scores depicted the percentage of fatty food consumption resulting in a continuous variable.

Children's physical activity was surveyed with accelerometers (Actigraph GT1M and ActiTrainer) with cutoffs for moderate to vigorous physical activity (MVPA) according to Sirard et al.[29], resulting in a continuous variable of daily minutes spent in MVPA.

The accelerometers were worn around the waist for 3 consecutive days and had to be taken off for swimming, showering or bathing, and during sleep. The parents were asked to keep records of each time the device was taken off in an accelerometer diary. Information on daylight duration was obtained by month for each study center from astronomical tables available at www.timeanddate.com. Daylight duration is given in decimal hours. Temperature data (monthly average) was based on climate tables at www.woeurope.eu. Both, daylight duration and temperature were included as continuous variables in the analysis.

**Statistical Analysis**

Differences in continuous variables were compared using the Student *t*-statistics, while the $?^2$ statistic was used for comparison of categorical variables. To estimate the association between sleep duration and overweight controlled for confounding factors, we fitted logistic regression models, including variables that were related with both, sleep and overweight in univariate analysis and that accounted for =10% change in the estimate for sleep duration in our general model (model 1). The significance level was set at a = 0.01 to account for the elevated sample size. In a second step we conducted the same regression stratified by European region (northern vs. southern) to check for possible differences in the effect estimate for sleep duration categories (model 2). Subsequently we created our final model including region as an additional control variable (model 3). Tests for interaction were conducted, including interaction terms for region per sleep duration and age group per sleep duration in the final model. Statistical analysis was done with SAS Version 8.2 (SAS Institute, Cary, North Carolina, USA).

**RESULTS**

There were slightly less children from southern than from northern Europe in the present study sample and the proportion of school children was a little higher than the proportion of preschool children. The proportion of boys and girls was about equal (Table 3.1).

Student *t*-statistics indicated that school children slept on average 0.33 h (99% CI 0.28; 0.39) less than preschool children. Sleep duration also differed significantly between overweight and normal weight children, with normal weight children sleeping on average 0.34 h (99% CI 0.28; 0.41) more than overweight children. Accordingly, sleeping >10 h (median of sleep distribution in present data) was more common among normal weight children than among overweight children (56.7 vs. 41.0%, $P < 0.001$). Figure 3.1 shows the distribution of sleep duration by weight status.

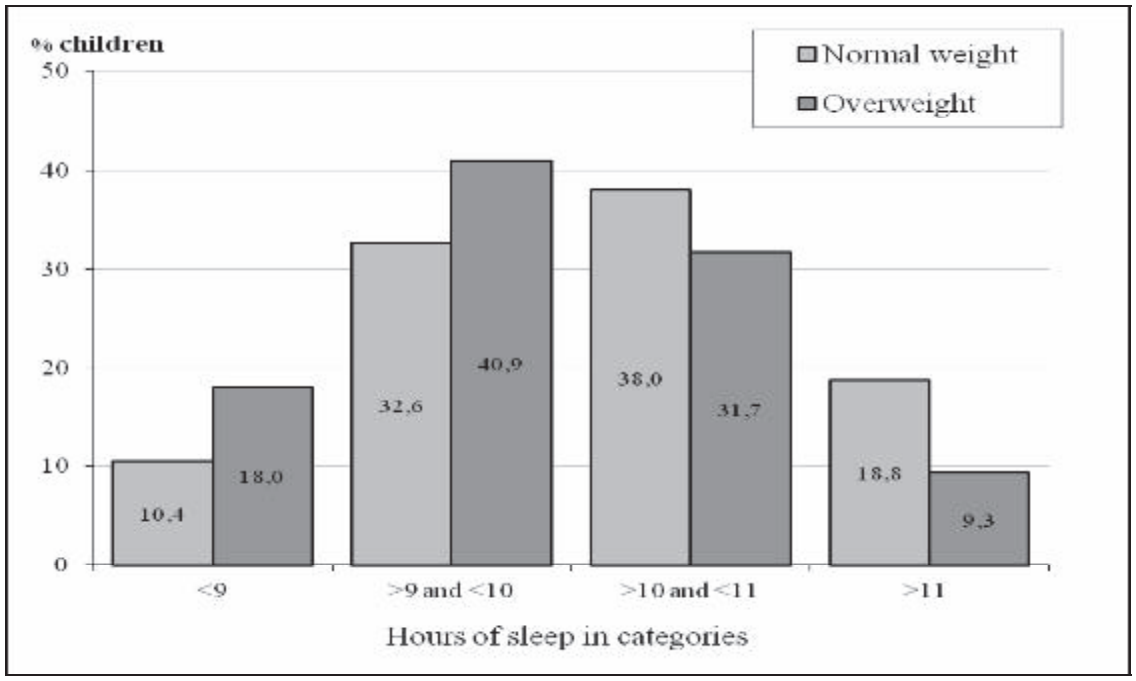


**Figure 3.1: Sleeping hours per night by weight**

A clear gradient in sleep duration could also be seen between regions, with children from northern Europe sleeping 0.59 h (99% CI 0.54; 0.64) longer than children in southern Europe. The percentage of children who slept >10 h per night was 40.1% in southern and 65.5% in northern countries ($P < 0.001$). The distribution of sleep duration by region is shown in Figure 3.2.

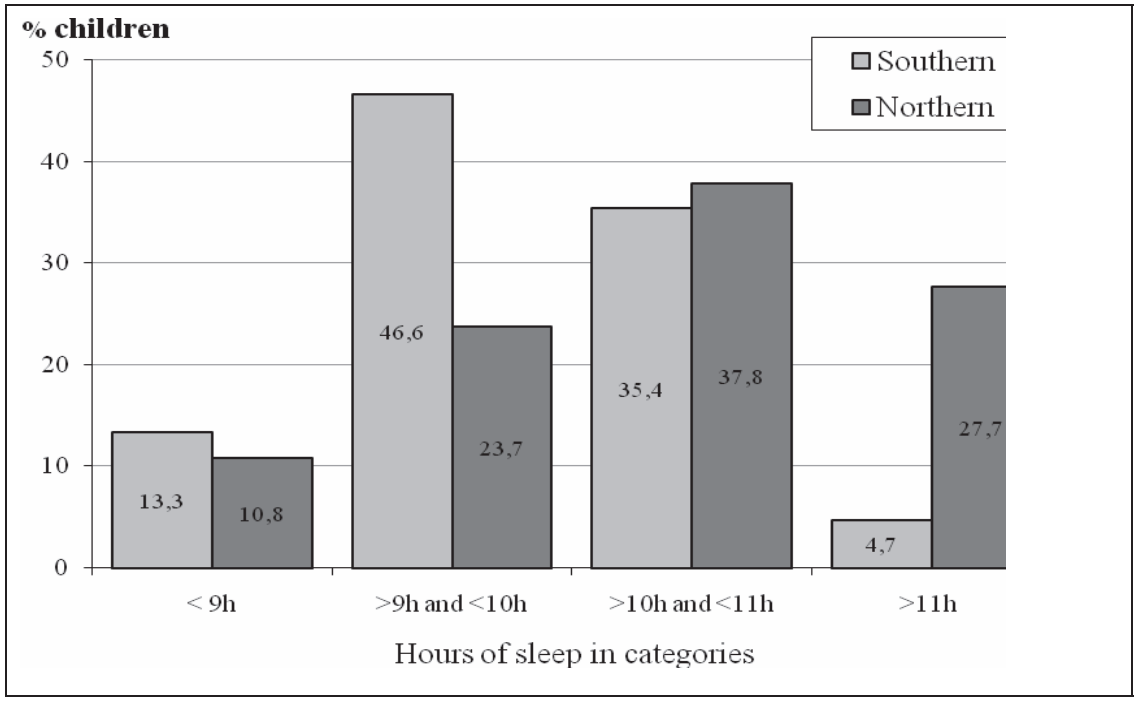


**Figure 3.2: Sleeping hours per night by region**

An overview of the association between possible confounder variables and sleep as well as overweight is given in Table 3.1. Age and temperature fulfilled the criteria for inclusion in multivariate analysis, and we therefore included them as covariables in our models.

**Table 3.1: Characteristics of study sample and associations of possible confounder variables with overweight and minutes of sleep duration**

| Variable | N (%) | Mean (SD) | Association with overweight | | Association with sleep duration | |
|---|---|---|---|---|---|---|
| | | | OR (99% CI) | P-value | ß (99% CI) | P-value |
| Region (southern Europe) | 3579 (45.5) | - | 2.82 (2.43; 3.29) | <0.001 | -37.7 (-40.98; -34.44) | <0.001 |
| School children | 4348 (54.0) | - | 2.04 (1.76; 2.39) | <0.001 | -20.94 (-24.33;-17.54) | <0.001 |
| Age | 7867 (100) | 6.0 (1.8) | 1.23 (1.18; 1.28) | <0.001 | -6.32 (-7.23; 5.41) | <0.001 |
| Female sex | 3864 (49.1) | - | 1.20 (1.04; 1.39) | <0.001 | 1.04 (-2.39; 4.48) | 0.411 |
| Low education | 1202 (15.3) | - | 1.86 (1.55; 2.23) | <0.001 | -2.28 (-7.07; 2.48) | 0.217 |
| Daily screen time (>3h/day) | 1421 (18.1) | - | 1.45 (1.21; 1.73) | <0.001 | -24.2 (-28.98; -20.15) | <0.001 |
| MVPA (<15 min/day) | 6805 (86.5) | - | 1.64 (1.29; 2.08) | <0.001 | 0.94 (-4.09; 5.97) | 0.631 |
| Fatty food consumption | 7867 (100) | 10.7 (5.9) | 0.96 (0.95; 0.98) | <0.001 | 0.54 (0.25; 0.83) | <0.001 |
| Daylight duration | 7867 (100) | 11.6 (2.8) | 0.98 (0.95; 1.01) | 0.023 | -2.94 (-3.56; -2.33) | <0.001 |
| Temperature | 7867 (100) | 9.2 (5.5) | 1.06 (1.05; 1.08) | <0.001 | -1.42 (-1.73: -1.11) | <0.001 |

A dose-dependent association between sleep duration and overweight could be observed in all models (Table 3.2). Taking a sleep duration =11 h as the reference category, the crude ORs for sleep duration ranged from 1.73 (99% CI 1.33; 2.25) for 10 to 11 h to 3.81 (99% 2.85; 5.09) for =9 h. In model 1 the associations persisted and were still significant if adjusted for the above mentioned co-variables with ORs of 1.36 (99% CI 1.05; 1.79) for 10 to 11 h and 2.89 (99% CI 2.15; 3.89) for =9 h of sleep. Similar results to those of model 1 could be seen in stratified analysis (model 2), even if not all associations remained significant. Estimates for sleeping =9 h differed slightly between northern and southern Europe, with the ORs being 1.70 (99% CI 1.13; 2.58) in the north

and 2.84 (99% CI 1.57; 5.12) in the south. Also model 3 showed a dose-dependent relationship, with sleeping <9 h accounting for a more than twofold risk of being overweight (OR = 2.22; 99% CI 1.64; 3.02). Inclusion of an interaction term did not show significant results (P = 0.075) and accounted for an only marginal change in estimate in this model. Stratified by age, model 1 resulted in higher estimates for school children than for preschool children.

**Table 3.2: Associations of sleep duration and overweight (reference >11 h). Results are presented as OR (99%CI)**

| | =11h and >10h | =10h and >9h | =9 h |
|---|---|---|---|
| **Crude OR** | | | |
| Preschool | 1.37 (0.96; 1.96) | 1.82 (1.27; 2.61) | 2.03 (1.32; 3.14) |
| School | 1.92 (1.27; 2.89) | 3.02 (2.02; 4.51) | 5.12 (3.31; 7.92) |
| All | 1.73 (1.33; 2.25) | 2.67 (2.07; 3.45) | 3.81 (2.85; 5.09) |
| **Model 1*** | | | |
| Preschool | 1.18 (0.82; 1.70) | 1.52 (1.05; 2.19) | 1.85 (1.19; 2.89) |
| School | 1.78 (1.18; 2.69) | 2.64 (1.76; 3.96) | 4.57 (2.93; 5.11) |
| All | 1.36 (1.05; 1.79) | 1.91 (1.47; 2.49) | 2.89 (2.15; 3.89) |
| **Model 2**** | | | |
| **North** | | | |
| Preschool | 0.97 (0.62; 1.53) | 0.98 (0.57; 1.67) | 0.77 (0.36; 1.64) |
| School | 1.67 (1.00; 2.77) | 2.21 (1.30; 3.78) | 3.19 (1.76; 5.78) |
| All | 1.17 (0.85; 1.63) | 1.40 (0.99; 1.99) | 1.70 (1.13; 2.58) |
| **South** | | | |
| Preschool | 1.12 (0.51; 2.67) | 1.45 (0.64; 3.30) | 2.31 (0.97; 5.54) |
| School | 1.11 (0.51; 2.44) | 1.46 (0.68; 3.15) | 3.20 (1.43; 7.17) |
| All | 1.15 (0.65; 2.03) | 1.47 (0.84; 2.57) | 2.84 (1.57; 5.12) |
| **Model 3***** | | | |
| Preschool | 0.93 (0.63; 1.36) | 1.08 (0.73; 1.61) | 1.38 (0.87; 2.19) |
| School | 1.46 (0.96; 2.22) | 1.88 (1.23; 2.86) | 3.53 (2.24; 5.54) |
| All | 1.10 (0.84; 1.45) | 1.36 (1.03; 1.80) | 2.22 (1.64; 3.02) |
| | | | |
| *adjusted for age, temperature | | | |
| **Model 1 stratified by European region | | | |
| ***Model 1 + European region | | | |

In the analysis stratified by region (model 2), no association between sleep and overweight could be seen in preschool children. In school children the estimates were higher in northern countries than in southern countries, where the only significant

association and the highest estimate was observed for sleeping <9 h (OR = 3.20; 99% CI 1.43; 7.17).

