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Sleep and behaviour and cognition in European children – Results from the EU Child Cohort Network

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List of Abbreviations

AASM	American Academy of Sleep Medicine
ALSPAC	Avon Longitudinal Study of Parents and Children
CHOP	Childhood Obesity Project
CI	Confidence interval
EDEN	Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant
ELFE	Étude Longitudinale Française depuis l'Enfance
EUCCN	European Union Child Cohort Network
INMA	INfancia y Medio Ambiente Project
OR	Odds ratio
SD	Standard deviation
SWS	Southampton Women's Survey

1. Abstract

Background:

Insufficient sleep duration has been suggested to have negative effects on children's behaviour and cognitive abilities. Research in this area has so far been mainly focused on children in school age and on parent-reported sleep duration.

Aims:

The aim of this cumulative thesis was to study sleep duration in European preschool and schoolchildren and to investigate whether device-measured as well as parent-reported short sleep duration is associated with more behavioural problems and lower cognitive performance. Publication I was focused on a cross-sectional analysis of device-measured sleep duration derived from 8-year-old European schoolchildren and its association with internalizing and externalizing behaviour problems. Publication II was focused on parent-reported sleep duration from preschool children from five European cohorts and its association with behavioural and cognitive outcomes at 5 years of age.

Methods:

Data were drawn from the European Union Child Cohort Network (EUCCN) that was initiated in the Horizon 2020 project LifeCycle. In Publication I, secondary data from the CHOP study that was carried out in five European countries (Belgium, Germany, Italy, Poland, Spain), were analyzed. The SenseWear™ Armband 2 was used to measure sleep duration. Internalizing and externalizing problems were parent-rated using the *Child Behavior Checklist*. To investigate whether sleep duration is associated with behaviour, logistic regression models were applied. In Publication II, data from five European cohorts (ALSPAC, SWS (United Kingdom); EDEN, ELFE (France); INMA (Spain)) were analyzed. Sleep duration was measured with parental questionnaires. Behaviour was assessed by parents who filled out the *Strengths and Difficulties Questionnaire*. The *Wechsler Preschool and Primary Scale of Intelligence* or the *McCarthy Scales of Children's Abilities* were used by psychologists to assess language and non-verbal intelligence. A two-stage individual participant data meta-analysis was performed. Adjusted generalized linear regression models were used in each cohort and effect estimates were combined with random-effects meta-analysis.

Results:

In Publication I, we analyzed data from 406 8-year-old schoolchildren. In Publication II, data from 11.920 preschool children were available for the analysis of behavioural outcomes and data from 2981 preschool children for the analysis of cognitive outcomes. The average sleep duration in preschool children was 11h 54min per day (SD: 1h 01min) and in schoolchildren 9h 15min per night (SD: 40min). Sleep duration varied between the different countries. Children from Middle Europe tended to sleep longer on average than children from South or East Europe, regardless of age. Looking at preschool children, we found that one hour more sleep per day at 3.5 years of age was associated with lower internalizing behaviour percentile scores (adjusted mean difference: -1.27; 95% CI -2.22, -0.32) and with lower externalizing behaviour percentile scores (adjusted mean difference: -2.39; 95% CI -3.04, -1.75) at 5 years of age. The associations between sleep duration and language and non-verbal intelligence showed trends towards an inverse association, albeit with imprecise estimates. Looking at 8-year-old schoolchildren, 66.7% of our sample met the sleep duration recommendation of the American Academy of Sleep Medicine (AASM) for children aged 6 to < 13 years (9-12 hours of sleep per night). Children who slept one hour more per night had a lower risk for internalizing problems (adjusted OR: 0.51; 95% CI 0.29, 0.91). Adhering to the sleep duration recommendation of the AASM reduced the risk for internalizing problems (adjusted OR: 0.45; 95% CI 0.21, 0.99). Sleep duration and externalizing problems were not associated.

Conclusions:

Results of the two publications highlight that a longer sleep duration during preschool years as well as in primary-school years is associated with fewer internalizing behaviour problems. Sleep duration and externalizing behaviour showed an association in preschool children, but not in schoolchildren. It emphasizes the need to ensure sufficient sleep duration as early as in preschool years for the optimal development of mental health of children. Findings also underline that paediatricians should monitor sleep as one of the potential factors that can contribute to behavioural problems. The association of sleep duration with cognitive outcomes could not be clearly answered and need replication in a larger sample of children.

2. Zusammenfassung

Hintergrund:

Es gibt Hinweise, dass eine unzureichende Schlafdauer negative Auswirkungen auf das Verhalten und die kognitiven Fähigkeiten von Kindern hat. Die Forschung in diesem Bereich hat sich bisher hauptsächlich auf Kinder im Schulalter und auf die von eltern-berichtete Schlafdauer konzentriert.

Ziele:

Das Ziel dieser kumulativen Arbeit war es, die Schlafdauer von europäischen Vorschul- und Schulkindern zu untersuchen und herauszufinden, ob eine von Geräten gemessene oder von eltern-berichtete kurze Schlafdauer mit mehr Verhaltensproblemen und schlechteren kognitiven Fähigkeiten assoziiert ist. Publikation I umfasste eine Querschnittsanalyse der Schlafdauer von 8-jährigen europäischen Schulkindern, die gerätegestützt erfasst wurde, und deren Assoziation mit internalisierenden und externalisierenden Verhaltensproblemen. Publikation II konzentrierte sich auf die eltern-berichtete Schlafdauer von 3.5 Jahre alten Vorschulkindern aus fünf europäischen Kohorten und deren Assoziation mit verhaltensbezogenen und kognitiven Merkmalen im Alter von 5 Jahren.

Methoden:

Die verwendeten Daten stammen aus dem European Union Child Cohort Network (EU-CCN), das im Rahmen des Horizon 2020 Projekts LifeCycle entstand. In Publikation I wurden Sekundärdaten aus der CHOP-Studie analysiert, die in fünf europäischen Ländern (Belgien, Deutschland, Italien, Polen, Spanien) durchgeführt wurde. Das SenseWear™ Armband 2 wurde zur Messung der Schlafdauer verwendet. Internalisierende und externalisierende Verhaltensprobleme wurden von Eltern anhand der *Child Behavior Checklist* bewertet. Um zu untersuchen, ob die Schlafdauer mit dem Verhalten assoziiert ist, wurden logistische Regressionsmodelle angewandt. In Publikation II wurden Daten aus fünf europäischen Kohorten (ALSPAC, SWS (Großbritannien); EDEN, ELFE (Frankreich); INMA (Spanien)) untersucht. Die Schlafdauer wurde mit Fragebögen gemessen, die von Eltern ausgefüllt wurden. Das Verhalten wurde von Eltern beurteilt, die den *Fragebogen zu Stärken und Schwächen* ausfüllten. Die *Wechsler Preschool and Primary Scale of Intelligence* oder die *McCarthy Scales of Children's Abilities* wurden von Psychologen zur Bewertung der Sprache und der nonverbalen Intelligenz verwendet. Eine zweistufige individuelle Teilnehmerdaten Meta-Analyse wurde durchgeführt. In jeder Kohorte wurden

generalisierte lineare Regressionsmodelle verwendet und die Effektschätzer mit einer Meta-Analyse mit zufälligen Effekten kombiniert.

Ergebnisse:

In Publikation I wurden Daten von 406 8-jährigen Schulkindern analysiert. In Publikation II waren Daten von 11.920 Vorschulkindern für die Analyse von Verhaltensproblemen verfügbar und Daten von 2.981 Vorschulkindern für die Analyse von kognitiven Fähigkeiten. Die durchschnittliche Schlafdauer bei Vorschulkindern betrug 11 Std. und 54 Min. pro Tag (SD: 1 Std. 1 Min.) und bei Schulkindern 9 Std. und 15 Min. pro Nacht (SD: 40 Min.). Die Schlafdauer variierte zwischen den verschiedenen Ländern. Kinder aus Mitteleuropa tendierten dazu, im Durchschnitt länger zu schlafen als Kinder aus Süd- oder Osteuropa, unabhängig vom Alter. Bei den Vorschulkindern konnten wir feststellen, dass eine Stunde mehr Schlafdauer pro Tag im Alter von 3.5 Jahren mit niedrigeren Perzentilwerten für internalisierendes Verhalten (bereinigte mittlere Differenz: -1.27; 95% CI -2.22, -0.32) und externalisierendes Verhalten (bereinigte mittlere Differenz: -2.39; 95% CI -3.04, -1.75) im Alter von 5 Jahren verbunden war. Die Assoziationen zwischen Schlafdauer und Sprache oder nonverbaler Intelligenz zeigten Tendenzen zu einer inversen Assoziation, allerdings mit ungenauen Schätzungen. Bei den 8-jährigen Schulkindern erfüllten 66.7% unserer Stichprobe die von der American Academy of Sleep Medicine (AASM) empfohlenen Schlafdauer für Kinder im Alter von 6 bis < 13 Jahren (9-12 Stunden Schlaf pro Nacht). Kinder, die eine Stunde mehr pro Nacht schliefen, hatten ein geringeres Risiko für internalisierende Probleme (bereinigte OR: 0.51; 95% CI 0.29, 0.91). Die Einhaltung der von der AASM empfohlenen Schlafdauer reduzierte das Risiko für internalisierende Probleme (bereinigte OR: 0.45; 95% CI 0.21, 0.99). Schlafdauer und externalisierende Probleme waren nicht assoziiert.

Schlussfolgerungen:

Die Ergebnisse aus den beiden Publikationen verdeutlichen, dass eine längere Schlafdauer im Vorschulalter sowie im Grundschulalter mit weniger internalisierenden Verhaltensproblemen verbunden ist. Schlafdauer und externalisierendes Verhalten zeigte eine Assoziation bei Vorschulkindern, aber nicht bei Schulkindern. Dies unterstreicht die Notwendigkeit, bereits im Vorschulalter für eine ausreichende Schlafdauer zu sorgen, um eine optimale Entwicklung der psychischen Gesundheit von Kindern zu gewährleisten. Die Ergebnisse zeigen auch, dass Kinderärzte Schlaf als einen der potenziellen Faktoren, die zu Verhaltensproblemen beitragen können, beobachten sollten. Der Zusammenhang zwischen der Schlafdauer und kognitiven Fähigkeiten konnte nicht eindeutig geklärt werden und sollte mit einer größeren Stichprobe von Kindern wiederholt werden.

3. Introduction

3.1 Background

Children's mental health problems have emerged as one of the leading challenges for public health in this century (1). Worldwide, the prevalence of mental health problems in children and adolescence is estimated to be around 10 to 20% (2, 3). The case of Europe shows that 9 million children and adolescents between the age of 10 and 19 years are experiencing mental health problems (4). In particular, anxiety and depression are listed among the most common five causes of the total disease burden in European children and adolescents (5).

Mental health is as important as physical health and plays a key role in every stage of life. The World Health Organization defines mental health as "a state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community" (6). Especially, the ability to apply social, emotional and cognitive skills to cope with daily life, is an essential component of good mental health (7).

Mental health problems during childhood can interfere with a child's developmental potential and impact health outcomes in later life (8). Childhood is considered as a sensitive developmental period in life in which the foundations for health in adulthood are built (9, 10). Many mental disorders have their roots in childhood. In about half of the cases, the development of first symptoms starts before the adolescent age (11, 12). A systematic review of studies with a prospective longitudinal design has shown that having mental health difficulties as a child increases the risk for mental disorders as an adult (13). Mental health disorders in adulthood can be associated with various consequences like poorer academic performance, higher levels of unemployment and worse physical health (14). Therefore, it should be a priority to start prevention and interventions early in life to protect mental health and well-being of children and to improve long term mental health outcomes.

