SLEEP & HEALTH DURING THE FIRST 1000 NIGHTS

Margreet Harskamp-van Ginkel

Sleep and health during the first 1000 nights

Margreet W. Harskamp-van Ginkel

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To all (my) small and big sleepers…..

When the night has come
And the land is dark
And the moon is the only light we'll see
No, I won't be afraid
Oh, I won't be afraid
Just as long as you stand, stand by me

Stand by Me – Ben E. King

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Nederlandse samenvatting

Tijdens mijn werk als jeugdarts krijg ik vaak vragen over slaap. ‘Midden in de nacht met een huilende baby op de arm of een wakkere peuter bij je in bed sta je er alleen voor. En natuurlijk doe je dan wat je kunt als ouder’. Maar vragen over slaap krijg ik niet alleen bij baby’s; ook tieners en hun ouders worstelen met vragen rondom vermoeidheid en slaap. De ouders van tieners geven vaak aan dat hun zoon of dochter al een slechte slaper was als baby. Ik vroeg mij als jeugdarts en onderzoeker af wanneer slaapproblemen en risicofactoren voor slaapproblemen ontstaan. Is dit al in de eerste 1000 dagen en nachten van een menselijk leven (tussen conceptie en de tweede verjaardag)?

Slaap speelt een belangrijke rol in het bevorderen van een gezonde leefstijl voor kinderen en volwassenen. Uiteindelijk brengen we een groot deel van ons leven slapend door. De aanname voor dit proefschrift was dat het ontwikkelen van goede slaapgewoonten vroeg in het leven kan resulteren in een levenslang voordeel, niet alleen voor de slaap zelf, maar ook voor de algehele gezondheid. Als dat zo is, dan zou de omgeving en jeugdgezondheidszorg kinderen en hun ouders misschien beter moeten helpen om al jong gezonde slaapgewoonten te ontwikkelen.

De overkoepelende onderzoeksvragen in dit proefschrift zijn:

1: Wat is het verband tussen slaap in de eerste 1000 nachten en lichamelijke gezondheid op kinderleeftijd (tussen 4 en 12 jaar)?

2: Wat zijn mogelijke voorspellers van slaapproblemen en wat zijn zorgbehoeften van ouders rondom slaap in de eerste 1000 nachten?

Allereerst geeft **hoofdstuk één** een algemene inleiding op het onderwerp en onderbouwing van de onderzoeksvragen. **Hoofdstuk twee** beschrijft het verband tussen slaaptekort in de zwangerschap en lichamelijke gezondheid op kinderleeftijd. We gebruikten hiervoor data van kinderen van de Amsterdamse ABCD-studie en het Griekse Rhea cohort. We onderzochten kinderen waarvan de moeders een slaaptekort hadden in de zwangerschap. We zagen dat deze kinderen gemiddeld een hogere Body Mass Index, middelomtrek en bloeddruk hadden op de leeftijd van 4-11 jaar en bijna anderhalf keer zo vaak overgewicht en obesitas. Deze bevinding over slaaptekort in de zwangerschap is nieuw en niet eerder beschreven. Het ondersteunt de theorie dat de gezondheid van moeder tijdens de zwangerschap langetermijneffecten op het kind kan hebben. We hebben ook gekeken hoe dit kan. Moeders met slaapgebrek hadden vaker zwangerschapsdiabetes en een kortere zwangerschapsduur wat weer

gerelateerd was aan een hogere Body Mass Index. Dit wijst op zowel stress als ontsteking gerelateerde onderliggende mechanismen.

In **hoofdstuk drie** vatten we al het gepubliceerde onderzoek tot 2019 naar het verband tussen slaap op babyleeftijd en de kans op overgewicht tijdens de kinderjaren samen. Er waren niet veel kwalitatief goede studies en samenvattend vonden we inconsistent bewijs voor een verband tussen de slaapduur van baby's tijdens de eerste twee levensjaren en de lichaamssamenstelling tijdens de latere kinderjaren.

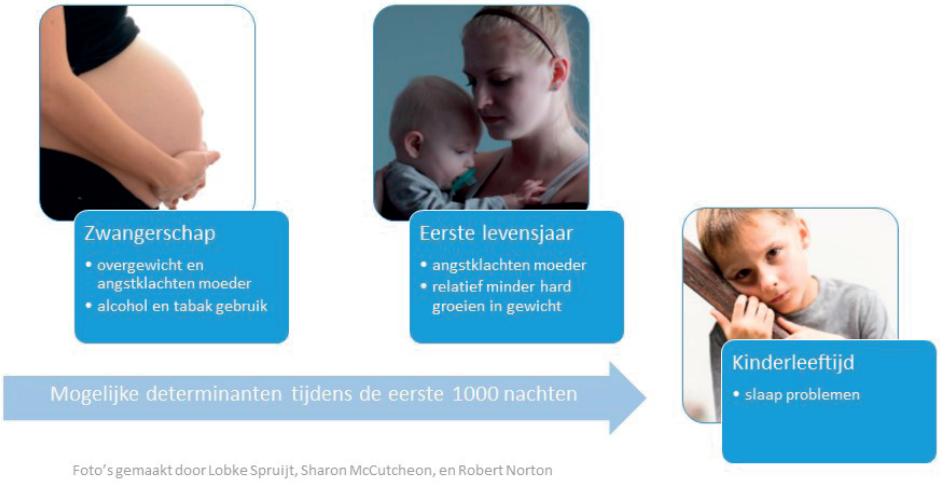
Figuur 1: slaapproblemen in de zwangerschap

In **hoofdstuk vier** onderzoeken we of ontevredenheid van ouders over slaap bij baby's van vier tot zes maanden samenhangt met slaapproblemen in het tweede levensjaar. We gebruikten hiervoor data van 1471 kinderen van het Sarphati Cohort. Jeugdverpleegkundigen en jeugdartsen in Amsterdam noteerden tijdens consulten bij leeftijd vier tot zes maanden of ouders tevreden waren over hun baby's slaap (Figuur 2). Een kwart (26%) van de ouders was niet tevreden.

Figuur 2: monitoring van groei tijdens periodieke gezondheidsonderzoeken bij de Jeugdgezondheidszorg

Tussen de 1e en 2e verjaardag vulden ouders een vragenlijst in over het slaapgedrag van hun peuter. Opnieuw ervaarde een kwart (27%) van de ouders slapen als een probleem. Peuters van wie ouders al ontevreden waren over hun slaap als baby, hadden bijna twee keer zo vaak problematisch slaapgedrag. Hun ouders ervaarden het slapen vaker als een probleem. Ontevredenheid van ouders over slaap van hun baby's lijkt dus een voorspeller voor latere slaapproblemen in de peutertijd. Als we slaapproblemen vroeg signaleren, kunnen we ouders meer gerichte voorlichting geven. Professionals kunnen we beter uitrusten om deze adviezen te geven.

In **hoofdstuk vijf** gaan we dieper in op mogelijke vroege voorspellers van slaapproblemen. Het vinden van voorspellers van slaapproblemen, zowel tijdens de zwangerschap als in de kindertijd, kan helpen om de slaapgezondheid te verbeteren. De voorspellers voor een hogere slaapprobleemscore op de leeftijd van zeven tot acht jaar zijn samengevat in *Figuur 3*. Tijdens de zwangerschap waren mogelijke voorspellers overgewicht en angst bij de moeder, en alcohol- en tabaksgebruik tijdens het eerste trimester. Tijdens de kindertijd waren angst bij de moeder en een minder goede gewichtsgroei bij de baby gerelateerd aan slaapproblemen in de latere kindertijd.



Figuur 3: gevonden verband tussen de gezondheid van moeders en slaapproblemen bij kinderen in ***hoofdstuk vijf***

Hoofdstuk zes beschrijft de perspectieven van ouders van baby's die buitengewoon veel huilen. We vonden vier thema's (*Figuur 4*), allemaal gerelateerd aan vertrouwen in de professional. Ouders hebben behoefte aan zorgprofessionals die hen serieus nemen (erkenning), medische expertise hebben om een lichamelijke oorzaak uit te sluiten, en met een plan van aanpak komen. Het is niet altijd de ernst van het huilen die bepaalt wanneer ouders hulp zoeken, maar soms juist de uitputting van de ouders. Hoe het met ouders gaat moet daarom ook besproken worden.

Figuur 4: vier thema's in de zorgbehoefte van ouders bij overmatig huilen van hun baby.

Hoofdstuk zeven geeft een algemene discussie over de bevindingen van het proefschrift. Onze belangrijkste conclusies zijn:

a) Slaap en gezondheid van moeder en kind beïnvloeden elkaar wederzijds
b) Slaap en gezondheid worden gedurende de eerste 1000 nachten beïnvloed door meerdere omgevingsfactoren
c) Slaapproblemen bij kinderen komen regelmatig voor en kunnen samengaan met buitengewoon veel huilen van baby's en mentale klachten van ouders.
d) Slaapproblemen lijken te blijven bestaan van babyleeftijd tot kindertijd.

Onze bevindingen ondersteunen de theorie dat er langer bestaande veranderingen kunnen optreden bij een kind in de eerste 1000 dagen en nachten. Deze veranderingen worden beïnvloed door de omgeving in de baarmoeder en het vroege leven. We vonden omgevingsfactoren tijdens de zwangerschap en de kindertijd die een sterke associatie hadden met slaapproblemen op latere leeftijd.

We hebben verschillende onderzoeksmethoden gebruikt in dit proefschrift, waardoor we meer inzicht hebben gekregen in de complexiteit van slaap gedurende de eerste 1000 nachten van ons leven. We weten nu beter hoe vaak problemen voorkomen, maar ook hoe ouders dit ervaren en wat de behoeften van ouders zijn. Onze studies konden van zowel moeders als vaders gegevens gebruiken, wat waardevolle informatie oplevert over gezinskenmerken, mogelijke risicofactoren en het perspectief van ouders. Het perspectief van vaders blijft wel relatief onderbelicht. Op basis van onze observatiegegevens kunnen we geen oorzakelijk verband claimen of voorspellen hoe interventies de slaap en gezondheid van baby's kunnen verbeteren. Er is meer onderzoek nodig om de slaapgezondheid in alle gezinnen te verbeteren. We bevelen toekomstig onderzoek aan naar: 1) het meten van de slaapgezondheid van baby's; 2) verbetering van de slaapgezondheid van kinderen door onderliggende factoren van slaap te veranderen; en 3) het verband tussen slaapgezondheid en lichamelijke gezondheid van ouders en kinderen.

Onze eindconclusie is dat slaapproblemen bij baby's regelmatig voorkomen en vaak samengaan met buitengewoon veel huilen van baby's en psychische klachten van ouders. Tijdens de eerste 1000 nachten beïnvloeden slaap en gezondheid van moeder en kind elkaar. Slaapproblemen kunnen tijdens de eerste 1000 nachten voortkomen uit verschillende omgevingsfactoren en kunnen aanhouden vanaf de babyleeftijd tot de latere kindertijd. Gezondheidszorgondersteuning moet, naast het verlichten van het huilen van baby's of slaapproblemen, ook aandacht besteden aan het welzijn van de ouders.

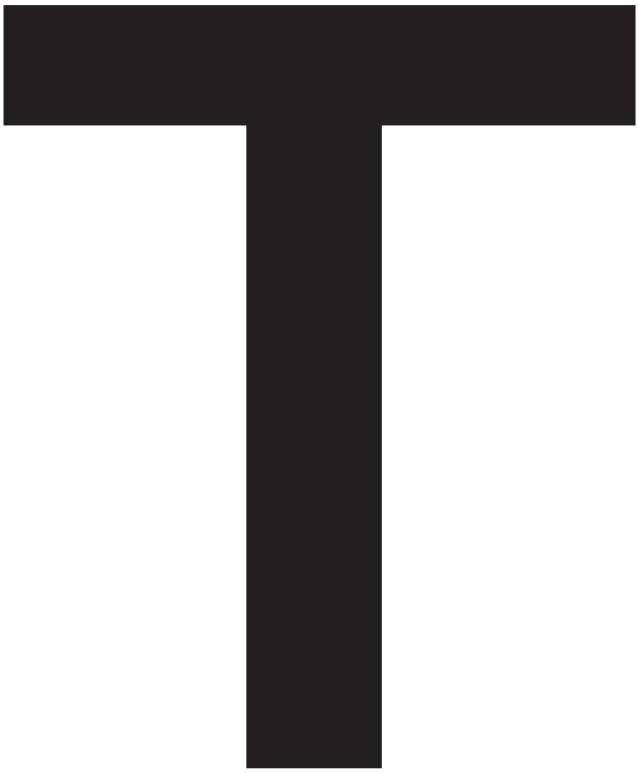
Slotwoord voor alle ouders

Ik wil me in dit proefschrift kort apart richten tot (aanstaande) ouders. Als ouder wil je gewoon het beste voor je kind en volg je je ouderlijke instincten. Na de geboorte zoek je een ritme en routine in het voeden en volg je de ontwikkeling en groei van je kind. De eerste lachjes, hapjes en stapjes gaan veel makkelijker als je (beiden) uitgeslapen bent. Goed slapen is meer dan de hele nacht doorslapen. Hoe je als ouders het slapen van je kind ervaart wordt gevormd door culturele waarden, normen en overtuigingen. Dit bepaalt ook of je er over praat met anderen en hulp zoekt als het even niet vanzelf gaat.

Na het lezen van (delen van) dit proefschrift besef je je dat:

- goede slaap niet vanzelfsprekend is tijdens de zwangerschap en de kindertijd (de eerste 1000 nachten),
- de gezondheid verbeteren door slaap niet makkelijk is als:
  - o je zwanger bent en onregelmatig werkt
  - o je zwanger bent en stress hebt
  - o je baby veel troost nodig heeft in de nacht
  - o je zelf moe bent en je kinderen vaak uit bed komen ’s nachts.

Met dit proefschrift wil ik ouders niet extra onder druk zetten door ze simpelweg aan te sporen om goed te slapen. Je kunt als ouder slaapgezondheid niet alleen verbeteren! Ik pleit voor een gezonde omgeving voor gezinnen, die hun slaapritme bevordert en factoren zoals stress vermindert. Professionals willen graag meer handvatten om gezinnen te begeleiden. Wetenschappelijk bewijs voor specifieke interventies is zeer welkom, maar ook scholing aan professionals. Dit proefschrift bespreekt dat het doel van professionele steun niet alleen is om het huilen of de slaapproblemen van baby’s te ‘genezen’, maar ook om aandacht te besteden aan hoe het met jou als ouder gaat.



Thesis summary

Components of childhood sleep health

- *sleep efficiency*
  - o sleep latency,
  - o nocturnal wakefulness
- **experienced sleep quality**
  - o bedtime resistance,
  - o bedtime parental behaviors,
  - o feeling rested in the morning,
  - o nightmares.

Given the importance of sleep for both our physical and mental health, developing good sleep health is pivotal. In the introductory *chapter 1* we describe that the development of sleep starts during the period between conception and a child's second birthday, in this thesis referred to as the first 1000 nights of life. In this period fetal brain structures develop, as is the child's sleep-wake rhythm. The environment of the child is known to influence adaptive responses and potential epigenetic mechanisms. This was first hypothesized by Barker and is also known as 'fetal programming'. Emergent themes in fetal programming are effects of psychological or physiological stress during the first 1000 nights. Sleep health during this period could be one of these stressors and we therefore studied the association with later childhood sleep and health.

The overall theme of this thesis is a public health perspective on sleep during the first 1000 nights. The axiom is that developing good sleeping habits early on in life, may result in a life-long benefit, not only for sleep itself, but also for cognitive and behavioral development and cardio-metabolic health.

The first research question was **'What is the association of sleep during early stages of life (between conception and the second birthday) and childhood cardio-metabolic health outcomes (age 4-12 years)?'** This research question was addressed in chapters 2 and 3.

Chapter 2 describes the association between gestational sleep deprivation and childhood body composition and blood pressure, using combined data from a Dutch (ABCD) and Greek (Rhea) birth cohort. Sleep deprivation of the expecting mother was, at ages 4-11 years, associated with adverse cardio-metabolic outcomes of the child (higher BMI, waist circumference and diastolic blood pressure). Children born to mothers with sleep deprivation in pregnancy had an increased risk of having childhood overweight and obesity. Mothers with sleep deprivation more often had gestational diabetes and a shorter gestational age, which partly mediated the association with childhood weight status, indicating both stress-related and inflammatory underlying mechanisms.

Chapter 3 involves a systematic literature review of the evidence on the association between sleep during infancy and childhood body composition. We found inconsistent evidence for an association between infant sleep duration during the first two years of life and body composition during later childhood.

The second research question was **'What are potential determinants and parental health care needs regarding sleep in early life (between conception and the second birthday)?'** This question was addressed in *chapters 4, 5 and 6*.

In *chapter 4* we studied expressed discontent regarding infant sleep during early health check-ups (at 4 and 6 months of age). Based on data from the Amsterdam Sarphati Cohort, infant sleep problems were a common complaint, with 1 out of 4 infants having problematic sleep. We also studied persistence of parental discontent. Infants whose parents expressed concerns about sleep at early health check-ups were more likely to develop problematic sleep in the second year of life. While causality cannot be claimed, this finding is of clinical relevance. By registering parental discontent, Youth Health Care or pediatric clinics may be able to identify a group of infants at risk for later problematic sleep who could benefit from selective prevention efforts.

In *chapter 5*, we took a deeper dive into potential early determinants of sleep problems. Identifying potential modifiable risk factors for sleep problems, both during pregnancy and in infancy, can inform strategies to improve sleep health. Several potential determinants during pregnancy and infancy, that were associated with a higher sleep problem score at age 7-8 years, are summarized in **Figure 1**. During pregnancy, potential determinants were maternal overweight and anxiety, and alcohol and tobacco use during the first trimester. During infancy, maternal anxiety and relative infant weight loss were associated with later childhood sleep problems.

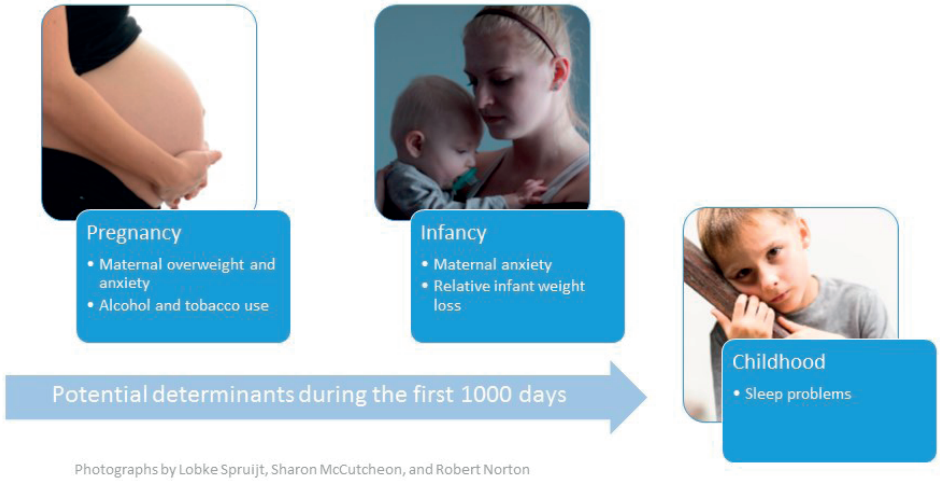


Figure 1: found association between maternal health and childhood sleep problems in chapter 5

In *chapter 6*, we investigated parental perspectives and health care needs, during the first months after birth, in families that were referred to medical specialists for excessive infant crying. Regarding assessment of infant crying and support by medical professionals, we identified four interrelated themes (**Figure 2**), all related to confidence in the professional (theme 1). While excessive crying is how the problem started, it is not the severity of crying that determines when parents seek help (theme 2 and 3). Instead parental exhaustion and feelings of failure (theme 4) were the motivation for the timing to search health care support after a longer period of infant crying.

Figure 2: themes describing parental need for medical support while dealing with excessive infant crying

Chapter 7 provides a general discussion on the thesis findings. Our main conclusions are:

A. Sleep and health of mother and child have a bi-directional relationship and are affected by multiple environmental factors during the first 1000 nights.
B. Infant problematic sleep is common and often coincides with excessive infant crying as well as mental complaints in parents.
C. Problematic sleep seems persistent from infancy to childhood.

Our findings support the hypothesis of fetal programming in the development of sleep health. Fetal programming is affected by the in-utero and early life environment. We found environmental determinants during pregnancy and infancy that had a strong association with later childhood sleep problems.

We used both quantitative and qualitative methods in this thesis, which increased our understanding of the complexity of sleep during the first 1000 nights of life. We perceive the use of mixed methods as a strength of this thesis, as it provides both insights in the prevalence as well as the perceived burden and needs of parents. Our studies were able to include data from both mothers and fathers in quantitative and qualitative analysis, which provides valuable information on family characteristics, potential determinants and parental perspectives. Especially the perspective of fathers is relatively understudied. Based on our observational data we cannot claim

causality or predict how interventions can improve infant sleep and health. Future studies are needed to develop and implement evidence-based strategies to improve sleep health in all families. We recommend future studies on: i) measurement of infant sleep health; ii) improving sleep health by modifying determinants of sleep; and iii) the association between sleep health and cardio-metabolic health.

Our final conclusion is that infant sleep problems are common and often coincide with excessive infant crying as well as mental complaints in parents. During the first 1000 nights, sleep and health of mother and child have a bi-directional relationship. Sleep problems can originate from various environmental factors during the first 1000 nights and can be persistent from infancy to later childhood. Health care support should, in addition to alleviating infant crying or sleep problems, also address parental wellbeing.

1

General introduction and thesis outline

Sleep is an important behavior that allows us to function throughout our lives (1). Sleep is as essential as water and food (2), and without sufficient sleep, the brain cannot function properly (3). A lack of sleep results in an impaired ability to concentrate and respond quickly, to learn and create new memories. A structural lack of sleep also increases the risk of obesity, diabetes, cardiovascular disease and depression (4, 5). The biological mechanisms underlying these effects are through an impact of sleep on adaptive and innate immunity (6).

Given the importance of sleep for both our physical and mental health, developing good sleep habits is pivotal (1, 6). Sleep habits are initially developed during pregnancy and infancy when physiologic structures are formed and evolve during human lifetime (2, 7). The period between conception and a child's second birthday is popularly phrased as 'the first 1000 days of life' (8, 9). In this dissertation on sleep, I will further refer to this period as the first 1000 nights, as most sleep occurs during nighttime, also for infants. As a reader please consider in sentences containing 'parents' also other main caregivers.

This introductory chapter provides an overview of the current knowledge on infant sleep, sleep development, potential determinants and associated health effects during the first 1000 nights to put the subsequent chapters of this thesis into perspective. The aim and outline are discussed at the end of this chapter.

What is sleep?

Sleep is a complex and dynamic process, and despite decades of research, we still have an incomplete understanding of what sleep entails (1). The ability to fall asleep is hypothesized to depend on two internal biological mechanisms (Textbox 1): circadian rhythms and sleep-wake homeostasis (10). Circadian rhythms determine the body rhythm of rest, metabolism and activity using neural or hormonal communication (most well-known example is melatonin), and even continues in the absence of cues. Sleep-wake homeostasis keeps track of our need to sleep and is influenced by the time since we last slept and by light (daylight, but also screen light) detected by the retina (eye) (12).

Textbox 1: Internal biological mechanisms of sleep timing (10, 11).

Circadian rhythm: biological clock with 'sleep gates' and 'wake maintenance zones'

Sleep-wake homeostasis: pressure to sleep, depending on how long we are awake it causes us to sleep longer and deeper.

The process of falling asleep and consolidating sleep is a result of a conscious choice (to take rest, most often in bed) and the ability to fall asleep (internal biological

mechanism) and is therefore a cognitive behavior. Adults and older children make the conscious choice to respond to sleepiness by going to bed, but the sleep of young children is more timed by their parents and therefore a contextual behavior (with both intrinsic and extrinsic factors) (13). In the following paragraphs we will further discuss the main theories on how sleep develops during the first 1000 nights of life and beyond.

The development of sleep

There are a series of milestones in the development of infant sleep in these first 1000 nights (Textbox 2). The foundation for sleep is laid during pregnancy when the fetus develops a sleep-wake rhythm. This sleep-wake rhythm is instilled by the development of a biological clock, and brain structures of this biological clock are already active in the 18th week of pregnancy (14). The biological clock is trained via nutritional and hormonal stimuli of the mother that reach the fetus' brain structures through the placenta. An example of a nutritional stimulant is the rhythm of food intake of the mother, an example of a hormonal stimulant is synchronization to the light-dark cycle by maternal melatonin passing through the placenta (12).

Textbox 2: Milestones in sleep development:

- 18th week pregnancy: brain structured developed (14)
- Synchronization to maternal rhythm by melatonin through the placenta (12)
- In the first weeks after birth: Day-night differences stimulated by light-dark cycles and feeding schemes
- From age 3 months: decrease in daytime sleep and improved infant self-soothing (15-18)
- Age 6 months to 5 years: Change in sleep cycles (2, 18)

A few days after birth, maternal or placental production of melatonin is, considering the short half-life of melatonin, most likely not affecting neonatal melatonin concentrations (19). Infants develop their own rhythmic melatonin excretion after 9 to 12 weeks of age, a process that is delayed by approximately nine weeks in premature born infants. Until 8–9 months after birth it can be negatively affected by preterm birth, but positively affected by alternating light-dark cycles and feeding schemes (19, 20). Light-dark cycles and feeding schemes can stimulate day-night differences in sleep of newborns after one week of age, but consolidated periods of sleep are not apparent until more than one to two months after birth (12, 21). The developing interaction of both circadian rhythms and sleep-wake homeostasis may be a key determinant for infant sleep-wake behavior (10). Proper alignment of both mechanisms that time sleep in the first few months after birth, results in circadian alertness peaking at the end of the afternoon (resulting in decreased daytime sleep duration around 3 months after birth in full-term born infants) and circadian sleep pressure counteracting decreasing sleep pressure during the nighttime, resulting in

increased sleep consolidation (10). After 3 months of age, infants also develop the skill of self-soothing that leads to further consolidation of night-time sleep (15-18).