If adjusted for geographic region (model 3), sleeping 9 to 10 h (OR = 1.88; 99% CI 1.23; 2.86) and <9 h (OR = 3.53; 99% CI 2.24; 5.54) was associated with overweight in school children, while no such association was observed in preschool children. The interaction term for region per sleep duration was not statistically significant nor did it account for relevant changes in estimate in any of the age groups.

## DISCUSSION

Our multivariate models confirmed the observation made in bivariate analyses, that shorter sleep duration is associated with a higher probability of being overweight. The association though appeared to be much stronger in school children than in preschool children. Our data showed only weak evidence that regional differences might act as an effect modifier in the association between sleep duration and overweight. However, adjustment for geographic region attenuated the association between sleep duration and overweight to some degree.

Data on sleep duration of children has been presented in studies from different countries and for different age groups[12,16,30,31] and attempts to define a "normal" sleep duration[16] have been undertaken. Our study demonstrated that sleep duration differs between regions even within Europe. Children from southern Europe seemed to sleep less than children from northern countries. In fact, cultural differences in sleep duration have been reported also in other studies.[15,26] The advantage of our study is that it presents comparable epidemiological data for European regions. As for the association between sleep duration and obesity, our data confirm findings from other cross-sectional studies.[1-5,7,8] Even if previous findings were largely consistent between countries and continents with regard to the direction of the association,[7] differences in effect sizes have been observed.[3,12] However, comparison of those results is hampered, due to differing study designs and methods. To account for this limitation we wanted to find out, whether the association between sleep duration and overweight would differ between geographic regions, in this case between children from northern and southern European countries. Differences between effect estimates could indicate that factors linked to geographic area such as cultural habits including behavioral differences or environmental factors might mediate the association between sleep duration and overweight. Detailed cross-cultural research on factors that may interact with or complete existing biological as well as behavioral hypotheses for the association between sleep and weight is limited. Based on our data, regional affiliation did not seem to considerably modify this association, although an adjustment for region accounted for relevant changes in the effect estimate for sleep, even if additionally adjusted for

environmental factors such as temperature in all models. This may be explained by factors that influence overweight and differ by country but are not associated with sleep duration and therefore were not included in our model (e.g., parental smoking habits[32]).

Age-stratified analysis showed a stronger association between sleep and overweight in school children than in preschool children and the relation seems to increase after transition from preschool to school. This contradicts a recent study that did not find any age dependency in the association between sleep duration and overweight.[33]

Based on a systematic review on the association between sleep duration and overweight in children, adolescents and adults, it has been suggested that the relationship between sleep duration and weight may weaken with age over the lifespan.[7] Our data showed an increasing effect with age in children below the age of ten, indicating that the association may decrease later in life. Hence, it would be of interest to detect if and at which age this possible inversion of the effect size takes place. To date, data on the impact of age on the association between sleep and overweight in children is limited, calling for a more detailed investigation of this topic in younger age groups.

One of the strengths of our study is the large dataset of international data with a population based sample, including children from different age groups which allows for stratified analyses with sufficient statistical power. Age differences between children with sleep information and children without sleep information were significant, but small and therefore should not distort the association under investigation. Sleep duration in large scale studies can be most objectively measured by means of accelerometry, while parental report seems to overestimate the objectively measured sleep duration.[1] However, we do not see any reason why this potential over reporting should be differential between parents of normal weight children as compared to parents of overweight children. A social desirability bias in reporting sleep-related data seems to be improbable because the possible association with overweight is not perceived by the general population. Last but not least, it may be mentioned that the study does not claim to be representative for the respective countries.

To the best of the authors' knowledge, this study is the first of its type to provide a large amount of comparable data from several European countries on the association between sleep duration and overweight in children. The results discussed above allow for the conclusion that geographic region and related factors—even if they did not seem to modify the association between sleep and overweight—should in any case be taken into consideration as a confounding factor for this association. The fact that sleep duration remained associated with overweight after adjustment for regional, behavioral and environmental variables—at least in school aged children—supports the hypothesis that a major part of the association may be explained by biological processes. To specify in

more detail the cultural and environmental characteristics playing a role in this context, longitudinal internationally comparable data on these aspects will be needed.

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# 4 Sleep duration and overweight in different stages of life

Sabrina Hense , Otmar Bayer

**Abstract**

Sleep deprivation is considered as a serious risk factor with a relevant public health impact due to its multiple effects, which we are just beginning to understand. This is underlined by the growing number of studies in the past decades that investigate especially the association between sleep duration and overweight.

This review gives an overview of the current state of research and potential biological mechanisms. The evidence from epidemiological studies suggests an association between short sleep duration and overweight in children as well as in adults. Different biological mechanisms have been discussed in this context, with a special focus on hormonal changes as the potential mediator. To include sleep in a comprehensive strategy to prevent overweight, intervention studies, that analyse the potentially protective effect of prolonged sleep duration, are necessary.

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**Zusammenfassung**

Schlafmangel ist aufgrund seiner vielfältigen Auswirkungen, deren Wirkmechanismen wir erst zu verstehen beginnen, als ernst zu nehmender Risikofaktor mit großer Public Health Relevanz zu sehen. Dies wird auch durch die steigende Zahl an Studien belegt, die sich speziell mit der Frage nach dem Zusammenhang zwischen Schlafdauer und Übergewicht befassen.

Die vorliegende Übersichtsarbeit gibt einen Überblick sowohl über den aktuellen Stand der Forschung zu diesem Thema als auch über mögliche biologische Mechanismen. Die Evidenz aus epidemiologischen Studien deutet sowohl bei Kindern als auch bei Erwachsenen auf einen Zusammenhang zwischen kurzer Schlafdauer und Übergewicht hin. Die Ergebnisse bei Kindern sind konsistenter, als bei Erwachsenen. Als Ursache des Zusammenhangs werden mehrere Mechanismen diskutiert, wobei vor allem hormonelle Veränderungen im Fokus stehen. Um Schlaf in eine umfassende Strategie zur Bekämpfung von Übergewicht einbeziehen zu können, sind nun Interventionsstudien erforderlich, die einen potentiellen protektiven Effekt von verlängerter Schlafdauer untersuchen.

## HINTERGRUND

Sowohl die Einstellung zu Schlaf als auch das Schlafverhalten haben sich in den letzten Jahrhunderten stetig verändert, der Schlafbedarf aus biologischer Sicht ist jedoch der gleiche geblieben. Unsere Vorstellungen von ‚richtigem' oder ‚gesundem' Schlaf variieren sowohl von Kultur zu Kultur als auch in Abhängigkeit vom aktuellen wissenschaftlichem Verständnis in Bezug auf diesen Zustand (1). Der Psychologe G. Stanley Hall erklärte vor bereits mehr als einem Jahrhundert, dass alles dafür getan werden solle, einen so tiefen und sowohl qualitativ als auch quantitativ einwandfreien Schlaf wie möglich zu fördern. Alles, was dieses Ziel ernsthaft beeinträchtigen könnte, solle gewissenhaft gemieden werden (2).

Dennoch wurde in den letzten Jahrzehnten eine Verkürzung der Schlafdauer berichtet. So zeigten zum Beispiel Untersuchungen aus den USA einen Rückgang der durchschnittlichen Schlafdauer um 1,5 bis 2 Stunden in den letzten 50 Jahren (3) und auch eine finnische Studie berichtete dieses Phänomen (4). Zeitgleich zur Reduktion der Schlafdauer wurde ein weltweiter Anstieg der Prävalenz von Übergewicht und Adipositas beobachtet und die Evidenz für Schlafdauer als einen neuen Risikofaktor für Übergewicht und Adipositas, der bereits im Kindesalter eine Rolle zu spielen scheint, wächst durch die stetig steigende Anzahl an Studien, die diesen Zusammenhang untersuchen (5-10). Übergewichtige Kinder haben ein erhöhtes Risiko, im Erwachsenenalter übergewichtig zu bleiben oder adipös zu werden, was wiederum das Risiko für chronische pathologische Zustände wie Diabetes Typ 2 oder kardiovaskuläre Erkrankungen erhöht (11). Vor diesem Hintergrund ist dem Thema Schlaf, und in diesem Fall vor allem der Schlafdauer, durchaus eine erhebliche Public Health Relevanz zuzuschreiben. Bedenkt man zudem, dass chronische Krankheiten wie Diabestes und Herz-Kreislauferkrankungen einen großen Anteil der Kosten im Gesundheitssystem ausmachen (12), ist ein detailliertes Verständnis des Zusammenhangs zwischen Schlaf und Gewichtsstatus auch aus gesundheitspolitischer Sicht wünschenswert.

Im Folgenden wird zunächst ein Überblick über die Entwicklung der Schlafdauer in verschiedenen Lebensphasen gegeben. Darauf aufbauend folgt eine Darstellung der in diesem Kontext diskutierten Mediatoren und biologischen Mechanismen, gefolgt von der Vorstellung von Verfahren zur Erfassung von Schlafmustern und des aktuellen Forschungsstandes bezüglich epidemiologischer Studien zu Schlaf und Übergewicht bei Erwachsenen und Kindern. Vor dem Hintergrund dieser Studienergebnisse werden abschließend mögliche Limitationen bezüglich der Untersuchung des Zusammenhangs zwischen Schlaf und Gewichtsstatus und aus den Ergebnissen resultierende Implikationen diskutiert.

Zu Schlafdauer und Übergewicht liegen bereits verschiedene Übersichtsarbeiten und Meta-Analysen vor. Erst kürzlich erschien ein systematischer Review, der alle bis

Anfang 2009 veröffentlichten Längsschnittstudien zum Thema zusammenfasst (13). Daher basiert die vorliegende Arbeit zum einen auf den Ergebnissen bereits bestehender Übersichten und ergänzt diese durch Originalartikel zum Thema, die seit Januar 2009 veröffentlicht wurden. Die Arbeit stützt sich hierbei vor allem auf Ergebnisse aus longitudinalen Studien, da Querschnittsdaten aufgrund ihres Designs nur bedingt Aussagen zu kausalen Zusammenhängen zulassen und eine solche Einschränkung in Hinblick auf die umfassende Datenlage nach Sicht der Autoren sinnvoll ist. Querschnittsstudien werden nur dann herangezogen, wenn sie die einzige verfügbare Evidenz zur jeweiligen Fragestellung darstellen.

## SCHLAF IN VERSCHIEDENEN LEBENSPHASEN

Die nächtliche Schlafdauer ist von diversen Faktoren abhängig und unterliegt einer hohen Variabilität zwischen Individuen. So zeigte eine aktuelle Studie, dass Schlafdauer nicht nur durch interne, sondern auch durch externe Faktoren wie zum Beispiel regionale und kulturelle Aspekte beeinflusst wird (14). Im Gegensatz hierzu gilt Schlafdauer innerhalb eines Individuums als sehr stabil (15). Das Schlafbedürfnis ändert sich jedoch in verschiedenen Lebensphasen und sinkt in der Regel mit dem Alter. Dementsprechend brauchen Säuglinge und Kleinkinder nach Angaben der Bundeszentrale für Gesundheitliche Aufklärung (BZgA) und der American Academy of Sleep Education zwischen 12 und 16 Stunden Schlaf über den Tag verteilt (polyphasisches Schlafmuster) (16;17). Circa die Hälfte dieser Zeit befinden Kinder sich in diesem Alter im so genannten REM Schlaf (Rapid Eye Movement). Diese Phase nennt sich auch ‚Traumschlaf', da hierbei am intensivsten geträumt wird. Bei Kindern im Kindergartenalter konzentriert sich der Schlaf bereits mehr auf die Nacht, wobei ca. 11-13 Stunden Schlaf pro Nacht empfohlen werden. Der Anteil an REM Schlaf sinkt hierbei auf circa 35%. Die Empfehlungen für Grundschulkinder sprechen für 10 bis 11 Stunden Schlaf pro Nacht (16;17) und für Jugendliche wird ein Schlafbedürfnis von ca. 9 Stunden berichtet (15). Erwachsene benötigen ungefähr 8 Stunden Schlaf pro Nacht und mit steigendem Alter kehren Menschen zum polyphasischen Schlafmuster zurück, wobei die kumulative Schlafdauer über den Tag verteilt in der Regel keinen großen Veränderungen unterliegt (15).