Mental health problems in children can have many different facets and early signs of mental health problems can be, amongst others, feelings of sadness, difficulties in concentrating or staying still, severe out-of-control behaviour, lack of problem-solving abilities or language delays (15). The symptoms mentioned can be divided into behavioural problems, specifically in internalizing and externalizing problems, and problems related to cognitive performance. Internalizing problems refer to inner-directed behaviours of a child and include anxiety and depression symptoms, emotions as sadness, fear or shyness, social withdrawal and somatic complaints (16). Externalizing problems are outer-directed behaviours of the child towards others or the environment including attention problems, hyperactivity, impulsivity, and aggressive or rule-breaking behaviour (16). Problems related to cognitive performance may be reflected in delayed language development, decreased attention, poor executive function or worse problem-solving skills.

As described earlier, childhood years are an important window of opportunity where children undergo rapid biological and emotional changes, and where behavioural as well as cognitive skills are developing (9, 10). Exposures that occur during developmentally sensitive periods are of special importance, because they can influence mental health outcomes of a person years into the future (10). Therefore, it is important to investigate behaviour and cognition in this time window to determine which early stressors they are associated with or influenced by.

The literature demonstrates that a variety of different factors, such as health-related, socio-demographic or lifestyle characteristics can impact mental health outcomes of children. Health-related characteristics like maternal depression have been shown to have a negative impact on the behavioural and cognitive development of a child (17). Other health-related factors such as maternal overweight and obesity before or during pregnancy can also have an effect on the development of behavioural problems and neurodevelopmental outcomes in children (18, 19). Additionally, socio-demographic factors like a low parental socio-economic status, characterized by a low education level and low income, have been described as being associated with behavioural problems and cognitive and language development in children (20, 21). Parental divorce or separation have also been reported to be associated with different aspects of mental health in later life (22). Furthermore, lifestyle factors like maternal smoking and alcohol consumption during pregnancy or passive smoke exposure in a child’s early life have been shown to be linked to mental health problems in children (23-25).

Last but not least, sleep has also been suggested to be a risk factor for behavioural problems and lower cognitive performance in children (26-28). The literature shows that adequate sleep quantity and quality contribute to overall health and well-being of a child, supports a child’s healthy development, and is fundamental for maintaining optimal cognitive and emotional functioning (28-30). As sleep habits but also behaviour and cognition are in development during childhood years, it provides potential for prevention and intervention. Therefore, it is of clinical importance to understand the relationship between sleep and mental health. Sleep is a modifiable factor that can be potentially addressed through specific intervention strategies. Additionally, sleep can be an early indicator for parents and paediatricians to detect evolving mental health problems in a child (31).

The need for sleep as well as sleep patterns change throughout the life course. In the first weeks of life, a newborn's circadian rhythm is not yet fully developed and is mainly characterized by several short sleep episodes, which are more determined by whether the infant is hungry or satiated than whether it is day or night (32, 33). The circadian rhythm begins to develop in the further course of the first year of life, when also the amount of nighttime sleep increases and the amount of daytime sleep decreases (33). Frequent night wakings in early childhood are typical (32). Most toddlers and preschool-aged children take daytime naps until they are around 4 years old (34). As children get older, their sleep duration decreases steadily and becomes shorter due to later bedtimes and unchanged or earlier wake times (32, 34).

The question of how much sleep is appropriate for a child depends mainly on the age of the child (35). The American Academy of Sleep Medicine (AASM) developed age-appropriate recommendations for the amount of sleep that is required on a regular basis to facilitate optimal health in children (36): for infants aged 4 months to < 1 year, 12 to 16 hours of sleep per day including naps are recommended (no recommendations were possible for infants under the age of 4 months, because of a lack of studies in this age group); toddlers between 1 and < 3 years of age should sleep between 11 to 14 hours per day including naps; for preschool children aged 3 to < 6 years, 10 to 13 hours of sleep per day including naps are recommended; children aged 6 to < 13 years should sleep 9 to 12 hours per day; for adolescents between 13 and 18 years of age, 8 to 10 hours sleep per day are recommended. To establish these recommendations, a literature review was undertaken as well as several rounds of discussing and voting by an expert panel (36). Such recommendations on sleep duration are fundamental to give parents and paediatricians an idea of healthy sleep behaviours and to inform intervention strategy planning (30). In addition to sufficient sleep duration, also other aspects of healthy sleep need to be taken into account, such as good sleep quality and an appropriate sleep rhythm (36).

In paediatric research, there are several different methods available for measuring sleep quantity in children: polysomnography, actigraphy, diaries and questionnaires. The gold-standard of sleep measurement is polysomnography, which is usually performed in sleep laboratories for one or two nights (37). Multiple sensors are attached to the body to measure a wide variety of neurophysiological parameters during sleep. In children, it is usually used as a diagnostic tool for example to diagnose sleep disorders (37). Since it is an expensive and time-consuming procedure, it is rather not suitable for studies with large populations like observational studies (37). Additionally, it can be difficult to apply in younger children, because they have to spend the night in an unfamiliar environment, which might be frightened and can bias and complicate the measurements (38). Other less cumbersome device-based methods are actigraphy measurements. An actigraphy device is usually worn for several consecutive nights on the wrist, arm or ankle, depending on the age group and the device (ActiGraph: wrist, ankle; SenseWear Armband: arm). During sleep, activity data is recorded with different axes and sensors at certain intervals (e.g. in 1 min epochs) (39). These parameters are used to estimate sleep-wake patterns using special algorithms (39). Advantages of actigraphy devices are that they document the day-to-day variability of sleep and record the normal sleep behaviour in the home setting of a child (40). Measurement inaccuracies may result when external motion is recorded or the device is removed (37). To control the latter and thus the quality of the actigraphy measurement, complementary sleep diaries are often used. They represent the personal or parent perception of each night sleep (38). Since sleep diaries need to be completed on a daily basis, they put a higher burden on the parents or the child than questionnaires, but are less prone to recall bias (40). The most common sleep measurement method used in children are parent-reported or self-reported questionnaires, depending on the age of the child. They are especially suitable for studies with many participants, because they are relatively cost-effective. Sleep questionnaires have the advantage that they are easy to handle and put a low burden on the respondent (parents or children), however, the collected information can be influenced by recall or response bias (37).

A review of literature on worldwide trends on sleep duration in 5 to 18 year old children has shown that children and adolescents sleep nowadays less compared to the past (41). Reasons for this may be attributed to lifestyle changes as increased screen-based activities like television watching, and computer or mobile-phone use which can result in delayed bedtimes (42). However, the decrease in sleep duration that was observed in children is of concern. A growing body of evidence shows that insufficient sleep has negative effects on children's daytime functioning resulting in more behavioural problems, reduced emotional regulation, impaired cognitive function and poorer academic achievement (27, 28).

Especially for school-aged children and adolescents, the association between sleep duration and behavioural and cognitive outcomes is becoming increasingly evident. Astill et al. (29) concluded in a meta-analysis that shorter sleep duration is associated with lower cognitive performance and more problem behaviour in 5- to 12-year-old children. A systematic review on the relationship between sleep and various health outcomes in children between the ages 5 to 17 years showed that there is an association between longer sleep duration and better school performance, emotional regulation and well-being (30). Matricciani et al. (43) demonstrated in a review of reviews that there is consistent evidence that longer sleep duration is associated with better emotional health in children and adolescents.

The available findings from these studies, however, are primarily relying on sleep duration that was reported by parents or was self-reported, e.g. from questionnaires or diaries. In contrast, studies in children measuring sleep duration with devices like actigraphy measurements are rare (30, 44, 45). Research has shown that parents' subjective reports of their children's sleep tend to overestimate sleep duration compared to measurements with devices (46, 47). Dayyat et al. (46) reported that parents overestimate their children's actual sleep duration by around one hour per night, in comparison with actigraphy measurements.

To date, device-based measurements for sleep have predominantly been applied in experimental studies, in which sleep duration is manipulated to examine its impact on behaviour and cognitive performance in children. They showed that sleep restriction has negative effects on emotional functioning and regulation as well as attention and memory (48, 49). In the field of observational studies, there are just a few studies that have measured sleep duration with devices and examined its relationship with problem behaviour in children. Therefore, we concluded that further studies with device-measured sleep data are needed to investigate the relationship of sleep and behaviour. This research gap was addressed in Publication I of this doctoral thesis (50).

While there have been many studies in schoolchildren and adolescents focusing on the association of sleep with behavioural and cognitive outcomes as previously described, there is a lack of studies with children under 5 years of age in this research field (44, 51, 52). Preschool years are an unique time window in which the brain matures, the sleep wake rhythm develops rapidly and sleep habits are shaped (53). Insufficient and poor sleep during this period of life may influence a child's development stronger than at later ages (44). It is therefore of importance to know whether the associations observed in older children are already visible as early as in preschool age. The scarce evidence in this research field shows the need for examining the potential association between sleep duration and behavioural symptoms and cognitive outcomes in preschool-aged children. Combining a large amount of data from different European pregnancy and birth cohorts, we wanted to address this research gap in Publication II of the present doctoral thesis (54).

3.2 Outline

The overarching aim of this cumulative doctoral thesis is to examine if sleep duration has an influence on behavioural and cognitive outcomes in European preschool-aged and school-aged children. To address the current research gaps described previously, device-measured sleep duration was the focus in Publication I and preschool-aged children were the focus in Publication II. Outcomes of interest were internalizing and externalizing behaviour in both publications as well as language and non-verbal intelligence in Publication II.

For the analyses, data from the European Union Child Cohort Network (EUCCN) were used, specifically data from six cohorts: Avon Longitudinal Study of Parents and Children (ALSPAC), United Kingdom (55); Childhood Obesity Project (CHOP), Belgium, Germany, Italy, Poland, Spain (56); Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant, (EDEN), France (57); Étude Longitudinale Française depuis l'Enfance (ELFE), France (58); INfancia y Medio Ambiente Project, (INMA), Spain (59); and Southampton Women's Survey (SWS), United Kingdom (60). The EUCCN has been established by the Horizon 2020 project LifeCycle and is a consortium of 18 European and one Australian pregnancy and birth cohorts (61). Together, these cohorts cover a large part of the lifecycle, from the preconception period, through pregnancy until childhood and adolescence. In the course of the project a large amount of variables around different early life-stressors like socio-economic, lifestyle and environmental factors, and different outcomes around cardiovascular, respiratory and mental health have been harmonized (62). The EUCCN is a findable, accessible, interoperable and reusable (FAIR) data resource (61). The harmonized data from each cohort is stored on local servers hosted by the participating institutions. After approval of the research proposal by the institution, researchers get access to the specific data and perform analyses via a central analysis server using the R-based platform DataSHIELD (63). It allows joint analysis of data from different cohorts without the need to exchange data at an individual level.

The following two publications are part of this cumulative doctoral thesis:

(I) **Guerlich K**, Gruszfeld D, Czech-Kowalska J, Ferré N, Closa-Monasterolo R, Martin F, Poncelet P, Verduci E, Koletzko B and Grote V. Sleep duration and problem behaviour in 8-year-old children in the Childhood Obesity Project. Eur Child Adolesc Psychiatry 31 (3): 519–527 (2022). https://doi.org/10.1007/s00787-021-01731-8

(II) **Guerlich K**, Avraam D, Cadman T, Calas L, Charles MA, Elhakeem A, Fernández Barrés S, Guxens M, Heude B, Ibarluzea J, Inskip H, Julvez J, Lawlor DA, Murcia M, Salika T, Sunyer J,Tafflet M, Koletzko B, Grote V and Plancoulaine S. Sleep duration in preschool age and later behavioral and cognitive outcomes: an individual participant data meta-analysis in five European cohorts. Eur Child Adolesc Psychiatry 33 (1): 167-177 (2024). https://doi.org/10.1007/s00787-023-02149-0

Each publication focused on a different sleep duration measurement method (device-based measurement, parent-reported measurement) and a different age group (preschool children, primary school children). In the following, the specific aims of each publication are described more in detail. The full-texts of the two publications and the contribution of the applicant are listed in the separate chapters 5 to 7.