Physiologically the sleep of infants differs from adults with a higher proportion of REM (rapid eye moment) sleep and delta (stage 3-4 of non-REM) sleep. Another difference is that their sleep cycles are shorter (40-50 minutes in comparison with 75-100 minutes for children aged four and older). Sleep cycles become gradually longer between the age of six months and five years while the percentage of REM sleep decreases (2, 18).

Definition and measurement of infant sleep health

At all ages, healthy sleep can be defined as: sufficient and regular sleep with a good sleep quality (Textbox 3) (22). Good sleep health is characterized by subjective satisfaction, appropriate timing, adequate duration, high efficiency, and sustained alertness during waking hours (1). The measurement of sleep health in infants and young children is different from adults. Therefore, specific methods to assess child sleep health are available, including direct methods such as polysomnography, actigraphy, videosomnography, and parent-reported measures such as sleep diaries and questionnaires (23-27).

Textbox 3: components of sleep health (1, 22)

- **sleep efficiency**
  - o sleep latency,
  - o nocturnal wakefulness
- **experienced sleep quality**
  - o bedtime resistance,
  - o bedtime parental behaviors,
  - o feeling rested in the morning,
  - o nightmares.

In assessing infant sleep quantity, the difference is that delayed sleep onset and frequent awakenings can only be registered by parents if an infant calls for attention by crying or calling. Alternatively, sleep can be registered by devices such as accelerometers or video camera's (23, 28).

In assessing childhood sleep quality, bedtime resistance and required parental bedtime behaviors are important additional aspects of parent-perceived sleep quality (29).

Development and prevalence of sleep problems during the first 1000 nights.

In this thesis we investigate both maternal and infant sleep as determinants of later health. Parental sleep difficulties during pregnancy and postnatal period can have multiple origins and are not surprising, given the many physiological, psychological and circumstantial changes during this period. Pregnancy-related symptoms such as frequent urination and difficulty finding a comfortable sleep position diminish sleep health in women (30). In a recent meta-analysis the prevalence of insomnia symptoms

during pregnancy was determined to be 38% (95% CI 32-45%) (31). The majority of women report sleep disruption (100%), inadequate sleep (76%) and symptoms of sleep disorders during pregnancy (54-57%) (30, 32).

Maternal insomnia and short sleep are observed to have a high stability between the third trimester of pregnancy and the child's second birthday (33). After birth, parental sleep deficits and reduced sleep quality are to be expected due to infant sleep patterns and nighttime feeding. Parents of newborn infants might be affected differently by their infants' fragmented sleep, depending on the sleep deprivation they have already built-up due to pregnancy, work or stress. For this reason, parental mental health is often considered as a confounding factor leading to information bias in the reporting on infant sleep. The prevalence of infant sleep problems ranges widely, depending on used definitions and information resources. The estimated mean prevalence is 20-30% (34) with a reported peak prevalence of 40% at the age of eight months (35).

Parents with preterm born infants or infants not exposed to light-dark cycles after birth due to hospitalization or family practices can expect even more sleeping problems. Misalignment of circadian rhythms and sleep-wake homeostasis could play part in delayed sleep consolidation in the first year of life in this population. We found no studies on the relationship between sleep problems during pregnancy and infant sleep problems. Such a relationship may exist as the fetal biological clock is trained via nutritional and hormonal stimuli of the mother through the placenta (12).

Improving cardio-metabolic health in the first 1000 nights

The environment in which the embryo, fetus and young child grows and develops is known to influence adaptive responses and potential epigenetic mechanisms which may underlie life course health and wellbeing (7, 11, 37). This was first hypothesized by Barker and is now known as 'fetal programming'. Fetal programming can affect susceptibility to non-communicable diseases. The high prevalence of these diseases (including obesity, type 2 diabetes, hypertension, coronary heart disease, chronic lung and kidney disease, musculoskeletal disorders, some cancers and some mental illnesses) has stimulated interest in this field and led to the formation of an international society for developmental

Textbox 4: Environmental aspects that influence child development identified by International Society of DOHaD (7):

- maternal, fetal and infant nutrition
- toxins
- pregnancy in teenager or older women
- psychological or physiological stress

Heart of framework to promote, protect and support children's development (36):

- nurturing care that parents provide
- parental support by services, programs and an enabling environment

origins of health and disease (DOHaD) (7). The DOHaD hypothesis has gained interest over several decades, especially in the last decade. The hypothesis includes environmental aspects that influence child development, as displayed in textbox 4. Improving health during the first 1000 nights requires broader system changes on the family and societal level (Textbox 4). Quoting the Lancet Early Childhood Development Series Steering Committee 'strong biological, psychosocial, and economic arguments exist for intervening as early as possible to promote, protect, and support children's development' (38). The Lancet committee developed a framework to promote children's development through a multi-sectoral approach (36). At the heart of this framework is the nurturing care that parents provide to their young children. Parents can be supported by services and programs and an enabling environment (38). Internationally and on a Dutch national level the importance of the first 1000 nights has been campaigned, e.g. with UNICEF's 'Early Moments Matter' campaign and the Dutch Ministry of Health's action program 'Kansrijke Start' (39, 40). Locally the Amsterdam Healthy Weight Approach (AAGG) had gradually shifted its attention from older children to 0-2-year-olds around the start of the research described in this dissertation (41).

Professionals and policy advisors aim to identify and change modifiable risk factors to support parents in making healthy choices and enhance child health. For parents, the first 1000 nights are a natural moment for lifestyle changes, as they are more aware or made aware of their lifestyle choices (text box 5). Many parents for example quit smoking or improve their diet 'to have a healthy baby' (42). Parents develop ways of nurturing infant care: from safe baby beds to milk-feeding, and from vaccinations to eating vegetables (43).

Textbox 5: lifestyle during the first 1000 nights from parental perspective.

"So he is now two months and I am trying to let him sleep in his own bed during all naps. But it's just not working, so I pick him up again and take him with me in a baby carrier. It's not me to let children cry … especially young infants"

"We had ideas on how to care for our infant. During pregnancy we discussed things and mostly agreed, but that was more regarding older ages, like eating the crusts of bread for example. But when he was born and really enjoyed being carried around I thought it would spoil him and I was busy doing the 'right' thing.
Until I realized: what is the 'right thing'? It might be different for every child."
(quotes from qualitative study in *Chapter six*)

Not only the effects of nutrition on outcomes in childhood and adulthood are an emergent theme in the DOHaD field, but also the effects of psychological or physiological stress during the first 1000 nights. Sleep health during this period could be one of these stressors of influence. Poor sleep in children has been associated with increased risk of overweight and poor sleep in adults has been associated with overweight as well as cardiovascular disease (5, 44-48). If poor sleep during infancy is related to higher adiposity

or impaired growth during childhood remains unclear as reviews report inconclusive evidence for this association (49, 50). The effects of gestational sleep on later cardio metabolic health of the child has not been investigated to date, but gestational sleep deprivation has been associated with maternal psychological health (51) and with increased gestational weight gain and pregnancy complications (52-54), as well as adverse perinatal outcomes (55-59).

Overall aim, research questions and outline

The overall aim of this thesis is to contribute to the knowledge on sleep during the first 1000 days and nights, specifically the associations with cardio-metabolic health, potential determinants of infant sleep, and parental health care needs regarding sleep in early life.

The first research question is **'What is the association of sleep during early stages of life (between conception and the second birthday) and childhood cardio-metabolic health outcomes (age 4-12 years)?**

Chapter two describes the association between gestational sleep deprivation and childhood body composition and blood pressure, using the combined data from Amsterdam (ABCD) and Greek (Rhea) birth cohorts.

Chapter three involves a systematic literature review of the evidence on the association between sleep during infancy and childhood body composition.

The second research question is **'What are potential determinants and parental health care needs regarding sleep in early life (between conception and the second birthday).**

Chapter four describes the prevalence of parental discontent with infant sleep and feeding during the first two years of life. We investigated the reasons of parental discontent during the first six months after birth and the association with problematic sleep in the second year of life. This chapter aims to gain insight in the public health importance to support parents who are discontent with infant sleep during wellbeing child visits.

Chapter five explores potential determinants of sleep problems using data from the Amsterdam (ABCD) birth cohort. Knowledge on environmental factors associated with sleep during the first 1000 nights is crucial for informing evidence-based policies

aimed at improving sleep habits and treating sleep problems (universal and indicated prevention).

Chapter six describes the parental health care needs regarding infant crying, which often coincides with sleeping problems in the first months after birth.

Finally, *chapter seven* provides a general discussion on sleep and health in the first 1000 nights, we reflect on methodological considerations and provide recommendations for future research, professionals, policy makers and parents.

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Gestational sleep deprivation is associated with higher offspring BMI and blood pressure

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ABSTRACT

Study objectives: The objective of this study was to evaluate the association between gestational sleep deprivation and childhood adiposity and cardio metabolic profile.

Methods: Data were used from two population-based birth cohorts (Rhea study and Amsterdam Born Children and their Development study). A total of 3,608 pregnant women and their children were followed up until the age of 11 years. Gestational sleep deprivation was defined as six or fewer hours of sleep per day, reported by questionnaire. The primary outcomes included repeated measures of body mass index (BMI), waist circumference, body fat, serum lipids, systolic and diastolic blood pressure levels in childhood. We performed a pooled analysis with adjusted linear mixed effect and Cox proportional hazards models. We tested for mediation by birthweight, gestational age and gestational diabetes.

Results: Gestational sleep deprivation was associated with higher BMI (beta; 95%CI: 0.7; 0.4, 1.0 kg/m^2) and waist circumference (beta; 95%CI: 0.9; 0.1, 1.6 cm) in childhood, and increased risk for overweight or obesity (HR; 95%CI: 1.4; 1.1, 2.0). Gestational sleep deprivation was also associated with higher offspring diastolic blood pressure (beta; 95%CI: 1.6; 0.5, 2.7 mmHg). The observed associations were modified by sex (all p-values for interaction<0.05); and were more pronounced in girls. Gestational diabetes and shorter gestational age partly mediated the seen associations.

Conclusions: This is the first study showing that gestational sleep deprivation may increase offspring's adiposity and blood pressure, while exploring possible mechanisms. Attention to glucose metabolism and preterm birth might be extra warranted in mothers with gestational sleep deprivation.

Statement of Significance

A suboptimal intrauterine environment is now a recognized risk factor to overweight/obesity and higher blood pressure during later life. The vast majority of pregnant women experience significant sleep disruption however, whether gestational sleep deprivation affects offspring adiposity and blood pressure in childhood remains unclear.

This is the first study showing that gestational sleep deprivation may increase offspring's adiposity and blood pressure. By exploring possible mechanisms with formal mediation analysis, we recognize that attention to glucose metabolism and preterm birth might be extra warranted in mothers with gestational sleep deprivation. Besides sleep duration, future studies should also investigate the role of sleep quality during pregnancy.

INTRODUCTION

A suboptimal intrauterine environment is now a recognized risk factor to overweight/obesity and higher blood pressure during later life[1,2]. Pregnancy is a period when life-style interventions are encouraged, and parents are aware of their choices. Current interventions are mainly focussed on maternal physical activity and/or a healthful diet, and appear effective in decreasing gestational weight gain and diabetes, with some evidence for positive maternal and child outcomes[3-6].

During pregnancy the great majority of women experience significant sleep disorders including increased rates of inadequate sleep[7,8]. Sleep disorders in pregnancy have been associated with increased gestational weight gain and pregnancy complications such as hypertension, pre-eclampsia and gestational diabetes mellitus[9,10], as well as with adverse perinatal outcomes including intrauterine growth restriction, low birthweight and preterm birth[11-16], longer labor, more pain during labor, and caesarean sections[12,16]. Some of these factors, such as gestational diabetes, pre-term delivery and birthweight[11-16], have also been associated with child's risk of overweight/obesity and cardio metabolic status[17-21], suggesting a plausible link between the two. Yet there is a lack of human studies linking gestational sleep disruption with child's cardio metabolic health or exploring potential mediating pathways.

Current evidence to support the hypothesis that sleep disorders during pregnancy has long-term cardio-metabolic effects on offspring comes solely from mice studies. Sex dimorphism has been found in a mice study on metabolic dysfunction due to late gestational sleep fragmentation; male offspring had higher food intake, body weight, visceral fat mass and insulin resistance and lower adiponectin levels, but not female offspring. Dyslipidemia was apparent in both male and female offspring after gestational sleep deprivation[22]. Two other mice studies found that gestational sleep deprivation increases blood pressure in offspring via alterations in cardiovascular autonomic regulation and renal morpho-functional changes[23,24]. The effects of gestational sleep deprivation were similar between male and female mice, but in females the effects were bigger in mice that underwent an ovariectomy and lacked female hormones.

In epidemiologic studies, poorer sleep in children has been associated with metabolic risk, adiposity and altered lipid profile[25-30], and these effects in children have been more prominent in girls compared to boys[25,31,32]. As far as we know, there is no published human-based research on the role of sleep during pregnancy on childhood obesity and metabolic health. Our aim was to evaluate the association between gestational sleep

deprivation and childhood adiposity and cardio metabolic profile in a pooled analysis of mother-child pairs from two European birth cohorts, with attention to possible interaction by sex and plausible factors mediating these associations.

METHODS

Study population

This study utilized data from two European birth cohorts, the Greek "Rhea" birth cohort[33] (n=1363) and the Dutch Amsterdam Born Children and their Development (ABCD) study[34] (n=12,379). Both studies are population-based birth cohorts that started during pregnancy. Children from the Rhea cohort were examined at ages four (n=879) and six (n=606) years, while children from the ABCD study were examined at ages five (n=3260), ten (n= 2162) and eleven years (n= 935).

Gestational sleep deprivation

Information on sleeping habits of the participating mothers of the Rhea cohort was collected through a computer-assisted interview in the third trimester of pregnancy (median (25^{th} -75^{th}) gestational week: 32 (31-35) week) [13]. Sleep duration was obtained by the following close-ended question: "During the past month, how many hours did you sleep per day?. The mother reported sleep duration as five or fewer hours, six to seven hours; eight to nine hours; and ten or more hours[13]. Sleep deprivation was defined as five or fewer hours of sleep. Information on gestational sleep duration was available in 685 children with available outcome data at age four years and in 436 children with data available at age six years.

Pregnant women in the ABCD-study received a written questionnaire (median ((25^{th} -75^{th}) gestational week: 16 (14-18) week) and were asked an open-ended question: "How many hours did you sleep or rest lying down per day (of 24 hours) on average in the past week". Sleep deprivation was defined as 6 or fewer hours of sleep, compared to five for Rhea, in order to account for the extra daytime resting hours that were reported. Information on gestational sleep duration during pregnancy was available in 3191, 2112 and 917 children with available outcome data at age 5, 10 and 11 years old, respectively.

Gestational sleep deprivation was used as a binary variable to assess the associations of extremely short gestational sleep with the outcomes of interest instead of sleep duration differences in hours. The cut-off was set at five hours of sleep for Rhea and at six hours for ABCD due to differences in the sleep questionnaires administered in

the two cohorts. We decided on this as extremely short sleep is generally considered as unhealthy, whereas sleep duration needs may vary from person to person and differ across cultures. However, as sensitivity analysis we also used two additional cut-offs at 5 and 7 hours of sleep in both cohorts.

Child outcome measurements

Child anthropometry

In the Rhea cohort, trained research assistants measured children's weight and height during the follow-up visits, using validated scales (Seca 354 baby scale, SecaBellisima 841; Seca Corporation, Hanover, MD) and stadiometers (Seca 210 measuring mat, Seca 213; Seca Corporation) according to standard (operating) procedures[35]. Waist circumference was measured in duplicate to the nearest 0.1 cm in the standing position, at the high point of the iliac crest at the end of a gentle expiration, using a flexible tape measure (Seca 201). At age four years we estimated child percentage of body fat (% BF) from subscapular and triceps skinfolds using Slaughter et al. skinfold-thickness equations[36]. At age six years we measured bioelectric impedance analysis (BIA) using a tetra-polar device (Bodystat 1500) and calculated % BF using a pediatric specific BIA equation[37].

In the ABCD study we measured children during ABCD health checks. We measured height to the nearest millimeter using a Leicester portable height measure (Seca); weight to the nearest 100 gram using a Marsden weighing scale, (model MS-4102); and waist circumference to the nearest millimeter midway between the costal border and the iliac crest using a Seca measuring tape. % BF was measured by arm-to-leg bioelectrical impedance analysis with a 1500MDD machine (Bodystat Ltd, Douglas, Isle of Man, British Isles). At age five years we used calculations based on equations adapted from Lohman et al. and Kushner et al[38]. At age eleven years we used age-specific calculation formulas adapted from Deurenberg et al[39]. At age ten years, child weight and height to the nearest 100 gram and millimeter, were ascertained as part of the regular preventive Child Health Care in the Netherlands, performed by qualified nurses and physicians.

For both cohorts we defined overweight using the same procedure. First, we calculated BMI (weight/height^2) [38] and then categorized children into normal, overweight or obese according to the cutoff points for sex and age proposed by the International Obesity Task Force (IOTF) definitions[40].

Blood Pressure

In the Rhea cohort, trained research assistants measured systolic and diastolic blood pressure levels in sitting position on the child's right arm, using an automatic oscillometric device with a cuff of appropriate size for arm circumference. The average of three consecutive measurements with 1 minute intervals was used for analysis[41].

In the ABCD study systolic and diastolic blood pressure were measured with the Omron 705 IT device (Omron Healthcare Inc, Bannockburn, IL, USA) with its appropriate cuff size (arm circumference 17–22 cm) [42]. Blood pressure was measured twice on the right arm in sitting position, with the arm supported at heart level. These two measurements were considered valid if they did not differ by more than 10 mmHg, otherwise blood pressure was measured a third time. Systolic and diastolic blood pressure (mmHg) were calculated by taking the mean value of the two valid measures.

Lipid profile

In the Rhea cohort, we analyzed serum lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) by standard enzymatic methods (Medicon, Greece) on an automatic analyzer (AU5400 high-volume chemistry analyzer; Olympus America, Inc., Melville, New York). In the ABCD study at age 5 years, capillary blood was collected in the morning after an overnight fast, as a part of the study health check[43]. We used an ambulatory collection kit (Demecal kit: LabAnywhere, Haarlem, The Netherlands) [44] to determine fasting plasma total cholesterol, triglycerides and, LDL-C and HDL-C[42]. At age 11 years, 3 hour fasting capillary blood was collected and analysed with the point-of-care-analyser Alere Cholestech LDX machine using Lipid Profile and GLU cassettes (Cholestech Alere Health, Hayward, CA, USA) [45].

As a sensitivity analysis we also used age and gender specific z-scores for the outcomes BMI and blood pressure. Serum lipids included: fasting plasma, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

Statistical Analysis

We conducted descriptive analysis using standard univariate statistic procedures (chi-square, t-test). We compared mother-child pairs with normal sleep duration or gestational sleep deprivation for baseline characteristics between cohorts. Additionally, we compared the mother-child pairs with follow-up and complete data on covariates (participants) to mothers that participated in the study during pregnancy but missed information on one or more covariates on follow-up after pregnancy (non-participants) per cohort.

Our main analysis was a pooled analysis of the Rhea and ABCD cohorts. For continuous outcomes we used linear mixed models and for overweight/obesity we used Cox proportional hazards models. Linear mixed models included random effects for cohort and child and a random slope for child age. Mixed models also included an interaction term between the exposure and child age at examination. Child age at examination in the interaction term was used categorically (4, 5, 6, 10 and 11 years in the models for BMI; 4, 5, 6, and 11 years in the models for all other outcomes). The overall effect of the exposure was evaluated using the marginal effects and the difference between the two groups was tested using Wald's test. The associations are reported in terms of beta coefficients and their corresponding 95% Confidence Intervals (CIs). In Cox proportional hazards models, shared frailties for cohort were introduced in order to account for the shared risk within each cohort and Hazard Ratios (HR) and 95% CIs were reported. Birth was considered as the time of study entry and age at study visit as the time scale in our analysis. The exact age at the visit during which the child first became overweight/obese was used as the time of event. Children who did not become overweight/obese during follow-up were censored at the end of study follow-up or when lost to follow-up. The proportional hazards assumption was tested using both graphical inspection methods and Schoenfeld residuals.

We constructed a directed acyclic graph (DAG) based on previous knowledge and selected the set of confounders using DAGitty version 3.0 (**Figure S2.1**) [46]. The confounders included in all models were maternal age at conception, parity (nulliparous, multiparous), maternal smoking early in pregnancy (yes/no), pre-pregnancy BMI (normal weight/overweight/obese), maternal education (low/middle/high) and maternal origin (country of cohort/other). Child sex and age at assessment (years) were also included. Models with blood pressure as an outcome were further adjusted for child height and BMI and models with lipids as an outcome were further adjusted for child BMI. In order to evaluate potential effect modification by sex we included a multiplicative exposure-sex interaction term in each model.

As a sensitivity analysis we performed a random effects meta-analysis. For this we obtained cohort specific estimates using mixed effects models with child random effects and a random slope for child age for continuous outcomes and Cox proportional hazards models for binary outcomes. Consequently, we combined these estimates using random effects meta-analysis, in order to check the consistency with the pooled analysis and for quantifying heterogeneity among included studies with chi square test from Cochran's Q and I^2 statistics.

We tested if there was significant mediation by three plausible mediators (gestational diabetes; gestational age; and birthweight) on the association between gestational sleep deprivation and childhood BMI and other outcomes **(Figure 2.1**). We made two separate mediator models with structural equation modeling; the first one with the continuous mediators gestational age and birthweight as parallel mediators; the second one with gestational diabetes as a single binary mediator. The second model included only mother-child pairs from the ABCD study, as gestational sleep deprivation was measured in early pregnancy, before the diagnosis of gestational diabetes would be made.

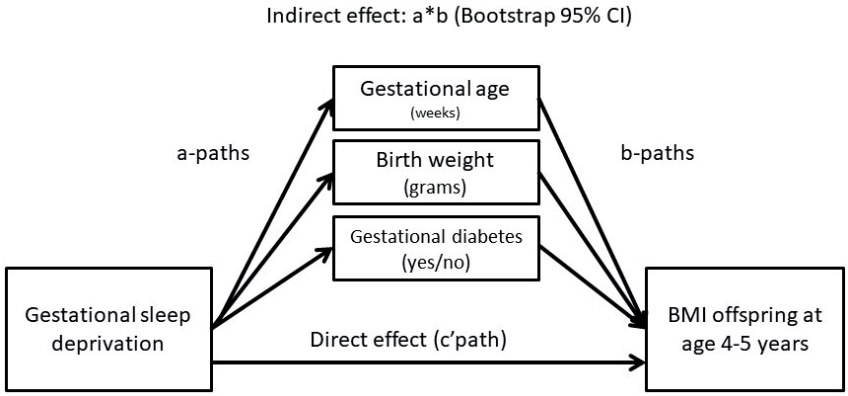

Figure 2.1: Mediation model. Theoretical model for mediation: the a-path reports the change in gestational age or birthweight (continuous mediators) or the odds ratio for gestational diabetes (binary mediator) if the mother had gestational sleep deprivation; and the b-path reports the increase in offspring BMI at age four to five years associated with a 1 point increase of each mediator. The c' path reports the direct effect of gestational sleep deprivation on offspring BMI.

The a-path of a mediator reports the association between gestational sleep deprivation and the mediator and the b-path reports the association between the mediator and offspring BMI at age four to five years. The indirect effect is a product of the a- and b-path. A 95 percentile bootstrap CI was calculated based on 1,000 bootstrap resamples for the indirect effect (ab), in order to test for significance. The total indirect effect is a sum of both indirect effects in a parallel model. The total direct effect (c'-path) refers to the association between gestational sleep deprivation and offspring BMI, corrected for the b-path. The total effect (c-path) is the association between gestational sleep deprivation and offspring BMI. The following confounders were added to the simple adjustment model: child sex, age at assessment (years). Considering the small numbers in each group, we did not perform a mediation analysis with full adjustment for all confounders.

All analyses were conducted using Stata version 13 and 15 and significance level for all 2-sided tests was set at the 5% level. We used capture program for mediation analysis.

RESULTS

Participant characteristics

In the present analyses complete data on exposure, outcome and covariates were available in a total of 661 and 453 Rhea mother-child pairs at ages four and six years, respectively and in a total of 2947, 1957 and 874 ABCD mother-child pairs at ages five, ten and eleven years, respectively.