## BIOLOGISCHE MECHANISMEN

Als Ursache des Zusammenhangs zwischen Schlafdauer und Körpermasse werden mehrere, möglicherweise konkurrierende Mechanismen diskutiert. Im Folgenden werden die verschiedenen Hypothesen und die zugrunde liegenden biologischen Zusammenhänge dargestellt.

Die wohl intuitivste Hypothese in Bezug auf den Zusammenhang zwischen Schlaf und Übergewicht geht davon aus, dass verhaltensbezogene Mechanismen der Assoziation

zugrunde liegen. Demnach haben Menschen in einer Umgebung mit Nahrungsüberfluss, wenn sie weniger schlafen, schlicht mehr Zeit, um Nahrung aufzunehmen (18). In einer Studie bei erwachsenen Männern konnte dieser simple Zusammenhang nicht bestätigt werden (19). Untersuchungen bei Jugendlichen zeigten hingegen einen erhöhten Konsum von fetthaltigen Lebensmitteln bei Teilnehmern mit kurzer Schlafdauer (20). Ferner wird berichtet, dass Schlafmangel mit *verminderter Impulskontrolle* und einer *reduzierten Fähigkeit zur Gratifikationsverzögerung* einhergeht, was wiederum mit vermehrter Nahrungsaufnahme in Verbindung gebracht wird (21).

Für eine gegensätzliche Richtung der Assoziation zwischen Schlafdauer und Körpermasse spricht die Beobachtung, dass das Gehirn als bedeutender Glukoseverbraucher im Schlaf weniger *Glukose* aufnimmt (22). Dies würde für einen geringeren BMI bei Personen mit kurzer Schlafdauer sprechen.

Weitere Hypothesen beziehen sich vor allem auf endokrine Faktoren, die als Mediatoren zwischen Schlaf und Gewichtszunahme diskutiert werden.

Eines der in diesem Zusammenhang diskutierten Hormone ist *Somatotropin* (STH) (23;24), ein im Hypophysenvorderlappen gebildetes Peptidhormon, welches das Wachstum fördert und im Non-REM-Schlaf sezerniert wird. Dies könnte bei Kindern und Jugendlichen mit Schlafmangel zu einer kleineren Körpergröße und somit zu einem höheren BMI (Körpergewicht/Körpergröße²) führen. Allerdings fand sich in den Daten des Kinder- und Jugendgesundheitssurveys 2003-2006 (KiGGS) kein Zusammenhang zwischen Größe und altersadjustierter Schlafdauer (25), was gegen diese Hypothese spricht. Ein anderer möglicher Einfluss von STH auf das Körperfett besteht in der Modulation der Lipoproteinlipase-Aktivität (26). *Lipoproteinlipase* ist ein Enzym, das beim Transfer von Fett aus Transportproteinen im Fettgewebe eine Schlüsselrolle spielt (27). Durch Schlafmangel erniedrigtes STH, konsekutive Disinhibition und damit vermehrte Aktivität des Enzyms könnten auf diesem Weg zu einer erhöhten Fettspeicherung führen.

Weitere Faktoren, die im vorliegenden Kontext zunehmend diskutiert werden, sind die Hormone *Ghrelin* und *Leptin*. Ghrelin ist ein appetitsteigerndes Hormon, das vom Magen produziert wird. Leptin dagegen wirkt appetithemmend und wird hauptsächlich vom Fettgewebe produziert. Wie in Labor- (28;29) und epidemiologischen Studien (30;31) gezeigt wurde, geht eine verkürzte Schlafdauer mit erhöhten Ghrelin- und erniedrigten Leptinspiegeln im Blut einher. Beides könnte einerseits somit den negativen Zusammenhang von Körpermasse und Schlafdauer erklären. Andererseits steigt der Leptinspiegel mit der Körperfettmasse, was den Zusammenhang zwischen Schlaf, Leptin und Übergewicht komplex macht und bei dahingehenden Analysen zu berücksichtigen ist.

Des Weiteren spielt *Insulin* als anaboles Hormon eine wichtige Rolle im Energiehaushalt. Es regelt die Glukoseaufnahme aus dem Blut und wirkt lipogenetisch. Sollte das Insulin für die schlafbedingte Gewichtszunahme verantwortlich sein, würde man eine erhöhte Ausschüttung des Hormons und/oder eine gesteigerte Insulinsensibilität erwarten. Tatsächlich aber belegen Laborstudien (32) sowie epidemiologische (33;34) Untersuchungen bei Schlafmangel einheitlich eine geringere Glukosetoleranz; die dort verwendeten zusammengesetzten Maße für Insulinresistenz (homeostatic model assessment HOMA) und Ergebnisse des oralen Glukosetoleranztests verwehren allerdings den Einblick in die zugrunde liegenden Mechanismen. Die Insulinsekretion ist tageszeitunabhängig im frühen Schlaf (vermehrt im so genannten slow-wave-sleep) erhöht und fällt dann im späteren Schlaf ab (35). In diesem Zusammenhang ist es interessant, dass eine Beobachtungsstudie an 27 normalgewichtigen Personen zeigte, dass bei weniger als 6,5 Std. Schlaf eine Erhöhung der C-Peptid-Spiegel nachweisbar war, was eine erhöhte Insulinsekretion anzeigt (36).

Ein weiteres Hormon, was im Zusammenhang mit Schlaf und Übergewicht diskutiert wird, ist *Kortisol*. Kortisol ist ein kataboles, Zucker mobilisierendes Steroidhormon mit einem breiten Wirkungsspektrum. Neben seinen Auswirkungen auf den Kohlenhydrathaushalt hat es vor allem Effekte auf den Fettstoffwechsel und den Proteinumsatz. Studien im Labor zeigten teils niedrigere (37), teils unveränderte (38;39) teils höhere (40) Kortisolspiegel nach Schlafentzug unterschiedlichen Grades. Die konkrete Rolle, die Kortisol bezüglich des Zusammenhangs zwischen Schlaf und Übergewicht spielt, ist dementsprechend weitgehend unklar.

Generell zeigt dieser kurze Abriss, dass aktuell zwar zahlreiche Hypothesen über biologische Mechanismen und potentielle Mediatoren in der Assoziation zwischen Schlafdauer und der Entstehung von Übergewicht vorliegen, die Forschung aber bis heute noch weit von einem detaillierten Verständnis dieses Zusammenhangs entfernt ist.

## MESSUNG VON SCHLAFDAUER

Die Erfassung von Schlafverhalten und Schlafdauer stellt besonders im Rahmen von epidemiologischen Studien ein Problem dar.

Während in experimentellen Laborstudien Schlaf präzise aufgezeichnet und ggf. experimentell beeinflusst werden kann, ist dies in epidemiologischen Studien aufgrund organisatorischer und finanzieller Begrenzungen in der Regel nicht möglich. Zudem ist es wahrscheinlich, dass das Schlafverhalten durch die künstliche Situation im Schlaflabor beeinflusst wird. Aussagen über das Schlafverhalten im Alltag sind somit anhand solcher Daten nur begrenzt möglich.

Daher müssen in populationsbasierten Studien andere Methoden für die Erfassung der Schlafdauer angewendet werden. Die eingesetzten Instrumente zur Erhebung der Schlafdauer variieren erheblich zwischen den den Autoren bekannten Studien und reichen von einfachen Fragebögen zum Schlafverhalten über Schlaftagebücher bis hin zu objektiven Messverfahren mittels Akzelerometrie. Akzelerometrie ist ein Verfahren zur Erfassung von Schlaf-Wachmustern und zirkadianen Rhythmen durch Bewegungs- und Beschleunigungsmessung. Akzelerometer werden zur Schlafmessung in der Regel am Handgelenk getragen und gelten aktuell als die valideste Methode für Schlaferfassung in epidemiologischen Studien (41).

Da kurze, akute Schlafdeprivation z. T. andere Folgen hat als eine längerfristig verkürzte Schlafdauer (42), besteht die Stärke epidemiologischer Studien darin, habituelle Schlafgewohnheiten zu erfassen. Dies gilt jedoch besonders für Fragebogen-basierte Studien, da die Tragedauer von Akzelerometern begrenzt ist; sie beträgt in den meisten Studien lediglich einen Tag, gelegentlich bis zu einer Woche (43). Aufgrund der hier dargestellten methodischen Unterschiede in der Messung von Schlafdauer wird ein direkter Vergleich von Studienergebnissen, die auf unterschiedlichen Messmethoden basieren, erschwert.

## EPIDEMIOLOGIE

Im Rahmen der Literaturrecherche in Pubmed ergaben sich bei der Suche nach ("sleep"[MeSH Terms] OR "sleep"[All Fields]) AND ("overweight"[MeSH Terms] OR "overweight"[All Fields]) 967 Treffer für den Zeitraum Januar 2009 bis April 2011. Nach dem Ausschluss von Artikeln, die sich nicht spezifisch mit dem Zusammenhang zwischen Schlafdauer und Übergewicht im Rahmen von populationsbasierten Studien befassten, lagen insgesamt 26 neue Artikel zum Thema vor, wovon 7 Studien longitudinale Ergebnisse zur Fragestellung lieferten (44-50).

Im Folgenden wird der aktuelle Forschungsstand bezüglich der epidemiologischen Literatur zu Schlafdauer und Übergewicht für Erwachsene und Kinder getrennt zusammengefasst.

### Erwachsene

Den Autoren lagen 11 Längsschnittstudien (Tabelle 4.1) bei Erwachsenen bezüglich des Einflusses von Schlafdauer auf Übergewicht vor (46-48;50-57). Davon wurden 4 Studien nach Januar 2009 veröffentlicht und waren somit in keiner bis heute erschienenen Übersichtsarbeit zu dem interessierenden Thema einbezogen (46-48;50).

Insgesamt waren die Ergebnisse bei Erwachsenen inkonsistent.

**Table 4.1: Übersicht über Studien mit Längsschnittdaten zum Zusammenhang zwischen Schlafdauer und Übergewicht bei Erwachsenen (nach Erscheinungsjahr).**

| Autor, Jahr (Ref) | Follow-Up Dauer | N | Alter bei Beginn der Studie | BMI Messung | Schlafmessung | Ergebnisse |
|---|---|---|---|---|---|---|
| Lopez-Garcia, 2001 (55) | 2 Jahre | 3,576 | > 60 | Gemessener BMI | Persönliches Interview | Kein Zusammenhang bei Männern. U-förmiger Zusammenhang bei Frauen. |
| Hasler, 2004 (53) | | 496 | 27 | Berichteter BMI | Fragebogen | Negativer Zusammenhang. |
| Patel, 2006 (56) | | 68,183 (Frauen) | 30-55 | Berichteter BMI | Fragebogen | Negativer Zusammenhang. |
| Gangwisch, 2005 (52) | 10 Jahre | 6,981 | 32-49 | Berichteter BMI bei Studienbeginn, bei Follow-Up selbst berichteter BMI | Fragebogen | Kein Zusammenhang. |
| Littman, 2006 (54) | | 173 | 50-75 | Berichteter BMI | Fragebogen | Kein Zusammenhang. |
| Stranges, 2007 (57) | 5 Jahre | 10,308 | 35-55 | Berichteter BMI | Fragebogen | Kein Zusammenhang. |
| Chaput, 2008 (51) | | 276 | 21-64 | Gemessener BMI | Fragebogen | U-förmiger Zusammenhang. |
| Lauderdale, 2009 (47) | | 612 | 18-30 | Gemessener BMI | Akzelerometrie | Kein Zusammenhang zwischen Schlafdauer und Übergewicht |
| Hairston, 2010 (46) | 5 Jahre | 1,107 | 18-81 | Gemessener BMI | Fragebogen | U-förmiger Zusammenhang bei <40 Jährigen. Kein Zusammenhang bei >40 Jährigen. |
| Nishiura, 2010 (48) | | 2,623 | 40-59 | Gemessener BMI | Fragebogen | Negativer Zusammenhang. |
| Watanabe, 2010 (50) | | 35,247 | unklar | Gemessener BMI | Fragebogen | Negativer Zusammenhang bei Männern. Kein Zusammenhang bei Frauen. |

So berichteten mehrere Studien einen klaren negativen Zusammenhang zwischen Schlafdauer und Übergewicht (48;50;53;56). Andere Studien hingegen fanden einen U-förmigen Zusammenhang, d. h. Übergewicht kam gehäuft sowohl bei kurzer als auch bei langer Schlafdauer vor, wobei der niedrigste BMI in den meisten Fällen mit einer Schlafdauer von 7 bis 8 Stunden assoziiert war (46;51;55). Wiederum andere Studien fanden überhaupt keine Assoziation zwischen Schlaf und Übergewicht oder Fettleibigkeit (46;47;50;52;54;55;57). Erwähnenswert ist hierbei, dass die einzige Studie, die Schlaf nicht mithilfe eines Fragebogens sondern mittels Akzelerometrie erfasst hat, im Längsschnitt keinen Zusammenhang mit Übergewicht fand (47).