(I) The aim of Publication I was to investigate the association of device-based measured sleep duration with behavioural outcomes (internalizing and externalizing behaviour) in schoolchildren aged 8 years from five European countries. Additionally, sleep duration differences between sex and countries were studied. Data from the CHOP study were used.

(II) The aim of Publication II was to study the associations between parent-reported sleep duration in preschool age (3.5 years) and behavioural problems and cognitive outcomes in 5-year-old children from five European birth-cohorts. Additionally, sleep duration differences between countries were described. Data from five cohorts were used: ALSPAC, EDEN, ELFE, INMA and SWS.

4. Publication list

This cumulative doctoral thesis consists of the following two publications:

Publication I:

Guerlich K, Gruszfeld D, Czech-Kowalska J, Ferré N, Closa-Monasterolo R, Martin F, Poncelet P, Verduci E, Koletzko B and Grote V. Sleep duration and problem behaviour in 8-year-old children in the Childhood Obesity Project. Eur Child Adolesc Psychiatry 31 (3): 519–527 (2022). https://doi.org/10.1007/s00787-021-01731-8

"Sleep duration and problem behaviour in 8-year-old children in the Childhood Obesity Project" is an original research article published in the peer-reviewed Journal *European Child & Adolescent Psychiatry*. It appeared online on February 24, 2021 and in print in March 2022.

Publication II:

Guerlich K, Avraam D, Cadman T, Calas L, Charles MA, Elhakeem A, Fernández-Barrés S, Guxens M, Heude B, Ibarluzea J, Inskip H, Julvez J, Lawlor DA, Murcia M, Salika T, Sunyer J, Tafflet M, Koletzko B, Grote V and Plancoulaine S. Sleep duration in preschool age and later behavioral and cognitive outcomes: an individual participant data meta-analysis in five European cohorts. Eur Child Adolesc Psychiatry 33 (1): 167-177 (2024). https://doi.org/10.1007/s00787-023-02149-0

"Sleep duration in preschool age and later behavioral and cognitive outcomes: an individual participant data meta-analysis in five European cohorts" is an original research article published in the peer-reviewed Journal *European Child & Adolescent Psychiatry*. It appeared online on February 7, 2023 and in print in January 2024.

According to the InCites Journal Citation Reports the impact factor of the Journal *European Child & Adolescent Psychiatry* was 6.4 in 2022. In the *Pediatrics* category it was ranked at place 7 of 130 journals in 2022, among the top 5% of journals.

Further scientific publications (not part of the doctoral thesis)

- Cadman T, Elhakeem A, Vinther JL, Avraam D, Carrasco P, Calas L, Cardol M, Charles MA, Corpeleijn E, Crozier S, de Castro M, Estarlich M, Fernandes A, Fossatti S, Gruszfeld D, **Guerlich K**, Grote V, Haakma S, Harris JR, Heude B, Huang RC, Ibarluzea J, Inskip H, Jaddoe V, Koletzko B, Luque V, Manios Y, Moirano G, Moschonis G, Nader J, Nieuwenhuijsen M, Andersen AM, McEachen R, Pinot de Moira A, Popovic M, Roumeliotaki T, Salika T, Marina LS, Santos S, Serbert S, Tzorovili E, Vafeiadi M, Verduci E, Vrijheid M, Vrijkotte TGM, Welten M, Wright J, Yang TC, Zugna D, Lawlor DA. Associations of maternal educational level, proximity to greenspace during pregnancy, and gestational diabetes with Body Mass Index from infancy to early adulthood: A proof-of-concept federated analysis in eighteen birth cohorts. Am J Epidemiol. Epub ahead of print (2023). https://doi.org/10.1093/aje/kwad206
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5. Contribution to the Publications

5.1 Contribution to Publication I

Guerlich K, Gruszfeld D, Czech-Kowalska J, Ferré N, Closa-Monasterolo R, Martin F, Poncelet P, Verduci E, Koletzko B and Grote V. Sleep duration and problem behaviour in 8-year-old children in the Childhood Obesity Project. Eur Child Adolesc Psychiatry 31 (3): 519–527 (2022). https://doi.org/10.1007/s00787-021-01731-8

For the first publication data from the Childhood Obesity Project (CHOP) were used. The study is coordinated at the Dr. von Hauner Children's Hospital at the LMU University Hospital Munich, in collaboration with four European partners from Spain (Universitat Rovira i Virgili, IISPV, Reus), Belgium (Centre Hospitalier Chretien St. Vincent, Liege-Rocourt; Université Libre de Bruxelles, Brussels), Poland (Children's Memorial Health Institute, Warsaw) and Italy (University of Milan, Milan). CHOP is part of the EU Child Cohort Network that was established in the LifeCycle project. Nine co-authors from the study centers were included. The contribution of co-authors to Publication I included either the conceptualization and design of the CHOP trial and research or the data collection at study sites as well as the critical review of the manuscript.

My contribution to Publication I include:

- Contribution to the conception and design of the research question
- Data preparation for analysis
- Statistical analyses of data and interpretation of results
- Creation of the figure and tables in the manuscript
- Drafting and finalizing of the manuscript
- Coordination of communication with the 9 co-authors and revisions of the manuscript based on input from co-authors
- Preparation and submission of the manuscript to the Journal *European Child & Adolescent Psychiatry*
- Revision of the manuscript based on peer-reviewers' comments, point-by-point response to peer reviewers' comments
- Proof read of the accepted manuscript

5.2 Contribution to Publication II

Guerlich K, Avraam D, Cadman T, Calas L, Charles MA, Elhakeem A, Fernández-Barrés S, Guxens M, Heude B, Ibarluzea J, Inskip H, Julvez J, Lawlor DA, Murcia M, Salika T, Sunyer J,Tafflet M, Koletzko B, Grote V and Plancoulaine S. Sleep duration in preschool age and later behavioral and cognitive outcomes: an individual participant data meta-analysis in five European cohorts. Eur Child Adolesc Psychiatry 33 (1): 167-177 (2024). https://doi.org/10.1007/s00787-023-02149-0

For the second manuscript data from five European cohorts were used: Avon Longitudinal Study of Parents and Children (ALSPAC), Etude des Determinants pre et postnatals du developpement et de la sante de l'Enfant (EDEN), Etude Longitudinale Francaise depuis l'Enfance (ELFE), INfancia y Medio Ambiente Project (INMA) and Southampton Women's Survey (SWS). All cohorts are part of the EU Child Cohort Network that was established in the LifeCycle project. 19 co-authors from the participating cohorts were included. The contribution of co-authors to Publication II included either contributions to the collection, harmonization, analysis or interpretation of data or contributions to the design of the research as well as the critical review of the manuscript.

My contribution to Publication II include:

- Substantial contribution to the conception and design of the research question
- Writing of an analysis plan
- Assistance in obtaining data access agreements with the participating cohorts
- Data preparation for analysis
- Statistical analyses of data and interpretation of results
- Creation of the figures and tables in the manuscript
- Drafting and finalizing of the manuscript
- Coordination of communication with the 19 co-authors and revisions of the manuscript based on input from co-authors
- Preparation and submission of the manuscript to the Journal *European Child & Adolescent Psychiatry*
- Revision of the manuscript based on peer-reviewers' comments, point-by-point response to peer reviewers' comments
- Proof read of the accepted manuscript

6. Publication I

Original title: Sleep duration and problem behaviour in 8-year-old children in the Childhood Obesity Project

Authors: Guerlich Kathrin; Gruszfeld Dariusz, Czech-Kowalska Justyna, Ferré Natàlia, Closa-Monasterolo Ricardo, Martin Francoise, Poncelet Pascale, Verduci Elvira, Koletzko Berthold and Grote Veit

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ORIGINAL CONTRIBUTION

Sleep duration and problem behaviour in 8-year-old children in the Childhood Obesity Project

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Abstract
There is growing evidence that insufficient sleep has negative effects on the mental health of children. The aim of this study is to examine the associations between device-measured sleep duration and internalizing and externalizing problems in 8-year-old children. The study is a secondary analysis of data from the Childhood Obesity Project conducted in five European countries. Nocturnal sleep duration was measured with the SenseWear™ Armband 2. Parents rated their child's internalizing and externalizing problems on the Child Behaviour Checklist. Behaviour scores were dichotomized at the 90th percentile based on sex- and country-specific *z*-scores. Logistic regression models were applied to test the associations between sleep duration and behaviour. Data were available for 406 8-year-old children. The average sleep duration was 9.25 h per night (SD: 0.67) with 1464 nights measured in total. The sleep duration recommendation of the American Academy of Sleep Medicine for school-aged children (9–12 h) was met by 66.7% of children. One hour of additional sleep per night significantly reduced the risk of having internalizing problems (adjusted OR = 0.51; 95% CI 0.29–0.91). Children who adhered to the sleep duration recommendation had a lower risk for internalizing problems (adjusted OR = 0.45; 95% CI 0.21–0.99). Sleep duration and externalizing problems showed no significant association. Longer sleep duration was associated with a reduced risk of having internalizing problems but not externalizing problems. Results highlight that it is important to ensure adequate sleep duration throughout primary-school years for the optimal emotional health of children. Trial registration number: NCT00338689. Registered: June 19, 2006.

Keywords Sleep quantity · Child Behaviour Checklist · Emotional health · Behavioural problems · Schoolchildren

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Abbreviations

AASM	American Academy of Sleep Medicine
CBCL	Child Behaviour Checklist
CHOP	Childhood Obesity Project
CI	Confidence interval
GHQ	General Health Questionnaire
OR	Odds ratio
SD	Standard deviation

Background

Up to 20% of children and adolescents worldwide experience mental health problems [1, 2]. It represents one of the major public health challenges in the current century [3]. Internalizing problems, like anxiety and depression, and externalizing problems, like hyperactivity, inattention or aggression, have their onset often in childhood or adolescents with tracks into adulthood [4, 5]. Therefore, it is necessary to identify potential risk factors to develop effective intervention strategies. The literature shows that health-related factors like smoking and alcohol in pregnancy or maternal overweight [6], psychosocial stressors like depression and violence [6, 7] and socio-economic factors like poverty and low education [8] can have an effect on internalizing and externalizing problems in children. Sleep might be an additional modifiable stressor that needs to be considered [9, 10].

Sleep is essential for children's healthy development and contributes to normal mental functioning and health. Insufficient sleep is associated with negative effects on learning, memory, concentration and school performance in children [10]. Chaput et al. [11] reported in a systematic review that longer sleep duration is associated with better emotional regulation and higher quality of life in 5- to 17-year-old children and adolescents. A recent review on sleep and its relation to behaviour in preschool children demonstrated that a higher quantity of sleep is associated with better behavioural and cognitive outcomes [12]. Astill et al. [13] conducted a meta-analysis showing small but significant associations of shorter sleep duration with poorer cognition and problem behaviour in healthy school-aged children between the ages of 5 and 12 years.