Table 2.1: Maternal and infant characteristics

	Overall N=3608	Rhea N=661	ABCD N=2947	P-value*
	No. (%) or Mean ±SD	No. (%) or Mean ±SD	No. (%) or Mean ±SD	
Maternal characteristics				
Maternal age at conception (years)	31.6 (4.6)	29.8 (4.9)	32.0 (4.5)	<0.001
Maternal education				<0.001
Low	181 (5.0)	103 (15.6)	78 (2.6)	
Middle	805 (22.3)	337 (51.0)	468 (15.9)	
High	2622 (72.7)	221 (33.4)	2401 (81.5)	
Maternal origin-non native	717 (19.9)	31 (4.7)	686 (23.3)	<0.001
Parity- Nulliparous	1965 (54.5)	305 (46.1)	1660 (56.3)	<0.001
Smoking in early pregnancy-yes	487 (13.5)	223 (33.7)	264 (9.0)	<0.001
Pre-pregnancy BMI (kg/m^2)	23.3 (4.1)	24.7 (4.8)	22.9 (3.8)	<0.001
Underweight and normal weight (BMI <25 kg/m^2)	2764 (76.6)	426 (64.4)	2338 (79.3)	<0.001
Overweight (BMI 25-30 kg/m^2)	606 (16.8)	147 (22.2)	459 (15.6)	
Obese (BMI ≥30 kg/m^2)	238 (6.6)	88 (13.3)	150 (5.1)	
Gestational characteristics				
Gestational diabetes	110 (3.1)	60 (9.2)	50 (1.7)	<0.001
Gestational age at delivery (weeks)	39.2 (1.8)	38.2 (1.5)	39.5 (1.7)	<0.001
Cesarean section	739 (20.5)	330 (49.9)	409 (13.9)	<0.001
Gestational sleep deprivation	144 (4.0)	37 (5.6)	107 (3.6)	0.020
Infant characteristics				
Female	1785 (49.5)	309 (46.7)	1476 (50.1)	0.121
Birth weight (g)	3424.7 (542.2)	3208.8 (448.6)	3473.1 (549.6)	<0.001
Ever Breastfed	2929 (82.0)	558 (86.9)	2371 (80.9)	<0.001

*Univariate analysis with chi square or T-test. BMI: Body Mass Index

Table 2.1 shows maternal and infant characteristics. In total 144 (4.0%) mothers were sleep deprived during the index pregnancy (5.6% in Rhea and 3.6% in ABCD). Cardio metabolic characteristics of the children are presented in **Table S1**. In the Rhea-cohort, 21.4% of the children was overweight at age six years and 11.0 % was obese; whereas in the ABCD-cohort 7.1 % of the children was overweight at age five years and 1.5 % was obese. In the ABCD, sociodemographic characteristics of the mothers with gestational sleep deprivation varied significantly from mothers with adequate gestational sleep; they had higher rates of gestational diabetes (6.5% versus 1.5%); and children were born at lower gestational age (39.1 versus 39.5 weeks) and with a lower birthweight (3364 versus 3477 grams). Besides parity we did not see these differences in the Rhea cohort (**Table S2.2**). Non response analysis revealed that participants were of higher education and lower BMI-pregnancy in both cohorts compared to lost to follow up mother-child pairs (**Table S2.3**).

Gestational sleep deprivation and childhood cardio metabolic health

Table 2.2 shows the association of gestational sleep deprivation with child BMI, waist circumference, body fat, blood pressure and the risk of overweight/obesity after adjusting for covariates.

Gestational sleep deprivation was associated with higher child BMI (beta 0.7 kg/m^2 (95% CI: 0.4, 1.0)), waist circumference (beta 0.9 cm (95% CI: 0.1, 1.6)) and diastolic blood pressure (beta 1.6 mmHg (95% CI: 0.5, 2.7)) but not with % body fat (beta 0.7 % (95% CI: -0.3, 1.7)). Children born to mothers with sleep deprivation in pregnancy had 40% increased risk of overweight and obesity (HR 1.4 (95% CI:1.1, 2.0)). There were no significant associations with child lipid profile (**Table S2.4**).

There was significant effect modification by sex on the observed associations (P- values for interaction<0.05; **Table 2.2**). When stratified by sex, short sleep duration in pregnancy was significantly associated with higher DBP, BMI and risk for overweight/obesity in girls only, whereas these associations in boys were smaller and not significant. The adverse associations of short maternal sleep with child's waist circumference and SBP was also stronger in girls compared to boys, however the interactions did not reach statistical significance (**Table 2.2**).

Sensitivity analysis

When using age and sex specific z values for BMI and blood pressure, we also found BMI and diastolic BP to be associated with gestational sleep deprivation in girls (**Table S2.5**).

Table 2.2: A longitudinal pooled analysis of associations between gestational sleep deprivation and adiposity and blood pressure during childhood adjusting for potential confounders and testing for sex interaction

	Rhea & ABCD (n=3608)									
	Overall			Boys			Girls			
Outcomes	N	Estimate (95%CI)	P-value	N	Estimate (95%CI)	P-value	N	Estimate (95%CI)	p-value	P-interaction with sex
BMI (kg/m^2) [a]	3607	**0.7 (0.4, 1.0)**	**<0.001**	1823	0.5 (0.0, 1.0)	0.050	1784	**0.9 (0.4, 1.3)**	**<0.001**	**0.046**
Overweight or obese [b d]	3607	**1.4 (1.1, 2.0)**	**0.019**	1823	0.9 (0.5, 1.5)	0.663	1784	**2.2 (1.5, 3.3)**	**<0.001**	**0.004**
Waist circ. (cm) [a]	3601	**0.9 (0.1, 1.6)**	**0.031**	1818	0.4 (-0.8, 1.6)	0.498	1783	**1.3 (0.2, 2.3)**	**0.018**	0.167
Body fat (%)[a]	3590	0.7 (-0.3, 1.7)	0.164	1816	0.7 (-0.7, 2.1)	0.332	1774	0.7 (-0.7,2.1)	0.319	0.957
Systolic BP (mmHg) [a c]	3491	0.5 (-0.8, 1.8)	0.416	1758	-0.4 (-2.2, 1.5)	0.687	1733	1.8 (-0.1, 3.6)	0.063	0.135
Diastolic BP (mmHg) [a c]	3485	**1.6 (0.5, 2.7)**	**0.006**	1753	0.3 (-1.3, 1.9)	0.726	1732	**2.8 (1.2, 4.3)**	**0.001**	**0.045**

Gestational sleep deprivation was defined as at least 5 and 6 hours for Rhea and ABCD cohort respectively. All models are adjusted for child sex, age at assessment (years), parity (nulliparous, multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre-pregnancy BMI (normal weight/overweight/obese), maternal origin (country of cohort/other) and maternal education (low/middle/high).

[a] Beta coefficient and 95% confidence intervals as marginal effect estimates obtained by mixed effects models with cohort and child random effect and age interaction

[b] Hazard ratios and 95% confidence intervals obtained by Cox proportional hazard models with shared cohort frailties.

[c] Additionally adjusted for child height and BMI at assessment

[d] Defined with use of the BMI cutoff point for sex and age that was proposed by the International Obesity Task Force

BMI: Body Mass Index, BP: Blood pressure, bold faceted text indicated significant associations (p-value<0.05)

The second sensitivity analysis showed us that using the same cut-off of ≤5 hours of sleep/day for gestational sleep deprivation in both cohorts made the associations stronger and still significant, even with a prevalence of gestational sleep deprivation of 2%. When we used ≤7 hours as a cut-off in both cohorts the prevalence of gestational sleep deprivation was 19% and associations remained significant for overweight/obesity and blood pressure in girls (**Table S2.6**).

The random effects meta-analysis of the cohort specific estimates from the mixed models confirmed the girl-specific associations of short maternal sleep during pregnancy with BMI, waist circumferences and blood pressure (**Figure 2.2** and **Tables S2.7**). The associations were stronger and only significant in the ABCD-cohort, compared to the Rhea-cohort. There was significant interaction by age for the association with BMI; waist circumference; total cholesterol and LDL as the effects of gestational sleep deprivation became stronger with age (**table S2.8**). The I-squared statistic for BMI was suggestive for heterogeneity of the effect in the two studies (I^2=71.6, p-value=0.061) but the stratification according to child sex, revealed evidence for heterogeneity among boys (I^2=71.6, p-value=0.115) and not among girls (I^2=0.0%, p-value=0.323). No heterogeneity was observed for the other outcomes (I^2=0.0%, p-values<0.1) (**Figure 2.2**).

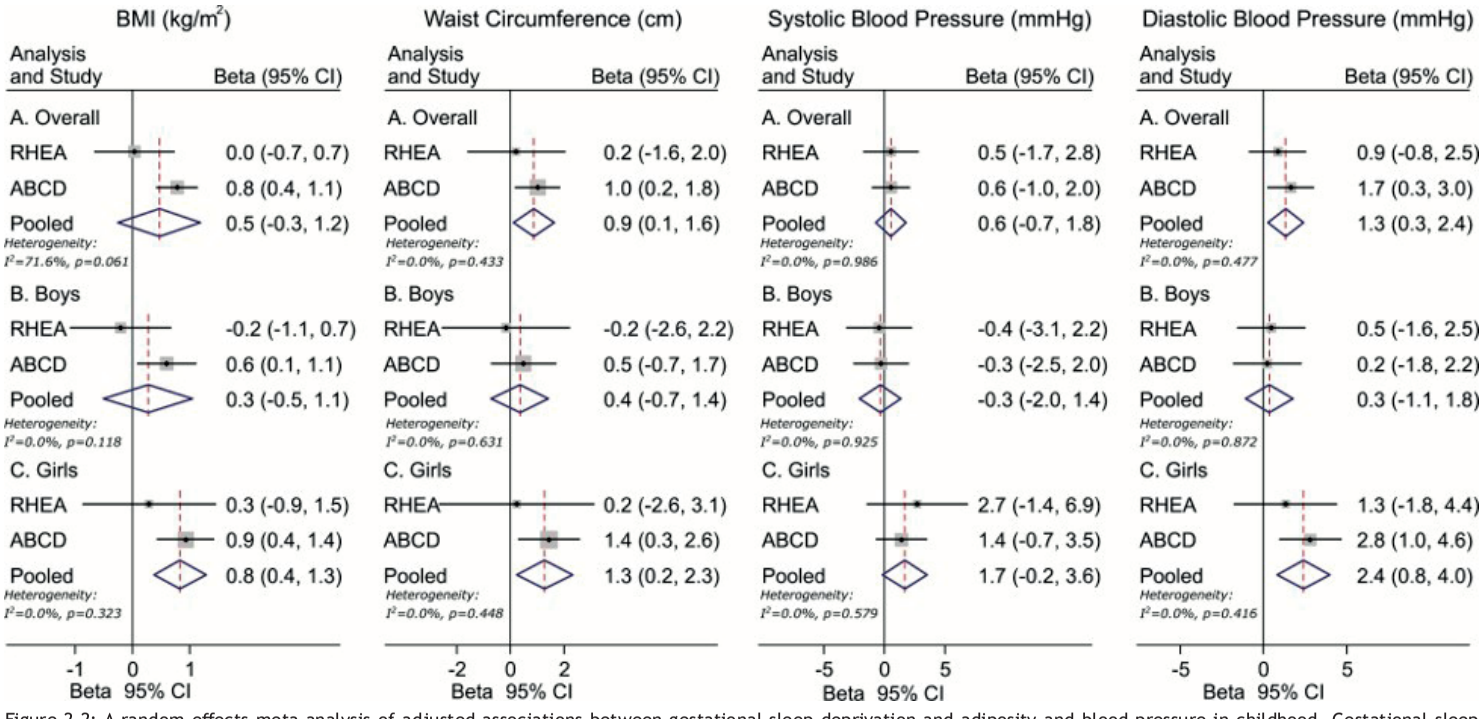

Figure 2.2: A random effects meta-analysis of adjusted associations between gestational sleep deprivation and adiposity and blood pressure in childhood. Gestational sleep deprivation was defined as at least 5 and 6 hours for Rhea (n= 661) and ABCD cohort (n=2,947) respectively. Cohort specific estimates were obtained by mixed effects models with child random effects and a random slope for child age. Cohort-specific estimates were adjusted for child sex, age at assessment (years), parity (nulliparous, multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre-pregnancy BMI (normal weight/overweight/obese), maternal origin (country of cohort/other) and maternal education (low/middle/high). Models for blood pressure were additionally adjusted for child height and BMI at assessment.

Table 2.3: Mediation by gestational age; birthweight; and gestational diabetes in the association between gestational sleep deprivation and offspring BMI at ages four to five years.

		Sleep → Mediator (a-path) measure of association	Mediator → BMI (b-path) measure of association	Mediation (a x b)
Single mediator model with binary mediator (ABCD n=2947)	Gestational diabetes at delivery (yes/no)	**OR 4.51**	ß **1.10**	**5.25 (1.35, 21.28)**
	Total direct effect (c' path)			**0.52 (0.24, 0.80)**
Multiple paralell mediator model with continuous mediators (ABCD& Rhea, n=3607)	Gestational age (weeks)	ß **-0.48**	ß **-0.12**	**0.06 (0.02, 0.10)**
	Birthweight (gram)	ß-77	ß **0.001**	-0.04 (-0.09, 0.01)
	Total indirect effect			0.02 (-0.02, 0.057)
	Total direct effect (c' path)			**0.49 (0.23, 0.75)**

Gestational sleep deprivation was defined as at least 5 and 6 hours for Rhea and ABCD cohort respectively. Mediation model based on structural equation modelling, adjusted for child sex and age at assessment (years). Bold faceted text indicates significant associations (p-value<0.05). OR: odds ratio

Mediation by gestational diabetes, gestational age and birthweight

Table 2.3 presents results for the mediation analysis on BMI. The total direct effect (c' path) was 0.5, meaning that children of mothers with gestational sleep deprivation had a 0.5 kg/m^2 higher mean childhood BMI.

Gestational diabetes was a significant mediator in the association between gestational sleep deprivation and offspring BMI. Mothers with gestational sleep deprivation during early pregnancy had 4.5 times higher odds of gestational diabetes (a-path), and gestational diabetes was associated with a mean increase of1.1 kg/m^2 in offspring BMI. The confidence interval of the indirect effect was wide, due to small numbers. Gestational age was also a significant mediator in the association between gestational sleep deprivation and offspring BMI, leading to on average a 0.06 point higher BMI. We found that children of mothers with gestational sleep deprivation were born with half a week shorter gestational age (a-path), and that a shorter gestational age was associated with a higher offspring BMI (b-path). Both indirect effects were found significant as the bootstrap confidence interval of the indirect effects did not contain zero, even though the numbers for gestational diabetes were small resulting in a wide confidence interval.

Low birthweight was not a significant mediator. The effect of gestational sleep deprivation on birthweight was not significant (a-path), but a higher birthweight was associated with a higher offspring BMI (b-path).

Apart from the BMI outcome, we also tested mediation for the other metabolic outcomes of interest. Gestational diabetes was a mediator for overweight/obesity, waist circumference, and % body fat, but not for DBP and SBP. Gestational age was a mediator for overweight/obesity and waist circumference. Low birthweight was not a mediator for the outcomes of interest (**Table S2.9**).

DISCUSSION

This is the first human epidemiological study showing that gestational sleep deprivation could be associated with offspring cardio metabolic profile. Children born to mothers with short sleep duration during pregnancy had higher adiposity and blood pressure levels with associations being more pronounced in girls than in boys and the effects becoming stronger with age. The effect estimates for each cohort separately were in the same direction, but stronger and significant in the ABCD cohort. The associations with adiposity were partly mediated by gestational diabetes and shorter gestational age.

Both sleep duration and sleep quality are known to change during pregnancy[47]. A recent meta-analysis found that about half of pregnant women experience poor sleep quality and that median sleep quality decreases from the second to third trimester[48]. Studies in the general population, as well as in pregnant women, suggest that sleep disturbances may alter the neuroendocrine homeostasis of the body, with an increased activity of the sympathetic nervous system and hypothalamic–pituitary system, as well as the stress and pro-inflammatory responses which are associated with numerous health consequences[49,50]. Syntheses of findings from epidemiological studies in general populations suggest that lack of sleep is associated with obesity and a wide range of adverse cardio metabolic outcomes affecting both adults and children[51-54].

Importantly, during pregnancy the adverse physiologic response to sleep deprivation may lead to a suboptimal intra-uterine environment, with subsequent effects on the placenta function, direct maternal and foetal effects, but also with long-term consequences[2,49]. Gestational sleep disruption has been associated with gestational diabetes, pre-term delivery and birthweight[11-16], factors also being associated with child's risk of overweight/obesity and cardio metabolic status[17-21], thus may be involved in the causal pathway. In agreement with that, for the association between gestational sleep deprivation and offspring BMI, overweight, waist circumference and % body fat, we found partly mediation by gestational diabetes. Mothers with gestational sleep deprivation during early pregnancy had higher odds of gestational diabetes during

later pregnancy and consequently gestational diabetes was associated with higher offspring BMI. The underlying pathogenic mechanisms behind gestational diabetes and the abnormal metabolic risk profile in offspring are unknown, but epigenetic changes induced by exposure to maternal hyperglycaemia during fetal life may be implicated in impaired insulin sensitivity in the offspring[55].

We also found that part of the association between gestational sleep deprivation and offspring adiposity in our cohort was mediated by gestational age; children of mothers with gestational sleep deprivation were born on average half a week earlier, and that was associated with a small increase in offspring BMI. Studies suggest the balance between pro- and anti-inflammatory cytokines may vary in each trimester, and sleep deprivation can adversely affect pro-inflammatory response with endothelial dysfunction in the placenta, which along with impaired glucose metabolism and can lead to preterm labor[14,56,57]. This causal pathway is further supported by another cohort study showing that obesity at the age of 2 years among children who were born extremely preterm was associated with perinatal systemic inflammation[58].

We found interaction by sex in our associations, with associations being more pronounced in girls than in boys. A sex-specific effect of poor sleep has also been observed by epidemiological studies in children, where sleep disruption was associated with more prominent effects on metabolic risk, adiposity and altered lipid profile in girls compared to boys[25,31,32]. Also, during pregnancy sexual dimorphisms have been observed in the effects of maternal obesity on childhood growth[17]. A possible mechanism could be differences in placenta function between boys and girls, which are caused by differences in gene expression in response to maternal health[59]. The differences in adaptation between males and females may be context, species and stage specific, and therefore it is difficult to say whether one sex copes better than the other[59]. Our findings in human are not in line with studies in mice, where associations between sleep fragmentation were stronger in male offspring[22] and sleep deprivation had similar associations with blood pressure in both sexes[23,24]. In a mouse study with female offspring the effects of gestational sleep deprivation were bigger in females that underwent a ovariectomy and lacked female hormones[24]. Future research could investigate if there is still interaction by sex when the children reach adolescence.

Strengths and limitations

Our study has several strengths. We were able to test longitudinal mediation in a large number of mother-infant pairs from different countries. By doing this we were able to test potential mechanisms for the association between gestational sleep deprivation and adiposity. In the mediation analysis the number of mothers with gestational

sleep deprivation and gestational diabetes was low, but we still found a significant mediation effect with the minimal adjustment set. However, these results should be interpreted with caution due to the small sample size. Although our data are observational, the sequence of events and associations over time might implicate causal relationships. All data were collected prospectively and outcome measurements during childhood were all performed by research staff. Third, we tested the association in a pooled analysis from two cohorts, but we do also provide cohort specific estimations for the benefit of quantifying the heterogeneity between cohorts and plotting the associations.

There were several limitations, mostly inherent to the cohorts' study design. Our exposure variable of gestational sleep deprivation was composed from a self-administered questionnaire and therefore recall bias and possible under- or over reporting may occur. We measured sleep at two different points during pregnancy, during the third (Rhea) and second (ABCD) trimester, capturing two stages of pregnancy. Effects of sleep duration, as well as sleep duration itself, may vary during pregnancy, and that may, besides other unknown factors, explain the different associations between the two cohorts. Also, the phrasing of the sleep question differed between both cohorts. Therefore, we used different cut-offs in the main analysis, correcting for resting time during the day that was included in the ABCD-study. However, our sensitivity analysis where two different common cut-offs in both cohorts were used, showed the same associations. We have no details about the timing of sleep during the day- and night-time, e.g. the effects of nocturnal sleep might be different from day-time naps, and we have no information about gestational weight gain in the ABCD-cohort. Moreover, there are important differences in demographics between the two cohorts, causing some heterogeneity in our analysis. There are higher rates of maternal smoking; obesity; gestational diabetes; and cesarean section in the Rhea cohort. The smaller numbers in the RHEA cohort (for the random effects meta-analysis n=661 versus n=2,947 for ABCD cohort) resulted in limited power which might be one of the reasons for the non-significant findings in this cohort. However, effect estimates were in the same direction, specifically with regard to stronger associations in girls. Nevertheless, the random effects meta-analysis indicates low to moderate heterogeneity for most of the outcomes, and pooled analysis was adjusted for cohort and other relevant covariates. Due to numerical difficulties we were not able to provide a measure of risk (OR or RR) for overweight/obesity, instead we calculated Hazard Ratios assuming that the development of overweight/obesity happened at the exact time of the follow-up visit. Structural equation models (SEMs) allowed us to assess multiple potential mediators but it makes strong assumptions that the relations between all variables are unconfounded. For this reason we consider the mediation analysis an explorative

study and do not claim causality. Lastly, loss to follow up over the years of childhood caused our analysis to have a lower rate of mothers with short sleep duration in the participant group versus non-participants. We hypothesize that this difference was most likely attributed to higher loss to follow up rates in non-Greek or non-Dutch origins, as ethnicity was previously shown to be associated with shorter sleep duration in a Dutch population[60], and we corrected our analyses for that.

Gestational sleep deprivation and clinical implications

Pregnancy is a period where lifestyle interventions are encouraged and parents are more aware of their choices[61]. Healthy gestational sleep has several perinatal benefits, whereas based on our findings, it probably also has positive long-term effects on childhood cardio metabolic health. Primary prevention may be limited to few socioeconomic factors previously related to sleep deprivation, for example ethnicity and occupation[62]. But also secondary prevention could have a great impact for mothers with sleep disturbances already in early pregnancy. Closer monitoring for glucose metabolism and preterm birth might be extra warranted in mothers with sleep deprivation during pregnancy. Although sleep needs may vary by age and gender, both the National Sleep Foundation and American Academy of Sleep Medicine and Sleep Research Society have recommended seven to nine hours of sleep per 24 hours for adults[63,64]. In a sensitivity analysis we found that the associations are stronger for more severe sleep deprivation (≤5 compared to ≤7 hours). During some circumstances sleeping more than nine hours per night might be appropriate too and for other it is uncertain if this is associated with health risk. There are no official sleep recommendations for pregnant women, but we postulate based on our findings that sleep deprivation (meaning a sleep duration of less than six hours) should be avoided at any stage during pregnancy.

Future perspectives

Future studies should be done to replicate our findings in other populations, different stages of pregnancy, and to further study the underlying mechanism. Also, the associations we found for gestational sleep deprivation with child adiposity and blood pressure should be further explored in relation not only to sleep deprivation, but also in relation to sleep quality during pregnancy. We tested potential mechanisms with an explorative mediation analysis. Further research on the effects of gestational sleep deprivation on gestational diabetes and shorter gestational age and subsequent childhood metabolic health are needed to investigate causality and opportunities for prevention. We tested for 3 potential perinatal mediators, however other potential mediators (e.g. childhood lifestyle and sleep) could exist during gestation and early life which may warrant further study. There is one published research protocol of a

prospective cohort study that investigates the effects of circadian rhythm on birth and infant outcomes, which can replicate the studied associations[65].

Conclusion

Our study is the first analysis on the association between maternal sleep duration during pregnancy and later childhood health. We used data from two ethnical and demographical diverse European cohorts and found that gestational sleep deprivation may be associated with increased risk for overweight and higher blood pressure in offspring, up until the age of eleven years, with more pronounced significant effects in girls than boys. Gestational diabetes and gestational age partly mediated these effects, pointing to altered glucose metabolism and inflammatory pathways as possible biological mechanisms underlying the observed associations.