Eine Meta-Analyse aus dem Jahr 2008, welche sich jedoch ausschließlich auf Daten aus Querschnittsstudien bezieht, ergab, dass Personen mit einer Schlafdauer von 5 Stunden oder weniger häufiger übergewichtig waren als Personen mit mehr Schlaf (gepooltes geschätztes Odds Ratio 1.55; 95% KI: 1.43 bis 1.68; basierend auf 17 Studien) (58). Zudem wurde hier ein linearer Zusammenhang zwischen Schlafdauer und Gewichtsstatus gefunden (gepoolter Effektschätzer von -0.35 kg/m² BMI pro h Schlaf; 95% KI: -0.57 bis -0.12; basierend auf 7 Studien).

Neben den zahlreichen Studien zu Schlafdauer und Übergewicht im Sinne eines erhöhten BMI deuten aktuelle Studien darauf hin, dass der Zusammenhang zwischen Schlafdauer und Körpermasse vor allem durch einen erhöhten Anteil an Fettgewebe zu erklären sein könnte (59). So hatten in der Study of Osteoporotic Fractures (SOF) und Osteoporotic Fractures in Men Study (MrOS) Teilnehmer, die weniger als 5 Stunden schliefen, einen erhöhten Körperfettanteil verglichen mit Teilnehmern, die 7 – 8 Stunden schliefen. Zudem zeigten diese Studien einen Effekt von Schlafdauer auf die Fettverteilung. Studienteilnehmer mit kurzer Schlafdauer hatten dementsprechend einen höheren Bauchumfang als Teilnehmer mit ‚normaler' Schlafdauer.

**Kinder**

Insgesamt 11 Längsschnittstudien untersuchten den Zusammenhang zwischen Schlafdauer und Übergewicht bei Kindern (5;6;10;44;45;49;60-64), wovon 3 nach Januar 2009 publiziert worden sind (44;45;49). Diese Ergebnisse erwiesen sich als weitaus konsistenter als die Resultate von Studien mit Erwachsenen (Tabelle 4.2). So zeigten fast alle hier zusammengefassten Studien einen klaren Zusammenhang zwischen kurzer Schlafdauer und Übergewicht. Die einzigen nicht signifikanten Ergebnisse lieferten 2 Studien bei Kindern, die bei der Ersterhebung älter als 5 Jahre waren (44;45). Der Zusammenhang zeigt sich also anscheinend mit zunehmendem Alter weniger deutlich.

**Table 4.2: Übersicht über Studien mit Längsschnittdaten zum Zusammenhang zwischen Schlafdauer und Übergewicht bei Kindern (nach Erscheinungsjahr).**

| Autor, Jahr | Follow Up Dauer | N | Alter bei Beginn der Studie | BMI Messung | Schlafmessung | Ergebnisse |
|---|---|---|---|---|---|---|
| Agras, 2004 (5) | 9,5 Jahre | 150 | 0 | Gemessener BMI | Fragebogen von Eltern auszufüllen | Negativer Zusammenhang. |
| Reilly, 2005 (10) | 5 Jahre | 5,493 | 2 | Gemessener BMI | Fragebogen von Eltern auszufüllen | Negativer Zusammenhang. |
| Snell, 2007 (62) | 5 Jahre | 1,441 | 3-12 | Gemessener BMI | Tagebuch von Eltern auszufüllen | Negativer Zusammenhang. |
| Lumeng, 2007 (61) | 3 Jahre | 1,364 | 9-11 | Gemessener BMI | Fragebogen von Eltern auszufüllen | Negativer Zusammenhang. |
| Gillman, 2008 (6) | 3 Jahre | 1,579 | 0 | Berichteter BMI | Persönliches Interview mit der Mutter | Negativer Zusammenhang. |
| Taveras, 2008 (63) | 3 Jahre | 915 | 0 | Gemessener BMI | Persönliches Interview mit der Mutter | Negativer Zusammenhang. |
| Touchette, 2008 (64) | 6 Jahre | 1,138 | 0 | Berichteter BMI | Fragebogen von der Mutter auszufüllen | Negativer Zusammenhang. |
| Landhius, 2009 (60) | 32 Jahre | 1,037 | 0 | Gemessener BMI | Fragebogen von Eltern auszufüllen | Negativer Zusammenhang. |
| Bell, 2010 (44) | 5 Jahre | 1,930 | 0-13 | Berichteter BMI | Tagebuch von den Eltern auszufüllen | Negativer Zusammenhang bei Kindern zwischen 0-4 Jahre. Kein Zusammenhang bei Kindern zwischen 5-13 Jahre. |
| Calamaro, 2010 (45) | 1 Jahr | 13,586 | 12-18 | Berichteter BMI | Persönliches Interview | Kein Zusammenhang. |
| Seegers, 2011 (49) | 4-7 Jahre | 1,916 | 6 | Berichteter BMI | Fragebogen von Eltern auszufüllen | Negativer Zusammenhang. |

In der bereits erwähnten Meta-Analyse aus dem Jahr 2008, die den Zusammenhang zwischen Schlaf und Gewicht anhand von Daten aus Querschnittsstudien untersuchte, wurde diese Assoziation auch bei Kindern analysiert (58). Der gepoolte Schätzer (gepooltes geschätztes Odds Ratio 1.89; 95% KI: 1.46 bis 2.43; basierend auf 12 Studien) zeigte eine deutlich höhere Übergewichtsprävalenz bei Kindern mit kurzer Schlafdauer.

Eine Studie deutet darauf hin, dass auch bei Kindern der Zusammenhang zwischen Schlafdauer und Übergewicht (definiert durch BMI) zu einem erheblichen Teil durch einen Zusammenhang zwischen Schlafdauer und einem erhöhten Anteil an Fettgewebe

zu erklären ist, was durch aktuelle, noch unpublizierte Analysen bestätigt wird (25;65). Ferner war nach den Ergebnissen dieser Studien der Zusammenhang mit Schlafdauer besonders bei Kindern mit hohem BMI ausgeprägt. Es ist jedoch zu erwähnen, dass den Analysen nur Querschnitts- und keine Längsschnittsdaten zugrunde lagen.

## KRITISCHE BEWERTUNG MÖGLICHER LIMITATIONEN

Neben den bereits erwähnten Schwierigkeiten bei der Erfassung von Schlafmustern können bei der Untersuchung des Zusammenhangs zwischen Schlafdauer und Übergewicht weitere methodische Aspekte eine mögliche Rolle spielen.

So fällt auf, dass vor allem die Studien keine bzw. schwächere Zusammenhänge zeigten, die einen linearen Zusammenhang zwischen Schlafdauer und Gewichtsstatus modelliert haben (47;52;54;57). Lineare Modelle, die die Expositionsvariable als kontinuierliche Variable einbeziehen, sind generell anfälliger für eine Unterschätzung des Effektes, wenn Messfehler oder Messungenauigkeiten vorliegen (66) – wie es bei der Erfassung von Schlaf wahrscheinlich ist. Modelle, die die Schlafdauer dagegen als kategorisierte Variable einbeziehen, sind gegenüber solchen Ungenauigkeiten robuster und können die Form der Beziehung detaillierter beschreiben. Die Inkonsistenzen in den Ergebnissen könnten also zum Teil durch die eben beschriebenen Unterschiede in der statistischen Modellierung des Zusammenhangs begründet liegen.

Ein weiterer Aspekt ist die Definition von kurzer und langer Schlafdauer; diese variierte zwischen den Studien bei Erwachsenen von weniger als 5 Stunden bis hin zu weniger als 8 Stunden bzw. mehr als 7 oder zwischen 9 und 10 Stunden Schlaf. Bei Kindern unterschieden sich die Definitionen vor allem in Abhängigkeit vom Alter der untersuchten Population. Insgesamt zeigte sich jedoch in den hier zusammengefassten Studien in Bezug auf den Zusammenhang zwischen Schlafdauer und Übergewicht kein Muster nach Definition von kurzer oder langer Schlafdauer.

Zudem wird durch Publikationsbias das Bild in der Literatur möglicherweise verzerrt, indem Studien, die keinen Zusammenhang zwischen Schlaf und BMI finden, nicht veröffentlicht werden.

## SCHLUSSFOLGERUNG

Insgesamt deutet die Evidenz aus wissenschaftlichen Studien darauf hin, dass eine zu geringe Menge an Schlaf mit einem erhöhten Risiko für Übergewicht verbunden sein könnte und dass dieser Zusammenhang vor allem bei jüngeren Populationen eine Rolle zu spielen scheint.

Generell sollte der Effekt von Schlaf auf den Gewichtsstatus trotz der weitgehend signifikanten Studienergebnisse jedoch nicht überschätzt werden. So ergaben nicht publizierte Analysen anhand bevölkerungsbezogener Daten von 3 – 10 jährigen Kindern

aus dem aktuellen KiGGS (Analysedaten wie in Bayer et al. 2009 (25)) nach Adjustierung für Störgrößen eine erklärte Varianz des BMI-z-Wertes von weniger als einem halben Prozent (Tabelle 4.3).

**Table 4.3: Anteil der BMI (z-Wert)-Varianz, die durch verschiedene Einflussfaktoren nach Adjustierung für die übrigen aufgelisteten Größen erklärt wird. Schätzung aus multiplem linearen Regressionsmodell anhand von KiGGS-Daten.**

| Einflussfaktor | Partielles $R^2$ x 100 (%) |
|---|---|
| BMI der Mutter | 4,24 |
| Geburtsgewicht | 2,26 |
| Rauchen in der Schwangerschaft | 0,74 |
| Altersbezogene Schlafdauer | 0,39 |
| Konsum elektronischer Medien | 0,26 |
| Soziale Schicht des Vaters | 0,18 |
| Bis zum 4. Monat voll gestillt | 0,04 |

Im Vergleich zu anderen beeinflussbaren Risikofaktoren ist dies dennoch ein relevantes Ergebnis. Geht man zudem davon aus, dass der Zusammenhang zwischen Schlaf und Gewichtsstatus bei Kindern mit höherem BMI ausgeprägter ist (25), würden von einer Verlängerung der Schlafdauer genau diejenigen profitieren (nämlich die Übergewichtigen), bei denen eine BMI-Reduktion erstrebenswert ist.

Eine 2008 erschienene Übersichtsarbeit warnte jedoch davor, eine Verlängerung der Schlafdauer als generelles Mittel der BMI-Reduktion zu empfehlen, bevor härtere wissenschaftliche Evidenz für den Zusammenhang und die hierbei agierenden Mechanismen und den Effekt von Interventionen auf Schlaf gegeben ist (67). Kritikpunkte waren dabei vor allem die bereits erwähnte Validität der Schlafmessung, mit der Empfehlung wiederholte, objektive (Akzelerometrie) Messungen durchzuführen, wie es bereits in einer Studie getan wurde, die keinen Zusammenhang fand (47). Zudem wird derzeit in den USA eine randomisierte Studie bei Adipösen durchgeführt, deren Intervention in der Verlängerung der habituellen Schlafdauer besteht (68).

Vor dem Hintergrund der hier dargestellten Ergebnisse und der bereits beschriebenen Tatsache, dass in verschiedenen Populationen eine Reduzierung der durchschnittlichen Schlafdauer beobachtet wurde, wird die Public Health Relevanz von Schlaf als möglicher neuer Risikofaktor für die Entstehung von Übergewicht sowohl im Erwachsenen- vor allem aber bereits im Kindesalter deutlich. Die Aspekte, die Schlafdauer beeinflussen und mit den Folgen von inadäquater Schlafdauer einhergehen, sind multifaktoriell und komplex. Aus epidemiologischer Sicht ist es daher von großem Interesse, die damit verbundenen Mechanismen zu verstehen, um die Bedeutung von Veränderungen im Schlafverhalten interpretieren zu können und möglicherweise entsprechende Empfehlungen zu entwickeln. Um dies zu gewährleisten, sind weitere epidemiologische Studien zur konkreten Untersuchung von Faktoren, die Schlaf beeinflussen, von biologischen Mechanismen im Zusammenhang zwischen Schlaf und Übergewicht und vom Effekt schlafbezogener Interventionen, erforderlich. Hierbei sollte ein besonderer Fokus auf das Kindesalter gesetzt werden, da zum einen in dieser Lebensphase die Grundlage für die Entwicklung von Schlafmustern und Schlafverhalten geschaffen wird und zum anderen in diesem Alter eine Übergewichtsprävention besonders erfolgreich zu sein scheint (69). Einen ersten Schritt in diese Richtung zeigt eine Publikation basierend auf Daten aus verschiedenen europäischen Ländern, die Unterschiede und Determinanten der Schlafdauer bei Kindergarten- und Schulkindern untersuchte und einen starken Einfluss von kulturellen und regional bedingten Aspekten fand (14).