However, researchers concluded that the available evidence of these studies is mainly based on parent- or self-reported sleep duration whereas more objective sleep measurement methods in children are rarely used [11, 12]. Subjective reports like questionnaires or sleep diaries often overestimate the actual sleep duration and are susceptible to reporting bias compared to device-based measurement methods like accelerometer or polysomnography [14]. Device-measured sleep is mainly used in experimental studies which have consistently shown effects of decreased sleep duration on emotional regulation, affective responses and moodiness in children and adolescents [15–17]. Only a few observational studies in children looked at associations of device-measured sleep duration and problem behaviour. They reported associations of short sleep duration with internalizing and externalizing problems as well as hyperactivity/impulsivity symptoms in school-aged children [18–20].

The main objective of our study was to examine the association of night sleep duration, measured with an accelerometer, with internalizing or externalizing symptoms in 8-year-old children, assessed with the Child Behaviour Checklist, a standardized screening questionnaire on mental health [21].

Patients and methods

Study design and study population

The underlying study uses data from the Childhood Obesity Project (CHOP), a double-blind randomized controlled intervention trial (ClinicalTrials.gov: NCT00338689. URL: http://clinicaltrials.gov/ct2/show/NCT00338689), initiated in 2002. Across five European countries (Belgium, Germany, Poland, Italy, Spain), 1678 healthy infants were recruited during their first eight weeks of life and randomized to either receive a higher or lower protein-content formula, with a reference group of breastfed children as control. The primary aim of the trial was to investigate whether different levels of protein-content in infant formula have an effect on infant growth and later risk of obesity. Detailed information on the whole study is published elsewhere [22, 23]. For this secondary analysis we used data from the 8-year follow-up ($N = 589$). Local ethical committees approved the trial and parents and children gave their informed consent. All research was conducted in accordance with the Declaration of Helsinki.

Sleep duration

The nocturnal sleep duration was measured with the SenseWear™ Armband 2 (BodyMedia Inc., Pittsburgh, PA) in 8-year-old children. As intended in the study protocol, children wore the device day and night on at least three consecutive days for at least 20 h per day. For the analyses, we included all children with at least two nights of sleep measurements. The SenseWear™ Armband is worn on the right arm over the triceps muscle and collects data in 1 min epochs through five sensors: two-axis accelerometer, heat flux, galvanic skin response, skin temperature and near body temperature [24]. The two-axis accelerometer measures whether the child is lying or not. The body heat sensor can detect non-wear-time and prevents from identifying non-wear-periods as sleep [25]. Studies have shown that the SenseWear™ Armband can give good sleep estimates compared to polysomnography [25, 26].

Sensor parameters combined with anthropometric data were edited with the Professional InnerView Software 6.1 (BodyMedia Inc., Pittsburgh, PA), which uses an undisclosed algorithm to distinguish between sleep and wake periods. Due to the lack of standardization of scoring rules for the armband, data were processed guided by scoring rules used in other studies with device-based measurements [27]. In contrast to other devices, the armband measurement differentiates lying and sleeping time. Therefore, we defined the nocturnal sleep duration as time from sleep onset (first minute of at least 3 consecutive minutes scored as lying down followed by at least 1 min scored as sleeping) to sleep offset (last minute of at least 5 consecutive minutes scored as lying). We applied the scoring rules to timeframes from 6 pm to 11 am as we could not see regular sleep duration periods during daytime.

We categorized the children in two sleep groups based on age-appropriate recommendations of the American

Academy of Sleep Medicine (AASM) (9–12 h sleep per night: yes/no) [28]. Based on the armband-wear-dates the season of measurement was defined (winter [Dec–Feb], spring [Mar–May], summer [June–Aug], autumn [Sept–Nov]).

Internalizing and externalizing problems

At the 8-year follow-up parents rated their child's behaviour on the Achenbachs' Child Behavior Checklist (CBCL 6/18). The CBCL is a widely used, standardized questionnaire with 113 symptom items assessed on a three-point Likert scale ('not true = 0', 'somewhat or sometimes true = 1', 'very true or often true = 2') [21]. From the responses, eight subscales (anxious/depressed, withdrawn/depressed, somatic complaints, rule-breaking behaviour, aggressive behaviour, thought problems, attention problems, social problems) and three broadband scales (internalizing, externalizing, total) are evaluated. The internalizing score, consists of the sum of the three subscales anxious/depressed, withdrawn/depressed and somatic complaints. The externalizing score, includes the subscales rule-breaking and aggressive behaviour. The CBCL has strong internal consistency ranging from 0.78 to 0.97 and a good test–retest reliability ($r = 0.90$) [29].

CBCL scores were z-standardized by sex and country to get each child's standing relative to other children of the same sex and country in the sample [30]. All CBCL scales were positively skewed, which is typical for problem behaviour scores in a general population where most of the children have relatively low scores. Therefore, to define high internalizing and externalizing problems, we decided to dichotomize the CBCL scales at the 90th percentile of the calculated z-scores (cut-offs: internalizing problems: 1.53, externalizing problems: 1.32) following other studies [31, 32].

Covariates

Additional to gender and country, various parental background information were collected at study entry. The highest education level reached by one of the parents was assessed according to the International Standard Classification of Education 1997 levels and defined as low (level 0–2), middle (level 3–4) or high (level 5–6) [33]. The mother reported her smoking status during pregnancy (yes/no) and her age at the child's birth (years). During the 8-year follow-up the current mental health status of the mother, or in some cases of the father was measured with the General Health Questionnaire (GHQ-12) and z-standardized by country and respondent [34]. A higher GHQ-12 score represents poorer mental health.

Statistical analyses

Night sleep duration was presented in decimal hours. Sex- and country-specific CBCL z-scores were calculated by subtracting the individual score from the corresponding country- and sex-specific mean and dividing it by the corresponding country- and sex-specific standard deviation. Differences in problem behaviour scores and nocturnal sleep duration were assessed by t-test and ANOVA. We applied logistic regression models to test the associations between night sleep duration and internalizing (low/high) or externalizing (low/high) problems at 8 years of age. The main predictor of the models was nocturnal sleep duration analysed as continuous (hours) and categorical data (adherence to AASM-recommendation: yes/no). Sex and country were regarded as fixed covariates for adjustment in the base models. Additional covariates for the adjusted models were selected based on a p-value < 0.25 in bivariate analyses (Online Resource Table 1) and the literature: highest education level reached by one of the parents, smoking in pregnancy, mother's age at child's birth and GHQ-12 z-score [6–8, 35].

Excluding children with only two nights of sleep measurements from logistic regression models, we performed a sensitivity analysis with children who had at least three nights of sleep recording as intended in the study protocol. In an additional sensitivity analysis we did not adjust for sex and country in the logistic regression models as they are already incorporated in the CBCL z-scores.

Statistical significance was assumed at a maximum error probability of 0.05. Statistical analysis was carried out with SPSS (IBM SPSS Statistics 26).

Results

At the 8-year follow-up 589 children participated. CBCL data were available for 524 children (89.0%). The participation rate in armband measurement was 75.4% (444 children). CBCL scores of children who took part in the armband measurement did not differ from those who did not participate. Complete data on CBCL and sleep measurements were available for 416 children; further ten children were excluded from analysis with only one night of sleep recording. Thus, 406 children remained for the final analysis (Fig. 1). In 39 cases, fathers instead of mothers filled in the CBCL, but as there were no detectable differences of scores between fathers or mothers, we analysed them together.

Table 1 shows the characteristics of the study children and their parents. About one-third of the participating children were from Spain. Most of the parents had a middle or high level of education. Every tenth child was categorized to have high internalizing or externalizing problems as defined

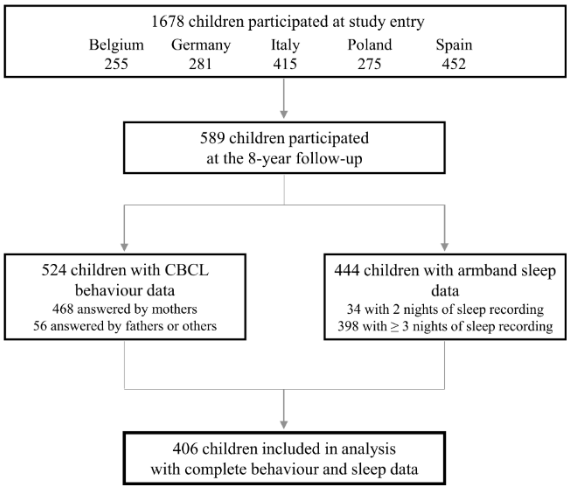

Fig. 1 Number of participating children and available data

by decile and 27% of these children had both internalizing and externalizing problems.

Overall, we measured sleep duration for 1464 nights ranging from 2 to 5 nights per child. Children slept on average 9.25 h per night (SD: 0.67). We could not observe significant differences in night sleep duration due to day of sleep measurement (weekday or weekend day). Sixty-seven percent of children slept on average within the recommended range of 9–12 h per night. Boys had significantly ($p < 0.001$) shorter night sleep durations (about 15 min less) than girls (Table 2). Sleep duration differed between countries, with children from Belgium and Germany showing a longer nocturnal sleep duration than children from Italy and Spain (Table 2). There was no significant difference in sleep duration measurements based on seasons.

Table 3 shows the associations of night sleep duration (continuous in hours and dichotomized) with internalizing and externalizing problems (low/high). An increase of 1 h sleep duration per night was significantly related to a lower risk of having internalizing problems (adjusted OR = 0.51; 95% CI 0.29, 0.91). Further, children who adhere to the recommendation of the AASM had a lower risk for internalizing problems (adjusted OR = 0.45; 95% CI 0.21, 0.99). Base models delivered similar results (Online Resource Table 2). A poorer mental health status of the mother or father (GHQ-12 *z*-score) was significantly associated with a higher risk of internalizing problems of the child in both adjusted models (OR = 1.63; 95% CI 1.23, 2.17; OR = 1.64; 95% CI 1.24, 2.18), while none of the other covariates showed a significant association with internalizing problems.

Nocturnal sleep duration in hours and externalizing problems showed no significant association (adjusted OR = 0.77; 95% CI 0.44–1.35). Further, there was no association between adherence to AASM recommendation and externalizing problems (adjusted OR = 0.53; 95% CI 0.25–1.16). Base models obtained similar results (Online Resource Table 2). A poorer mental health status of the mother or father was significantly associated with a higher risk of externalizing problems of the child in both adjusted models (OR = 1.56; 95% CI 1.19, 2.05; OR = 1.55; 95% CI 1.18, 2.03). Furthermore, the mother's age at child's birth showed a significant association with externalizing problems (adjusted OR = 0.91; 95% CI 0.83, 0.99; adjusted OR = 0.91; 95% CI 0.83, 0.99). None of the other covariates were significantly associated with externalizing problems.