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SUPPLEMENTAL INFORMATION

Table S2.1: Age specific cardiometabolic outcomes in Rhea and ABCD birth cohorts

	Rhea N=661	ABCD N=2947	Rhea N=436	ABCD N=1951	ABCD N=874
	No. (%) or Mean ±SD	No. (%) or Mean ±SD	No. (%) or Mean ±SD	No. (%) or Mean ±SD	No. (%) or Mean ±SD
Follow up	**4 years**	**5 years**	**6 years**	**10 years**	**11 years**
Age at assessment (years)	4.2 ± 0.2	5.7 ± 0.5	6.6 ± 0.3	10.6 ± 0.4	11.8 ± 0.4
BMI (kg/m^2)	16.4 ± 1.9	15.5 ± 1.5	17.0 ± 2.6	17.4 ± 2.6	17.6 ± 2.5
Overweight[a]	94 (14.2)	210 (7.1)	93 (21.4)	210 (10.8)	64 (7.3)
Obese[a]	50 (7.6)	45 (1.5)	48 (11.0)	38 (2.0)	8 (0.9)
Waist circumference (cm)	53.6 ± 4.8	52.5 ± 3.7	58.6 ± 6.9	NA	62.4 ± 6.0
Body fat (%)	19.3 ± 5.8	23.4 ± 6.7	24.6 ± 6.9	NA	23.2 ± 5.6
Systolic BP (mmHg)	90.2 ± 7.5	97.8 ± 8.6	95.2 ± 8.9	NA	105.2 ± 8.7
Diastolic BP (mmHg)	53.5 ± 5.1	58.0 ± 8.0	54.9 ± 6.6	NA	60.4 ± 6.7
Total Cholesterol (mg/dl)	155.5 ± 26.8	156.4 ± 26.2	162.4 ± 23.7	NA	157.6 ± 25.0
Triglycerides (mg/dl)	71.1 ± 27.4	57.6 ± 26.8	68.5 ± 33.8	NA	87.5 ± 48.8
HDL (mg/dl)	49.0 ± 11.0	50.2 ± 11.6	58.1 ± 12.2	NA	57.2 ± 12.3
LDL (mg/dl)	92.3 ± 23.0	90.4 ± 24.9	90.8 ± 20.6	NA	83.1 ± 21.1

BMI: Body Mass Index, BP: Blood pressure, HDL: High density lipoprotein, LDL: Low density lipoprotein, SD: Standard deviation.

a: Defined with use of the BMI cutoff point for sex and age that was proposed by the International Obesity Task Force

Table S2.2: Maternal and infant characteristics of the participants with available outcome data according to gestational sleep duration status

	Rhea		ABCD	
	Adequate gestational sleep N=624	Gestational sleep deprivation N=37 (5.6%)	Adequate gestational sleep N=2840	Gestational sleep deprivation N=107 (3.6%)
	No. (%) or Mean ±SD	No. (%) or Mean ±SD	No. (%) or Mean ±SD	No. (%) or Mean ±SD
Maternal age at conception (years)	29.7 ± 4.9*	31.7 ± 4.7 *	32.0 ± 4.5	31.6 ± 5.3
Maternal education				
Low	95 (15.2)	8 (21.6)	67 (2.4)*	11 (10.3)*
Middle	316 (50.6)	21 (56.8)	434 (15.3)	34 (31.8)
High	213 (34.1)	8 (21.6)	2339 (82.4)	62 (57.9)
Maternal origin (Country of cohort (%))	592 (95.0)	37 (100.0)	2212 (77.9)*	49 (45.8)*
Parity (Nulliparous (%))	295 (47.3)*	10 (27.0) *	1621 (57.1)*	39 (36.4)*
Smoking in early pregnancy (yes (%))	208 (33.3)	15 (40.5)	246 (8.7)*	18 (16.8)*
Pre-pregnancy BMI (kg/m^2)	24.6 ±4.8	25.0 ± 5.2)	22.9 ± 3.8*	23.9 ± 4.4*
Underweight and normal weight (BMI <25 kg/m2)	404 (64.7)	23 (62.2)	2271 (80.0)	67 (62.6)
Overweight (BMI 25-30 kg/m2)	140 (22.4)	6 (16.2)	426 (15.0)	33 (30.8)
Obese (BMI ≥30 kg/m2)	80 (12.8)	8 (21.6)	143 (5.0)	7 (6.5)
Gestational diabetes (yes (%))	56 (9.1)	4 (10.8)	43 (1.5)*	7 (6.5)*
Gestational age at delivery (weeks)	38.3 ± 1.5	37.9 ± 1.5	39.5 ± 1.7*	39.1 ± 2.2*
Mode of delivery (Cesarean section)	311 (49.8)	19 (51.4)	396 (13.9)	13 (12.1)
Child sex (male (%))	328 (52.6)	24 (64.9)	1422 (50.1)	49 (45.8)
Birthweight (g)	3203.2 ± 450.9	3304.6 ± 401.0	3477.2 ± 546.2 *	3364.1 ± 624.5*
Breastfeeding duration (months)	4.2 ± 4.3	3.6 ± 4.5	4.9 (3.8)	4.2 (3.8)

*: significant difference ($p<0.05$) between groups with normal sleep versus sleep deprivation; BMI: Body Mass Index

Table S2.3: Maternal and infant characteristics of the participants, based on participation

Rhea & ABCD	Rhea		ABCD	
	Non-participants N= 425	Participants N= 661	Non-participants N= 4,776	Participants N=2,920
	No. (%) or Mean ±SD	No. (%) or Mean ±SD	No. (%) or Mean ±SD	No. (%) or Mean ±SD
Maternal characteristics				
Maternal age at conception (years)	28.8 ± 5.2 *	29.8 ± 4.9*	30.1 ± 5.5 *	32.0 ± 4.5 *
Maternal education				
Low	114 (28.1)*	103 (15.6)*	347 (7.4)*	78 (2.6)*
Middle	200 (49.3)	337 (51.0)	1328 (28.2)	468 (15.9)
High	92 (22.7)	221 (33.4)	3035 (64.4)	2401 (81.5)
Maternal origin (country of cohort (%))	360 (86.1) *	629 (95.3)*	2170 (45.4) *	686 (23.3) *
Parity (nulliparous (%))	158 (39.0) *	305 (46.1)*	2631 (55.1)	1660 (56.3)
Smoking in early pregnancy (yes (%))	146 (36.9)	223 (33.7)	467 (9.8)	264 (9.0)
Pre-pregnancy BMI (kg/m^2)	23.8 ± 4.9 *	24.7 ± 4.8 *	23.2 ± 4.2 *	22.9 ± 3.8 *
Gestational diabetes (yes (%))	31 (7.4)	60 (9.2)	108 (2.3)	50 (1.7)
Gestational sleep deprivation (yes (%))	34 (8.0)	37 (5.6)	402 (8.4) *	107 (3.6) *
Infant characteristics				
Gestational age at delivery (weeks)	38.2 ± 1.5	38.2 ± 1.5	39.0 ± 3.2 *	39.5 ± 1.7 *
Child sex (male (%))	210 (49.4)	352 (53.3)	2402 (50.6)	1471 (49.9)
Birthweight (g)	3140.6 ± 454.3 *	3208.8 ± 448.6 *	3385.5 ± 646.1 *	3473.1 ± 549.6 *

*: statistical difference P<0.05 between group with normal sleep versus sleep deprivation, BMI: body mass index

Table S2.4: A longitudinal pooled analysis of linear associations (β (95% CI)) between gestational sleep deprivation and serum lipid profile during childhood adjusting for potential confounder and testing for sex interaction

	Rhea & ABCD (n=2692)									
	Overall			Boys			Girls			
Outcomes	N	Estimate (95%CI)	P-value	N	Estimate (95%CI)	P-value	N	Estimate (95%CI)	P-value	P-interaction with sex
Total Cholesterol (mg/dl)	2692	-1.1 (-6.3, 4.2)	0.689	1391	-0.1 (-7.5, 7.3)	0.98	1301	-3.9 (-11.5, 3.8)	0.321	0.323
Triglycerides (mg/dl)	2692	0.3 (-6.2, 6.8)	0.924	1391	-3.4 (-12.4, 5.5)	0.454	1301	2.8 (-6.9, 12.6)	0.567	0.501
HDL(mg/dl)	2692	-0.2 (-2.5, 2.2)	0.872	1391	1.8 (-1.6, 5.3)	0.303	1301	-2 (-5.2, 1.3)	0.245	0.224
LDL (mg/dl)	2692	0.4 (-4.4, 5.2)	0.882	1391	-1.3 (-8, 5.3)	0.697	1301	-0.1 (-7.2, 7)	0.977	0.672

Gestational sleep deprivation was defined as at least 5 and 6 hours for Rhea and ABCD cohort respectively. All estimates are marginal effects obtained by mixed effects models with cohort and child random effect and age interaction
All models are adjusted for child sex, age at assessment (years), parity (nulliparous, multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre pregnancy BMI (normal weight/overweight/obese), maternal origin (country of cohort/other), maternal education (low/middle/high) and for child BMI at assessment.
BMI: body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein, CI: Confidence Interval

Table S2.5: A longitudinal pooled analysis of linear associations (β (95% CI)) between gestational sleep deprivation and BMI and blood pressure z-scores during childhood adjusting for potential confounder and testing for sex interaction

	Rhea & ABCD (n=3608)									
	Overall			Boys			Girls			
Outcomes	N	Estimate (95%CI)	P-value	N	Estimate (95%CI)	P-value	N	Estimate (95%CI)	p-value	P-interaction with sex
Z-BMI	3607	**0.2 (0.0, 0.3)**	**0.043**	1823	0.1 (-0.2, 0.3)	0.636	1784	**0.3 (0.1, 0.5)**	**0.010**	0.162
Z-Systolic BP [a]	3491	0.1 (-0.1, 0.2)	0.447	1758	-0.1 (-0.3, 0.1)	0.554	1733	0.2 (0.0, 0.4)	0.058	0.092
Z-Diastolic BP [a]	3485	**0.2 (0.1, 0.3)**	**0.004**	1753	0.0 (-0.2, 0.2)	0.810	1732	**0.4 (0.2, 0.6)**	**<0.001**	**0.027**

Gestational sleep deprivation was defined as at least 5 and 6 hours for Rhea and ABCD cohort respectively. All models are adjusted for child sex, age at assessment (years), parity (nulliparous, multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre-pregnancy BMI (normal weight/overweight/obese), maternal origin (country of cohort/other) and maternal education (low/middle/high).
BMI: Body Mass Index, BP: Blood pressure, CI: Confidence Interval, bold faceted text indicated significant associations (p-value<0.05)
a Additionally adjusted for child height and BMI at assessment

Table S2.6: A longitudinal pooled analysis of associations between gestational sleep deprivation (defined as ≤5 and ≤7 hours per night in both cohorts) and adiposity and blood pressure during childhood adjusting for potential confounder and testing for sex interaction

gestational sleep deprivation defined as ≤5 hours per night in both cohorts (exposed n (%)= 66 (2 %))										
	Rhea & ABCD (n=3608)									
	Overall			**Boys**			**Girls**			
Outcomes	**N**	**Estimate (95%CI)**	**p-value**	**N**	**Estimate (95%CI)**	**P-value**	**N**	**Estimate (95%CI)**	**p-value**	**P-interaction with sex**
BMI (kg/m^2) [a]	**3607**	**1.5 (0.8, 2.1)**	**<0.001**	**1823**	**1.2 (0.2, 2.1)**	**0.018**	**1784**	**1.8 (1.0, 2.7)**	**<0.001**	**0.047**
Overweight or obese [b d]	**3607**	**1.6 (1.1, 2.3)**	**0.020**	1823	0.9 (0.5, 1.6)	0.649	**1784**	**3.0 (1.8, 5.0)**	**<0.001**	**0.001**
Waist circ. (cm) [a]	**3601**	**1.5 (0.2, 3.0)**	**0.029**	1818	1.2 (-1.1, 3.6)	0.296	**1783**	**2.3 (0.5, 4.1)**	**0.011**	0.163
Body fat (%)[a]	**3590**	**2.3 (0.6, 4.1)**	**0.007**	1816	2.4 (-0.2, 5.1)	0.069	1774	2.2 (-0.2, 4.5)	0.070	0.939
Systolic BP (mmHg)[a c]	3491	1.5 (-0.9, 3.8)	0.217	1758	-0.6 (-4.5, 3.2)	0.739	**1733**	**6.3 (3.0, 9.7)**	**<0.001**	**0.004**
Diastolic BP (mmHg) [a c]	3485	**2.4 (0.4, 4.4)**	**0.016**	**1753**	-0.6 (-3.9, 2.6)	0.693	1732	**6.1 (3.5, 8.8)**	**<0.001**	**0.017**
gestational sleep deprivation defined as ≤7 hours per night in both cohorts (exposed n (%)= 687 (19 %))										
	Overall			**Boys**			**Girls**			
BMI (kg/m^2) [a]	3607	0.1 (-0.0, 0.3)	0.098	1823	0.1 (-0.1, 0.4)	0.387	1784	0.2 (-0.1, 0.4)	0.137	**0.041**
Overweight or obese [b d]	3607	1.1 (0.9, 1.3)	0.351	1823	0.8 (0.6, 1.1)	0.161	**1784**	**1.4 (1.1, 1.8)**	**0.008**	**0.006**
Waist circ. (cm) [a]	3601	0.1 (-0.3, 0.5)	0.511	1818	-0.1 (-0.6, 0.5)	0.804	1783	0.4 (-0.2, 0.9)	0.184	**0.035**
Body fat (%)[a]	3590	0.3 (-0.1, 0.8)	0.163	1816	0.3 (-0.4, 1.0)	0.422	1774	0.4 (-0.3, 1.1)	0.217	0.666
Systolic BP (mmHg) [a c]	3491	0.3 (-0.4, 0.9)	0.375	1758	-0.1 (-1.0, 0.9)	0.891	**1733**	**1.0 (-0.0, 1.9)**	**0.054**	0.204
Diastolic BP (mmHg) [a c]	3485	0.4 (-0.2, 0.9)	0.205	1753	-0.1 (-0.9, 0.8)	0.871	**1732**	**0.9 (0.1, 1.6)**	**0.036**	0.257

All models are adjusted for child sex, age at assessment (years), parity (nulliparous, multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre-pregnancy BMI (normal weight/overweight/obese), maternal origin (country of cohort/other) and maternal education (low/middle/high).

a Beta coefficient and 95% confidence intervals as marginal effect estimates obtained by mixed effects models with cohort and child random effect and age interaction

b Hazard ratios and 95% confidence intervals obtained by Cox proportional hazard models with shared cohort frailties.

c Additionally adjusted for child height and BMI at assessment

d Defined with use of the BMI cutoff point for sex and age that was proposed by the International Obesity Task Force.

BMI: Body Mass Index, BP: Blood pressure, CI: Confidence Interval; bold faceted text indicated significant associations (p-value<0.05)

Table S2.7: Random effects meta-analysis of the cohort specific adjusted associations between gestational sleep deprivation and adiposity and blood pressure in childhood

		RHEA (n= 661)	ABCD (n=2,947)	Random Effect Meta-analysis				
Outcome	**Analysis**	**Beta (95% CI)**	**Beta (95% CI)**	**Beta (95% CI)**	**P-value**	**I^2**	**Q-test**	**P-value for heterogeneity**
BMI (Kg/m^2)	Overall	0.0 (-0.7, 0.7)	**0.8 (0.4, 1.1)**	0.5 (-0.3, 1.2)	0.201	71.6%	3.52	0.061
	Boys	-0.2 (-1.1, 0.7)	**0.6 (0.1, 1.1)**	0.3 (-0.5, 1.1)	0.485	59.1%	2.45	0.118
	Girls	0.3 (-0.9, 1.5)	**0.9 (0.4, 1.4)**	**0.8 (0.4, 1.3)**	**<0.001**	0.0%	0.98	0.323
	Interaction	0.4 (-0.2, 1)	1.1 (-0.2, 2.4)	0.5 (0.0, 1.0)	0.058	0.0%	0.92	0.338
Waist Circumference (cm)	Overall	0.2 (-1.6, 2.0)	**1.0 (0.2, 1.8)**	**0.9 (0.1, 1.6)**	**0.022**	0.0%	0.62	0.433
	Boys	-0.2 (-2.5, 2.2)	0.5 (-0.7, 1.7)	0.4 (-0.7, 1.4)	0.517	0.0%	0.23	0.631
	Girls	0.2 (-2.6, 3.1)	**1.4 (0.3, 2.6)**	**1.3 (0.2, 2.3)**	**0.017**	0.0%	0.58	0.448
	Interaction	0.8 (-0.6, 2.2)	2.2 (-1.1, 5.6)	1.0 (-0.3, 2.3)	0.125	0.0%	0.58	0.445
Body fat (%)	Overall	0.8 (-1.1, 2.7)	0.5 (-0.6, 1.7)	0.6 (-0.4, 1.6)	0.223	0.0%	0.05	0.831
	Boys	0.2 (-2.2, 2.5)	0.7 (-0.9, 2.4)	0.5 (-0.8, 1.9)	0.434	0.0%	0.15	0.695
	Girls	1.7 (-1.7, 5)	0.3 (-1.2, 1.9)	0.6 (-0.8, 2.0)	0.423	0.0%	0.50	0.481
	Interaction	-0.4 (-2.6, 1.8)	1.2 (-2.7, 5)	0.0 (-1.9, 1.9)	0.983	0.0%	0.46	0.497
Systolic BP (mmHg)[a]	Overall	0.5 (-1.7, 2.8)	0.6(-1.0, 2.1)	0.6(-0.7, 1.8)	0.388	0.0%	0.00	0.986
	Boys	-0.4 (-3.1, 2.2)	-0.3 (-2.5, 2.0)	-0.3(-2.0, 1.4)	0.704	0.0%	0.01	0.925
	Girls	2.7 (-1.4, 6.9)	1.4 (-0.7, 3.5)	1.7 (-0.2, 3.6)	0.074	0.0%	0.31	0.579
	Interaction	1.3 (-1.6, 4.3)	3.0 (-1.8, 7.7)	1.8 (-0.7, 4.3)	0.161	0.0%	0.34	0.560
Diastolic BP (mmHg)[a]	Overall	0.9 (-0.8, 2.6)	**1.7 (0.3, 3.0)**	**1.3 (0.3, 2.4)**	**0.013**	0.0%	0.51	0.477
	Boys	0.5 (-1.6, 2.4)	0.2 (-1.8, 2.2)	0.3 (-1.1, 1.8)	0.641	0.0%	0.03	0.872
	Girls	1.3 (-1.7, 4.4)	2.8 (1.0, 4.7)	**2.4 (0.8, 4.0)**	**0.003**	0.0%	0.66	0.416
	Interaction	2.5 (-0.1, 5.2)	1.2 (-2.4, 4.7)	2.0 (-0.1, 4.2)	0.062	0.0%	0.37	0.543

Cohort specific estimates were obtained by mixed effects models with child random effects and a random slope for child age. Gestational sleep deprivation was defined as at least 5 and 6 hours for Rhea and ABCD cohort respectively.

All models are adjusted for child sex, age at assessment (years), parity (nulliparous, multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre-pregnancy BMI (normal weight/overweight/obese), maternal education (low/middle/high). BMI: Body Mass Index, BP: Blood pressure, CI: Confidence Interval; bold faceted text indicated significant associations (p-value<0.05)

a: Additionally adjusted for child height and BMI;

Table S2.8: Cohort and age specific associations between gestational sleep deprivation and adiposity, blood pressure and serum lipids in childhood

	Rhea 4 years		ABCD 5 years		Rhea 7 years		ABCD 10 years		ABCD 11 years		p-interaction with age
Outcomes	**Estimate (95%CI)**	**P-value**	**Estimate (95%CI)**	**P-value**	**Estimate (95%CI)**	**P-value**	**Estimate (95%CI)**	**P-value**	**Estimate (95%CI)**	**P-value**	
BMI (kg/m^2)[a]	-0.1 (-0.8, 0.5)	0.661	**0.3 (0.0, 0.6)**	**0.025**	0.6 (-0.2, 1.3)	0.145	**0.9 (0.4, 1.5)**	**0.001**	**0.9 (0.0, 1.9)**	**0.043**	<0.001
Overweight / obese[b c]	**1.6 (1.0, 2.6)**	**0.037**	**1.6 (1.1, 2.3)**	**0.018**	1.3 (0.6, 2.7)	0.573	**1.6 (1.2, 2.2)**	**0.004**	1.5 (0.6, 3.6)	0.339	Not applicable
Waist circ. (cm)[a]	-0.5 (-2.1, 1.1)	0.554	0.6 (-0.1, 1.3)	0.119	**1.6 (-0.3, 3.4)**	**0.098**	NA		**2.0 (-0.3, 4.2)**	**0.082**	0.031
Body fat (%)[a]	0.4 (-1.5, 2.4)	0.65	0.3 (-0.9, 1.6)	0.573	**1.7 (0.0, 3.3)**	**0.046**	NA		1.6 (-0.4, 3.5)	0.116	0.625
Systolic BP (mmHg)[a d]	1.0 (-1.6, 3.7)	0.443	0.1 (-1.5, 1.7)	0.875	-0.5 (-3.5, 2.5)	0.742	NA		2.0 (-1.3, 5.4)	0.237	0.757
Diastolic (mmHg)[a d]	1.5 (-0.4, 3.4)	0.119	1.0 (-0.5, 2.5)	0.187	-0.4 (-2.9, 2.1)	0.743	NA		**4.0 (1.4, 6.6)**	**0.003**	0.289
Total Chol. (mg/dl)[a e]	**9.6 (0.2, 19.1)**	**0.046**	-6.9 (-14.1, 0.4)	0.062	-4.4 (-13.4, 4.6)	0.339	NA		-6.8 (-17.4, 3.7)	0.204	0.027
Triglycerides (mg/dl)[a e]	4.1 (-5.5, 13.8)	0.398	-1.1 (-8.5, 6.2)	0.763	-7.9 (-25.0, 9.2)	0.365	NA		-9.9 (-30.0, 10.2)	0.336	0.490
HDL(mg/dl)[a e]	0.3 (-3.5, 4.2)	0.861	0.4 (-2.8, 3.6)	0.816	-0.2 (-4.5, 4.1)	0.92	NA		-1.6 (-6.6, 3.4)	0.534	0.671
LDL (mg/dl)[a e]	**8.4 (0.3, 16.5)**	**0.043**	-5.6 (-12.4, 1.2)	0.108	-3 (-10.6, 4.5)	0.429	NA		-3.7 (-12.5, 5.2)	0.414	0.029

Gestational sleep deprivation was defined as at least 5 and 6 hours for Rhea and ABCD cohort respectively. All models are adjusted for child sex, age at assessment (years), parity (nulliparous, multiparous), maternal smoking early in pregnancy (yes/no) maternal age at conception, pre-pregnancy BMI (normal weight/overweight/obese), maternal origin (country of cohort/other) and maternal education (low/middle/high). BMI: Body Mass Index, SBP: Systolic Blood pressure, DBP: Diastolic Blood pressure, HDL: High density lipoprotein, LDL: Low density lipoprotein, NA: not available; bold faceted text indicated significant associations (p-value<0.05.

a Beta coefficient and 95% confidence intervals

b Hazard ratios and 95% confidence intervals

c: Defined with use of the BMI cutoff point for sex and age that was proposed by the International Obesity Task Force

d: Additionally adjusted for child height and BMI at assessment

e: Additionally adjusted for child BMI at assessment

Table S2.9: Mediation by gestational age; birthweight; and gestational diabetes in the association between gestational sleep deprivation and other outcomes at ages four to five years.

		Outcome	Mediation
Single mediator model with binary mediator (ABCD n=2947)	Gestational diabetes at delivery(yes/no)	Overweight/obesity[a]	**0.28 (0.04, 0.55)**
		Waist circumference	**3.36 (0.47, 6.63)**
		% body fat	**5.32 (0.92, 9.50)**
		DBP	0.31 (-0.06, 0.79)
		SBP	0.15 (-0.26, 0.62)
Multiple paralell mediator model with continuous mediators (ABCD& Rhea, n=3607)	Gestational age (weeks)	Overweight/obesity[a]	**0.01 (0.00, 0.01**)
		Waist circumference	**0.15 (0.04, 0.29)**
		% body fat	-0.01 (-0.09, 0.07)
		DBP	-0.01 (-0.02, 0.00)
		SBP	-0.00 (-0.01, 0.01)
	Birthweight (gram)	Overweight/obesity[a]	-0.00 (-0.01, 0.00)
		Waist circumference	-0.10 (-0.24, 0.03)
		% body fat	0.02 (-0.03, 0.07)
		DBP	0.01 (-0.00, 0.03)
		SBP	0.01 (-0.00, 0.03)

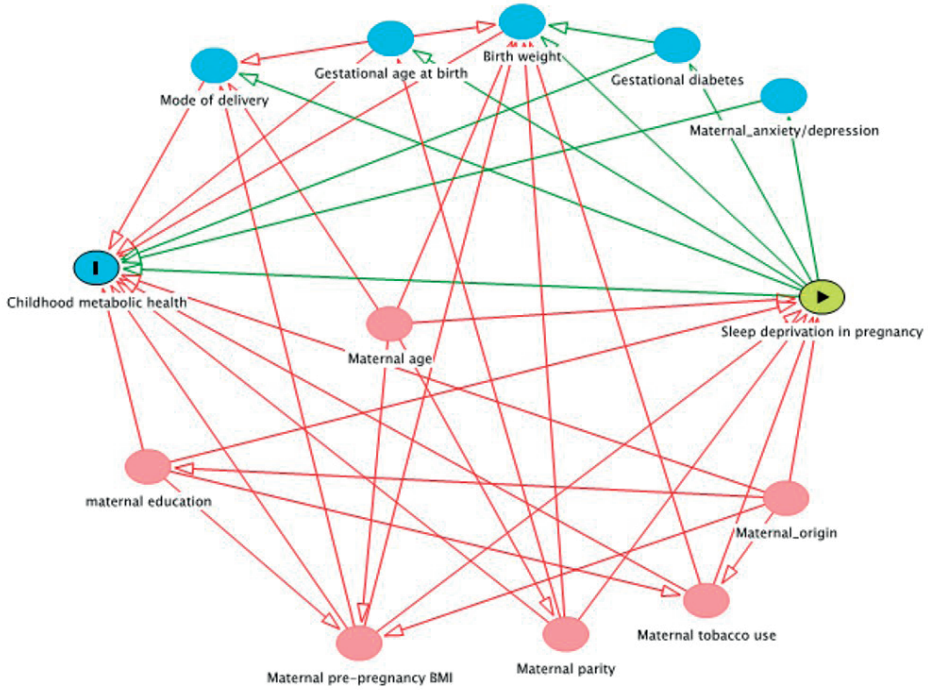
Gestational sleep deprivation was defined as at least 5 and 6 hours for Rhea and ABCD cohort respectively. SBP: Systolic Blood pressure, DBP: Diastolic Blood pressure. Bold faceted text indicated significant associations (p-value<0.05).

a: Defined with use of the BMI cutoff point for sex and age that was proposed by the International Obesity Task Force

Figure S2.1: Directed acyclic graph for the association between gestational sleep deprivation and cardio-metabolic health in childhood.

Green node with mark: exposure of interest; Blue node with mark: outcome of interest; blue node: ancestor of outcome; red node: ancestor of exposure. All red nodes are variables we controlled for in adjusted models.

Figure S2.1: Directed acyclic graph for the association between gestational sleep deprivation and cardio-metabolic health in childhood.
Green node with mark: exposure of interest; Blue node with mark: outcome of interest; blue node: ancestor of outcome; red node: ancestor of exposure. All red nodes are variables we controlled for in adjusted models.



3

Sleep during infancy and associations with childhood body composition. A systematic review and narrative synthesis.

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ABSTRACT

Introduction: Prevention of childhood overweigh should start as early as possible preferably in 'the first 1000 days of life'. Sleep is one of the modifiable health behaviors during this age period, besides dietary intake and physical activity. Aim of this systematic review is to summarize the existing literature regarding the association between sleep during infancy (age ≤24 months) and body composition measures during childhood (age ≤12 years).