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# 5 Sleep duration and cardiovascular related mortality

Sabrina Hense, Terry Boyle, Jennifer Girschik, Lin Fritschi

**Background:** Several studies have presented associations between sleep duration and cardiovascular mortality. Meta-analyses showed a U-shaped association, when separately comparing short or long to normal sleep duration. This could underestimate the dose effect of sleep. The purpose of this report to quantify the dose dependency of the association between sleep duration and cardiovascular mortality based on the relevant literature.

**Methods:** A systematic literature review for studies on sleep duration and cardiovascular mortality was conducted. For the meta-analysis, spline regressions with pooled estimates for sleep duration categories based on risk ratios (RR) from original studies were applied.

**Results:** The analyses showed an increased cardiovascular mortality risk depending on sleep duration in both sexes. For stroke and CVD the strongest association was seen with sleeping more than 7.5 hours, showing similar patterns in men and in women. For CHD the effects were stronger, with different directions for men and women - short sleep was associated with CHD in men (RR=2.22; 95% CL: 1.09-4.50), while in women long sleep duration (10 hrs. or more) increased the risk for CHD related death (RR=1.91; 95% CL: 1.30-2.80). A U-shaped pattern was seen only for CHD. Tests for linearity were significant for CHD and CVD ($p<0.01$), but not for stroke.

**Conclusion:** The previously observed U-shaped association between sleep duration and cardiovascular mortality is explained by the effect on CHD. Our results suggest that a distinction needs to be drawn between types of cardiovascular outcomes and that the effect differs by sex, especially the relationship between sleep duration and CHD related mortality.

**Keywords:** sleep, dose-response, stroke, coronary heart disease, cardiovascular disease, men, women

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## BACKGROUND

Already more than a century ago, the psychologist G. Stanley Hall [1] suggested that 'everything possible should be done to favour sleep as deep and sound in quality and usually as long in quantity as possible, and everything that seriously interferes with this end should be sedulously avoided'. Research over the past few decades has reinforced this philosophy, with a number of different health outcomes linked with poor sleep. An adequate amount of sleep is now believed to be important for optimal health and functioning throughout life [2]. However, a decrease in sleep duration has been observed over the last decades, due to social as well as environmental changes within western societies [3, 4]. Increased mortality and morbidity is associated with both, too little sleep or too much sleep [5].

Several studies have presented associations between sleep duration and cardiovascular mortality [6-16]. Two recent meta-analyses on sleep duration and cardiovascular events and mortality have been published, and both have concluded that the relationship between sleep and cardiovascular mortality is U-shaped [17, 18]. However, both these papers presented separate analyses for long sleep duration versus average sleep duration and short sleep duration versus average sleep duration. The dichotomisation of sleep duration into short versus normal or long versus normal leads to a loss of information and could possibly underestimate the dose effect of sleep duration on the outcomes under investigation. New methods are available which can be used to perform dose-response meta-analyses. Therefore the purpose of this report was to systematically review the existing epidemiological literature on the association between sleep duration and cardiovascular related mortality and to quantify the dose dependency of these associations based on the relevant literature.

## METHODS

### Literature search

Relevant original articles were identified by searching the MEDLINE database (National Library of Medicine, Bethesda, MD) of articles published between 1950 and November 2010 for studies examining the relationship between sleep duration and cardiovascular mortality. Exposure definition was limited to nocturnal sleep duration and the outcome definition was death due to cardiovascular disease, including cardiac events (e.g. myocardial infarction, angina pectoris, stroke). The primary search was performed for the terms "sleep" AND ("mortality" OR "death"). The search was repeated in February 2011 to identify any new publications. Additionally, reference lists of original and reviewed articles were reviewed and a citation index search in Web of Science was conducted to search for further studies. Relevant publications in English, German, Italian and Spanish language were considered for inclusion.

**Inclusion and exclusion criteria**

Only studies that fulfilled all of the following criteria were eligible for analysis: a) original article; b) peer reviewed; c) population based; d) observational; e) prospective cohort design; f) conducted in humans; g) follow up period of at least three years; h) assessment of nocturnal sleep duration as baseline exposure; i) death recorded prospectively as outcome; and k) at least three sleep duration categories. Studies were excluded if one or more of the following criteria applied: a) case control design; b) patient population; c) population with sleep disorders or insomnia; or d) information on daytime sleep only.

**Assessment of study quality**

All publications obtained from the above presented search were screened and data were extracted separately by two independent investigators. Information on extracted articles included first author's surname, year of publication, year of data collection, country of data origin, source of outcome data, duration of follow up, number of participants who were lost to follow up, sleep duration assessment method. A grading of the studies was done according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [19]. Where discrepancies occurred with the quality grading a third independent review was conducted and consensus was sought.

**Data extraction**

Risk ratios (RR) and corresponding 95% confidence intervals (CIs) were extracted for each sleep duration category presented in each paper. Information on sample characteristics including number of participants and deaths in each group, age of participants, gender, as well as covariates controlled for in multivariate analysis were also extracted. Four studies did not contain sufficient data for extraction and inclusion in the analysis. Three of these studies did not contain information on the number of cases by sleep duration category [12, 20, 21], and one study did not present results for men and women separately [8].

**Statistical analysis**

For each RR, the midpoint of each exposure interval was considered to be the exposure level. For unbounded categories, it was assumed that the width of the interval was equal to that of the nearest interval. The effect sizes were recalculated, using the Excel macro outlined in Hamling et al [22], so the lowest dose (or the two lowest doses combined if the lowest dose was less than 5 hours) was the referent category in studies where that was not already the case. The results of the studies were pooled using two-stage random effects, as described by Greenland and Longnecker [23], using a user-written

Stata program [24]. This method estimates the dose-response trend while taking into account the correlation between effect sizes presented in individual studies.

To assess whether the dose-response relationship was non-linear, sleep duration was modelled using restricted cubic splines with 3 knots. The knots were taken from the model with the best goodness of fit. Postestimation commands were used to recalculate the results so that 7.5 hours was the reference dose.

Between-study heterogeneity was assessed using the $I^2$ statistic. $I^2$ values of 25%, 50% and 75& were considered to indicate low, moderate and high heterogeneity respectively [25]. We attempted to assess the possibility of publication/small-study bias using Egger's regression asymmetry tests and visual inspection of funnel plots, however the small number of studies in each meta-analysis made the output from these tools unreliable.

Separate analyses were conducted for males and females. All analyses were performed using Stata version 11.1 (StataCorp, College Station, TX, USA).

**RESULTS**

The search strategy yielded 5533 references, of which 5528 were excluded after title, abstract and full-text review (Figure 5.1).

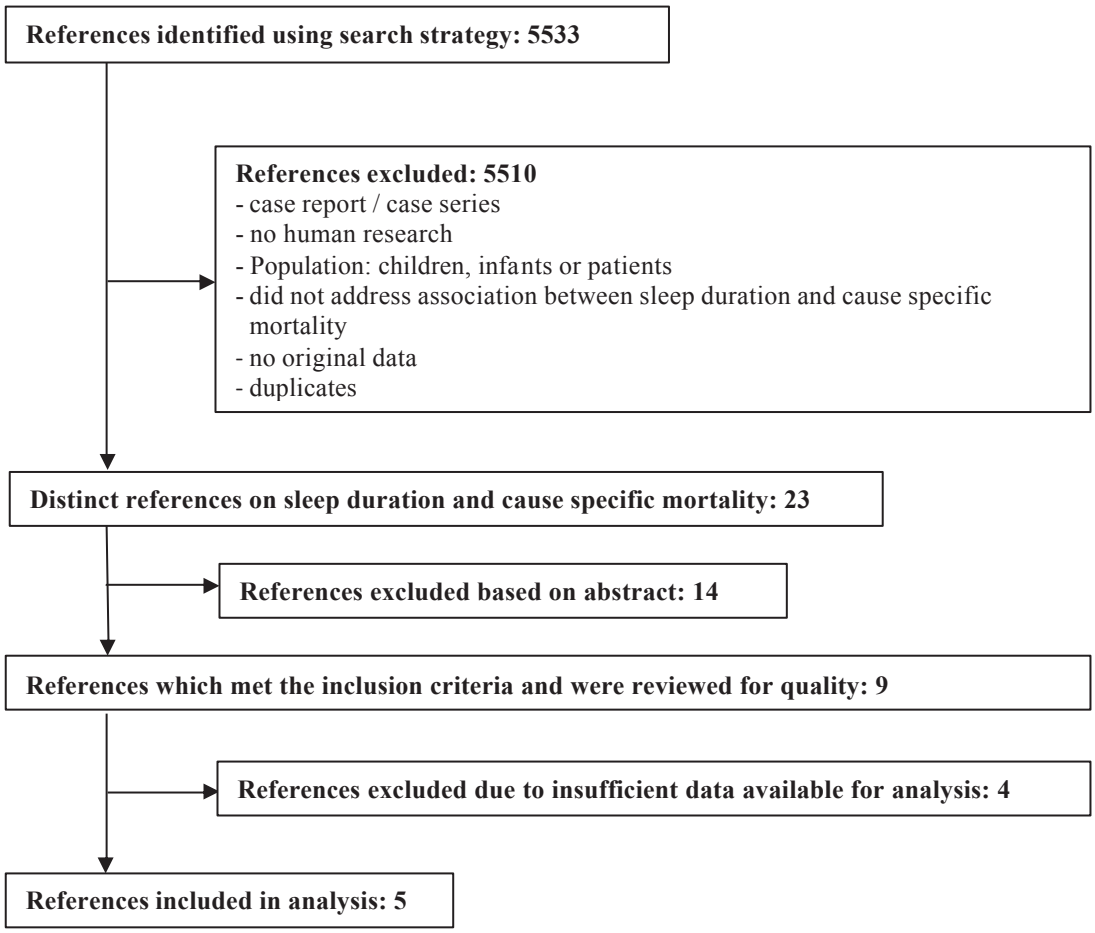


**Figure 5.1: Study selection process**

## Table 5.1: Description of included studies

| Author | Year | Country | Cohort | Outcome | Outcome assessment | Exposure assessment | Total sample/ men/ women | Age* | Quality score | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|
| Amagai | 2004 | Japan | Jichi medical school cohort study | Stroke/ CHD | Death certificate | Questionnaire | 11325/ 4419/ 6906 | 19-93 | 8 | age, systolic blood pressure, totla cholesterol, BMI, smoking, alcohol intake, education, marital status |
| Heslop | 2002 | Scotland | Scottish workplaces | CVD | Death certificate | Questionnaire | 6797/ 5819/ 978 | <65(m)/ <60(f) | 6 | age, marital status, social class, diastolic blood pressure, blood cholesterol level, BMI, FEV, Hours of recreational activity per week, alcohol intake, smoking, self-perceived stress |
| Ikehara | 2009 | Japan | JACC study | Stroke/ CHD/ CVD | Death certificate | Questionnaire | 89634/ 41489/ 57145 | 40-79 | 9 | age, BMI, history of hypertension, history of diabetes, alcohol consumption, smoking, education level, hours of exercise, hours of walking, regulra employment, perceived mental stress, depressive symptoms, frequency of fresh fish intake |
| Shankar | 2008 | Singapore | Singapore Chinese Health Study | CHD | Death certificate | Questionnaire | 58044/ 25552/ 32492 | 45-74 | 8 | age, dialect group, education, year of recruitment, BMI, smoking, alcohol intake, moderate physical activity, dietary intakes of total calories, fruit, vegetables, fiber, total fat, cholesterol, weekly use of vitamin/mineral supplements, (menopausal status, ever use of postmenopausal hormone therapy) |
| Suzuki | 2009 | Japan | Shizuoka study | CVD | National Vital Statistics Database | Questionnaire | 11395/ 5825/ 5570 | 65-85 | 8 | age, sex, BMI, Smoking, alcohol intake, frequency of physical activity, SES, mental health, hypertension, diabetes |

* at baseline

## Table 5.2: Description of excluded studies

| Author | Year | Country | Cohort | Outcome | Outcome assessment | Exposure assessment | Total sample/ men/ women | Age* | Quality score | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|
| Burazeri | 2003 | Israel | Kiryat Yovel Community Health Study | CVD | National Population Registry | Questionnaire | 1842/ 841/403 | ≥50 | 7 | age, BMI, self-appraised health, activities of daily living, diabetes, CHD, congestive heart failure, alcohol consumption, systolic blood pressure, homocysteine, glucose and albumin |
| Ferrie | 2007 | Great Britain | Whitehall II | CVD | National Population Registry | Questionnaire | 9781 at phase 1 and 7729 at phase 3 | 35-55 | 8 | age, sex, marital status, employment grade, smoking status, physical activity, alcohol consumption, self-related health, BMI, systolic blood pressure, cholesterol, physical illness, modified General Health Questionnaire score, prevalent CHD |
| Lan | 2007 | Taiwan | Survey of Health and Living Status of the Elderly | CVD | National Population Registry | Interview | 3079/17 48/1331 | ≥64 | 7 | age, marital status, monthly income, cigarette smoking, alcohol consumption, BMI, exercise, disease history and depression |
| Patel | 2004 | United States | Nurses Health Study | CVD | Next of Kin, Postal Services and/or National Population Registry | Questionnaire | 82969 women | 30-55 | 6 | Age, smoking, alcohol consumption, physical activity, depression, history of snoring, BMI, history of disease and shiftwork history |

* at baseline

After exclusion of studies according to the search strategy and inclusion criteria, five studies contributed to the present analysis. They reported risk estimates for at least three sleep duration categories and offered data sufficient for meta-analysis for males and females separately (Table 5.1). Three of those studies were conducted in Japan, one in Singapore, and one in Scotland. The cohorts varied in sample size from 6,797 to 89,634 and included ages from 19 to 93. Two studies reported deaths due to stroke, three studies reported deaths due to coronary heart disease (CHD) and 3 studies reported deaths due to cardiovascular disease (CVD).