Sensitivity analysis on the sample with three or more nights of sleep recording and without adjusting for sex

Table 1 Characteristics of participating children and their parents

	N = 406[a]
Age in years, mean (SD)	7.93 (0.08)
Girls, *n* (%)	215 (53.0)
Country, *n* (%)	
Belgium	42 (10.3)
Germany	57 (14.0)
Poland	93 (22.9)
Italy	78 (19.2)
Spain	136 (33.5)
Highest education level reached by one of the parents, *n* (%)	
High	167 (41.2)
Middle	199 (49.6)
Low	35 (8.7)
Mother's age at child's birth in years, mean (SD)	31.09 (4.68)
Smoking in pregnancy, *n* (%)	111 (27.4)
GHQ-12 *z*-score, mean (SD)	0.00 (1.01)
Nocturnal sleep duration in decimal hours, mean (SD)	9.25 (0.67)
Adherence to AASM[b] recommendation, *n* (%)	271 (66.7)
Season of sleep duration measurement, *n* (%)[c]	
Winter	132 (32.5)
Spring	120 (29.6)
Summer	57 (14.0)
Autumn	97 (23.9)
Number of nights measured per child, mean (SD)	3.61 (0.67)
CBCL results, *n* (%)	
High internalizing problems	40 (9.9)
High externalizing problems	40 (9.9)

AASM American Academy of Sleep Medicine, *CBCL* Child Behaviour Checklist, *GHQ* General Health Questionnaire, *SD* standard deviation

[a]Missings: education parents = 5; mother's age = 1; smoking in pregnancy = 1; GHQ-12 = 24

[b]9–12 h sleep per night

[c]Meteorological classification of season: winter = December, January, February; spring = March, April, May; summer = June, July, August; autumn = September, October, November

Table 2 Nocturnal sleep duration of participating children by sex, country and season of sleep duration measurement

	Nocturnal sleep duration in decimal hours	
	mean (SD)	*p* value
Sex		
Boys	9.11 (0.65)	**< 0.001**
Girls	9.36 (0.66)	
Country		
Belgium	9.74 (0.69)	**< 0.001**
Germany	9.51 (0.63)	
Poland	9.19 (0.55)	
Italy	9.11 (0.67)	
Spain	9.10 (0.65)	
Season[a]		
Winter	9.30 (0.61)	0.63
Spring	9.19 (0.67)	
Summer	9.21 (0.83)	
Autumn	9.26 (0.63)	

Significant *p* values are marked in bold

SD standard deviation

[a]Meteorological classification of season: winter = December, January, February; spring = March, April, May; summer = June, July, August; autumn = September, October, November

and country delivered similar results (Online Resource Tables 3 and 4). Online Resource Table 5 shows the associations of night sleep duration with the subscales of internalizing and externalizing problems. There was no significant association in a specific subscale.

Discussion

The present study investigated device-measured nocturnal sleep duration and its association with internalizing and externalizing problems in 8-year-old children from five European countries. Besides sex and country differences in sleep durations, we observed that an increase of 1 h sleep duration per night or the adherence to the AASM recommendation was significantly related to a lower risk of having internalizing problems even when controlling for other variables, while sleep duration and externalizing problems were not associated.

Some observational and experimental studies looked at device-measured sleep and different spectrums of problem behaviour in children. Most of the observational studies have a cross-sectional design. In the study of Nixon et al. [18] sleep of 519 7-year-old children was measured by actigraphs and dichotomized into less than 9 h and more than 9 h sleep per night. Similar to our results, less than 9 h sleep was significantly associated with higher emotional lability scores compared to children sleeping more than 9 h per night. Externalizing symptoms like attention deficit or hyperactivity disorder scores did not differ with sleep duration. Emotional lability scores and externalizing symptoms were measured by the Conners Rating Scale Parent Form. However, the results were based on sleep duration of just one night measurement. Another actigraph-study observed that a decreased sleep duration was not associated with parent-reported CBCL externalizing symptoms in 49 school-aged children but with teacher-reported externalizing symptoms measured by the Teacher's Report Form [19]. The results suggest that externalizing problems seem to be more evident in the school environment than at home. This could be a reason why we did not find an association between sleep and parent-reported externalizing problems.

Table 3 Adjusted associations between nocturnal sleep duration and internalizing and externalizing problems of children at 8 years of age

N = 376	High internalizing problems[a]			High externalizing problems[a]		
	OR [95% CI]	*p* value	R^2	OR [95% CI]	*p* value	R^2
Nocturnal sleep duration in h	0.51 [0.29, 0.91]	**0.02**	13.7	0.77 [0.44, 1.35]	0.36	13.6
Adherence to AASM recommendation[b]	0.45 [0.21, 0.99]	**0.046**	13.0	0.53 [0.25, 1.16]	0.11	14.5

Significant *p* values are marked in bold

All models were adjusted for sex, country, highest level of education reached by one of the parents, mother's age at child's birth, smoking in pregnancy and mother/father GHQ-12 *z*-score

AASM American Academy of Sleep Medicine, *OR* Odds Ratio, R^2 Nagelkerkes R^2, *95% CI* 95% confidence interval

[a]Low internalizing and externalizing problems were defined as scores below the 90th percentile on the internalizing and externalizing scale of the CBCL and high internalizing and externalizing problems as scores at the 90th percentile or higher on the internalizing and externalizing scale of the CBCL

[b]9–12 h sleep per night

Paavonen et al. [20] showed that 280 8-year-old children with less than 7.7 h of sleep per night, measured by actigraphs, had an increased risk for behavioural problems like hyperactivity/impulsivity symptoms using maternal ratings of the ADHD Rating Scale IV. Differences to our results can be due to other cut-offs to define short sleep (7.7 vs. 9 h in our study) and the focus on attention problems and hyperactivity symptoms rather than on aggressive and rule-breaking behaviour. As attention problems and hyperactivity are not part of the CBCL externalizing score, this spectrum of behavioural problems was not included in our analysis.

Longitudinal studies with objective sleep measurement methods are relatively rare in children and have suggested that reduced sleep is associated with an increased risk of future occurrence of emotional and externalizing symptoms [36, 37].

A few studies in children have examined experimentally induced sleep deprivation. Vriend et al. [15] showed in 8- to 12-year-old children that going to bed 1 h later for four nights relative to the typical bedtime had significant consequences on emotion regulation and positive affective responses measured by the parent-reported Emotion Questionnaire and an Affective Response Task. Another study in 50 adolescents aged 14–17 years reported that sleep restriction to 6.5 h in bed per night for five nights resulted in poorer emotional regulation and more feelings of anxiety, anger and tension (self-reports on Profile of Moods States) compared to the healthy sleep duration group (10 h in bed per night for five nights) [16]. Gruber et al. [17] observed that a restriction of sleep over five nights in 7- to 11-year-old children had negative effects on emotionality and moodiness in school, measured by the Conners' Global Index—Teachers, compared to children with extended sleep. These findings imply that even a modest sleep restriction of a realistic amount of sleep over a few nights can weaken the ability to regulate emotions, which can lead to problem behaviour in children. This emphasizes the importance of perceiving sleep as a potentially modifiable factor in children's emotional health.

In the literature, several hypotheses try to explain how sleep and behaviour might be related. The overnight therapy hypothesis for example proposed that sleep provides a timeframe for resetting the neuronal systems [38]. One experimental study in adults showed that severe sleep deprivation leads to a more intense amygdala response to negative emotional stimuli compared to individuals who were not sleep-deprived [39]. As this system is involved in the affect regulation and processing of emotions, insufficient sleep can have negative impacts on emotional regulation and mood. The applicability of this hypothesis for children needs further clarification.

Our analysis showed sex and country-specific differences in sleep duration. Girls slept on average 15 min longer than boys, a finding which is consistent with previous studies in school-aged children [40, 41]. The cause for the observed sex difference is still unclear, but there is some support that girls are more sensitive to their sleep requirements and that parenting styles or socio-cultural effects may play a role [40, 41].

Nocturnal sleep duration differed between countries, with children from middle Europe (Germany, Belgium) showing a longer sleep duration than children in southern (Italy, Spain) or eastern (Poland) countries. This is in line with results from the IDEFICS study that reported significant differences between sleep durations in eight European countries, with children from northern countries sleeping longer than children in middle or southern Europe [42]. One reason could be cultural differences in sleep habits [42]. Norms and expectations regarding normal and problematic sleep of children may differ between countries and can lead to various bedtime routines. In addition, social demands like school starting times can vary in countries and regulate the sleep of school-children differently [43].

Strengths and limitations

One strength of the study is the multicentre design with participants from metropolitan areas of five European countries. This makes it possible to generalize the results to other European children with similar demographic backgrounds and living conditions.

Another strength includes the device-measured nocturnal sleep duration. The gold standard for sleep measurements is laboratory measurements like polysomnography, which are not applicable in larger epidemiological studies. The SenseWear™ Armband is easy to handle and does not disturb the usual sleep habits of children [25, 26]. There is a paucity of validation studies for the SenseWear™ Armband and its use for sleep in normative samples of children. Two studies have shown that the armband was less accurate on an individual level compared to polysomnography measurements which prevents the armband from being used as a clinical tool [25, 26]. Furthermore, due to the lack of standardization of scoring rules for the armband, we based our sleep definition on scoring rules used in actigraph-studies even if we used an arm placement and not a wrist or waist placement [27].

It is difficult to directly compare the results of accelerometer-studies with our study due to various devices used and a different number of days measured. One limitation of our study is the relatively short observation time from 2 to 5 nights. The AASM recommends for actigraph studies a recording time for a minimum of 72 h and other studies reported four to seven nights [44, 45]. However, our measurements provided reasonable values for night sleep duration and are comparable to a meta-analysis of actigraphically-measured sleep in 6- to 8-year-old children (range of the pooled mean sleep duration: 8.53–9.43 h) [46].

Furthermore, the CBCL assessment was based on parent-reported data and could be affected by socially desirable answers despite guaranteed anonymity. Parents' expectations regarding a normal or problematic behaviour of children could have been affected the scores. Additionally, the selection of externalizing problem items in the CBCL does not cover attention problems and hyperactivity. Nevertheless, the CBCL is a well-standardized screening tool fitting exactly for the age group and is designed to be filled by parents.

A further limitation is the cross-sectional design of the study that does not allow an interpretation of longitudinal relationships.

Conclusion

In a cross-sectional multicentre study in 8-year-old European children, each additional hour of nocturnal sleep duration and the adherence to the AASM recommendation reduced the risk of having internalizing problems. Externalizing problems were not associated with night sleep duration.

Adequate sleep duration throughout primary-school years is important for children's optimal emotional health. Pediatricians should consider sleep as a potential risk factor for internalizing problems in children. Further research on longitudinal associations is needed to determine whether short sleep is a cause or consequence of problem behaviour.

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Author contributions KG analyzed the data and drafted and finalized the manuscript. DG, JCK, NF, RCM, FM, PP and EV conducted the study, entered data at study sites, and critically reviewed the manuscript. BK designed the research and critically reviewed the manuscript. VG designed the research, participated in the data analysis, and critically reviewed the manuscript. All authors approved the final manuscript.

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Data availability The authors support sharing data with other researchers for legitimate research purposes. However, the study is still ongoing and data cannot yet be anonymized as we currently plan a further follow-up. Therefore, according to the General Data Protection Regulation and the institution's data protection rules individual study participant data cannot be put in the public domain but can only be shared after establishing a written data sharing agreement ensuring that collaborating researchers do not violate privacy regulations and are in keeping with informed consent that is provided by study participants. Written requests to access the data may be submitted to: office.koletzko@med.uni-muenchen.de.

Code availability Statistical analysis was carried out with SPSS (IBM SPSS Statistics 26).

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All research was conducted in accordance with the Declaration of Helsinki. Local ethics committees of each study center approved the trial: Belgium (Comité d'Ethique de L'Hopital Universitaire des Enfants Reine Fabiola; No. CEH 14/02), Germany (Bayerische Landesärztekammer Ethik-Kommission; No. 02070), Italy (Azienda Ospedaliera San Paolo Comitato Etico; No 14/2002), Poland (Instytut Pomnik-Centrum Zdrowia Dziecka Komitet Etyczny; No 243/KE/2001), and Spain (Comité ético de investigación clínica del Hospital Universitario de Tarragona Joan XXIII).

Consent to participate Parents and children gave their written informed consent.

Consent for publication Not applicable.