Methods: We registered the protocol of this systematic review (PROSPERO registration no. CRD42018087088) and conducted the review following the PRISMA statement. We searched for papers published until July 31st 2019 reporting on longitudinal associations with a minimal follow-up of 6 months. Methodological Quality was assessed and a narrative synthesis was performed.

Results: We included 19 studies. Sleep was reported as sleep duration (n=18) or sleep problems (n=2). Sleep was assessed at least once before the age of 12 months in 14 out of the 19 studies. Methodological quality was rated as strong for five studies; moderate for five studies; and weak for nine studies.

Conclusion: This narrative synthesis found inconsistent evidence that longer infant sleep duration during the first two years of life is associated with a healthier body composition during childhood.

INTRODUCTION

Childhood obesity is becoming a permanent problem in our society even at the toddler age (1, 2). Because childhood obesity often tracks into adulthood (3) prevention should start as early as possible, preferably in 'the first 1000 days of life': between conception and second birthday (4). Childhood obesity risk factors during the first 1000 days that are modifiable and identified in a recent systematic review include: higher maternal pre-pregnancy BMI, prenatal tobacco exposure, maternal excess gestational weight gain, and accelerated infant weight gain (5). Less consistent evidence was found for curtailed infant sleep, bedtime routine with bottle feeding at age nine months, bottle feeding at age 24 months, and introduction of solid food intake before age four months (5). Curtailed infant sleep and bedtime routine have recently been under the attention of pediatricians and youth health care workers and healthy sleep is part of newly developed lifestyle interventions during infancy (4, 6-10). Infant sleep problems can be problematic and include sleep latency and night awakenings, both leading to reduced sleep duration, quality and efficiency (% of time spent in bed that the child really sleeps). Systematic reviews and meta-analysis so far have looked at the association and dose-response effects of sleep duration at age 0-4 years (11, 12) and age 0-18 years (13-15) and concluded that there is an inverse association between sleep duration and weight gain. From these reviews we cannot conclude if infant sleep duration is a determinant of childhood overweight, as these reviews did not investigate infant age separately. Also, new studies in infants have been published that are not included in the last reviews. Infant sleep is different from childhood sleep in timing (frequent day-time naps, nighttime wakening's), initiation (feeding, pacifiers, room or bedsharing) and optimal measurements (diaries versus accelerometry detecting the duration of laying and sleeping in bed or other places).

Infancy (age 0-2 years) is a defining period in life and overweight prevention should ideally start as early as possible. Sleep is one of the modifiable health behaviors during this age period, besides dietary intake and physical activity. Aim of this systematic review is to summarize the existing literature regarding the association of sleep duration and sleep problems during infancy (age ≤24 months) with body composition outcomes during childhood (age ≤12 years).

METHODS

Protocol and registration

We registered the protocol of this systematic review with the International Prospective Register of Systematic Reviews (PROSPERO; Registration no. CRD42018087088; available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087088. We conducted the review following the Preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement for reporting systematic reviews and meta-analysis (16).

Information sources and search strategy

We searched Ovid MEDLINE and EMBASE for papers published from inception until July 31st 2019 in collaboration with a clinical librarian (J.G.D). Detailed search terms and MeSH terms are provided in appendix 1. The search strategy can be displayed as the following Boolean combination of concepts: ([children 0-2 yrs] AND [sleep duration] AND [body composition and adverse cardiometabolic outcomes]) OR [relevant cohorts|-studies]. No language limitation or filter was applied. In addition, we reviewed the reference lists from the relevant articles and earlier published review articles.

Study selection

Eligible studies were longitudinal studies with a minimal follow-up time of 6 months, reporting the determinant sleep (either duration or problems) at any age between 0 and 24 months and as outcome BMI, another indicator of weight status up till 12 years of age. We included all definitions of sleep problems or different measurements of sleep quality or sleep duration. Two independent reviewers (MH and TV, IH or KA) screened titles and abstracts using Rayyan, a web-app for screening titles and abstracts (17). Reviewers were blinded for each other's decision and discrepancies were discussed until consensus was reached. Full texts were screened for eligibility by MH and in case of doubt screened by TV as well. If more than one study analyzed associations in the same children at the same age, we selected the study that reported the most complete analysis for that age period, preferring continuous outcomes over binary outcomes and panel data over linear regressions on single determinants.

Data extraction

Data extraction was performed by MH and checked by TV or IH for all articles, using a predefined data extraction table. Discrepancies were discussed until consensus was reached. We chose to present the adjustment model with the most complete set of covariates, also if this included confounders that could be considered potential mediators in a causal pathway. We additionally report confounders that were considered, but not included in the final model. **Table 3.1** presents associations with

BMI or weight-for-age outcomes, **Table 3.2** associations with other body composition measures.

Methodological quality assessment

For the assessment of the methodological quality of the studies we used a tool adapted from the 'Effective public health practice project quality assessment tool', see **Table S3.1** (18). We choose this tool as a specific tool on quantitative analysis in the public health field. We customized our criteria list and the corresponding judgment rules so they were fitting longitudinal cohort and interventional studies. We assessed the following five dimensions; selection bias; confounding; measurement; study attrition; and data-analysis. Each dimension was judged as strong; moderate; or weak based on two questions. For the global quality rating of a paper, no weak ratings resulted in a strong rating; one weak rating in a moderate rating; and two or more weak ratings in a weak rating. For a strong quality of the dimension confounding, the analysis had to adjust for at least: maternal BMI; socioeconomic status/maternal education/income; ethnicity; and birthweight/dysmaturity/baseline BMI. Studies that not adjusted for maternal BMI were qualified as weak, regardless of other covariates, as we value maternal BMI as an important predictor for childhood BMI (19).

The customized tool was pretested by assessing four articles by three independent researchers and improved by specifying sleep duration measurement methods. At the same time researchers also improved their quality assessment skills by discussing discrepancies in these first four articles. Thereafter all articles were assessed by two independent researchers (MH and TV or IH) using the tool as displayed in appendix 2. If needed references were checked for study protocol details and selection procedures. Inconsistencies were discussed and resolved between the two researchers.

Narrative synthesis

A best evidence synthesis was applied to summarize the results for the association between sleep duration and body composition outcomes and draw conclusions regarding the level of evidence (**Table 3.3**). We based the rating system on that of Chinapaw et al. (20), consisting of four levels (i.e. strong, moderate, inconsistent and insufficient). The levels of evidence take into account the number, the methodological quality, and the consistency of outcomes of the studies:

- Strong evidence: consistent findings in multiple (≥2) high-quality studies.
- Moderate evidence: consistent findings in one high-quality study and at least one moderate quality study, or consistent findings in multiple (≥2) moderate-quality studies.
- Inconsistent evidence: inconsistent findings in multiple (≥2) studies.
- Insufficient evidence: only one study available.

Following the directions of Chinapaw et al. (20), results were considered consistent when at least 75% of the studies showed results in the same direction and when the results were significant ($P < 0.05$). If there were two or more high-quality studies, we disregarded the studies of low methodological quality in the evidence synthesis. Associations are considered significant per study if 75% of the tests found significant associations in the same direction per outcome.

RESULTS

Description of included studies

We identified 7,539 unique records through database searches and four records through hand search. After titles and abstracts were screened 7,471 records were excluded **Figure 3.1**). We assessed 77 full-text articles for eligibility and excluded 58 full texts (reasons displayed in **Figure 3.1**). Four studies were excluded after comparison with other publications from the same cohorts as they studied similar associations, but with binary outcomes or single outcomes versus panel data (7, 21-23).

We included 19 studies in the systematic review (**Tables 3.1 and 3.2**). Two studies were based on analyses from the same cohort; project Viva (24, 25), presenting different follow-up times. Data across studies involved 51,963 unique participants. Studies were published between 2008 and 2019, with 10 of the 19 published in 2016 or later. All studies had a longitudinal design: 14 observational studies (24-37) and five randomized clinical trials (6, 38-41) were included.

Sleep was reported as sleep duration (n=18) or sleep problems (n=2). Sleep was assessed at least once before the age of 12 months in 14 out of the 19 studies. Sleep duration was measured by parental report of sleep duration (n=8), Brief Infant Sleep Questionnaire (n=2); 24h activity diary (n=2); and accelerometry (waist-worn n=2, thigh worn n=1). Eight studies reported a combined sleep duration (deprivation score) for an age range. Sleep duration was reported as 24h sleep duration (n=14); nighttime sleep duration (n=3); both night- and daytime sleep duration separately (n=1); nap duration (n=1); or sleep variability (n=2). Sleep problems were defined by the Zuckerman definition by two papers (26, 34). Alamian compared three sleep definitions: Zuckerman (42); Richman (43); and Lozoff (44) (26).

Methodological quality was rated as strong for five studies; moderate for five studies; and weak for nine studies. Weak ratings were often due to selection bias, low response rates at baseline and poor study attrition at follow-up (see **Table S3.1**).

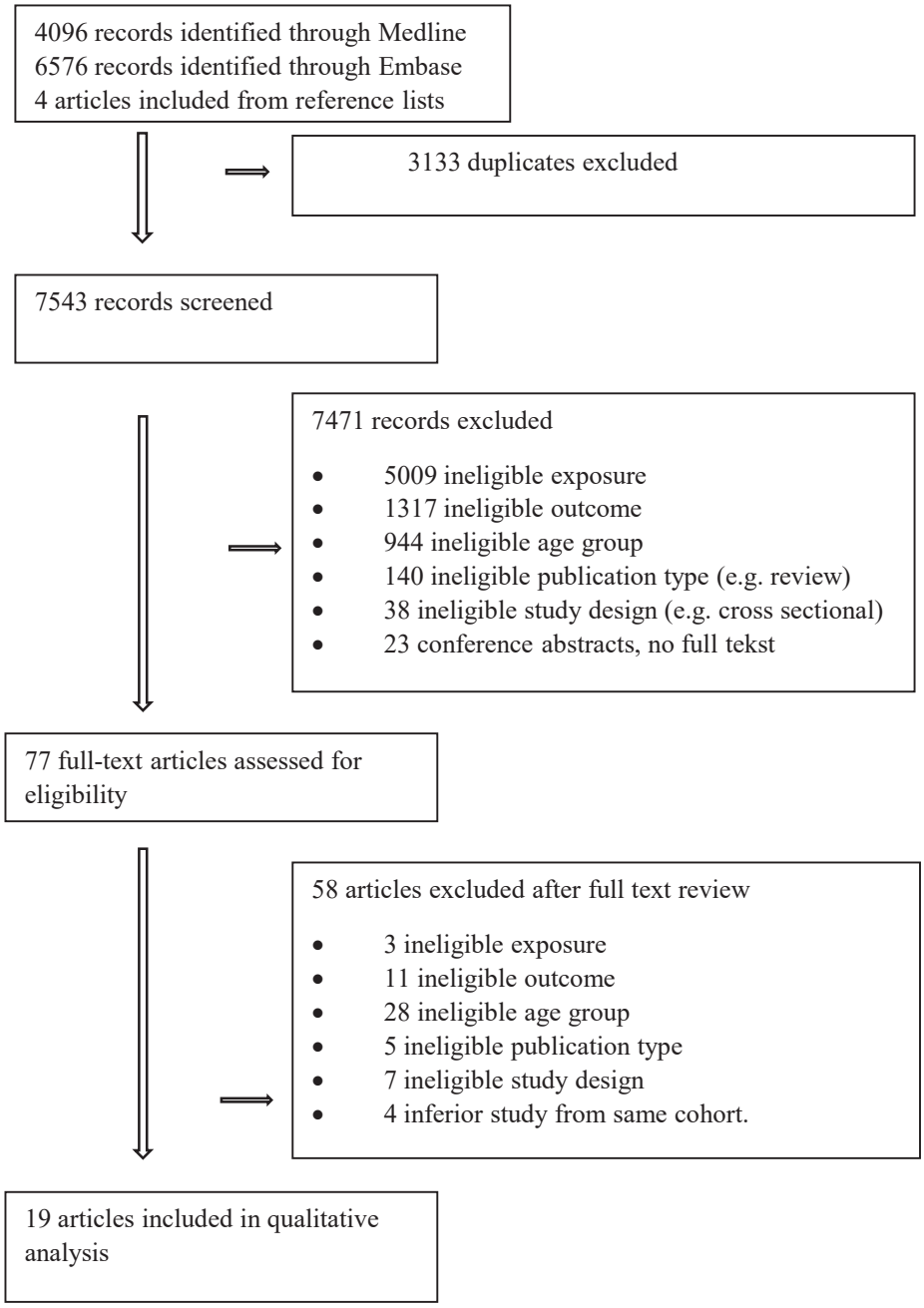

Figure 3.1: PRISMA flow diagram for the identification, screening, eligibility, and inclusion of studies.

Table 3.1: Summary of studies assessing the association between sleep and BMI or weight for age z-score/category sorted by methodological quality, assessment and age at exposure.

Author, publication year,	Observational/ trial (n, age at sleep measurement, cohort/study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (reference values, parental report/ measured by trained staff, age)	Analysis	Relevant outcome/ main results β (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis *	Quality Assessment
Kupers 2015 (33)	Observational, (n=2475, 4 months, GECKO, the Netherlands)	24h sleep duration (parental report)	weight-for-age z-score, (Dutch 1997 reference, measured between age 6-12 and 12-24 months).	Linear regression, multiple imputation for covariates,[1]	weight-for-age z-score at: age 6-12 months: β -0.00011 (-0.00020, -0.00002) age 12-24 months: β -0.00003 (-0.00008, 0.00002)	**total** $\frac{1}{2}$	strong
Derks, 2017 (29)	Observational (n=4277, 2; 6; and 24 months, Generation R, the Netherlands)	24h sleep duration (parental report)	BMI SD scores (Dutch reference, measured at age 6 years)	Linear regression, multiple imputation.[2]	sleep duration at : age 2 months: β -0,018 (-0.026, -0.009) (n=3909) age 6 months: β -0.008 (-0.018, 0.002) (n=3293) age 24 months: β -0.008 (-0.027, 0.011) (n=4277)	**total** $\frac{1}{3}$	strong

Table 3.1: Summary of studies assessing the association between sleep and BMI or weight for age z-score/category sorted by methodological quality, assessment and age at exposure. (*continued*)

Author, publication year,	Observational/ trial (n, age at sleep measurement, cohort/study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (reference values, parental report/ measured by trained staff, age)	Analysis	Relevant outcome/ main results ß (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis *	Quality Assessment
Derks, 2019 (40)	non-randomized quasiexperimental trial, (n=314 2; 4; 12 months, PEAS Kids Growth Sudy, Australia)	24h sleep duration (24-hour diary)	BMI score at age 4; 6; and 10 years (z-score in sensitivity analysis with similar results)	multivariable linear regression[3]	for sleep duration at different months of age: BMI at age 4 years: 2 months: ß -0.04 (-0.12, 0.05) 4 months: ß -0.01 (-0.09, 0.06) 12 months: ß 0.01 (-0.07, 0.08) BMI at age 6 years: 2 months: ß -0.04 (-0.13, 0.06) 4 months: ß 0.04 (-0.05, 0.13) 12 months: ß -0.02 (-0.12, 0.09) BMI at age 10 years: 2 months: ß 0.04 (-0.15, 0.22) 4 months: ß 0.10 (-0.06, 0.27) 12 months: ß -0.06 (-0.24, 0.12)	**total** $\frac{0}{9}$	strong
Zhou, 2015 (37)	Observational, (n=799, 3; 6; 9; 12; 18; and 24 months, GUSTO, Singapore)	24h sleep duration (BISQ)	BMI (measured at age 3; 6; 9; 12; 18; and 24 months)	mixed model without random effects in which sleep duration and BMI values at all time points were entered, stratified by ethnicity[4]	overall ß -0.014 (-0.030, 0.001) Chinese: -0.006 (p>0.05) Indian: 0.002 (p>0.05) Malay: -0.042 (-0.071, -0.012)	**total** $\frac{1}{4}$	strong

Table 3.1: Summary of studies assessing the association between sleep and BMI or weight for age z-score/category sorted by methodological quality, assessment and age at exposure. (*continued*)

Author, publication year,	Observational/ trial (n, age at sleep measurement, cohort/study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (reference values, parental report/ measured by trained staff, age)	Analysis	Relevant outcome/ main results β (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis *	Quality Assessment
Collings, 2017 (28)	Observational, (n=1338, 6; 12; 19; 24; and 36 months, Born-in-Bradford-1000, UK)	24h sleep duration, combined from parental report at age 6, 12, 19, 24 and 36 months.	BMI z-scores (UK reference, measured at age 6, 12, 19, 24 and 36 months)	mixed effect regression analysis with repeated measurements.[5]	Change in SD BMI per 1 SD higher sleep duration (compared to 12-13 h/day at 24 months) stratified by ethnicity, because of significant interaction by ethnicity. South Asian (n=756): β -0.030 (-0.061, -0.00016) p ≤0.05 with significant interaction by follow-up time, suggesting that the inverse association strengthened over time. Reversed negative association with sleep duration as outcome. White: β -0.0047 (-0.042, 0.033). Unchanged in sensitivity analysis.	**total** $\frac{1}{2}$	strong
Sha, 2017 (34)	Observational (n=519, 1; 3; 6; 8; and 12 months, China)	24h sleep duration, *sleep problems (hours; or yes/no by Zuckerman definition,* parental report)	weight-for-age z-score (WHO, measured, age 1, 3, 6, 8 and 12 months,)	Pooled effects model.[6]	Sleep duration: β -0.192 (SE 0.013, p<0.001) *Sleep problems:* *β -0.136 (SE 0.125, p=0.278)*	not applicable	moderate

Table 3.1: Summary of studies assessing the association between sleep and BMI or weight for age z-score/category sorted by methodological quality, assessment and age at exposure. (*continued*)

Author, publication year,	Observational/ trial (n, age at sleep measurement, cohort/study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (reference values, parental report/ measured by trained staff, age)	Analysis	Relevant outcome/ main results ß (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis *	Quality Assessment
Klingenberg, 2012 (32)	Observational (n=311, 9 and 18 months, SKOT, Denmark)	24h sleep duration (parental report)	BMI z-score (WHO, measured at age 3 years) .	Linear regression,[7]	9 months: ß -0.008 (-0.13, 0.12) 18 months: ß -0.010 (-0.07, 0.05).	not applicable	moderate
Miyakoshi, 2018 (35)	Observational (n=31.463, 18 months, Japan)	nighttime sleep duration (parental report, categorized as short; middle (reference); long; or irregular)	overweight (IOTF, measured at age 3 years)	multiple logistic regression models[8]	short sleep duration OR 1.10 (0.95, 1.28) long sleep duration OR 0.79 (0.66, 0.96) irregular sleep duration OR 0.73 (0.51, 1.06)	not applicable	moderate
Diethelm, 2011 (30)	Observational (n=481, 18 and 24 months, DONALD, Germany)	24h sleep duration (consistently short (<13h) versus Consistently Long (>13h), parental report)	BMI z-score and category (German reference data/ IOTF, measured between age 2 and 7 years)	Linear and logistic regression[9]	gain in BMI between age 2 and 7: Consistent short versus consistent long: ß 0.073 (SE 0.18, p=0.3) overweight at age 7 years for consistent short versus consistent long: OR 1,5 (0.8 -2.8)	not applicable	moderate

Table 3.1: Summary of studies assessing the association between sleep and BMI or weight for age z-score/category sorted by methodological quality, assessment and age at exposure. (*continued*)

Author, publication year,	Observational/ trial (n, age at sleep measurement, cohort/study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (reference values, parental report/ measured by trained staff, age)	Analysis	Relevant outcome/ main results β (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis *	Quality Assessment
Tuohino, 2019 (36)	Observational (n=889, 3; 8; and 18 months, CHILD-SLEEP birth cohort, Finland)	24h sleep duration: short versus normal/ long (lowest quartile), BISQ (8 months subsample with accelerometry (thigh-placed, n=350))	overweight, defined as > internal 90th % of age- and sex-adjusted BMI (Finnish national reference data), 24 months)	logistic regression[10]	3 months: OR 1.56 (1.02, 2.38) 8 months: OR 0.78 (0.49, 1.27) 18 months: OR 0.87 (0.52, 1.46)	not applicable	weak
Taveras, 2008 (25)	Observational (n=915, 6; 12; and 24 months, project Viva, USA)	24h sleep duration (<12 versus ≥12h) (weighted average of 3 data points, parental report)	BMI z score and category, (CDC, measured at age 3 years)	Linear and logistic regression[11]	BMI- z- score: β 0.16 (0.02, 0.29) Obesity (≥P95 versus P5-85): OR 2.04 (1.07, 3.91)	not applicable	weak

Table 3.1: Summary of studies assessing the association between sleep and BMI or weight for age z-score/category sorted by methodological quality, assessment and age at exposure. (*continued*)

Author, publication year,	Observational/ trial (n, age at sleep measurement, cohort/study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (reference values, parental report/ measured by trained staff, age)	Analysis	Relevant outcome/ main results β (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis *	Quality Assessment
Taveras, 2014 (24)	Observational (n=1046, 6; 12; and 24 months, Project Viva, USA)	24h sleep duration (<12 versus ≥12 h, weighted average of 3 data points, parental report)	BMI z score (CDC, measured at age 7 year) obesity= ≥95th % versus normal weight (<85)	Linear and logistic regression. Imputation for covariates (1 imputed value for each missing value)[12]	β 0.15 (0.02, 0.28) Obesity (≥P95 versus P5-85) OR: 1.36 (0.84, 2.21)	not applicable	weak
Wang, 2019 (38)	Randomized Clinical Trial (n=1704, 6; and 14 months, BeeBOFT, the Netherlands)	24 h sleep duration (parental report)	BMI z-score (WHO, measured at age 14 and 36 months)	Linear regression[13]	6 months: β -0.005 (SE 0.010) 14 months: β -0.002 (SE 0.015)	not applicable	weak
Alamian, 2016 (26)	Observational (n=895, 6 and 15 months, SECCYD, USA)	Sleep problems (yes/no at 6 and/or 15 months according to three definitions, parental report)	BMI category (CDC, measured at age 12 years)	Multinomial logistic regression[14]	overweight (P85-95 versus <P85) per definition of sleep problems: Zuckerman OR 1.68 (1.11, 2.55) Richman: OR 1.76 (1.05, 2.97) Lozoff: OR 1.07 (0.66, 1.74) No association with obesity (≥P95)	not applicable	weak

Table 3.1: Summary of studies assessing the association between sleep and BMI or weight for age z-score/category sorted by methodological quality, assessment and age at exposure. (*continued*)

Author, publication year,	Observational/ trial (n, age at sleep measurement, cohort/study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (reference values, parental report/ measured by trained staff, age)	Analysis	Relevant outcome/ main results β (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis *	Quality Assessment
Hiscock, 2011 (31)	Observational (n=2741), 8.7 months, LSAC, Australia)	24h sleep duration (two days activity diaries)	BMI z-score (CDC, measured at age 2-3 years)	Linear regression.[15]	β -0.0002 (-0.0005, 0.0001)	not applicable	weak
Bolijn, 2015 (27)	Observational (n=1658, 2 years, KOALA, the Netherlands)	Nighttime and daytime sleep duration (parental report)	BMI-z-score and category (Dutch references, parental report age 5; 6;7;8; and 9 years)	Linear and logistic general estimating equation, persistence of associations over time of follow-up was evaluated by testing for interaction by age at the BMI measurement. Missings in covariates were imputed from all other variables using regression with addition of residuals from random cases.[16]	Nighttime: β -0.082 (-0.120, -0.044) Daytime: β -0.011 (-0.065, 0.043) overweight/obesity (≥P85): Nighttime: OR 0,86 (0.76, 0.97) Daytime: OR 1.10 (0.91, 1.33) No significant interaction by age of BMI measurement	not applicable	weak

Table 3.1: Summary of studies assessing the association between sleep and BMI or weight for age z-score/category sorted by methodological quality, assessment and age at exposure. (*continued*)

Author, publication year,	Observational/ trial (n, age at sleep measurement, cohort/study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (reference values, parental report/ measured by trained staff, age)	Analysis	Relevant outcome/ main results ß (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis *	Quality Assessment
Wake, 2011 (6)	Randomized Controlled Trial, n=193, 7;10; and 12 months and 6 years, Kids Sleep Study, Australia	nighttime sleep duration (single predictor from 4 measurements, parental report)	BMI z-score and category (CDC/ IOTF measured at age 6 years)	Random effects linear and logistic regression,[17]	For 1 hour increase in sleep time: BMI z-score: ß 0.001 (-0.01, 0.01 p=1.0) OR overweight/obese versus normal: 0.9 (0.3, 2.4) p=0.8) No intervention effect (delivered at 8 months) on BMI z-score or overweight	not applicable	weak
Taylor, 2018 (41)	Randomized Controlled Trial (n=292, age 12 and 24 months, POI, New Zealand)	24h sleep duration (accelerometry, waist-worn)	BMI z-score (WHO, measured at age 5 years)	Linear regression models using isometric log-ratio coordinates[18]	12 months: ß -0.24 (SE 0.24) 24 months: ß -0.43 (SE 0.28)	not applicable	weak
Zhang, 2019 (39)	Randomized Controlled Trial (n=153, age 20 months, GET UP!Study, Australia)	24h sleep duration; nap duration; nighttime sleep duration; sleep variability (actipgraphy, waist-worn)	BMI z-score (internal sample standardization, measured at age 32 months)	Linear mixed models[19]	24h sleep duration: ß -0.01 (-0.13, 0.10); nap duration: ß 0.41 (0.14, 0.68); nighttime sleep duration: ß -0.08 (-0.20, 0.03); sleep variability: ß 0.08 (-0.19; 0.35)	not applicable	weak

*: only studies with strong quality are included in the narrative synthesis on the association between sleep duration and BMI- or weight-for-age-z-scores. BISQ: Brief Infant Sleep Questionnaire; BMI: Body Mass Index; CDC: Centers for Disease Control and Prevention; CI: Confidence Interval; CFI: Comparative Fit Index; IOTF: International Obesity Task Force; OR: Odds Ratio;; RMSEA: Root Mean Squared Error of Approximation; SE: standard error; SES: socioeconomic status ; WHO: World Health Organization.