**Table 5.3: Risk Ratios with 95% CL by sleep duration category in males and females**

| Dose (Hours) | Stroke | CHD | CVD |
|---|---|---|---|
| **Males** | | | |
| 5 | 0.93 (0.66-1.30) | 2.22 (1.09-4.50) | 0.93 (0.84-1.04) |
| 5.5 | 0.94 (0.72-1.24) | 1.88 (1.06-3.30) | 0.94 (0.87-1.03) |
| 6 | 0.96 (0.78-1.17) | 1.59 (1.04-2.43) | 0.96 (0.90-1.02) |
| 6.5 | 0.97 (0.85-1.11) | 1.34 (1.01-1.78) | 0.97 (0.93-1.01) |
| 7 | 0.99 (0.92-1.05) | 1.14 (0.99-1.31) | 0.99 (0.97-1.01) |
| 7.5 | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| 8 | 1.02 (0.96-1.09) | 1.02 (0.88-1.18) | 1.02 (1.00-1.04) |
| 8.5 | 1.07 (0.95-1.22) | 1.08 (0.81-1.44) | 1.06 (1.02-1.11) |
| 9 | 1.18 (0.98-1.43) | 1.14 (0.74-1.76) | 1.15 (1.07-1.24) |
| 9.5 | 1.31 (1.00-1.72) | 1.21 (0.68-2.16) | 1.26 (1.13-1.40) |
| 10 | 1.46 (1.02-2.08) | 1.28 (0.62-2.64) | 1.37 (1.19-1.59) |
| **Females** | | | |
| 5 | 0.93 (0.68-1.27) | 1.35 (0.96-1.89) | 0.90 (0.65-1.25) |
| 5.5 | - | - | 0.90 (0.69-1.16) |
| 6 | 0.93 (0.79-1.10) | 1.08 (0.90-1.30) | 0.89 (0.74-1.08) |
| 6.5 | 0.93 (0.84-1.03) | - | 0.89 (0.79-1.01) |
| 7 | 0.95 (0.90-1.00) | 0.94 (0.88-1.00) | 0.92 (0.87-0.98) |
| 7.5 | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| 8 | 1.07 (1.00-1.14) | 1.13 (1.05-1.22) | 1.12 (1.04-1.20) |
| 8.5 | 1.14 (1.01-1.30) | 1.29 (1.11-1.50) | 1.25 (1.09-1.44) |
| 9 | 1.23 (1.01-1.49) | 1.47 (1.17-1.85) | 1.41 (1.14-1.73) |
| 9.5 | 1.31 (1.01-1.70) | 1.67 (1.23-2.27) | 1.58 (1.20-2.08) |
| 10 | 1.41 (1.02-1.95) | 1.91 (1.30-2.80) | 1.77 (1.25-2.51) |

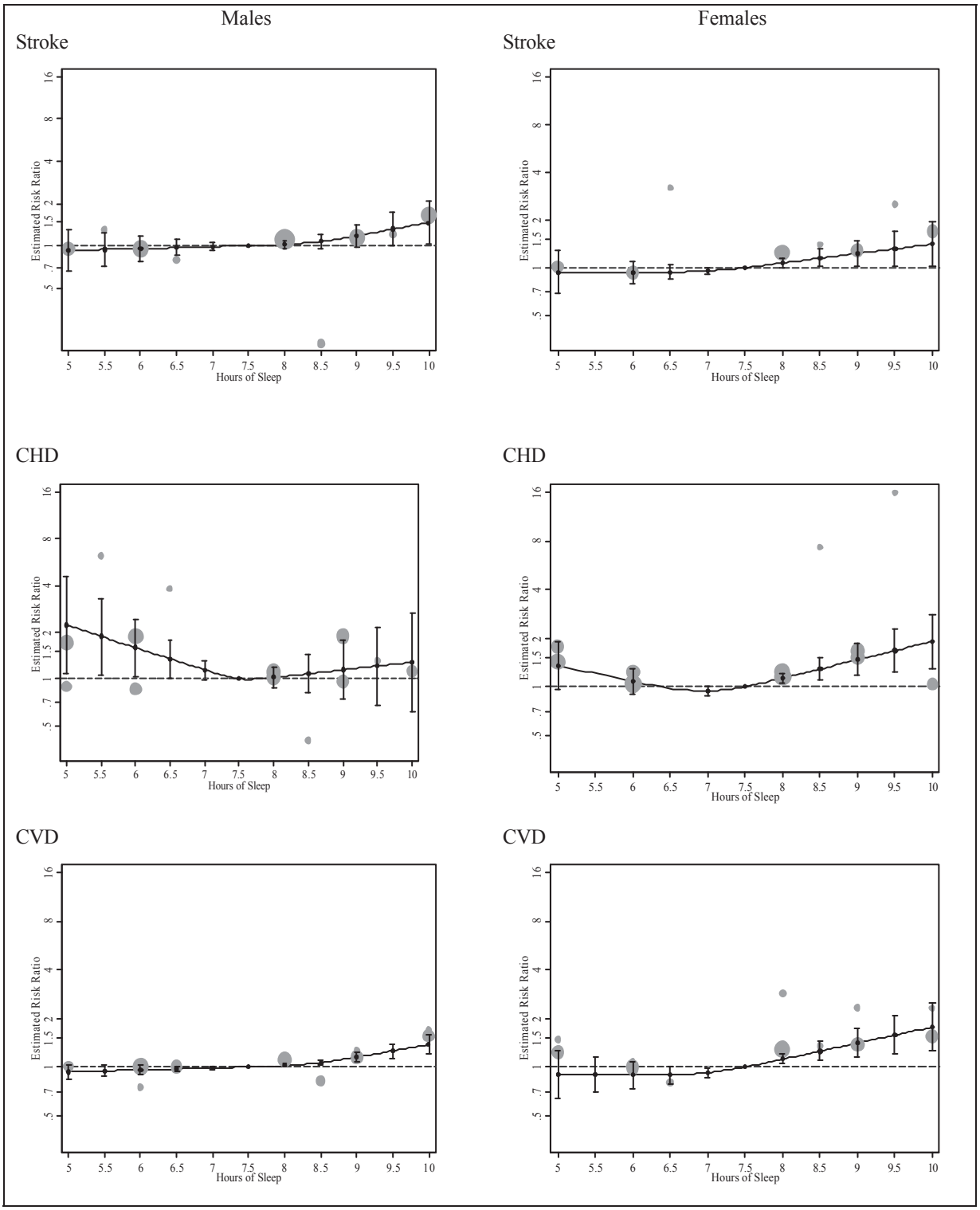


**Figure 5.2: Cubic spline regression of mortality risk by sleep duration, by outcome and sex. Bubbles are weighted by the inverse of the standard error of each sleep duration category (a larger bubble indicates less standard error).**

For stroke mortality (Figure 5.2 and Table 5.3), those sleeping 10 hours or more had a statistically significant increase in risk of stroke which was similar for men (1.46 95% CL 1.02-2.08) and women (1.41; 95% CL 1.02-1.95) but there was no change in risk for those in the lowest sleep duration category (5 hours or less).

The test for non-linearity indicated that there was no significant evidence that the relationship was non-linear for men (p=0.059) or women (p=0.166). There was low heterogeneity in the stroke meta-analyses ($I^2$ = 23.2% for men and 23.1% for women).

For CHD mortality, males seemed to have a higher risk than females for shorter sleep – the risk for those sleeping 5 hours or less for males was 2.22 (95% CL 1.09-4.50), and for females was 1.35 (95% CL 0.96-1.89). However females had a higher risk than males for longer sleep – the risk for those sleeping 10 hours or more were 1.28 (95% CL 0.62-2.64) for males and 1.91 (95% CL 1.30-2.80) for females. The relationships were non-linear for both males and females (p<0.01 for both). Accordingly, the results from the cubic spline with knots at 7, 7.5, and 8 showed a U-shaped pattern for CHD for both males and females. For males, the mortality risk was higher for short than for long sleep duration while for females the risk was higher for long than for short sleep duration (Figure 5.2). Heterogeneity was moderate to high in the meta-analysis for males ($I^2$ = 78.3%) but low for females ($I^2$ = 26.1%).

For CVD mortality, risk was not raised for short durations of sleep for either sex, and was raised for long durations of sleep (10 hours or more) for men (1.37 (95% CL 1.19-1.59) and women (1.77; 95% CL 1.25-2.51). Again the relationships were non-linear (p<0.01) but did not show a clear U-shaped pattern. Instead, risks were relatively flat until they began to increase at about 7.5 hours of sleep. Heterogenetity was low for males ($I^2$ = 11.4%) and moderate for females ($I^2$ = 46.2%).

**DISCUSSION**

This study showed an increased cardiovascular mortality risk depending on sleep duration in both sexes. For stroke and CVD the association could mainly be seen with sleep durations of more than 7.5 hours and the pattern of the relationship seemed to be similar in men and in women. For CHD the effects of sleep duration were stronger, but the pattern of the association was different for men and women - short sleep duration was significantly associated with CHD in men, while in women long sleep duration seemed to increase the risk to a higher extent than short sleep duration.

There is no currently-accepted theory as to how sleep might influence cardiovascular related mortality, and potential theories are complicated by an apparent similar effect produced by both long and short sleep.

Studies have identified a number of possible metabolic pathways by which short sleep may influence cardiovascular related mortality and these have recently been reviewed [26]. The possible mechanisms include metabolic factors associated with obesity and diabetes such as: altered glucose metabolism; increased appetite due to changes in hormone levels that regulate appetite and energy expenditure (e.g. leptin and ghrelin); and lower energy expenditure (less motivation for activity) in those who are sleep

deprived. In addition, short sleep has been associated with higher blood pressure and coronary artery calcification [26]. Thirdly, short sleep has been shown to impact on the immune and neuro-endocrine systems which may influence disease progression and mortality.

The relationship between long sleep and cardiovascular related mortality is less well defined and, since many of the studies examining this question are cross-sectional, it may be that long sleep is a marker of underlying latent disease. There is some suggestion that people who self-report long sleep may actually be spending more time in bed, but not sleeping longer [27]. However, analyses of the Nurses Health Study suggested that depression, antidepressant use and unemployment were associated with reported long sleep duration and these may be intermediate factors which are possibly associated with cardiovascular mortality [28].

Our study has both strengths and limitations. This study is the first to use pooled estimates to examine the dose-response relationship between sleep duration and cardiovascular related mortality. While previous meta-analysis on this subject have been conducted, those studies have conducted their analysis separately for long and short sleepers (compared to normal sleepers) and there is the potential for this dichotomised analysis to underestimate any dose-response effect.

A limitation of this meta-analysis is the small number of studies available for inclusion. This is due in part to the fact that almost half of the eligible studies did not contain sufficient data for inclusion in the dose-response analysis. This has previously been identified as a problem for conducting dose-response meta-analysis. Bekkering et al found only 66% of cohort studies investigating diet and prostate or bladder cancer contained sufficient data to be usable for meta-analysis [29]. Although Bekkering et al found only a weak association between direction of association and the probability that the results were usable, they did find evidence that stronger associations were more likely to be presented with sufficient detail for inclusion [29]. This may result in inflated risk estimates. Our attempts to contact the authors of excluded studies to obtain more detailed information were unsuccessful.