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7. Publication II

Original title: Sleep duration in preschool age and later behavioral and cognitive outcomes: an individual participant data meta-analysis in five European cohorts

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ORIGINAL CONTRIBUTION

Sleep duration in preschool age and later behavioral and cognitive outcomes: an individual participant data meta-analysis in five European cohorts

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Abstract
Short sleep duration has been linked to adverse behavioral and cognitive outcomes in schoolchildren, but few studies examined this relation in preschoolers. We aimed to investigate the association between parent-reported sleep duration at 3.5 years and behavioral and cognitive outcomes at 5 years in European children. We used harmonized data from five cohorts of the European Union Child Cohort Network: ALSPAC, SWS (UK); EDEN, ELFE (France); INMA (Spain). Associations were estimated through DataSHIELD using adjusted generalized linear regression models fitted separately for each cohort and pooled with random-effects meta-analysis. Behavior was measured with the Strengths and Difficulties Questionnaire. Language and non-verbal intelligence were assessed by the Wechsler Preschool and Primary Scale of Intelligence or the McCarthy Scales of Children's Abilities. Behavioral and cognitive analyses included 11,920 and 2981 children, respectively (34.0%/13.4% of the original sample). In meta-analysis, longer mean sleep duration per day at 3.5 years was associated with lower mean internalizing and externalizing behavior percentile scores at 5 years (adjusted mean difference: − 1.27, 95% CI [− 2.22, − 0.32] / − 2.39, 95% CI [− 3.04, − 1.75]). Sleep duration and language or non-verbal intelligence showed trends of inverse associations, however, with imprecise estimates (adjusted mean difference: − 0.28, 95% CI [− 0.83, 0.27] / − 0.42, 95% CI [− 0.99, 0.15]). This individual participant data meta-analysis suggests that longer sleep duration in preschool age may be important for children's later behavior and highlight the need for larger samples for robust analyses of cognitive outcomes. Findings could be influenced by confounding or reverse causality and require replication.

Keywords Preschool sleep duration · Multi-cohort analysis · Internalizing behavior · Externalizing behavior · Language · Non-verbal intelligence

Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
CI	Confidence interval
EDEN	Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant
ELFE	Étude Longitudinale Française depuis l'Enfance
IPD	Individual participant data
INMA	INfancia y Medio Ambiente Project
MSCA	McCarthy Scales of Children's Abilities
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SWS	Southampton Women's Survey
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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Background

Healthy sleep is important for children's physical and mental health and can have a positive influence on future health trajectories of a child [1–3]. There is growing evidence that shorter sleep duration is associated with more behavioral problems and poorer cognitive outcomes, especially in school-aged children and adolescents [4–6]. Compared with the literature in schoolchildren there is a paucity of studies in younger children of preschool age investigating this relationship [7, 8].

Early childhood is a sensitive period where both brain maturation and sleep habits are developing with continuation throughout childhood [9]. Insufficient sleep in these early years of life can have lasting impacts on a child's development [8]. Chaput et al. [7] reported in a systematic review of 25 studies that shorter sleep duration was associated with poorer emotional regulation in children aged 0 to 4 years, while for sleep duration and cognitive development (16 studies) results were less clear. Authors concluded that the evidence was mainly based on cross-sectional studies and the high level of between-study heterogeneity made meta-analysis infeasible. Another systematic review of 26 studies on sleep and its relation to behavior and cognition in preschoolers by Reynaud et al. [8] suggested that a higher quantity and quality of sleep was associated with better behavioral outcomes and receptive vocabulary, but found no association for other cognitive outcomes. They concluded that mainly cross-sectional designs (69% of studies), incomplete adjustment for confounders, weak effect sizes and small sample sizes (< 500) limited the validity of the results. Both reviews showed that only a few studies in preschoolers have examined the relationship between sleep duration and later behavioral or cognitive outcomes. They tend to suggest negative associations between sleep duration and internalizing and externalizing problems as well as mixed results for language and non-verbal intelligence in healthy preschoolers [10–14]. With our study involving five European pregnancy and birth cohorts with available data on sleep duration and behavior and cognition, we aimed to examine these previously reported results in a larger sample of preschool aged children. The objective of our study was to investigate the associations between sleep duration in early childhood (~ 3.5 years) and later behavioral problems (internalizing and externalizing) and cognitive outcomes (language and non-verbal intelligence) in children (~ 5 years) using individual participant data.

Methods

Study design and study population

Our study used harmonized data from an international cross-cohort collaboration, the European Union Child Cohort Network established in the Horizon 2020 Project LifeCycle [15–17]. A cohort was eligible for our study if it had harmonized preschool sleep at 2 to 4 years of age and behavior (internalizing, externalizing) or/and cognition data (language, non-verbal intelligence) from ages 4 to 6 years. Five cohorts participated: ALSPAC (Avon Longitudinal Study of Parents and Children, United Kingdom, $n = 4847$ eligible children) [18, 19], EDEN (Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant, France, $n = 1015$ eligible children) [20], ELFE (Étude Longitudinale Française depuis l'Enfance, France, $n = 9100$ eligible children) [21], INMA (INfancia y Medio Ambiente Project, Spain, $n = 1348$ eligible children) [22] and SWS (Southampton Women's Survey, United Kingdom, $n = 134$ eligible children) [23]. Further details on each cohort are provided in Online Resource 1.

Preschool sleep duration

All cohorts measured child's preschool sleep duration using different parental questionnaires (Online Resource 2 Table 1). Parents reported the time their child usually went to sleep (ALSPAC, ELFE, SWS) or to bed (EDEN) and woke up in the morning, as well as the duration of daytime naps. In INMA the parents were asked to provide night and daytime sleep duration.

Cohorts harmonized total sleep duration in hours per day in preschool age (2-4 years) by summing nighttime and daytime sleep durations following a harmonization protocol. Sleep was assessed at a mean age of 3.1 years (SD: 0.1) in SWS, 3.2 years (SD: 0.1) in EDEN, 3.5 years (SD: 0.1, SD: 0.2) in ALSPAC and ELFE, respectively, and 4.4 years (SD: 0.2) in INMA.

To investigate a potential non-linear association between sleep duration and behavioral or cognitive outcomes, we categorized total sleep duration into thirds within each cohort based on tertiles (1st third includes children with the shortest sleep durations).

Internalizing and externalizing behavior problems

Data on behavior was available in three cohorts: ALSPAC, EDEN and ELFE. All cohorts used the parent version of the Strength and Difficulties Questionnaire (SDQ) to measure internalizing and externalizing problems in children. The SDQ is a standardized questionnaire for children from 4 to 16 years with 25 items assessed on a three-point Likert scale [24]. The questionnaire covers five scales: emotional symptoms, peer problems, conduct problems, hyperactivity and prosocial behavior, ranging from 0 to 10 each [24]. The emotional and peer problems subscales were combined into the internalizing score, while the externalizing score includes the scales conduct and hyperactivity problems, as

Table 1 Characteristics of the participating study population

	ALSPAC (UK) 1991–1992		EDEN (France) 2003–2006		ELFE (France) 2011	INMA (Spain) 1997–2008	SWS (UK) 1998–2002
	Internalizing/ Externalizing behavior	Language/ Non-verbal intelligence	Internalizing/ Externalizing behavior	Language/ Non-verbal intelligence	Internalizing/ Externalizing behavior	Language/ Non-verbal intelligence	Language/ Non-verbal intelligence
n	3010/3009	718/719	876/877	865/866	8034	1285	111
% of original sample	20.0	4.8	46.1	45.5	44.3	60.2	3.5
Child characteristics							
Sex, male, *n* (%)	1517 (50.4)	383 (53.3)	467 (53.2)	469 (54.2)	4172 (51.9)	649 (50.5)	63 (56.8)
Birth weight, gr, mean (SD)	3435 (523)	3479 (512)	3309 (490)	3304 (494)	3353 (470)	3262 (452)	3461 (560)
Gestational age, weeks, mean (SD)	39.9 (1.7)	40.0 (1.5)	39.7 (1.6)	39.7 (1.6)	39.7 (1.4)	39.9 (1.4)	39.6 (2.0)
First born, yes, *n* (%)	1282 (42.6)	335 (46.6)	418 (47.7)	410 (47.3)	3684 (45.9)	739 (57.5)	63 (56.8)
Sleep duration, hours:min, mean (SD)	11:30 (0:54)	11:30 (0:53)	12:36 (0:57)	12:36 (0:57)	12:18 (0:44)	10:24 (0:57)	11:30 (0:51)
Age sleep duration measurement, years, mean (SD)	3.5 (0.1)	3.5 (0.1)	3.2 (0.1)	3.2 (0.1)	3.5 (0.2)	4.4 (0.2)	3.1 (0.1)
Maternal characteristics							
Maternal age at birth, years, mean (SD)	29.1 (4.5)	29.5 (4.2)	30.3 (4.4)	30.3 (4.5)	31.1 (4.5)	32.0 (4.0)	29.4 (3.4)
Mother born abroad, yes, *n* (%)	127 (4.2)	31 (4.3)	19 (2.2)	20 (2.3)	591 (7.4)	86 (6.7)	7 (6.3)
High maternal education level, *n* (%)	457 (15.2)	116 (16.2)	552 (62.9)	519 (60.0)	5792 (72.1)	473 (36.8)	34 (30.6)
Smoking in pregnancy, yes, *n* (%)	551 (19.6)	133 (18.5)	186 (21.3)	198 (22.9)	1231 (15.4)	383 (29.8)	17 (15.3)
Postpartum depression, yes, *n* (%)	236 (7.8)	48 (6.8)	67 (7.7)	67 (8.1)	658 (8.2)	NA	NA
Household characteristics							
EUSILC-based household income[a], mean (SD)	7.1 (0.2)	7.1 (0.2)	7.4 (0.3)	7.4 (0.3)	7.5 (0.3)	7.1 (0.3)	7.3 (0.3)
Passive smoke exposure in the first year of life, yes, n (%)	986 (32.8)	205 (28.8)	364 (41.5)	364 (42.5)	2837 (35.3)	NA	17 (15.3)

Table 1 (continued)

	ALSPAC (UK) 1991–1992		EDEN (France) 2003–2006		ELFE (France) 2011	INMA (Spain) 1997–2008	SWS (UK) 1998–2002
	Internalizing/ Externalizing behavior	Language/ Non-verbal intelligence	Internalizing/ Externalizing behavior	Language/ Non-verbal intelligence	Internalizing/ Externalizing behavior	Language/ Non-verbal intelligence	Language/ Non-verbal intelligence
Outcome characteristics							
Age at outcome measurement, years, mean (SD)	4.1 (0.1)	4.1 (0.03)	5.6 (0.1)	5.6 (0.1)	5.5 (0.5)	4.9 (0.6)	4.4 (0.1)
Outcome raw score[b], mean (SD)	2.8 (2.3)/ 5.8 (3.2)[c]	101.1 (13.5) / 109.3 (14.5)	3.3 (2.5)/ 5.3 (3.7)	106.9 (13.7)/ 99.9 (13.5)	3.2 (2.6)/ 5.1 (3.3)	61.0 (15.6) / 53.7 (13.3)	111.3 (15.5)/ 105.2 (14.0)
Outcome percentile score[d], mean (SD)	42.5 (30.3)/ 45.1 (29.3)	NA	50.0 (28.1) / 49.9 (28.6)	NA	42.8 (30.2) / 44.4 (29.3)	NA	NA
Outcome standardized score[d], mean (SD)	NA	101.0 (14.8)/ 101.4 (14.9)	NA	100.0 (14.5)/ 100.6 (14.7)	NA	100.0 (14.9)/ 100.3 (14.6)	99.0 (15.4)/ 99.6 (15.5)

Data are given as mean (standard deviation) or number (percentage). Sample sizes are based on children with data on sleep duration, the specific outcome and all covariates

[a]Log-equivalised total disposable household income predicted using EUSILC data

[b]Behavior measured with the SDQ in all cohorts; language and non-verbal intelligence assessed by the WPPSI in ALSPAC, EDEN and SWS; assessed by the MSCA in INMA; the respective outcome names are displayed in the column header

[c]In ALSPAC internalizing raw score and externalizing raw score are available for 2944 and 2948 children, respectively

[d]The respective outcome names are displayed in the column header

ALSPAC Aavon Longitudinal Study of Parents and Children, *EDEN* Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant, *ELFE* Étude Longitudinale Française depuis l'Enfance, *INMA* INfancia y Medio Ambiente Project, *NA* not available or not harmonized by the specific cohort, *SWS* Southampton Women's Survey, *UK* United Kingdom

suggested for analyses in low-risk samples in the general population [25]. The SDQ is at least as good in detecting internalizing and externalizing problems compared to semi-structured interviews [26].