1: Confounders: paternal BMI, maternal pre-pregnancy BMI, age, diabetes and hypertension, educational level, gestational weight gain, smoking during pregnancy, gestational age, birth weight, gender, Dutch ethnicity, type of feeding at 3 months, childcare and mother working at age 3 months, complementary feeding at 4 months, family screen time at 6 months, household income, possibility of unrestricted moving at 9 months, one-parent family.
2: Confounders: maternal education level, BMI and psychiatric symptoms, ethnicity, birth weight, duration of breastfeeding, TV watching and baseline BMI.
3: Confounders: child sex, date of birth, child place of birth (Australia vs. other), maternal education, gestational age, BMI at birth, neighborhood SES, maternal BMI at child age 4 years.
4: Confounders: sex; maternal education; household income; pregnancy smoking and diabetes; birth weight and length; gestational age; maternal BMI and height; breastfeeding duration; media use and physical activity at age 24 months and age at measurements
5: Confounders: baseline age, follow-uptime, gender, SES, parity, gestational age, birth weight, season of birth,
maternal pregnancy age; smoking during pregnancy; and follow-up BMI, TV viewing, unhealthy snacking, fruit and vegetable intake.
Sensitivity analysis: breast feeding history, age introduced to solids, physical activity, bedtime regularity, maternal early pregnancy BMI, TV viewing after 6 pm and height.
6: Confounders: (number of) breastfeeding (per day),(number of) formula feeding (per day), complimentary feeding, outdoor activities, taking vitamin D, birthweight, gender, maternal education level, household income, gestational age, maternal and paternal smoking during pregnancy.
7: Confounders: birth weight, gestational age, duration of breastfeeding, maternal smoking during pregnancy, maternal BMI at 9 months
of examination, household income and highest educational levels of both parents at time. daytime napping and nocturnal awakenings had no putative effect on sleep duration.
8: Confounders: daycare (maternal or relatives); smoking family members; older siblings; breastfeeding; introduction of solid foods; regular mealtime; use of precooked foods; consumption of cow's milk; sugar-sweetened beverages; sweet or snacks; maternal age at delivery; smoking and alcohol consumption during pregnancy; pregnancy-induced hypertension; gestational age; birth weight; sex of the child and past medical history of allergic diseases.
9: Confounders: sex, birth year, birth weight (< 3000 g) and rapid weight gain (0 – 18 months of age). (high maternal education, maternal overweight, age, gestational age, birth order, fully breastfeeding, smoking in the household were considered but did not meet requirements to be included as confounders)
10: Confounders: age, birthweight, sex, maternal early pregnancy BMI; parental education level; maternal smoking during pregnancy; and breastfeeding (all Finnish speaking mothers in an ethnical non-diverse area)
11: Confounders:, maternal education, income, prenatal smoking history, race/ethnicity, birth weight, sex for length z scores at age 6 months, daily tv viewing and active play.
12: Confounders: maternal age, education, BMI and parity; ethnicity, child television viewing at mid-childhood
13: Confounders: age at sleep and BMI measurement; maternal age, education level, pre-pregnancy BMI, and parity; child gender, ethnic
background, birth weight, gestational age, duration of breastfeeding, and screen time at baseline; intervention groups; baseline BMI z-score.
14: Confounders: maternal education and poverty, family weight, sex, breastfeeding
15: Confounders: sex, weight for age adjusted for birth length.
16: Confounders: general (anthroposophic), maternal country of birth, age at hours/week of paid work, pre pregnancy BMI, smoking during pregnancy, pregnancy weight gain, , child gender, time at kindergarten, tv time, computer time, and time playing outside, day time sleep (for night time sleep analysis), exact age of child at BMI measurement, BMI at age 2 years.
17: Confounders: gender, maternal education level, family language English (yes/no), SES area code
18: RCT group; sex; primiparous; maternal education; household maternal BMI; and concurrent BMI z-score
19: Confounders: clustering effects (modelled as random group; baseline age; gender; SES; baseline z-BMI

Table 3.2: Summary of observational studies assessing the association between sleep duration and indicators of body composition other than BMI/weight sorted by methodological quality assessment and age at exposure.

Author, publication year.	Observational/ trial (n, age at sleep measurement, follow-up time, cohort/ study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (age, type and method of measurement)	Analysis	Relevant outcome/ main results Beta (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis	Quality assessment outcome
Derks, 2017 (29)	Observational (n=4144, 2; 6; and 24 months, Generation R, the Netherlands)	24h sleep duration (parental report)	FMI and FFMI SD scores (DEXA, internal standardization measured at age 6 years)	Linear regression, multiple imputation.[1]	sleep duration at : FMI-SD: age 2 months: ß -0.013 (-0.022, -0.004) age 6 months: -0.005 (-0.015, 0.005) age 24 months: -0.012 (-0.0035, 0.011) FFMI-SD: 2 months: -0.007 (-0.017, 0.003) 6 months: -0.010 (-0.022, 0.001) 24 months ß:-0.019 (-0.042, 0.004)	FMI $\frac{1}{3}$ FFMI $\frac{1}{3}$	strong

Table 3.2: Summary of observational studies assessing the association between sleep duration and indicators of body composition other than BMI/weight sorted by methodological quality assessment and age at exposure. (*continued*)

Author, publication year.	Observational/ trial (n, age at sleep measurement, follow-up time, cohort/ study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (age, type and method of measurement)	Analysis	Relevant outcome/ main results Beta (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis	Quality assessment outcome
Derks, 2019 (40)	non-randomized quasi experimental trial, (n=336, 2; 4; 12 months, PEAS Kids Growth Study, Australia)	24h sleep duration (24-hour diary)	FMI (measured at age 4; 6; and 10 years by multi frequency BIA)	multivariable linear regression[2]	for sleep duration at different months of age: FMI at age 4 years: 2 months: Ƀ -0.02 (-0.09, 0.06) 4 months: Ƀ 0.02 (-0.05, 0.09) 12 months: Ƀ 0.01 (-0.06, 0.08) FMI at age 6 years: 2 months: Ƀ -0.02 (-0.10, 0.06) 4 months: Ƀ 0.03 (-0.05, 0.11) 12 months: Ƀ -0.08 (-0.25, 0.09) FMI at age 10 years: 2 months: Ƀ 0.01 (-0.16, 0.19) 4 months: Ƀ 0.05 (-0.11, 0.21) 12 months: Ƀ -0.08 (-0.25, 0.09)	FMI $\frac{0}{9}$	strong
Collings, 2017 (28)	Observational , (n=1338, 6; 12; 19; 24; and 36 months, Born-in-Bradford-1000, UK)	24h sleep duration in 5 categories, combined from parental response at age 6, 12, 19, 24 and 36 months.	Sum skinfolds (left triceps, subscapular and thigh); % body fatt; and waist circumference (Holtain calipers, BIA, measured at age 6, 12, 19, 24 and 36 months)	mixed effect regression analysis with repeated measurements.[3]	Change in SD per 1 SD higher sleep duration (compared to 12-13 h/day at 24 months) stratified by ethnicity, because of significant interaction by ethnicity. South Asian (n=765): % body fat: Ƀ -0.029 (-0.053, -0.00042) waist circumference: Ƀ -0.0072 (-0.038, 0.023) sum skinfolds: Ƀ -0.013(-0.059, 0.033) White: small and non-significant results. All models unchanged in sensitivity analysis.	% body fat: $\frac{1}{2}$ Waist circumference $\frac{0}{2}$ Skinfolds $\frac{0}{2}$	strong

Table 3.2: Summary of observational studies assessing the association between sleep duration and indicators of body composition other than BMI/weight sorted by methodological quality assessment and age at exposure. (*continued*)

Author, publication year.	Observational/ trial (n, age at sleep measurement, follow-up time, cohort/ study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (age, type and method of measurement)	Analysis	Relevant outcome/ main results Beta (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis	Quality assessment outcome
Klingenberg 2012 (32)	Observational (n=311, 9 and 18 months, SKOT, Denmark)	24h sleep duration (parental report)	Sum of subscapular and triceps skin-folds (mm), % body fat, Body fat mass (kg). (Harpenden skin-fold caliper and DEXA measured at age 3 years)	Linear regression,[4]	Sum of skin folds 9 months: Β 0.289 (-0.16, 0.73). 18 months: Β -0.039(−0.24, 0.16). % Body Fatt 9 months: Β -0.001 (-0.003, 0.001). 18 months: Β 0.00005(-0.001, 0.001)	Skin folds $\frac{0}{2}$ % Body fatt $\frac{0}{2}$	moderate
Diethelm, 2011 (30)	Observational (n=481, 18 and 24 months, DONALD, Germany)	24h sleep duration (consistently short (<13h) versus Consistently Long (>13h), parental report)	FMI, and FFMI gain (derived from skinfolds, Holtain skinfold caliper, measured between age 2 and 7 years)	Linear regression (comparing linear trend between sleep duration group[5]	FMI: Β 0.03 (SE 0.11, p=0.04) FFMI: Β -0.12 (SE 0.11, p=0.8)	FMI $\frac{1}{1}$ FFMI $\frac{1}{1}$	moderate

Table 3.2: Summary of observational studies assessing the association between sleep duration and indicators of body composition other than BMI/weight sorted by methodological quality assessment and age at exposure. (*continued*)

Author, publication year.	Observational/ trial (n, age at sleep measurement, follow-up time, cohort/ study name, country)	Exposure (definition, cut-off values, method of measurement)	Outcome (age, type and method of measurement)	Analysis	Relevant outcome/ main results Beta (95% CI) OR (95% CI)	Observed significant associations per study for narrative synthesis	Quality assessment outcome
Taveras, 2008 (25)	Observational (n=915, 6; 12; and 24 months, project Viva, USA)	24h sleep duration (<12 versus ≥12h) (weighted average of 3 data points, parental report)	Sum subscapular and triceps skinfold (mm, Holtain skinfold calipers, measured at age 3 years)	Linear regression[6]	ß 0.79 (0.18, 1.40)	Skinfold $\frac{1}{1}$	weak
Wake, 2011 (6)	Randomized controlled trial, n=193, 7; 10; and 12 months and 6 years, Kids Sleep Study, Australia	nighttime sleep duration (single predictor from 4 measurements, parental report)	waist circumference (cm) (tape measured at age 6 years)	Random effects linear regression,[7]	For 1 hour increase in sleep time: ß -0.001 (-0.07, 0.07 p=1.0) No intervention effect (intervention delivered at 8 months) on waist circumference.	Waist circumference $\frac{0}{1}$	weak
Taylor, 2018 (41)	Randomized Clinical Trial (n=232, 12 and 24 months, POI, New Zealand)	24 sleep duration (accelerometry, waist worn)	FFMI, % body fat (DEXA scan, age 5 years)	Linear regression models using isometric log-ratio coordinates[8]	FFMI: 12 months: ß -0.46 (SE 0.32) 24 months: ß -0.32 (SE 0.35) % body fat: 12 months: ß -1.24 (SE 1.96) 24 months: ß -0.07 (SE 2.26)	FFMI $\frac{0}{2}$ % Body fatt $\frac{0}{2}$	weak

FMI: fat mass index; FFMI: fat-free mass index; DEXA: dual energy X-ray absorptiometry: BIA: bioelectrical impedance; WHO: World Health Organisation; SES: socioeconomic status; OR: Odds Ratio; CI: Confidence Interval; +: significant association; 0: no significant association.

1: Confounders: maternal education level, BMI and psychiatric symptoms, ethnicity, birth weight, duration of breastfeeding, TV watching and baseline BMI.
2: Confounders: child sex, date of birth, child place of birth (Australia vs. other), maternal education, gestational age, BMI at birth, neighborhood SES, maternal BMI at child age 4 years.
3: Confounders: baseline age, follow-uptime, gender, SES, parity, gestational age, birth weight, season of birth, and follow-up BMI, TV viewing, unhealthy snacking, fruit and vegetable intake. Sensitivity analysis: breast feeding history, age introduced to solids, physical activity,
bedtime regularity, maternal early pregnancy BMI, TV viewing after 6 pm and height.
4: Confounders: birth weight, gestational age, duration of breastfeeding, maternal smoking during pregnancy, maternal BMI at 9 months of examination, household income and highest educational levels of both parents at time. Daytime napping and nocturnal awakenings had no putative effect on sleep duration.
5: Confounders: sex, birth year, birth weight (< 3000 g) and rapid weight gain (0 – 18) gestational age, birth order fully breastfeeding, smoking in the household were considered but did not meet requirements to be included as confounders)
6: Confounders:, maternal education, income, pre pregnancy BMI, marital status, prenatal smoking history, race/ ethnicity, birth weight, sex
breastfeeding duration, weight for length z scores at age 6 months, age, daily tv viewing and active play.
7: Confounders: gender, maternal education level, family language English (yes/no), SES area code
8: Confounders: randomized RCT group; sex; primiparous; maternal education; household deprivation; ethnicity; maternal BMI; and concurrent BMI z-score

Association between sleep problems and weight-for-age z-score or BMI category

Two studies reported sleep problems using the Zuckerman definition i.e. waking 3 or more times per night, waking event lasting at least 1 h, or parental report of "severe" disturbance. Using this definition, Sha et al found no significant association between sleep problems at age 1; 3; 6; 8; and 12 months and weight-for-age z-score at the same ages in a pooled effects model (34). Alamian et al found that infants with sleep problems at age 6 and/or 15 months had 1.7 times higher odds of overweight at age 12 years (95% CI 1.05-2.97), but they found no association with obesity (26). With only these two studies from moderate and low quality we concluded there is no evidence for an association between infant sleep problems and childhood body composition.

Table 3.3: Level of evidence in narrative synthesis, presented per study, for the association between sleep duration and body composition measurement.

	Body Composition Measurement	Conclusion of narrative synthesis, based on found associations with sleep duration expressed by $\frac{p}{t}$
BMI and weight-for-age z-scores narrative synthesis from strong quality studies only	BMI	Inconsistent evidence for an association $\frac{1}{2}\ \frac{1}{3}\ \frac{1}{2}\ \frac{0}{9}\ \frac{1}{3}$
Other body composition measurements narrative study from strong, (moderate and weak) quality studies	FMI	Inconsistent evidence for an association $\frac{1}{3}\ \frac{0}{9}\ (\frac{1}{1})$
	FFMI	No evidence for an association $\frac{1}{3}\ (\frac{0}{1})\ (\frac{0}{2})$
	Sum skin folds	No evidence for an association $\frac{0}{2}\ (\frac{0}{2})\ (\frac{1}{1})$
	% body fat	No evidence for an association $\frac{1}{2}\ (\frac{0}{2})\ (\frac{0}{2})$
	Waist circumference	No evidence for an association $\frac{0}{2}\ (\frac{0}{1})$

$\frac{p}{t}$ with p standing for positive associations found in a study and t standing for total tested associations in a study.
$\frac{p}{t}$: strong quality studies
$(\frac{p}{t})$: moderate or weak quality studies

Narrative synthesis from studies on sleep duration

We decided that a meta-analysis of the association between sleep duration and body composition measurements was not in place, due to high levels of heterogeneity in outcomes and ages. Instead we performed a narrative synthesis on the association between sleep duration and BMI or weight-for-age z-score or category (**Table 3.1**)

and other body composition measures (**Table 3.2**). We did not include studies that assessed sleep problems as determinant. Found associations are displayed per study in **Table 3.3**.

Sleep duration and BMI or weight-for-age z-score or category

With more than two high quality studies available, we used only the five high quality studies of **Table 1** for this evidence synthesis. Four studies report inconsistent findings, with only significant associations for certain subgroups (28, 37), follow-up times (33) or ages (29). Therefore, we concluded there is inconsistent evidence for an association between infant sleep duration and childhood BMI or weight-for-age z-score/category.

Kupers et al. found that per one hour increase in 24h sleep duration at age 4 months, weight-for-age between 6 and 12 months decreased with 0.00011 (95%CI -0.00020, -0.00002), but associations were smaller and not significant at age 12-24 months (33). Derks et al. found that in the Generation R cohort per one hour increase in 24h sleep duration at age two months there was a significantly lower BMI SD score at age six years. (-0.018 (95%CI -0.026, -0.009)), but for sleep duration at age 6 and 24 months there was no significant association after adjustment for confounders and baseline BMI (29). The same first author found no association in the PEAS Kids Growth Study, where sleep duration was measured at 2; 4; and 12 months by 24-hour diary and BMI measured at age 4; 6; and 10 years (40). Zhou et al. found a significant negative association between sleep duration and BMI in Malay infants in their longitudinal mixed model and no significant association in Chinese and Indian infants in Singapore. In the overall group they found no significant association (37). Collings et al. only found a significant association after stratification by ethnicity. They measured sleep at age 6-36 months and found that per one SD higher sleep duration in South Asians, BMI at the same age range decreased with 0.030 SD (95%CI -0.061 to -0.00016). For white families this association was smaller and non-significant (28).

Sleep duration and other body composition measures.

With less than two high quality studies for all except one outcome, we used all eight studies of **Table 3.2** for the narrative synthesis on other body composition measurements. There was inconsistent evidence for an association between sleep duration and Fat Mass Index. Derks et al. found in Generation R a significant inverse association with Fat Mass Index at one out of 3 ages at which sleep duration was measured (29). The same first author found no association in the PEAS Kids Growth Study at three different ages at which sleep was measured and three ages at which Fat Mass Index was measured (40). Diethelm et al compared consistent short sleepers at age 18 and

24 months with consistent long sleepers and found that short sleepers had a 0.03 higher Fat Mass Index gain between age two and seven years (Standard error 0.11, p=0.04) (30).

There was no evidence for an association between sleep duration and Fat Free Mass Index; % Body fat; sum skin folds; and waist circumference (**Table 3.3**).

DISCUSSION

This systematic review summarizes the existing evidence on the longitudinal association between sleep duration and sleep problems during infancy (<24 months) and indicators of body composition during infancy or childhood. We assessed the methodological quality of each study and performed a narrative synthesis. There was inconsistent evidence for an association between infant sleep during the first 24 months of life and BMI, weight-for age z-scores and Fat Mass Index during childhood. The significant associations reflect small effects; each hour off additional 24-hour sleep during infancy was associated with a 0,0001 to 0,0300 point lower BMI. There was no evidence for an association with fat-free mass index, sum of skin folds; % body fat; and waist circumference.

Comparison with earlier reviews

This systematic review summarizes all longitudinal studies on infant sleep duration (age period 0-2 years) and childhood overweight and obesity. Prior reviews of longitudinal data for sleep during age 0-4 years (11, 12) and age 0-18 years (13-15) concluded that there is an inverse association between childhood sleep duration and weight gain, but that the underlying explanatory mechanisms are still uncertain. We cannot confirm this association in infants. Evidence for an association with sleep duration during infancy could also come from interventional studies. So far, results from three intervention studies on promotion of sleep quality and sleep duration during the first months of life have been published. Two of them showed healthier weight at age 1-2 years, but not necessarily due to longer sleep duration (8, 41, 45).

The first explanation for the lack of consistent evidence for an association is that sleep duration at infant age may only have a temporary effect on body composition, but not a longer-term effect. If so, this opens opportunity to change sleep habits at an early age to improve later healthy sleep habits and body composition. A second explanation for our findings can be the lack of high quality studies. Methodological quality was strong for only five out of 19 studies. These cohorts were more representative

of the base population from the start and had lower study attrition during follow-up. We encourage more high quality studies on infant sleep and growth, specifically in the first six months of life, as existing studies have considerable risk of bias. A third explanation may be the different methods of sleep measurement across studies.

Measurement of sleep during infancy

The measurement of sleep duration and quality during infancy is complex due to a combination of longer nighttime stretches of sleep and shorter daytime naps and subtle differences in movements between awake stages and sleeping stages. The three most common methods of measurement are: parental report by questionnaire (e.g. Brief Infants Sleep Questionnaire); parent-reported 24-hour activity-diaries; and accelerometry. A recent study by Tikotzky examined how well these three agree in the assessment of nocturnal wakefulness, but also sleep duration. They found that parents are only aware of nocturnal awakenings that involve signaling (e.g. crying), which makes parental report less valid after the age of six months when infants increasingly learn to self-soothe. They advise to use both objective and subjective measures of sleep, especially when measuring nocturnal wakefulness after the age of six months . They also found that sleep duration was more than 30 minutes longer based on diary report versus accelerometry at the ages of 3; 6; 12; and 18 months. They additionally conclude that parents report infant sleep more accurately by diary than by the Brief Infants Sleep Questionnaire (46). Accelerometry can provide an objective estimate of movement, but does not detect the difference between sleep and wakefully lying still in small infants. It is considered a valid method to estimate sleep duration in older children (47, 48), but under the age of two years, it is so far only valid for nighttime sleep duration

Sleep patterns and habits during infancy and toddlerhood differ across cultures (49, 50). According to the National sleep foundation, appropriate sleep duration for healthy newborns (0- 28 days after birth) ranges from 14 to 17 hours; for infants (0-12 months) from 12 to 15 hours; and for toddlers (one and two years of age) from 11 to 14 hours is (51). The cut-off values for short sleep duration that are used in the studies in this systematic review vary and might have altered the findings of individual studies and therewith of our review and narrative synthesis.

Strengths and limitations

A strength of this review is that we have performed a very thorough literature search guided by a clinical librarian (JD). Our search identified 19 longitudinal studies, of which only six were included in prior reviews. Our search for outcomes included all different body size measurements and body composition measurements. Another

strength is that we selected longitudinal studies with a follow up of at least 6 months, so we could study the sequence of events. Reversed causation was minimized by adjusting for baseline body composition in many studies. We could not investigate causal mechanisms due to a lack of studies that investigated these. We selected the most complete reported model of each study for data extraction, even if this included confounders that could be regarded as potential mediators in the causal pathway of an association between sleep and body composition outcomes. Ideally these co-variates should be taken out all models across studies, something that could be done in a future pooled analysis. A weakness of this review and narrative synthesis is heterogeneity of the studies. The measurements of the determinant (continuous 24 hour sleep duration) and outcomes (age- and sex-adjusted BMI or weight-for-age-scores) are very similar in all five strong quality studies in the narrative review, but not the age at which they were measured and the analyses did not consider the same confounders.

Implications

Despite the lack of evidence for an association between infant sleep and childhood body composition, attention to adequate sleep is important. Both parents and professionals need to be aware that adopting healthy sleep habits might be easier during early infancy than in later childhood and adulthood. The inconsistent finding in our narrative synthesis might be due to a lack of strong quality studies and due to heterogeneity. There is a need for more strong quality observational studies. We recommend future observational and interventional studies to incorporate other sleep measurements than sleep duration alone in their study design and to measure sleep at different ages (starting between age one or six months) with a combination of objective and subjective measures (46, 47, 52). Objective measures are accelerometry or video recording (47) and subjective measures are 24-hour activity/sleep diaries and validated questionnaires in which parents report sleep duration and regularity of bedtime as well as sleep quality, and sleep problems (53).

We assessed the methodological quality of each study with an adapted tool. Using this we have rated the validated questionnaires stronger than accelerometry, no matter of the specific outcome measurement. We recommend future researchers to qualify accelerometry in combination with parental report more accurate than parental report alone when nighttime or 24-hour sleep duration is measured after infant age of six months (46). For the measurement of infant sleep problems, we recommend standardized questionnaires (e.a. Brief Infant Sleep Questionnaire).

Conclusion

This systematic review provides a thorough overview of studies investigating the longitudinal association of sleep during infancy (<24 months) and body composition during childhood. There was inconsistent evidence for a longitudinal association between infant sleep duration and child body composition.