In addition, the included studies differed in a number of ways including: the study population; follow-up time; inclusion criteria; and the variables they adjusted for in their models. However, this study sought to minimise the potential impact of the study variability by undertaking a systematic assessment of study quality using tightly defined inclusion/exclusion criteria and by restricting our sample to high quality studies. For example, we excluded studies with less than three years of follow-up in order to minimise the potential for underlying disease to have confounded the effect estimates. In addition, our inclusion criteria contained a specified minimum set of potential

confounders and we used the adjusted estimates for our analysis. However, a consistent limitation of all the individual studies is that measures of sleep were all self-reported at a single point in time which may not be adequate for assessing the impact of sleep duration on long term health outcomes. In addition, none of the individual studies sought to differentiate between those that are naturally short/long sleepers and those experiencing insufficient/excessive sleep with associated negative outcomes. But as all the included studies shared these limitations they were of a consistent standard.

One feature that was not consistent between studies was the racial profile of the study-population. While racial variability has not been investigated for sleep and cardiovascular outcomes, there is some evidence to suggest that melatonin (a hypothesised mechanism for the relationship between shiftwork/sleep and cancer incidence) may not be the same between racial groups [30]. Four of the five included studies were conducted in Asian countries which may make these results less relevant for other populations. Finally, despite this meta-analysis using the adjusted estimates from each study, residual confounding and bias cannot be ruled out.

The U-shaped association between sleep duration and cardiovascular mortality that has been previously reported might be mainly explained by the association between sleep duration and CHD. Our results suggest that, concerning the effect of sleep on mortality, a distinction needs to be drawn between types of cardiovascular outcomes. Different mechanisms might be involved in the association between sleep duration and the respective endpoints and further research should consider these possible differences, with a special focus on the sex differences in the relationship between sleep duration and CHD.

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# 6 General discussion

The understanding of sleep duration and its role in the aetiology of cardio-metabolic health outcomes has gained increasing interest in epidemiological research in the last decades. This thesis investigates a wide scope of potentially relevant elements that deserve consideration in this context, particularly taking into account the impact of different stages of life.

The following chapter reviews the results presented above and critically discusses them against the background of previous findings, the biological mechanisms involved in the relationship and methodological aspects. Moreover, it gives a perspective on possible implications for public health and further sleep epidemiological research.

## 6.1 Main findings

Mean sleep duration has been reported for several age groups from different countries, suggesting regional differences in sleep duration [1-4]. This is confirmed by the IDEFICS data, where nocturnal sleep duration of European children aged 2 to 9 years differed significantly ($P < 0.001$) and up to 1.7 hours between countries in univariate as well as in multivariate analysis. Disparities between Northern, Southern and Eastern Europe were striking, with children from Northern countries sleeping the longest *(Chapter 2)*.

Interestingly, the factor that was found to mostly affect children's sleep duration was country affiliation. Age also had a significant effect in all models, but accounted for less differences in sleep duration than country. Of note, no association was found with environmental factors such as season or daylight duration. While other studies have reported a relationship of sleep duration with behavioral aspects, parental education level or lifestyle factors [4,5], association with these characteristics were not statistically significant in the IDEFICS data after adjustment for country. These findings indicate that regional affiliation, involving presumably cultural and socio-environmental characteristics, seem to supersede individual determinants of sleep duration that have been reported to influence children's sleep in previous studies *(Chapter 2)*.

The analyses in *Chapter 3* confirmed observations from other research groups showing that sleep duration is associated with a higher probability of being overweight in childhood [4,6-10]. The association between sleep and overweight was attenuated by an adjustment for geographic region, but there was no effect modification by region. Generally, the association appeared to be much stronger in school children than in preschool children probably reflecting extended exposure periods. These results seem to support the hypothesis, that a major part of the relationship is explained by biological processes that act similarly in the participating countries rather than by behavioral or environmental aspects that differ between regions.

According to the evidence from epidemiological studies reviewed in *Chapter 4*, a relationship between sleep duration and weight status can not only be seen in children but also in adults – even though the results are less consistent with increasing age. Different biological mechanisms have been invoked in this context (see Chapter 1.4.3), and a special influence has been attributed to hormonal changes including mainly the adipose tissue derived Leptin, the 'hunger hormone' Ghrelin and the carbohydrate and fat metabolism regulating Insulin as potential mediators.

A major cardio-metabolic outcome that has been found in previous studies to be associated with sleep duration in adults is cardiovascular mortality, where a U-shaped relationship has been suggested [11,12]. The meta-analysis presented in *Chapter 5* demonstrates a clear dose-effect relationship between sleep duration and cardiovascular mortality and it indicates that the suggested U-shape of the relationship is mainly explained by the effect of sleep duration on coronary heart disease (CHD). Of note, the association with deaths due to stroke and cardiovascular diseases in general (CVD) was mainly found for sleep durations of more than 7.5 hours, and the pattern of the relationship was similar in men and in women. The effects of sleep duration on CHD mortality were generally stronger, but the patterns of the association slightly differed by gender, with short sleep duration being significantly associated with CHD related death in men whereas, in contrast, long sleep duration increased the risk especially in women. This suggests that the mechanisms involved vary subject to the cardiovascular outcome and that they might have different relevance in men and women.

## 6.2 Tracking of cardio-metabolic risk factors

A relevant aspect in the epidemiological research on cardio-metabolic health is the analysis of the longitudinal development of risk factors for metabolic and cardiovascular events, which includes the assessment of 'tracking' of risk factors. Tracking can be defined as 1) the predictability of the measurement of a certain risk factor early in life for values of this factor in later life or 2) the stability of a specific factor over time [13]. In this context, a focus was set on overweight tracking especially against the background of the alarming worldwide epidemic of childhood obesity [14,15]. It has been suggested that excess childhood weight - resulting from the early establishment of metabolic imbalances and risk factors such as sleep deprivation - might plausibly increase the likelihood of cardiovascular disease in adulthood. In fact, prospective studies have been able to confirm a positive association between obesity in childhood and the presence of cardiovascular risk factors, such as elevated blood pressure, in adults [16,17] . Likewise, an independent relationship between BMI in young age and an increased risk for cardiovascular events in later life has been reported [18-21].

Against this background, inadequate sleep duration can be expected to play a role in the development of metabolic and cardiovascular disease in at least two ways. Firstly, as described above, as a proximal and direct risk factor that operates through several biological mechanisms in all stages of life, and secondly, as a distant risk factor, through its protracted effect on the development of chronic overweight which starts already in the young and tracks into adolescence and adulthood.

## 6.3 Methodological considerations

A clear definition of exposure and outcome parameters is a crucial element in any epidemiological research. Therefore, methods of sleep assessment and measurements of overweight and cardiovascular mortality as central indicators of cardio-metabolic health need to be reflected in terms of their potential limitations and require critical discussion. Furthermore, possible confounding or modifying factors that might play a role in the associations under investigations have to be considered in the appraisal of the evidence produced in this thesis.

### 6.3.1 Exposure assessment

The evaluation of sleep patterns is essential for the identification and management of sleep problems as well as for the accomplishment of reliable research on the effect of sleep on health outcomes. In this context, a distinction needs to be drawn between quality and quantity of sleep.

Sleep quality is an intuitive concept to anyone who has ever had a poor night's sleep. However, as a clinical construct it represents a complex mixture of attributes that are difficult to define and measure objectively. It includes a mixture of quantitative aspects such as the duration of sleep, time taken to get to sleep (sleep latency), times woken during sleep (arousals) as well as more subjective aspects such as 'depth', 'restfulness' and 'refreshment' [22,23]. The short term effects of decreased sleep quality, such as tiredness, fatigue, loss of concentration and injuries are well recognised [24]. However, as far as it concerns the longer term health effects, associations are seen with and have mainly been studied in relation to sleep duration but not sleep quality. Accordingly, sleep duration has been chosen as the outcome of interest in this thesis.

Sleep duration is measured differently in experimental sleep laboratory studies and in population based studies. In a sleep laboratory, sleep is carefully controlled and precisely monitored by means of polysomnography (PSG). Such a detailed supervision is generally not feasible in epidemiological studies due to the high organisational strain put on participants and investigators, as well as the economic demands. Therefore, population based studies are forced to apply different and more reductionist methods to assess and survey sleep. Instruments to collect data on sleep duration vary considerably between studies; they range from questionnaires on usual sleep patterns over diaries to

objective measurements, for example, by means of actigraphy. Actigraphy is a method used to study sleep-wake patterns and circadian rhythms essentially by assessing the acceleration of movements. Sleep actigraphs are generally watch-shaped and worn on the wrist of the non-dominant arm. In contrast to PSG, the study participant remains movable and does not necessarily need to be located in a laboratory while the required data is being recorded. Actigraphy is considered the most valid method for sleep measurement in large scale studies. However, devices and sensors with acceptable size and signal quality have only been developed very recently such that the number of epidemiological studies that have assessed sleep duration by means of these instruments is still very limited [4,25,26] . Thus, the data presented in this thesis is exclusively based on subjective instruments, such as questionnaires or diaries. Generally, subjective measurements seem to slightly overestimate sleep duration compared to objective methods in children as well as in adults [4,27]. However, since this misclassification is commonly believed to be non-differential, it tends to result in an underestimation of the associations under investigation [28].

### 6.3.2 Outcome assessment

***Overweight***

The body mass index (BMI) is the most commonly used proxy measure composition based on an individual's height and weight. It was proposed in the 19$^{th}$ century by the Belgian mathematician Adolphe Quetelet [29] and is defined as the individual's body weight divided by the square of its height (BMI = kg/m²). BMI as an indicator for body composition is often used in epidemiological studies due to its low effort and high feasibility.

According to the cut-off points from the World Health Organization, overweight in adults is defined as a BMI of $\geq$25 kg/m², while a BMI of $\geq$30 kg/m² indicates obesity. In children, the establishment of an international classification system has proved to be more complex due to constant age dependent changes in body composition during growth. Therefore BMI cut-off points for children are generally based on percentile curves. The International Obesity Taskforce (IOTF) has established a broadly used reference system with international age- and sex-specific cut-off points for children [30]. Alternatively, the application of allometric indices, which take into consideration growth parameters, are used to calculate body composition in young populations [31].

The adequacy of BMI as a proxy for body fat is questionable, since it does not appropriately take into account other body tissues, e.g. muscle mass. Accordingly, a very athletic person might be categorized as overweight according to its BMI due to the elevated muscle mass, despite carrying little fat. An alternative – and in particular in children probably more specific – assessment of body fatness is the measurement of the

skinfold thickness [32] or of waist circumference. Waist circumference is an indicator of abdominal fat, which has been suggested to be among the major risk factors for cardiovascular disease mortality [33]. Recent studies have reported an association between short sleep duration and waist circumference [9,34,35].

Dual energy X-ray absorptiometry (DXA) is considered to be one of the most valid and reliable reference methods for body composition assessment, and it is widely used to assess changes in body composition during weight loss in clinical settings [36]. However, the use of DXA is generally not feasible in epidemiological studies due to the high costs of the equipment, the exposure of volunteers to ionising radiation, and a lack of portability. A popular alternative to DXA is bioelectrical impedance analysis (BIA), which is a more applicable method to assess body composition showing good agreement rates with DXA measurements [36]. However, it has been suggested that the utility of BIA to estimate body composition is limited in children [37].

As for the results presented in this thesis, it needs to be kept in mind that they refer exclusively to BMI measurements, since no data based on other assessment methods was available. Alternative measurements might have yielded more precise results in this context with a higher statistical power. However, the very common use of BMI in epidemiological research indicates that this method is widely accepted as an indicator of body composition.

***Cardiovascular Mortality***

In cardiovascular epidemiology, the differentiation between incident cardiovascular events (morbidity) like myocardial infarction, stroke or heart failure, and death due to cardiovascular disease (mortality) plays a central role. Cardiovascular mortality implies an estimate of the proportion of a population that dies due to a cardiovascular event and is usually assessed based on information from death registers or institutions that hold the death certificates for the respective study region. Incidence rate refers to the number of new cardiovascular events in a population over a defined time period.

Cardiovascular mortality has declined consistently and significantly during the past decades, especially in the past 30 years [38-40]. Improvements in treatment of incident cardiovascular disease, in particular regarding the avoidance of the potential fatal outcomes, resulting in a dramatic decline of case fatality, e.g., of acute myocardial infarction, appear to be a major reason for this reduction [39]. Nevertheless, the incidence of cardiovascular events may drop less rapidly, or it may even increase, especially against the background of an alarming global prevalence of overweight, which is a major risk factor for cardiovascular events [41,42]. Thus, the investigation of the effects of risk factors on the incidence of cardiovascular events may be – from a public health point of view - more relevant than one that puts a focus on the mainly treatment- and

intervention-affected cardiovascular mortality. However, since the availability of cardiovascular disease incidence data is usually dependent on the existence of a population-based register, the numbers of studies investigating the incidence of cardiovascular events are rather limited. Accordingly, the studies included in the meta-analysis conducted in this thesis exclusively refer to mortality data (*Chapter 5*), and one needs to be aware that the association of sleep duration with incident cardiovascular disease may in fact be more direct and thus stronger than that observed with CVD deaths.