We used internalizing and externalizing percentile scores, which range from 0 to 100 and indicate the relative position of each child within his/her cohort and age group [17]. Higher percentile scores indicate more behavioral problems. Behavior was assessed at a mean age of 4.1 years (SD: 0.1) in ALSPAC, 5.5 years (SD: 0.5) in ELFE and 5.6 years (SD: 0.1) in EDEN.

Language and non-verbal intelligence

Data on language and non-verbal intelligence were available in four cohorts: ALSPAC, EDEN, INMA and SWS. In ALSPAC, EDEN and SWS, language and non-verbal intelligence were assessed by trained psychologists using the verbal and performance intelligence scale of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). The WPPSI is an intelligence test for children aged 2 to 7 years that provides subtests on verbal and performance intelligence domains [27]. The verbal score includes the subtests Information, Vocabulary and Word Reasoning, while the performance score includes the subtests Block Design, Matrix Reasoning and Picture Concepts. In INMA, language and non-verbal intelligence were assessed by a psychologist using the verbal and perceptual-performance domains of the McCarthy Scales of Children's Abilities (MSCA) [28]. This instrument is similar to the WPPSI and measures intelligence in children aged 2 to 8 years. The verbal scale consists of the subtests Pictorial Memory, Word Knowledge, Verbal Memory, Verbal Fluency and Opposite Analogies, while the perceptual-performance scale consists of the subtests Block Building, Puzzle Solving, Tapping Sequence, Right-left Orientation, Draw-a-design, Draw-a-child and Conceptual Grouping.

To allow comparison between the two tests, cohort-specific z-scores were calculated and standardized within each cohort to a mean of 100 and a SD of 15, following a harmonization protocol and the lead of other studies [29, 30]. Scores were measured at a mean age of 5.6 years (SD: 0.1) in EDEN and 4.9 years (SD: 0.6) in INMA. In ALSPAC (4.1 years (SD: 0.03)) and SWS (4.4 years (SD: 0.1)) they were measured in a subgroup of children.

Covariates

Potential confounders were identified based on the literature and selected with creating directed acyclic graphs [31–34] (Online Resource 2 Fig. 1).

The selected variables included sex, birthweight (kg), gestational age (weeks), birth order (first/later born), maternal age at birth (years), maternal education level according to International Standard Classification of Education 97/2011 (low/middle/high) [35, 36], whether the mother was born abroad (yes/no), maternal smoking in pregnancy (yes/no), the predicted equivalized total disposable household income at baseline [37], maternal postpartum depression (yes/no) (not harmonized in INMA/SWS) and child's passive smoke exposure in the first year of life (yes/no) (not harmonized in INMA). Cohort-specific information on variable collection and missing data is shown in Online Resource 2 Tables 2–3.

Statistical analyses

Analyses were performed in R (version 3.5.2) using DataSHIELD (version 6.1.0), a data analysis platform that enables federated analysis of data from different cohorts without physically sharing individual-level data [38–40].

We performed complete case analysis, including only participants with data on sleep, the specific outcome, and all covariates (Fig. 1). Of the 35,093 eligible children, 34.0% (11,920) had complete data for behavioral analyses, ranging from 20.0% in ALSPAC to 46.1% in EDEN. Of the 22,253 eligible children, 13.4% (2979–2981) had complete data for cognitive analyses, ranging from 3.5% in SWS to 60.2% in INMA.

We used two-stage individual participant data (IPD) meta-analysis to study the associations of sleep duration at age 3.5 years with behavioral and cognitive outcomes in children aged 5 years. Sleep duration was analyzed as continuous (decimal hours) and categorical variable (reference: 2nd third) to investigate the possibility that both shorter and longer sleep duration might be associated with the outcomes. For each outcome we constructed two models: a basic model adjusted for sex and age at outcome measurement and a model adjusted for other potential confounders. We conducted generalized linear regression analyses in each cohort and combined the effect estimates using

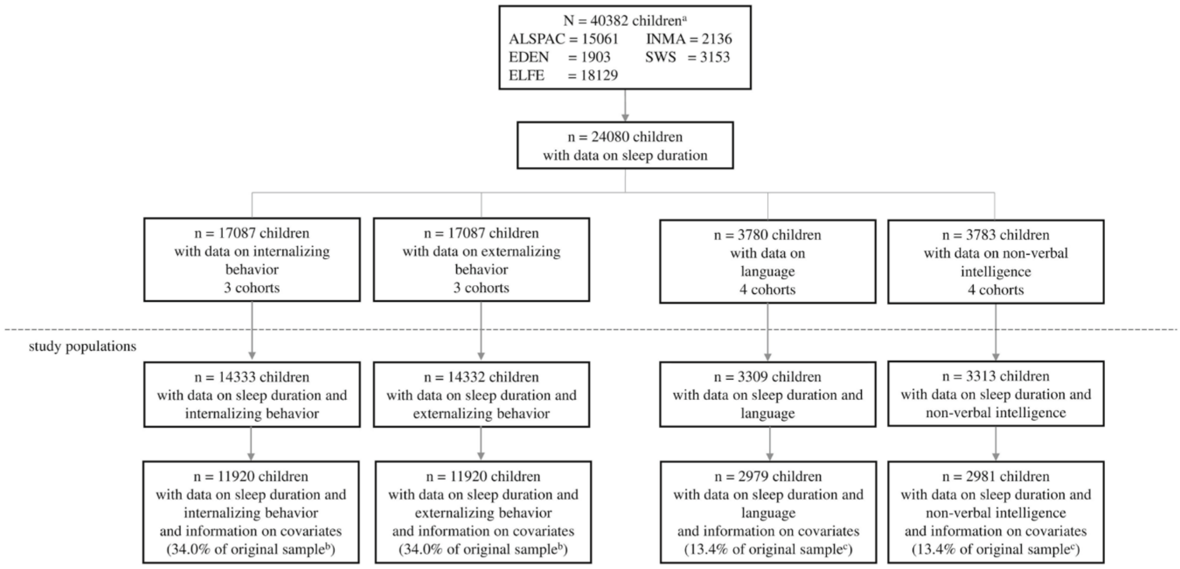

Fig. 1 Flow chart illustrating participants included in the study [a]N is based on all children with data on sex; [b]The original sample for behavior analyses consists of data from ALSPAC, EDEN and ELFE: $N=35{,}093$; [c]The original sample for cognition analyses consists of data from ALSPAC, EDEN, INMA and SWS: $N=22{,}253$. The same populations were used in both basic and adjusted models. *ALSPAC* Avon Longitudinal Study of Parents and Children, *EDEN* Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant, *ELFE* Étude Longitudinale Française depuis l'Enfance, *INMA* Infancia y Medio Ambiente Project, *SWS* Southampton Women's Survey

random-effects meta-analysis. For this we used the "rma" command with the restricted maximum likelihood estimator of the "metafor" package in R. Heterogeneity between cohorts was described using I^2 and τ^2 [41].

We performed several sensitivity analyses: (1) using a one-stage IPD meta-analysis approach, (2) using raw scores of internalizing/externalizing behavior, (3) excluding twins and children with congenital malformation or cerebral palsy as this could possibly effect sleep, behavior and cognition, (4) adjusting for TV watching duration at preschool age, and (5) excluding INMA because of their later sleep measurement.

Results

Table 1 shows the characteristics of the study population in each cohort divided by outcome. In both French cohorts mothers had higher education levels compared to mothers in the other cohorts. Children's sleep duration differed between countries, with children from France showing a longer sleep duration than children from the UK or Spain. It should be noted, however, that children in INMA were older than children in the other cohorts. Overall mean sleep duration was 11h54min per day (SD: 1h01min) (Online Resource 2 Table 3).

Characteristics of the analyzed and excluded samples were different. Children in the analyzed sample had longer sleep durations, slightly lower behavior percentile scores and higher language or non-verbal intelligence scores than excluded children. Mothers in the analyzed sample had higher education levels, smoked less during pregnancy and were less likely to be born abroad compared to excluded mothers (Online Resource 2 Table 3).

Associations between sleep duration and internalizing and externalizing behavior

Analyses examining the association between sleep duration and behavioral outcomes included 11,920 children from three cohorts (Fig. 1). Figs. 2a, b show that one hour of longer mean sleep duration per day at age 3.5 years was associated with lower internalizing and externalizing behavior percentile scores at 5.1 years (internalizing behavior: mean difference = − 1.27, 95% CI − 2.22, − 0.32; externalizing behavior: mean difference = − 2.39, 95% CI − 3.04, − 1.75). Heterogeneity between cohorts was moderate for internalizing behavior (I^2 = 42.0%) and low for externalizing behavior (I^2 = 0.0%) in adjusted models. ALSPAC showed a stronger negative association between sleep duration and behavioral outcomes than EDEN or ELFE. There was no evidence for a non-linear association between sleep duration and behavior (Online 2 Resource Table 9). Sensitivity analyses showed similar results (Online Resource 2 Tables 4–5, 8; Figs. 2–8).

Sleep duration and language and non-verbal intelligence

Analyses investigating the association between sleep duration and language or non-verbal intelligence included 2979 and 2981 children, respectively, from four cohorts (Fig. 1). Figures 3a, b show trends of inverse associations between sleep duration at age 3.7 years with either language or

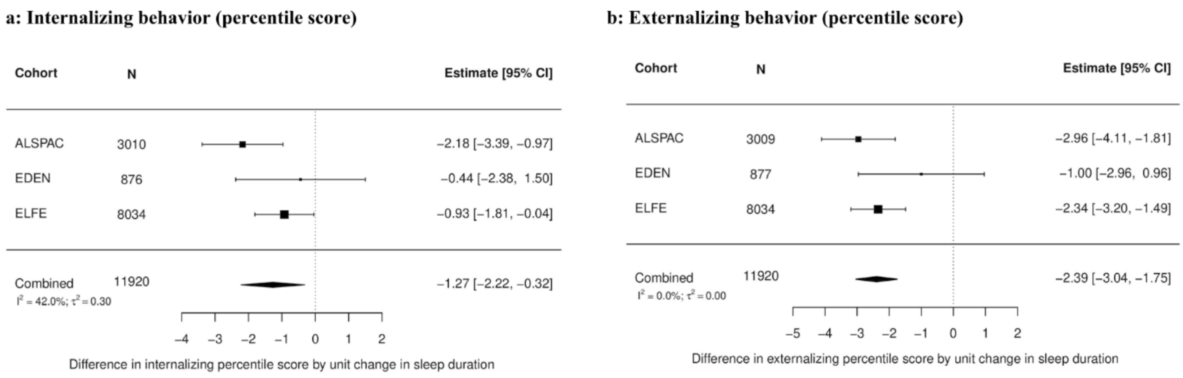

Fig. 2 Association between total sleep duration per day at mean age of 3.5 years and 2a) internalizing behavior (percentile score), 2b) externalizing behavior (percentile score) at mean age of 5.1 years using two-stage IPD meta-analysis – adjusted models Adjusted for sex of the child, age at outcome measurement, maternal age at birth, maternal education, postpartum depression, mother born abroad, birthweight, gestational age, siblings position, passive smoke exposure in the first year of life, EUSILC-based household income, *ALSPAC* Avon Longitudinal Study of Parents and Children, *CI* Confidence interval, *EDEN* Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant, *ELFE* Étude Longitudinale Française depuis l'Enfance, *N* Number of children included in the analysis; I^2 and τ^2 statistics represent between cohort heterogeneity

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non-verbal intelligence scores at 4.9 years, however, estimates were imprecise due to the relative small sample size and confidence intervals included null (language: mean difference = − 0.28, 95% CI − 0.83, 0.27; non-verbal intelligence: mean difference = − 0.42, 95% CI − 0.99, 0.15). Trends were mainly driven by ALSPAC, the oldest cohort. Between cohort heterogeneity in adjusted models was low (language: $I^2 = 0.0\%$, non-verbal intelligence: $I^2 = 4.4\%$). There was no evidence for a non-linear association between sleep duration and cognitive outcomes (Online Resource 2 Table 9). Sensitivity analyses delivered similar results (Online Resource 2 Tables 6–8; Figs. 9–13).