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SUPPLEMENTAL INFORMATION:

Supplement 3.1: search strategy

	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Search date: 11 January 2018	
#	Searches	Results
1	exp child/ or "schools, nursery"/ or infant/ or exp child welfare/	2152233
2	(infant? or infancy or toddler? or kid or kids or underage* or boy or boys or girl? or sibbling* or preschool* or childhood or child or children or schoolchild* or juvenile or minors or p?ediatric?).ab,kf,ti.	1910824
3	(("0" or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8" or "9" or "10" or "11" or "12") adj1 (age? or yr? or year?)).ab.	1223436
4	(("0" or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19" or "20" or "21" or "22" or "23" or "24") adj1 month?).ab.	1020689
5	(child or p?ediatric? or juvenile).jw.	570497
6	or/1-5 [children 0-2 yrs]	4357026
7	exp sleep/ or sleep wake disorders/	90862
8	((nap or napping or asleep or sleep* or doz* or nod* off or insomnia or awake* or hypersomnolence or hypersomnia or somnolence) adj2 (duration or time or hour? or minute? or measure*)).ab,kf,ti.	24256
9	((nap or napping or asleep or sleep* or doz* or nod* off or insomnia or awake* or hypersomnolence or hypersomnia or somnolence) adj3 (score or scale or index or questionnaire or interview or evaluation)).ab,kf,ti.	14332
10	(sleep adj2 depriv*).ab,kf,ti.	8022
11	((nap or napping or asleep or sleep* or doz* or nod* off or insomnia or awake* or hypersomnolence or hypersomnia or somnolence) and (insulin or cortis* or ghrelin or leptin)).ab,kf,ti.	6513
12	(bisq or brief infant sleep questionnaire or accelerometr* or sleep diar* or bedtime or wake up time).ab,kf,ti.	10297
13	or/7-12 [sleep duration]	118975
14	longitudinal.ab,hw,kf,ti.	276246
15	((assoc* adj3 (infancy or childhood)) or subsequent childhood or (points adj2 time)).ab,kf,ti.	89726
16	or/14-15 [longitudinal association]	357853
17	and/6,13,16	2232
18	(overweight or body mass or fat mass or fat free mass or lean mass or bmi or skinfold or skin fold or waist circumference).ab,hw,kf,ti.	334033
19	(diabet* or insulin or "c peptide").ab,hw,kf,ti.	893532
20	(hypertension or blood pressure).ab,hw,kf,ti.	774046
21	(cholesterol or triglyceride or metabolic profile).ab,kf,ti.	270091
22	or/18-21	1930264

23	(risk? or prevent*).ab,kf,ti.	3061955
24	22 and 23 [adverse future outcomes]	472629
25	and/6,13,24	1672
26	("born in bradford" or "study of women infant feeding" or (swift adj3 (study or cohort)) or koala or "generation R" or (project adj3 viva) or "growing up in whales" or "Study of Early Child Care and Youth Development" or SECCYD or birth cohort).ab,kf,ti.	15279
27	(nap or napping or asleep or sleep* or doz* or nod* off or insomnia or awake* or hypersomnolence or hypersomnia or somnolence).ab,kf,ti.	216751
28	26 and 27 [sleep AND relevant cohorts|studies]	289
29	(ACTRN126170009763 81 or NCT00125580 or NCT00359242 or NCT03191591).ab,kf.	2
30	28 or 29 [relevant cohorts|studies]	291
31	or/17,25,30	3832

Ovid Embase Classic+Embase <1947 to 2018 January 10>
Search date: 11 January 2018

#	Searches	Results
1	*child/ or *boy/ or *girl/ or exp *infant/ or *preschool child/ or *school child/ or *toddler/ or *child welfare/	229420
2	(infant? or infancy or toddler? or kid or kids or underage* or boy or boys or girl? or sibbling* or preschool* or childhood or child or children or schoolchild* or juvenile or minors or p?ediatric?).ab,kw,ti.	2316292
3	(("0" or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8" or "9" or "10" or "11" or "12") adj1 (age? or yr? or year?)).ab.	1706846
4	(("0" or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19" or "20" or "21" or "22" or "23" or "24") adj1 month?).ab.	1411628
5	(child or p?ediatric? or juvenile).jx.	637821
6	or/1-5 [children 0-2 yrs]	4663289
7	*sleep/ or *night sleep/ or *nonrem sleep/ or *rem sleep/ or *sleep pattern/ or *sleep quality/ or *sleep time/ or *sleep waking cycle/ or *sleep disorder/	82267
8	((nap or napping or asleep or sleep* or doz* or nod* off or insomnia or awake* or hypersomnolence or hypersomnia or somnolence) adj2 (duration or time or hour? or minute? or measure*)).ab,kw,ti.	36423
9	((nap or napping or asleep or sleep* or doz* or nod* off or insomnia or awake* or hypersomnolence or hypersomnia or somnolence) adj3 (score or scale or index or questionnaire or interview or evaluation)).ab,kw,ti.	24595
10	(sleep adj2 depriv*).ab,kw,ti.	11453
11	((nap or napping or asleep or sleep* or doz* or nod* off or insomnia or awake* or hypersomnolence or hypersomnia or somnolence) and (insulin or cortis* or ghrelin or leptin)).ab,kw,ti.	9560
12	(bisq or brief infant sleep questionnaire or accelerometr* or sleep diar* or bedtime or wake up time).ab,kw,ti.	14022
13	or/7-12 [sleep duration]	129457
14	longitudinal.ab,hw,kw,ti.	293061
15	((assoc* adj3 (infancy or childhood)) or subsequent childhood or (points adj2 time)).ab,kw,ti.	120991

16	or/14-15 [longitudinal association]	404714
17	and/6,13,16	2533
18	(overweight or body mass or fat mass or fat free mass or lean mass or bmi or skinfold or skin fold or waist circumference).ab,hw,kw,ti.	523915
19	(diabet* or insulin or “c peptide”).ab,hw,kw,ti.	1268278
20	(hypertension or blood pressure).ab,hw,kw,ti.	1149474
21	(cholesterol or triglyceride or metabolic profile).ab,kw,ti.	338654
22	or/18-21	2692729
23	(risk? or prevent*).ab,kw,ti.	3844265
24	22 and 23 [adverse future outcomes]	704128
25	and/6,13,24	2901
26	(“born in bradford” or “study of women infant feeding” or (swift adj3 (study or cohort)) or koala or “generation R” or (project adj3 viva) or “growing up in whales” or “Study of Early Child Care and Youth Development” or SECCYD or birth cohort).ab,kw,ti.	16378
27	(nap or napping or asleep or sleep* or doz* or nod* off or insomnia or awake* or hypersomnolence or hypersomnia or somnolence).ab,kw,ti.	298487
28	26 and 27 [sleep AND relevant cohorts|studies]	380
29	(ACTRN12617000976381 or NCT00125580 or NCT00359242 or NCT03191591).ab,cn,kw.	1
30	28 or 29 [relevant cohorts|studies]	381
31	or/17,25,30	5335
32	remove duplicates from 31	5233

Supplement 3.2: Quality Assessment Tool

Dimension	Criteria	Judgment rules	
Selection bias	(Q1) Are the individuals selected likely to be representative of the target population?	Strong:	Q1=1and Q2=1
	(1) very likely (e.g., randomly selected from target population), (2) somewhat likely (e.g., selected from a source/clinic/in a systematic manner); (3) not likely (e.g., self-referred); (4) can't tell	Moderate:	(Q1=1or2) and(Q2=2or4)
	(Q2) What percentage of selected individuals agreed to participate?	Weak:	(Q1=3)or(Q2=3) or(Q1=4 andQ2=4)
	(1) 80–100% agreement; (2) 60-79% agreement; (3) less than 60% agreement; (4) can't tell		
Confounding	(Q3) Were there important differences between normal and short sleepers or obese versus healthy weight?	Strong:	Q3=2orQ4=1
	(1) yes; (2) no; (3) can't tell	Moderate:	(Q3=1 or 3) andQ4=2
	(Q4) If yes, indicate the relevant confounders that were controlled for (in analysis)?	Weak:	(Q3=1or3) and(Q4=3or4)
	(1) at least maternal BMI; SES or maternal education/ income; ethnicity; birthweight/dysmaturity/baseline BMI (2) at least maternal BMI; (3) not maternal BMI; (4) can't tell		
Measurement	(Q5) Were tools to collect determinant/exposure valid and reliable?	Strong:	Q5=1andQ6=1
	(1) yes (validated sleep questionnaire (like BISQ), 24h activity diaries; (2) moderate: parental self-report, non-validated sleep problem questionnaire, accelerometry (3) no	Moderate:	Q5=1and Q6=2 or Q5=2and Q6=1
	(Q6) Were tools to collect outcome data valid and reliable?	Weak:	Q5=2 and Q6=2 or Q5=3
	(1) yes; measured by trained staff (2): parental self report		
Withdrawals and drop-outs	(Q7) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?	Strong:	Q8=1
	(1) yes; (2) no; (3) can't tell	Moderate:	Q8=2or4
	(Q8) Indicate the percentage of participants completing the study.	Weak:	(Q7=2 or 3) or(Q8=3or5)
	(1) 80–100%; (2) 60-79%; (3) less than 60%; (4) not applicable (i.e. retrospective), (5) can't tell		
Dataanalysis	(Q9) Are the statistical methods appropriate for the study design?	Strong:	Q9=1andQ10=1
	(1) yes ; (2) no; (3) can't tell	Moderate:	(Q9=1) and(Q10=2or3)
	(Q10) Point estimates and measures of variability are presented.	Weak:	(Q9=2or3) and(Q10=2or3)
	(1) yes; (2) no; (3) not applicable		

Criteria list, and the corresponding judgment rules for each dimension, for the assessment of the methodological quality of the studies included in this review adapted from the Effective Public Health Practice Project Quality Assessment Tool.

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES DICTIONARY

The purpose of this dictionary is to describe items in the tool thereby assisting raters to score study quality. Due to under-reporting or lack of clarity in the primary study, raters will need to make judgements about the extent that bias may be present. When making judgements about each component, raters should form their opinion based upon information contained in the study rather than making inferences about what the authors intended.

SELECTION BIAS

(Q1) Participants are more likely to be representative of the target population if they are randomly selected from a comprehensive list of individuals in the target population (score very likely). They may not be representative if they are referred from a source (e.g. clinic) in a systematic manner (score somewhat likely) or self-referred (score not likely).

CONFOUNDING

By definition, a confounder is a variable that is associated with the intervention or exposure and causally related to the outcome of interest. Even in a robust study design, groups may not be balanced with respect to important variables prior to the intervention. The authors should indicate if confounders were controlled in the design (by stratification or matching) or in the analysis. If the allocation to intervention and control groups is randomized, the authors must report that the groups were balanced at baseline with respect to confounders (either in the text or a table).

MEASUREMENT

Tools for primary outcome measures must be described as reliable and valid. If 'face' validity or 'content' validity has been demonstrated, this is acceptable. Some sources from which data may be collected are described below:

Self reported data includes data that is collected from participants in the study (e.g. completing a questionnaire, survey, answering questions during an interview, etc.).

Assessment/Screening includes objective data that is retrieved by the researchers. (e.g. observations by investigators).

Medical Records/Vital Statistics refers to the types of formal records used for the extraction of the data.

Reliability and validity can be reported in the study or in a separate study. For example, some standard assessment tools have known reliability and validity.

Table S3.1: Results of the quality assessment of the included studies, per dimension and overall

Author, year	Selection bias	Confounding	Measurement	Study attrition	Data analysis	Overall quality
Alamian, 2016	-	-	++	+	++	-
Bolijn, 2015	-	+	+	-	++	-
Collings, 2017	++	++	+	+	++	++
Derks, 2017	+	++	+	+	++	++
Derks, 2019	+	++	++	+	++	++
Diethelm, 2011	-	++	+	+	++	+
Hiscock, 2011	+	-	++	-	++	-
Klingenberg 2012	-	++	+	++	++	+
Kupers, 2015	+	++	+	++	++	++
Miyakoshi, 2018	++	-	+	+	++	+
Sha, 2017	+	-	+	++	++	+
Taveras, 2008	-	++	+	-	++	-
Taveras, 2014	-	+	+	-	++	-
Taylor, 2018	-	++	+	-	++	-
Tuohino, 2019	-	++	++	-	++	-
Wake, 2011	-	-	+	-	++	-
Wang, 2019	-	++	+	-	++	-
Zhang, 2019	+	-	+	-	++	-
Zhou, 2015	+	++	++	+	++	++

strong(++), moderate (+) or weak (-) . For the global quality rating of a paper, no weak ratings resulted in a strong rating; one weak rating in a moderate rating; and two or more weak ratings in a weak rating.

4

Parental discontent with infant sleep during the first two years of life.

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ABSTRACT

Background: Problematic sleep in infants can have a high impact on families. We examined parental discontent with infant sleep in the first six months of life and parent-perceived problematic sleep during the second year of life.

Methods: We used Sarphati Cohort data of 1471 children. During periodic youth health care visits in the first six months of life, professionals registered parental discontent with infant sleep. In the second year of life, parents filled out the Brief Infant Sleep Questionnaire (BISQ), from which we defined parent-perceived problematic sleep and BISQ-defined problematic sleep. We examined the association of parental discontent with infant sleep during the first six months with both BISQ-derived outcomes up to age two, using multivariable logistic regression analysis.

Results: 26% of parents were discontented with infant sleep during the first six months of life. During the second year of life, 27% of the parents perceived their child's sleep as problematic, and 9% of the infants had BISQ-defined problematic sleep. Early parental discontent with infant sleep was associated with parent-perceived problematic sleep [adjusted OR 2.50 (95% CI 1.91–3.28)], and BISQ-defined problematic sleep [adjusted OR 1.88 (1.11–3.17)].

Conclusions: Early registered parental discontent with infant sleep was a predictor of parent-perceived problematic sleep in early toddlerhood. Registering parental discontent during infancy might enable professionals to identify a group of infants at risk for later problematic sleep. We recommend screening and parental support for sleep difficulties in an early stage.

INTRODUCTION

Parent-reported infant sleep problems are highly prevalent during the first two years of life, with an estimated mean occurrence of 20-30% and reported peak occurrences of 40% at the age of eight months (1, 2). The likelihood of parent-reported sleep problems increases with a higher number of night awakenings and longer sleep latency. The broad range of reported occurrences of mild and severe sleep problems could be explained by underreporting in clinical registries and over reporting in observational studies (1, 3, 4). For example, not all parents seek medical help or wish to discuss infant sleep problems in the clinic setting, leading to underreporting of sleep problems in clinical registries, while prospective studies could find higher occurrences of sleep problems if they ask parents to confirm or deny sleep problems. Infant sleep problems could be of public health concern for several reasons. They have been associated with: (i) longer-term childhood cognitive and emotional development (5-9) (ii) cardio-metabolic outcomes during childhood (10-12); (iii) perceived quality of life and mental health of parents (13); (iv) parental work performance; and (v) health care costs (14-16).

Infant sleep evolves during the first two years of life as a result of intrinsic and parental-environmental factors (17). Intrinsic factors, such as maturation of the brainstem, are important due to their role in the sleep-wake cycle, cardiac vagal tone, and stress (18-20). Accompanied with the development of the circadian rhythm at week 10-12 (19, 21, 22), the development of self-regulation leads to consolidation of nighttime sleep (23). Self-soothing at sleep-onset and during night awakenings is a form of self-regulation and of great importance for the consolidation of nighttime sleep. An infant that cannot self-soothe will ask for parental soothing by crying. Parents can soothe by comforting and holding their infant, but also by feeding. More frequent nighttime feedings have been associated with long-term problematic sleep, although existing evidence is inconclusive (24, 25). Breastfeeding has been associated with more frequent night awakenings (>2 nights/week) at the age of one year old (26), but also with a lower risk of sleep-onset difficulties between age two and six years old (25). Self-regulation can be observed as early as the age of one month, improving significantly toward the age of three months (27), and more gradually during the rest of the first year (23, 28, 29). Improvement of self-regulation at this age could have long-term benefits since self-regulation develops significantly during the first months of life (27, 30). Infant feeding difficulties related to self-regulation could also increase the risk of later problematic sleep and could be a target for prevention through parental education.

Few studies investigated persistence of sleep problems or self-regulation problems during the first two years of life. Reported studies include 342 mother/child dyads from the HOMES cohort (representing <10% of all births in 2003 in Cincinnati, Ohio, USA (29)), 2352 children with standard home visit health care data (representing 80% of the population born between 2010 and 2013 in the Capital Region of Denmark (28)), and 4427 infants in the Bavarian Longitudinal Study (all born at risk, representing <10% of all live births between 1985 and 1986 in Southern Bavaria, Germany (5)). The three studies report a prevalence of sleep problems of around 10-20% (5, 28, 29) and a persistence of problematic sleep between the age of 6 months and 12, 24 and even 36 months (29), and between the age of 2-6 months and 8-11 months (28), and persistence of single and combined sleep problems between the age of 5 and 20 months (5). Authors recommend further research into screening of infant sleep problems and treatment, which are both not yet implemented in Dutch Public Health Services.

In Amsterdam, Public Health Services have started to address parental discontent with infant sleep during regular youth health care visits. However, it is unknown whether expressed parental discontent predicts later infant sleep problems. It is also unknown if population sleep health could be improved by targeted parental education and support. Parental lifestyle, expectations, and attitudes toward infant sleep have changed due to society's sociocultural and historical influences (31). Meanwhile, the same sociocultural and historical contexts influence how sleep experts view infant sleep, sleep problems, sleep training, night waking, and sleep consolidation (31). It is however not known if persistence of sleep problems has changed over recent decades. Therefore, we aimed to investigate parental discontent with infant sleep and feeding difficulties that could be related to self-regulation in a recent urban sample born between 2017 and 2020. We examined the association between parental discontent with infant sleep in the first six months of life and two parent-perceived problematic sleep outcomes in the second year of life. As a secondary aim, we assessed the association between parental discontent with infant feeding and parent-defined problematic sleep and BISQ-defined problematic sleep in the second year of life.

METHODS

Design and study population

We performed a longitudinal analysis of prospectively collected Sarphati Cohort data (www.sarphaticohort.nl). The Sarphati Cohort is a dynamic, multiethnic cohort study inviting all families of children aged 0-18 years receiving youth health care in the City of Amsterdam, the Netherlands. Parents of children are invited to participate in

the Sarphati Cohort through invitation letters by mail and communication materials during Public Health Service visits (e.g. leaflets, posters). The quality of the data is monitored through regular quality checks focusing on completeness of the registered health care data. The outcomes of these checks are discussed with the professionals responsible for registration. All children who receive youth health care in the Amsterdam region (99% of all children) and have a personal identification number are eligible for inclusion (32). The Sarphati Cohort represented 9.6% of the children up until age five years living in Amsterdam on December 31st 2021.

Data consist of health care data registered by youth health care professionals in digital health care files and digital parent questionnaires at age 12, 18 and 24 months. The Public Health Service of Amsterdam started recruitment for the Sarphati Cohort in October 2018. Informed consent was obtained by the Public Health Service of Amsterdam via a digital app from all participating parents. All procedures were approved by the Registration Committee of the Municipality of Amsterdam. Exemption from the Medical Research Involving Human Subjects Act (WMO) was granted by the Medical Ethical Committee of Amsterdam UMC, location AMC.

Measurements

Parental discontent

Data from the youth health care files provided information on the parental discontent with infant sleep (Are parents satisfied with their infant sleep?, categorized as content; partly discontented; or discontented). Nurses and medical doctors registered parental discontent during regular youth health care visits at age 4 and 6 months (for age ranges see **Table S4.1**). These visits last on average 20 minutes, addressing parental discontent, monitoring infant growth and development, and administering vaccinations. The consultation is based on topics, data is primarily gathered for care purposes and not for research purposes. If parents were partly discontented or discontented, professionals reported the cause of parental discontent using pre-categorized items (difficulty falling asleep, doesn't sleep in own bed, doesn't sleep uninterrupted, insufficient nocturnal sleep, too much nocturnal sleep, insufficient daytime sleep, too much daytime sleep, sleeps only when parent is present, moving in, for example, a car or baby carriage, with pacifier or while being fed, other).

Parental content with infant feeding was assessed during regular youth health care visits at the age of 0.5, 1, 2, 3, 4 and 6 months (for age ranges see **Table S4.1**). Feeding difficulties that could be related to self-regulation were: (i) drinking only small amounts; (ii) drinking too slowly or too quickly; (iii) irregular demand in feedings; (iv)

often nighttime feeding; (v) drinking too much; (vi) often being hungry; (vii) demanding more than milk production from mother; (viii) and often having colic attacks.

We classified parents as discontented if the professional registered parents to be partly discontented or discontented with the infant's sleep behavior at any Public Health Service visit during the first half year of life. As difficulties were only registered as the reason of discontent, they are not a registration of the prevalence of each difficulty (e.g. the prevalence of frequent night awakenings could not be determined with the data).

Brief Infant Sleep Questionnaire

The Brief Infant Sleep Questionnaire (BISQ) is a validated parental questionnaire assessing infant's sleep behavior (33). It involves: (i) sleep-wake rhythm; (ii) sleeping arrangement; (iii) situation until sleep-onset of the infant; (iv) and whether the parent considers the infant's sleep as problematic. Previous studies using the BISQ have defined problematic sleep as a binary outcome derived from three questions of the BISQ (33), or by a single question: 'Do you consider your child's sleep as a problem?' (5, 29).

We used both dichotomous outcomes derived from the BISQ data: (i) parent-perceived problematic sleep at either of the three ages derived from one single question (Do you consider your child's sleep as a problem?) (categorized as yes if 'a very serious problem; or a small problem', no if 'not a problem at all'); and (ii) 'BISQ-defined problematic sleep' when the parent reported at either of the three ages: <9 hours of sleep per night (between 7p.m. and 8a.m.), or >3 night awakenings between 7 pm and 8 am, or > 1 hour nocturnal wakefulness between 7p.m. and 8a.m. (33-35). All parents digitally filled out the BISQ about their infant's average sleep behavior over the previous two weeks at the age of 12, 18 and 24 months (pre-categorized questions displayed in **Table 4.3**).

Background characteristics

Infant's characteristics included: sex and gestational age at birth (weeks). Parents' characteristics included: (i) parental country of birth (both born in the Netherlands, one born abroad, or both parents born abroad); (ii) maternal educational level (High: tertiary education (International Standard Classification of Education 2011 (ISCED11) 5-8), Intermediate: upper or post-secondary education (ISCED11 3-4), Low: no education, pre-primary, primary and/or secondary education (non, ISCED11 0-2)); (iii) tobacco use during pregnancy (dichotomized yes/no); and (iv) maternal body mass index (BMI, kg/m^2). Infancy period characteristics included: (i) predominantly

breastfeeding (yes/no; at 0.5, 3 and 6 months); (ii) area code; and (iii) siblings in the household (dichotomized yes/no).

Data analysis

Data was analyzed using IBM SPSS Statistics version 21. Normality of the data was evaluated using histograms and Q-Q plots. Improbable values of maternal height and sleep duration were corrected as described in appendix. We present categorical variables in proportions and continuous variables as means with standard deviations (SD). Differences between the Sarphati sample and the total population were tested by one-way ANOVA for continuous outcomes and Chi-square test for categorical outcomes. All regression analyses were adjusted for: (i) sex; (ii) gestational age; (iii) parental country of birth; (iv) maternal educational level; (v) tobacco use during pregnancy; (vi) duration of breastfeeding; and (vii) presence of siblings in the household. We did not adjust for age during measurements as both determinant and outcome are computed measurements from several measurements during age 0 to 6 or 12 to 24 months. We used multiple imputation for missing information on covariates on all cases with both a determinant and one outcome measurement. Multiple imputation by chained equations (fixed seed; ten imputations) was performed on a separate database with only the necessary variables for the logistic regression analysis. Data was imputed for the independent variables 'BMI mother' and 'siblings in household' (13% and 12% missing data, respectively). We performed crude and multivariable logistic regression analyses on the multiple imputed dataset to examine the association between parental discontent with infant sleep and parent-perceived problematic sleep and BISQ-defined problematic sleep during the second year of life. We performed the same crude and multivariable logistic regression to examine the association between parental discontent with infant feeding and parent-perceived problematic sleep and BISQ-defined problematic sleep during the second year of life. As a sensitivity analysis we performed a complete case analysis for all predictors and outcomes.

RESULTS

Analysis sample

Figure 4.1 presents the flow chart resulting in a sample of 1471 infants born between 2017 and 2020 with information on both infant sleep and parent-perceived problematic sleep up to age 24 months.

Table 4.1 shows the study sample compared to all families with newborn infants in Amsterdam. Parents in the Sarphati Cohort sample were more often born in the Neth-

erlands (66% vs. 52%) and highly educated (94% vs. 67%) (**Table 4.1**). Also, parents who lived in the Nieuw-west district of Amsterdam or the south-eastern part of Amsterdam were slightly underrepresented in the Sarphati Cohort. In general, residents from these districts are less often of Dutch ethnicity and more often have lower incomes (36, 37).

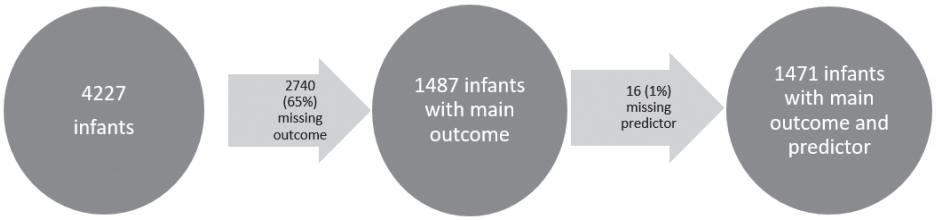

Figure 4.1: Flowchart analysis sample.

Table 4.1: Characteristics of the study sample and the source population.

	Study sample (n=1471)	n.	Newborn infants in Amsterdam
Year of birth	2017-2020		2018-2019
Sex (males)	49%	*1471*	51%
Gestational age (weeks, mean (SD))	40.3 (1.5)	*1440*	-
Parental country of birth		*1470*	
the Netherlands	66%		52%
Mixed (one parent from the Netherlands)	18%		48%
Both abroad	17%		
Educational level of mother	*	*1424*	*
High	94%		66%
Intermediate	5%		26%
Low	1%		8%
Household with multiple children (yes)	38%	*1290*	57%
Smoking during pregnancy (yes)	2%	*1375*	4%
Maternal post-pregnancy BMI (mean (SD))	22.7 (3.6)	*1269*	
Predominantly breastfeeding			
At 2 weeks	68%	*1445*	69%
At 3 months	41%	*1461*	43%
At 6 months	18%	*1471*	25%

N=total number of participants.

* High level includes tertiary education (International Standard Classification of Education 2011 (ISCED11) 5- 8), intermediate level includes upper or post-secondary education (ISCED11 3-4), low level includes no education/ pre-primary/primary and/or secondary education (non, ISCED11 0-2).

Persistence of parent-perceived problematic infant sleep

A total of 26% of parents were discontented with infant sleep during visits in the first six months of life (13% of 1065 visits at age four months and 22% of 1173 visits at age six months). Of the parents who were discontented with infant sleep at age four months, 53% reported interrupted sleep, 12% insufficient sleep during the night, and 10% trouble falling asleep. Of the parents who were discontented with infant sleep at age six months, 71% reported interrupted sleep, 9% insufficient sleep during the night, and 11% trouble falling asleep.