To ascertain a clear and possibly comparable definition of the specific outcome under investigation, diseases are coded according to the *International Classification of Disease* (ICD). In the ninth version of the ICD, codes from 390- 459 identify cardiovascular disease. In the ICD-10, cardiovascular disease is marked by the codes I00- I99. Unfortunately the choice and definition of the specific cardiovascular outcome in relation to sleep duration differ between the studies that could be included in the meta-analysis in *Chapter 5*. Some studies focus on cardiovascular diseases in general, others specify conditions such as stroke (ICD-10: I60–I69) or coronary heart disease (ICD-9: 410-414, 427.5, 429.2, 798; ICD-10: I20-I25). These differences limit comparability of reports from different studies using inconsistent endpoint definitions and they may also hamper conclusions about an effect of sleep on cardiovascular events in general, since different biological mechanisms that are dependent of the specification of the outcome under investigation, may be involved.

### 6.3.3 Confounding

Confounding is the distortion of a measure of effect of a certain exposure on an outcome due to the association of the exposure with factors that affect the occurrence of the outcome [43].

Socio-demographic and behavioural as well as regional characteristics are potential confounders in the relationship of sleep duration and cardio-metabolic health. A detailed description of their association with sleep duration in children is presented in *Chapter 2*. In the analyses presented herein, they do not seem to significantly affect the associations under study, such as with country of origin. Similarly, the relationship between sleep duration and overweight in childhood was controlled for potential confounding effects and, if appropriate, these factors were included in the final models of the analyses as described in *Chapter 3*.

In the meta-analysis on sleep duration and cardiovascular mortality (*Chapter 5*), the number, types and scales of covariates that were controlled for differed between studies – a problem inherent to any meta-analysis using published data [44]. Most of the studies adjusted for age and the main cardiovascular risk factors (BMI, hypertension, diabetes,

smoking). However, the variable sets within the single studies differed, leading to a combination of differently adjusted risk estimates that created the data base for the meta-analysis; e.g., only two of the studies that were included on the meta-analysis adjusted for depression or depressive symptoms that might confound the relationship between sleep duration and cardiovascular mortality (also see Chapter 6.3.4). Since no data set with individual data from the included studies was available, no adjustment for a uniform confounder set was possible and different non-controllable factors might distort the association under investigation. These aspects limit the explanatory power of the presented results and require confirmatory studies on the dose-effect of sleep duration on cardiovascular mortality. Alternatively, pooled analyses that gain access to and combine the individual data from the relevant studies within one model might give a more valid insight in this context.

Furthermore, undetected confounders or inadequate adjustments (due to e.g measurement errors [45]) leading to residual confounding may have affected the observed relationship. BMI deserves special attention in this context. As explained in Chapter 6.3.2, alternative assessment methods are likely to measure body composition more precisely than BMI and therefore might allow for more distinct adjustment in the relationship between sleep duration and cardiovascular mortality; e.g., waist circumference as a measure of abdominal fat was found to be a BMI-independent risk factor for cardiovascular mortality [46] and has also been reported to be associated with sleep duration [9,34]. Therefore, correction for waist circumference might allow for a more precise adjustment for body composition in the relationship under investigation. Since the studies included in the meta-analysis controlled exclusively for BMI in their multivariate models, their analyses may have been affected by possible residual confounding to a certain degree (*Chapter 5*). However, it is unlikely that the difference between BMI and waist circumference completely explains the observed effects.

Finally, part of the association between sleep duration and cardiovascular endpoints may also be considered as being mediated by body composition. From an epidemiological perspective, this implies that body composition – besides its role as a possible confounder - is a possible intermediate factor in the association under investigation. Hence, controlling for body composition could introduce some bias due to over-adjustment. Of note, despite adjustment for BMI, the effect of sleep duration on cardiovascular mortality persisted in most of the studies, which is a strong indicator for an independent association of sleep with CVD – over and above the body composition - mediated effect. Conceptually, this observation endorses the suggestion (Chapter 6.2) that sleep duration might affect the development of cardiovascular disease dually - as a direct and as a distant risk factor.

### 6.3.4 Effect modification

An effect modifier may or may not be a confounder [47]. Studying effect modification may contribute to the understanding of the association under investigation, whereas confounding is a bias not related to the causal pathways. The relationship between exposure and outcome differs between strata of the effect modifier, which might be of contextual relevance and has implications for the applicability of the results. Therefore, in the case of effect modification stratified analysis rather than adjustment for the respective variable is appropriate.

As one possible modification, the regional differences in sleep duration, overweight prevalence and cardiovascular mortality that have been found in this thesis and described in the literature, geographic affiliation needs to be taken into consideration. In the analysis on sleep duration and overweight in children from European countries a test for effect modification by region has been conducted, but failed to detect a statistically significant level of modification *(Chapter 3)*. With a sample size of nearly 8,000 children it is unlikely that the study was underpowered to detect a statistically significant result.

The most prominent among possible effect modifiers is age. In fact, differences between age groups in the association between sleep duration and overweight were also seen in our data: children below the age of six years showed a weaker association between sleep duration and overweight than older children (*Chapter 3*). Generally, the evidence from previous studies suggests a weakening relationship between sleep duration and overweight with age – but this concerned mainly a range covering age over the lifespan [48]. Our result indicates an inversion of the effect size at a certain stage of life. We propose that in younger children the association might be low due to the relatively short time that they have been exposed to inadequate sleep duration. With aging, exposure time increases, and thereby might develop an increasing effect of sleep duration on weight status. The evidence concerning this relationship in adolescent populations is limited, but the available studies congruently show an inverse association between sleep duration and BMI [49-53]. Unfortunately, we are not aware of comparable data on the effect size in different ages of young populations (say, e.g., 2-18 years) that were able to show until which age the effect size increases. Since sleep duration has been shown to be associated with hormonal imbalances, inadequate sleep might play an especially relevant role during adolescence, where multiple hormonal and developmental changes occur. The limited data in this context calls for further investigation of this topic in adolescent populations with the aim of obtaining a more detailed insight into the possible influences that sleep deprivation might have in this crucial stage of development.

Another frequent effect modifier is sex. In the analysis on sleep duration and overweight (*Chapter 3*) as well as in the relevant literature regarding this relationship, no clear sex pattern is seen. A different picture can be drawn for the effect of inadequate sleep duration on cardiovascular mortality, where sex differences were revealed in the association between sleep duration and coronary heart disease (*Chapter 5*). This appears to imply that different mechanisms might play a role, leading to elevated and statistically significant risk estimates for cardiovascular death in long sleeping women and in short sleeping men. However, the results suggest an increased – albeit less pronounced and statistically barely non significant - mortality risk also for short sleeping women. As for the elevated mortality risk in women reporting long sleep duration, one possible explanation might be underlying depression. Reported long sleep duration was found to be associated with depression in the Nurses Health Study [54] and the risk of cardiovascular death is elevated in people with depression [55]. Furthermore, the prevalence of depression is generally higher in women than in men [56]. Against this background and the fact that most of the studies included in the meta-analysis did not adjust for depressive symptoms, depression might confound the observed association between sleep duration and cardiovascular mortality. To further elucidate this aspect, the conduct of dedicated analyses may be necessary to investigate in detail the possible mechanisms involved in this context.

## 6.4 Conclusion

The observed results indicate a potential association between sleep duration and cardio-metabolic health and suggest a role of inadequate sleep patterns as a distant and as a direct risk factor for cardiovascular health outcomes. Implications for public health and suggestions for future research resulting from these findings will be briefly outlined in the following paragraph.

### 6.4.1 Public Health Implications

If one agrees that the need for sleep is similar for children and adults from diverse populations, then the results presented in *Chapter 2* and *Chapter 3* seem to endorse the hypothesis that sleep patterns are one of the factors that may underlie regional or country specific differences in cardio-metabolic conditions. In fact, children from Southern Europe fall short of the sleep recommendation of 11 to 13 hours for pre-school children, and of 10 to 11 hours for school children, that was published by the American Academy of Sleep Education [57]. By contrast, Northern European children seem to have sleep patterns that are more appropriate according to these guidelines. Consequently, children from Southern countries might run a higher risk of an unfavourable metabolic development, which is in line with the observed high prevalence of childhood overweight especially in Mediterranean countries (*Chapter 3*). Although data on cardiovascular events, occurring mainly in middle-age and elderly individuals, show relatively low incidence and mortality rates in these countries, the increase in prevalence of overweight and obesity in the region is being seen as the key feature which may in the long term undermine the Mediterranean advantage with regard to cardiovascular disease [41].

To counteract the trend of reduced sleep duration and inadequate sleeping patterns and its related health conditions already at the starting point, sleep experts have suggested taking on this subject in the educational systems in a structured and serious way. They criticise that children are taught about nutrition and regular exercise, but that the third critical ingredient of a healthy lifestyle, that is sleep, is barely touched upon [58]. Recommendations for sleep practices and sleep education programmes have been presented by several institutions [57-59]. For example, the American Academy of Sleep Medicine published several recommendations to help children sleep better and more adequately [57]. These guidelines include the following:

- Follow a consistent bedtime routine. Set aside 10 to 30 minutes to get your child ready to go to sleep each night.
- Establish a relaxing setting at bedtime.

- Do not let your child fall asleep while being held, rocked, fed a bottle, or while nursing.
- Interact with your child at bedtime. Don't let the TV, computer or video games take your place.
- Keep your children away from TV programs, movies, and video games that are not right for their age.
- At bedtime, do not allow your child to have foods or drinks that contain caffeine. This includes chocolate and sodas. Try not to give him or her any medicine that has a stimulant at bedtime. This includes cough medicines and decongestants.

Recommendations are also given from institutions in other countries [57-59], and the content is very similar in all of these references – disregarding cultural, socio-environmental and region specific differences of sleep.

The results of this thesis strengthen the view that these recommendations need to be seen also in the context of the respective cultural area where they are supposed to be implemented. They should be adapted to the cultural context so that, for example, recommendations for parents in Mediterranean countries should focus more on the adequate amount of sleep, while in other regions the above mentioned specific settings of sleep education might be more relevant. Since much of the information on healthy sleep in childhood is distributed and brought to the parents via the presentation of the child to a doctor, targeted education is needed for paediatric specialists [60] and they should be made aware of the country or culture specific aspect of sleep and advise the parents accordingly.

Additionally, different patterns were seen between countries with respect to factors that are not directly associated with sleep but might reflect a certain lifestyle or parenting style. For example, screen time, which can be seen as a proxy for sedentary behaviour, which in turn is associated with overweight as well as with cardiovascular mortality [61], was longest in the Mediterranean countries (*Chapter 2*). This – in combination with short sleep duration - might reflect a generally more unfavourable lifestyle with regard to cardio-metabolic health in these countries, primarily resulting in an elevated overweight prevalence (*Chapter 3*). Therefore, prevention programs should additionally take into account such possibly aggravating factors that can be addressed and modified already in childhood, where the cornerstone for cardio-metabolic health is laid.

### 6.4.2 Suggestions for future research

The presented results suggest sleep duration as a relevant risk factor for cardio-metabolic health, indicating a direct as well as an indirect impact (via overweight) on cardiovascular outcomes. However, more insight into these pathways and the complex

interactions in this context is needed, calling for – preferably prospective - studies that assess sleep duration as well as markers of cardio-metabolic health at different stages of life to show independent and possibly mediated effects of sleep. Such studies could additionally identify inadequate sleep as a possibly tracking risk factor with regard to cardio-metabolic outcomes. Furthermore, confirmatory and explanatory studies on the effect of sleep duration on cardiovascular outcomes that take into consideration co-morbidities, e.g. depression are required in order to develop appropriate evidence-based recommendations for adults.

Another aspect that requires further research are the regional differences in sleep patterns. Internationally comparable studies are needed to give a more detailed insight into the origins of these differences and in regional aspects of parenting practices concerning sleep in different cultures and nations. Such data would offer important additional perspectives for appropriate region-specific recommendations or educational programmes that counteract unhealthy sleep patterns already in the early years of life.

Further to this, deepening research on the impact of sleep quality rather than sleep duration only is desirable, since evidence for the effect of several other aspects of sleep quality, such as obstructive sleep apnea (OSA), misalignment of circadian rhythms (chronodisruption) or daytime sleep on cardio-metabolic health is limited or inconsistent [62-64]. In this context the development of instruments that thoroughly assess the miscellaneous elements of sleep quality might contribute to a more detailed insight in the complex relationship between sleep and cardio-metabolic health.

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