Discussion

In this meta-analysis of IPD from five European cohorts, we observed that a longer mean sleep duration per day in preschool age was associated with lower subsequent scores of internalizing and externalizing behavior at 5 years of age, while the associations between sleep duration and language or non-verbal intelligence were imprecise with trends toward an inverse association.

Our results extend the knowledge from the few available longitudinal studies on the association of sleep duration with behavior in normally developing preschoolers [10–12]. In a Norwegian cohort ($N = 32{,}662$) a dose–response association was found between parent-reported short sleep duration (≤ 10 h, 11-12 h vs. ≥ 13 h) at 18 months and the risk of internalizing and externalizing problems at age 5 years assessed by the Child Behavior Checklist [10]. Jansen et al. [11] showed that parent-reported sleep duration of less than 12.5 h at age 2 years was a risk factor for anxiety or depressive symptoms at age 3 years measured with the Child Behavior Checklist in 4782 children. In a sample of 1492 children a short sleep duration pattern before the age of 3.4 years was associated with higher hyperactivity-impulsivity scores at age 6 years [12]. All mentioned studies adjusted for pre-existing behavioral symptoms, to account at least partially for reverse causality, because pre-existing behavioral and cognitive traits are likely to influence sleep duration and correlate with equivalent traits at older ages [42]. Outcome at time of exposure measurement and exposure at time of outcome measurement were not available in the present study. Outcome misclassification needs to be additionally considered, as parents of children with more behavioral problems at an earlier age might report sleep duration as shorter than it is. This should be taken into account when interpreting our results.

The effect estimates obtained for internalizing and externalizing behavior percentile scores in our study were relatively small. Even though this difference may not be clinically relevant, it may reflect large differences at the population-level. Experimental studies with young children showed that even light levels of sleep deprivation over just a few days can impair the ability of emotion- and self-regulation, which are potential risk factors for problem behavior [43, 44].

There are some biological mechanisms that may explain the associations of sleep and behavioral outcomes. A systematic review of sleep and its associations with brain functions and structures in children suggested for example that shorter sleep duration is associated with greater reactivity in brain regions that are involved in emotion processing [45].

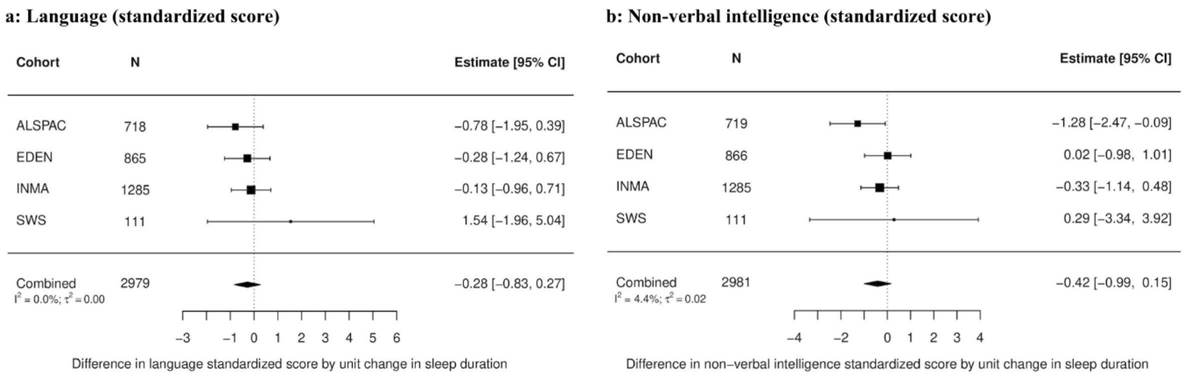

Fig. 3 Association between total sleep duration per day at mean age of 3.7 years and 3a) language (standardized score), 3b) non-verbal intelligence (standardized score) at mean age of 4.9 years using two-stage IPD meta-analysis–adjusted model Adjusted for sex of the child, age at outcome measurement, maternal age at birth, maternal education, mother born abroad, birthweight, gestational age, siblings position, smoking in pregnancy, EUSILC-based household income ALSPAC: Avon Longitudinal Study of Parents and Children, *CI* confidence interval, *EDEN*: Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant, *INMA* INfancia y Medio Ambiente Project, *SWS* Southampton Women's Survey, *N* number of children included in the analysis, I^2 and τ^2 statistics represent between cohort heterogeneity

Also studies in adults showed that sleep deprivation led to a stronger amygdala response to negative and neutral emotional images [46, 47]. This could result in less cognitive control over emotion processing leading to more irritability and negative affect [48]. In our study, we found an association with internalizing and externalizing problems which are closely related to emotional processes.

Previous studies reported mixed results of the association between sleep duration and cognition in preschool children [12–14, 49]. Touchette et al. [12] reported that children with persistently short sleep durations during preschool age scored lower on the Peabody Picture Vocabulary test at age 5 years, and children with a short sleep duration pattern before the age of 3.4 years had lower non-verbal intelligence skills assessed with the Wechsler Intelligence Scale at age 6 years. In contrast to our study, where only one time-point was analyzed, Touchette et al. [12] measured sleep at five time-points and created sleep patterns. Another study in 2800 children reported that children sleeping within the recommended sleep duration range of 11 to 14 h at age 2 years had better non-verbal intelligence as well as language scores at age 6 years than children with shorter or longer sleep [14]. Authors concluded that children with average sleep duration also most likely have normal levels in other developmental areas such as cognitive outcomes. Dionne et al. [13] showed in a sample of 1029 children that parental reports of night sleep duration at 30 months were not associated with receptive vocabulary assessed by the Peabody Picture Vocabulary Test at age 5 years, but with a higher day/night sleep ratio at 18 months, indicating less mature sleep consolidation. A study in 194 children showed a trend of an inverse association of mother-reported sleep duration at 24 months with verbal and non-verbal intelligence at age 3 years measured with the WPPSI [49].

The different findings show that further longitudinal studies with multiple sleep duration measurements, other sleep variables as day/night sleep ratio and larger sample sizes are needed to get a clearer picture of this potential relationship.

Strengths and limitations

Our study's major strength is the federated analysis approach which allowed analyses of IPD from five cohorts including children from three European countries. The consistent harmonization of variables between cohorts as well as the consistent adjustment for confounders in the analyses reduced between-study heterogeneity and strengthens reproducibility of the findings across cohorts. Another strength is that outcomes were measured with validated questionnaires (SDQ) and tests performed by trained psychologists (WPPSI, MCSA).

One limitation of our study is the complete case analysis. For behavioral analyses 34.0% of the original sample contributed, whereas this was just 13.4% for cognitive outcomes, in part because language and non-verbal intelligence were measured only in subgroups in ALSPAC and SWS. This potential loss of information leads to loss of statistical power and increases the uncertainty of the estimates. Complete case analysis assumes that the chance of being a complete case is independent of the outcome after adjusting for covariates [50]. We acknowledge that with the amount of missing data and the demonstrated differences between those included and not, it is plausible that selection bias has had some influence on our findings.

Sleep duration was based on parental reports in all cohorts. Studies have shown the tendency of parents to overestimate their child's real sleep duration compared to device-based measured sleep [51, 52]. While questions used to measure sleep duration were different across cohorts, the mean sleep duration in our study was similar to values in a meta-analysis of preschoolers (mean 11h54min) [53] and is within the range of 10 to 13 h recommended by the American Academy of Sleep Medicine for children aged 3 to 5 years [3], suggesting that it is rather cultural background that might play an important role in the specific country differences. The variation in sleep duration between the three countries that contributed to this study, are consistent with other studies showing that children from northern and middle European countries sleep longer than children in southern or eastern Europe [54, 55].

Methodological aspects in data acquisition might have affected the measured sleep duration, outcomes and covariates. However, great efforts were undertaken to harmonize data between cohorts [15–17]. The variable catalog with data source information is openly available at https://data-catalogue.molgeniscloud.org/catalogue/catalogue/#/networks-catalogue/EUChildNetwork/variables. The downside of the federated analysis approach is that it tends to use the lowest common denominator of available information for data harmonization, which can lead to residual confounding. Many confounders were reduced to binary variables (for example passive smoking (yes/no), birth order (first/later born) etc.) and ethnicity was approximated by whether the mother was born abroad or not, which will capture only a modest part of the complex influence of confounders on child sleep and outcomes.

Conclusion

Using IPD from five European cohorts, we showed that longer sleep duration at 3.5 years of age was associated with both lower internalizing and externalizing problem behavior scores at 5 years of age, while the evidence of an association of sleep duration with either language or non-verbal intelligence was imprecise. Our results suggest that longer sleep duration at early preschool ages may be important for later behavioral outcomes. These findings could be due to confounding or reverse causality and need replication.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00787-023-02149-0.

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Author contributions KG made substantial contributions to the design of the work, analyzed the data and drafted and finalized the manuscript. DA, TC, LC, M-AC, AE, SF-B, MG, BH, JI, HI, JJ, DAL, MM, TS, JS, MT made substantial contributions to the acquisition, analysis, or interpretation of data and critically reviewed the manuscript. BK made substantial contributions to the design of the work and critically reviewed the manuscript. SP and VG made substantial contributions to the design of the work, participated in the data analysis, and critically reviewed the manuscript. All authors approved the final manuscript.

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Data availability The data used in the analysis is not freely available as access is managed by each individual cohort. Researchers who want to use data from the EU Child Cohort Network can send a request to lifecycle@erasmusmc.nl (more information under https://lifecycle-project.eu/).

Code availability Statistical analysis was performed in R (version 3.5.2) using DataSHIELD (version 6.1.0).

Declarations

Conflict of interest Deborah A Lawlor has received support from Roche Diagnostics and Medtronic Ltd for research unrelated to that presented here.
All other authors have no competing interests to declare that are relevant to the content of this article.

Ethical approval All research was conducted in accordance with the Declaration of Helsinki. All participating cohorts received ethical approval from their local ethics committees (more details in Online Resource 1).

Consent to participate Parents and children gave their written informed consent.

Consent to publish Representatives from all participating cohorts reviewed the manuscript and gave consent for publication.

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