Table 4.2 presents detailed information on infant sleep behavior and parent-perceived and BISQ-defined problematic sleep in the second year of life. Average nocturnal sleep duration was stable around 11 hours while daytime sleep duration decreased from 2.5 to 2 hours. Sleeping arrangement was stable with around 90% of children sleeping in their own bed, whereas the situation at sleep-onset changed, with twice as many children being held or rocked falling asleep at age 12 months than at age 18 or 24 months. Sleep efficiency was stable at 12, 18 and 24 months, with a settling time until sleep-onset of around 0.2 hours; and mean number of night awakenings between 1.5 and 1.8, with a total duration of 0.3 to 0.4 hours.

Problematic sleep decreased during the second year of life, from 31 to 22% for parent-perceived problematic sleep and from 11 to 5% for BISQ-defined problematic sleep. The total occurrence of parent-perceived problematic sleep during the second year of life was 27% and the total occurrence of BISQ-defined problematic sleep was 9%. Only 53 (6% of 850) of the infants were defined as problematic sleepers by both BISQ-derived outcomes.

Parental discontent with infant sleep at the age of four and/or six months was associated with an increased risk of parent-perceived problematic sleep (adjusted OR 2.50 (95%CI 1.91–3.28)) and with BISQ-defined problematic sleep (adjusted OR 1.88 (95%CI 1.11–3.17)), both assessed at the age of 12, 18 and/or 24 months (**Table 4.3**).

Parental discontent with infant feeding

Table S4.2 presents registered parental discontent with infant feeding during clinic visits in the first six months of life. 19% of parents were discontented with infant feeding, due to difficulties that could be related to self-regulation at any time during this period. The reason for parental discontent with infant feeding differed by age. Infant colic attacks and demanding more milk than the breastmilk production of the mother were the most frequent reason during the first two months of life. Drinking

small amounts was the most frequent reason at the age of three months and frequent nighttime feeding at the age of four months and older. No significant associations were found between parental discontent with infant feeding at the age of 0-6 months and both outcomes (**Table 4.3**). The sensitivity analysis with complete cases produced the same results with slightly stronger associations (**Table S4.3**)

Table 4.2: Infant sleep behavior: description of BISQ outcomes (n=1471 infants with one or more measurements at 12, 18 and/or 24 months)

	12 mo.	n.	**18 mo.**	n.	**24 mo.**	n.	**12-24 mo.**	n.
Sleeping arrangement		*594*		*602*		*519*		*1471*
Own bed/crib.	90 %		90 %		91 %			
In parents' bed.	9 %		9 %		8 %			
Co-sleeper (attached to parents' bed), bassinet, infant seat, other.	2 %		1 %		1 %			
Situation till sleep-onset		*593*		*600*		*519*		
In bed alone.	71%		77%		75%			
In bed near parent.	11%		14%		17%			
Being held or rocked.	19%		9%		8%			
Often falls asleep while being fed (yes).	22%	*593*	13%	*600*	11%	*519*		
Settling time till sleep-onset. (hours, mean (SD))	0.2 (0.2)	*584*	0.3 (0.2)	*589*	0.3 (0.2)	*514*		
Sleep-onset time. (time hh:mm, mean (SD))	19:23 (1:37)	*593*	19:25 (1:49)	*593*	19:34 (2:09)	*519*		
Nocturnal sleep duration. (hours between 19:00-08:00, mean (SD))	11.1 (1.1)	*593*	11.2 (0.9)	*591*	11.0 (0.9)	*517*		
Night awakenings. (no. between 22:00-06:00, mean (SD))	1.8 (1.6)	*394*	1.5 (0.9)	*334*	1.6 (1.6)	*226*		
Nocturnal wakefulness. (hours between 22:00-06:00, mean (SD))	0.4 (0.6)	*390*	0.4 (0.7)	*332*	0.3 (0.6)	*223*		
Daytime sleep duration. (hours between 08:00- 19:00, mean (SD))	2.5 (0.7)	*592*	2.1 (0.5)	*593*	2.0 (0.9)	*513*		
parent-perceived problematic sleep (% yes)	**31%**	***593***	**22%**	***600***	**22%**	***519***	***27%***	**1471**
BISQ-defined problematic sleep (% yes)	**11%**	**390**	**8%**	**332**	**5%**	**221**	**9%**	***850***

N=total number of participants.

Table 4.3: Association between parental discontent at the age of 0-6 months* and parent-perceived problematic sleep and BISQ-defined problematic sleep at the age of 12, 18 and/or 24 months after multiple imputation.

	Parent-perceived problematic sleep#(n=1471) 400 cases^		BISQ-defined problematic sleep (n=850) 77 cases^	
	Crude OR (95% CI)	Adjusted α OR (95% CI)	Crude OR (95% CI)	Adjusted α OR (95% CI)
Parental discontent with infant sleep 4-6 months (yes)	**2.53 (1.94 - 3.30)**	**2.50 (1.91 - 3.28)**	1.56 (0.95, 2.56)	**1.88 (1.11-3.17)**
Parental discontent with infant feeding 0-6 month (yes)	1.12 (0.84 – 1.49)	1.19 (0.89 – 1.60)	1.02 (0.57, 1.82)	1.01 (0.55, 1.86)

*: Parental expressed discontent during consultation at any age between 0-6 months.; #: single BISQ question (% yes); **Bold** significant values (p<0.05). ^: explanation on cases definition and numbers; in the group of 1471 infants, 400 infants had parent-perceived problematic sleep. BISQ-defined problematic sleep could only be defined for 850 infants due to missing outcomes. In this group of 850 infants, 77 infants had BISQ-defined problematic sleep. α: Odds Ratio adjusted for sex (male/female), gestational age, maternal BMI, ethnicity parents (Dutch, mixed, other), educational level of mother (high, intermediate, low), siblings in the household (yes/no), tobacco use during pregnancy.

DISCUSSION

Occurrence of parent-perceived problematic sleep

This study examined parental discontent with infant sleep in the first six months of life and problematic sleep during the second year of life. Parental discontent with infant sleep at the age of 4-6 months was associated with later parent-perceived problematic sleep. Although we could not test persistence with repeated measurements of the same variable, this implies that prevention could already start in the perinatal period by promoting healthy sleeping habits before the age of six months. Registering parental discontent might enable professionals to identify a group of infants at risk for later problematic sleep who could benefit from selective evidence-based prevention with personalized parental education, advice or coaching based on the developmental stage and specific sleeping habits of their infants (e.g. structured bedtime routine, extinction-based approaches, cognitive behavioral therapy for insomnia, multicomponent infant behavioral treatment, or the Happiest Baby Method) (39-43). This type of selective prevention could be implemented alongside universal prevention through parental education for parents of all infants (44, 45).

Our longitudinal findings are in line with three previous studies examining persistence of problematic sleep based on different definitions, but at similar ages. The HOMES cohort (USA) found that problematic sleep at the age of six months was associated with problematic sleep at the age of 12, 24 and even 36 months (29). Their main outcome was based on parent-perceived problematic sleep, assessed by a similar question as that in the BISQ. A Danish study reported a positive crude association for

problematic sleep at the age of 2-6 months, with problematic sleep at the age of 8-11 months. Problematic sleep was registered by community health nurses using the Copenhagen Infant Mental Health Questionnaire during home visits. The observed association between professional-perceived problematic sleep and later sleep problems (univariate OR 2.02 (95% CI 1.41-2.90)) in the Danish cohort was similar to the association between parental discontent and later problematic sleep in our study (univariate OR 2.53 (95% CI 1.94 – 3.30)) (28). A large-scale German cohort study from the 1980s (>30 years earlier than our study sample) reported significant associations between single and combined sleep problems at the age of five months and sleep problems at the age of 20 months (5). They defined sleep problems at age five months as: "infant wakes up ≥ 2 times per night AND/OR Infant wakes up for ≥ 15 minutes at night". At 20 months they used parent-perceived problematic sleep by asking parents if they considered their infant's sleep as problematic, similar to our study. Despite the lower cut-off points for the BISQ in the German study, they observed a lower prevalence of sleep problems. We found higher rates of parent-perceived problematic sleep (20-30%) than the 10-20% observed in the three previous studies examining persistence of problematic sleep at similar ages. However, the potential explanations may be differences in the operationalization of problematic sleep across studies, cultural differences in parental and infant bedtime behavior, or an increase in sleep problems over the last 30 years. Despite the difference in prevalence, the association between infant sleep problems at age 4-6 months and infant sleep problems during the second year of life was quite similar (German cohort: adjusted OR of 2.08 (95% CI 1.60; 2.70), Dutch cohort 2.50 (95%CI 1.91–3.28)).

Sleep behavior of the infant

Our study made use of data registered as part of regular youth health care visits, implying that the identification of families at risk for infant problematic sleep could be part of routine health care. One out of four parents in our study sample (n=1471) were discontented with their infant's sleep. The peak of parent-perceived problematic sleep was at the age of 12 months, with 31% of parents being discontented. Our finding of a sleep duration of 13 per 24 hours lies within the normal range recommended by the National Sleep Foundation (46). The stable rate of infants who slept in their parents' bed during the first two years of life was in line with the results of a recent Spanish study (47) and two Dutch studies (48, 49). Based on our data, we cannot distinguish between co-sleeping that is reactive to perceived problematic sleep or intentional (e.g. cultural or parenting style-based) co-sleeping (31, 35). The percentage of infants who fell asleep while being held, rocked or fed until sleep-onset decreased toward the age of two years. However, the percentage of infants who fell asleep with a parent nearby increased toward the age of two years. An explanation might be that

children can verbally request the parent's presence in the second year of life. Also, bedtime routine may change toward reading bedtime stories, resulting in parental presence during sleep-onset. The percentages of assisted sleep-onset in our study are much lower than in a recent cohort of Brazilian families, reflecting cultural differences in parental bedtime routines (50). Parental presence during sleep-onset is an important factor when discussing sleep difficulties as it has been associated with the appearance of night awakenings and sleep-onset difficulties at the age of 12 months (51). Similar to findings in other studies (1, 3, 4), parents who were discontented about their infant's sleep at age four or six months most often reported interrupted sleep and difficulty falling asleep as reason. Reasons for parental discontent with their infant's sleep and feeding behavior were recorded with pre-categorized items. The item 'other' for discontent with infant sleep was selected by up to 28% of the parents, which suggests that there are other items which we did not take into account but can be of importance. The range of 20-30% of parent-perceived problematic sleep according to the BISQ was within the internationally estimated range (1).

The development of self-regulation and self-soothing skills is known to be influenced by parental and environmental factors, such as parental soothing methods and bedtime behaviors, which are bi-directionally related to infant behavior. Predictors of childhood problematic sleep have been investigated increasingly in recent years and potential determinants could be: (i) sex; (ii) gestational age; (iii) ethnicity; (iv) parental educational level; (v) tobacco use during pregnancy; (vi) duration of breastfeeding; and (vii) presence of siblings in the household (24, 25, 28, 52-54). Interventions based on modifying parental behaviors and cognition improve parental sleep-related behaviors and ultimately infant self-regulation and sleep (17).

We found no significant association between registered parental discontent with infant feeding and later problematic sleep, consistent with our previous finding in another Amsterdam-based cohort (the ABCD study) (24). Our study did not confirm the association between feeding problems at the age of 2-6 months and sleep problems at the age of 8-11 months observed by Olsen et al. (28). One explanation may be differences in the way feeding difficulties were reported. Our data is based on registrations of parental discontent during short clinic visits rather than home visits with a validated tool in the study by Olsen et al. We did not measure detailed feeding habits during the first months of life in this cohort and parental discontent might underestimate or overestimate feeding problems, leading to information bias.

Strengths and limitations

Our study has several strengths. Firstly, we are the first to examine the prevalence and persistence of parental discontent with infant sleep in a Dutch population. Secondly, we assessed parental discontent via a universal screening protocol that has already been implemented in the participating Public Health Service clinics. The Sarphati Cohort combines routine health care data with validated parent-report questionnaires into a longitudinal dataset. Parental discontent with infant sleep is not standardly documented in Dutch Public Health Service files. Professionals in Amsterdam actively discuss infant sleep during Public Health Service visits as well as quantitatively registering these data since 2017, which, to the best of our knowledge, is unique and provides an opportunity for screening and personalized early interventions. The quality of the data is optimized by training- and reflection meetings for professionals on how to fill out the Sarphati Cohort-specific questions on parental satisfaction. Another strength is the use of the validated BISQ.

A limitation of the study is information bias due to indirect registration of parental discontent. Health care professionals register parental discontent, meaning that their interpretation of the parental response can be biased by the impression of the professional regarding sleep behaviors of the infant and by the way parents express their discontent. Data is gathered for care purposes and not for research purposes, and sleep data may be missing if other health issues were more urgent during the consultation. Recall bias caused by, for example, parental mood, depressive symptoms, exhaustion or intermittent problems is another form of information bias that most likely affected our descriptive analysis. Two examples are: (i) that it increased the likelihood that the same parents expressed discontent during the first six months and in the second year of life (55); and (ii) that if the behavior of the infant is relatively worse on the day of the consultation or questionnaire, compared to an average day, parents may give a more negative answer to the main question, regarding the child's sleep to be problematic. We do however consider parent-reported sleep at this age the best available option for larger cohorts (56).

Another limitation of the Sarphati Cohort data is the external validity, as the Amsterdam population has on average a high income and educational level since housing prices in Amsterdam have increased substantially in recent years (57). Amsterdam is also more multiethnic than Dutch rural areas. This is reflected in our sample with a higher educational level compared to rural areas and a higher percentage of parents born outside the Netherlands (**Table 4.1**). Another limitation may be residual confounding due to maternal age, maternal sleep and other lifestyle factors. Addition-

ally, as parent questionnaires had been recently implemented, only a few parents had filled in the BISQ more than once.

Future recommendations

We recommend further research on which habits in the perinatal period are predictive for problematic sleep in later life. The following predictors might be of interest in future research projects: (i) maternal age; (ii) maternal alcohol use during pregnancy (24); (iii) maternal mental health during pregnancy and infancy (24, 28, 58); (iv) parental emotional availability (59); (v) (non-)sensitive parenting style (41, 60, 61); (vi) circadian rhythm of parents (62); (vii) bedtime routine practices (63); and (viii) screen time (television, touchscreens) (64).

Parents might consider other or additional habits and/or behaviors of the infant as problematic which are not included in the BISQ questionnaire. The revised BISQ questionnaire (BISQ-R) includes a wider array of sleep behaviors and outcomes and has an age-based norm-referenced scoring system. Use of the BISQ-R seems promising for future research projects, since an age-based norm-reference scoring system has been developed and tested for this tool (65). Research on Public Health efforts, such as behavioral interventions, to treat sleep problems as early as in the first six months of life is scarce (42, 45, 66-68). Public health efforts on prevention programs could provide further causal evidence regarding the infant's or parental factors that can be modified to improve sleep habits in infants.

Conclusion

Infants with registered parental discontent regarding sleep at the age of four and/or six months had parent-perceived problematic sleep in the second year of life more often. If confirmed in other studies, this implies that prevention could start in the perinatal period and that clinicians might be able to identify a group of infants and parents that could benefit from selective prevention to promote healthy sleeping habits.

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SUPPLEMENTS

Supplemental methods section:

Outliers of maternal height and weight were removed and replaced with missing values (i.e. if reported height and weight values corresponded to the data of the infant; 12 kg and 0.86 meter). Outliers of BISQ outcomes were removed and replaced with missing values if parents reported >14 hours of nocturnal sleep, >11 hours of daytime sleep, >8 hours nocturnal wakefulness, >4 hours settling time. We analyzed the age at each measurement point, removed and replaced outliers with missing values or transported the data to a measurement point corresponding with that certain age if there was not already data present. This was conducted according to the following age-ranges per measurement point: 1-2.9 weeks (0.5 month), 3-6 weeks (1 month), 7-10 weeks (2 months), 11-15 weeks (3 months), 16-19 weeks (4 months), 22-30 weeks (6 months), 47-57 weeks (12 months), 66-91 weeks (18 months), 94-114 weeks (24 months).

Table S4.1: Mean age (SD) per measurement moment

	Infant age (weeks)
Periodic Public Health Service visits	
0.5 month	1.8 (0.4)
1 month	4.6 (0.7)
2 months	8.4 (0.7)
3 months	13.3 (0.9)
4 months	17.7 (0.9)
6 months	26.7 (1.5)
BISQ questionnaires	
12 months	53.4 (1.3)
18 months	79.0 (1.2)
24 months	106.2 (2.2)

Table S4.2: Registered parental discontent, n= 1471

	% parents discontent, regarding:	
During clinic visits at infant age ..	**Sleep**	**Feeding***
0.5 months	not measured	7 % (n=1248)
1 month	not measured	6 % (n=1406)
2 months	not measured	3 % (n=1404)
3 months	not measured	4 % (n=1401)
4 months	13 % (n=1065)	3 % (n=1223)
6 months	22 % (n=1173)	2 % (n=1377)
During any visit between 0-6 months	*26 % (n=1379)*	*19 % (n=1471)*

N: total number of participants (varying per clinic visit). *: drinking only small amounts, drinking too slow or fast; irregular demand in feedings; often night-time feeding, drinking too much, often being hungry, demanding more than milk production of mother, and often having colic's.

Table S4.3: Association between parental discontent at the age of 0-6 months1 and parent-perceived problematic sleep and BISQ-defined problematic sleep at the age of 12, 18 and/or 24 months in complete cases.

	Parent-perceived problematic sleep[2] (n=1101) 292 cases[3]		**BISQ-defined problematic sleep (n=627) 45 cases[3]**	
	Crude OR (95% CI)	Adjusted[4] OR (95% CI)	Crude OR (95% CI)	Adjusted[4] OR (95% CI)
Parental discontent with infant sleep 4-6 months (yes)	**3.04 (2.28-4.05)**	**3.00 (2.23-4.03)**	**2.41 (1.31-4.44)**	**2.52 (1.31-4.84)**
Parental discontent with infant feeding 0-6 month (yes)	1.10 (0.78-1.55)	1.16 (0.82-1.65)	1.00 (0.47-2.14)	0.76 (0.32-1.85)

*: Parental expressed discontent during consultation at any age between 0-6 months.; #: single BISQ question (% yes); **Bold** significant values (p<0.05). ^: explanation on cases definition and numbers; in the group of 1101 infants, 292 infants had parent-perceived problematic sleep. BISQ-defined problematic sleep could only be defined for 627 infants due to missing outcomes. In this group of 627 infants, 45 infants had BISQ-defined problematic sleep. α: Odds Ratio adjusted for sex (male/female), gestational age, maternal BMI, ethnicity parents (Dutch, mixed, other), educational level of mother (high, intermediate, low), siblings in the household (yes/no), tobacco use during pregnancy.

5

Potential determinants during ‘the first 1000 days of life’ of sleep problems in school-aged children

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ABSTRACT

Study Objectives: Early life determinants of sleep problems are mostly unknown. The first 1000 days of life, the time between conception and a child's second birthday, is a period where the foundations for optimum health, growth and neurodevelopment are established. The aim of this explorative study is to identify potential early life determinants of sleep problems at age 7-8 years.

Methods: Data from the Amsterdam Born Children and their Development cohort study (n=2,746) were analyzed. Sleep problems at age 7-8 years were reported by the caregiver in the 'Child Sleep Habits Questionnaire'. A higher total score indicates more sleep problems. After multiple imputation (n=20), we studied multivariable associations between all potential determinants and sleep problems using regression analysis.

Results: A higher pre-pregnancy BMI was associated with more sleep problems at age 7-8 years (β 0.12 (95% CI 0.05, 0.18)). Children of mothers with symptoms of anxiety during pregnancy (β 0.06 (95% CI 0.03, 0.09)) and infancy period (β 0.04 (95% CI 0.00, 0.07)) had more sleep problems. Children of mothers drinking ≥1 glass of alcohol a day around 14 weeks of gestation had a two points higher sleep problem score (β 2.55 (95% CI 0.21, 4.89)) and children of mothers smoking ≥1 cigarette per day in that period had a one point higher score (β 1.07 (95% CI 0.10, 2.03)). Infants with relative weight loss (delta BMI-SD) had a higher sleep problem score during childhood (β -0.32 (95%CI -0.60, -0.04)).

Conclusions: We identified several potential determinants during pregnancy and infancy associated with childhood sleeping problems. We encourage further research into these and other potential determinants to replicate results and to identify underlying mechanisms.

INTRODUCTION

Sleep related problems are common among children, with prevalence rates reported up to 40% (1-7). Childhood sleep problems are associated with negative physical, emotional, behavioral and cognitive outcomes during childhood and later life, such as an increased risk of obesity, more symptoms of anxiety and depression and lower IQ scores (8-12).

The first 1000 days of life, the time between conception and a child's second birthday, is a period where the foundations for optimum health, growth and neurodevelopment are established (13, 14). During this period, neuronal and hormonal maturation play an important role in the development of normal sleep behavior and patterns (15-17). Hormonal changes due to the environment of the fetus and infant might have long-term consequences on sleep during lifetime. Few studies exist on the topic of early life origins of sleep problems. These studies observed an association between potential determinants within the first 1000 days and childhood sleep problems (e.g. nicotine exposure during pregnancy; parental emotional availability; and gestational age) (18-23). The most recent study by Fatima et al. found that girls had more trouble sleeping but less nightmares at age 14 years than boys. Nightmares were also associated with maternal smoking and poor dyadic adjustment during late pregnancy, premature birth and short or no breastfeeding (24). Potential determinants, not specific for the first 1000 days, that have been associated with sleep problems in school-aged children are lifestyle and health determinants (e.g. excessive screen use; difficult temperament; poor health; and affective disorders) (23, 25-27).

The aim of this study was to investigate potential determinants during the first 1000 days that are associated with higher sleep problem scores in school-aged children within a large prospective cohort study: the Amsterdam Born Children and their development (ABCD) study. Hereby we aimed to replicate previously observed associations with sleep, but also explore whether factors, within the first 1000 days of life, that are associated with cognitive development are also associated with sleep in school-aged children (28, 29).. This study will provide explorative information about potential determinants that could be used as focus areas for the development of effective strategies during the first 1000 days of life, to prevent sleep problems in later life.

METHODS

Design and study population

The data was retrieved from the ABCD study (www.abcd-study.nl). This is a large multi-ethnic prospective cohort study in the city of Amsterdam, the Netherlands. The main goal of the ABCD study is to examine and determine factors in early life (during pregnancy and infancy) that might explain subsequent differences in children's health. In depth details of this study can be found elsewhere (30). Between January 2003 and March 2004 all pregnant women living in Amsterdam were invited to participate in the ABCD study during their first antenatal visit to an obstetric caregiver. We only included children with complete information about sleep problems. Multiples, stillbirths and children with congenital abnormalities were excluded.

Approval of the study was obtained from the Central Committee on Research Involving Human Subjects in The Netherlands, the medical ethics review committees of the participating hospitals and from the Registration Committee of the Municipality of Amsterdam.

Sleep problems

Sleep problems were measured when the child was seven to eight years old by the Child Sleep Habits Questionnaire (CSHQ) completed by the mother or primary caregiver. The CSHQ is a 33-item questionnaire developed as a sleep screening tool for caregivers of school-aged children (31, 32). The responder was asked to report their child's average sleep behavior during the last typical week. The CSHQ includes eight subscales: sleep-onset delay, sleep duration, night wakening, parasomnias, daytime sleepiness, bedtime resistance, sleep anxiety and sleep disordered breathing. Items were rated on a 3-point scale; usually (5-7 times a week), sometimes (2-4 times a week), and rarely (0-1 time a week). A higher CSHQ score indicates more sleep problems on a continuous scale. We examined internal consistency of the CSHQ total sum score and each subscale separately by calculating correlations between items using a Cronbach's alpha. The total CSHQ sum score had an adequate internal consistency (α= 0.76). In order to describe the differences in potential determinants between children without and with sleep problems , we created a binary outcome with a cut-off at the 90th percentile. Average sleep duration at night and daytime per 24 hours was calculated by the parents and reported in hours and minutes per 24 hours.

Potential determinants

Potential determinants were all factors influencing the child during the first 1000 days based on prior research on childhood sleep and/or cognitive development, as

sleep problems in childhood are seen as a cognitive function or often closely related to cognitive functioning (18-24, 33). Information about the potential determinants was derived from the ABCD-study questionnaires; the Dutch Youth Health Care health records; pregnancy health records; and Perined (Dutch institute for registration concerning birth care). Mothers filled out the pregnancy questionnaire around 14 weeks of gestation, as they were invited after their first antenatal clinical visit in the first trimester. Most information about infancy was self-reported in the infancy questionnaire at age three months. Potential determinants are categorized into four categories (pregnancy; birth outcomes; infancy; and context) based on chronological order for theoretical understanding; to check correlation within each category; and for regression analysis per category.

Pregnancy

Pre-pregnancy BMI (kg/m^2) was computed from pre-pregnancy weight and height. Substance use was assessed as: alcohol use during pregnancy (<1 glass a day vs. ≥1 glass a day); smoking during pregnancy (<1 cigarette a day vs. ≥1 cigarette a day); drug use during pregnancy (cannabis (no, yes); cocaine (no, yes); xtc or speed (no, yes)); medicine use during pregnancy (painkillers (no, yes); sedatives or sleep medication (no, yes); antidepressants (no, yes)). Caffeine use during pregnancy (mg a day) was computed from the number of drinks including coffee, tea and caffeinated soft drinks. Maternal psychological wellbeing during early pregnancy was assessed on the domains of depression; anxiety and fatigue using the following questionnaires: Center for Epidemiologic Studies Depression (CES-D, depression symptoms score); the State-Trait Anxiety Inventory (STAI, anxiety symptoms score); and the Multidimensional Inventory for Fatigue (MFI, fatigue symptoms score) (34-36). A higher score on these questionnaires indicates more problems. Maternal sleep/resting duration (hours a day) during pregnancy was part of the MFI. We created a binary variable for gestational diabetes (37) (pre-existent or gestational (yes/no)) from pregnancy records.

Birth outcomes

We categorized children as low birth weight when they had a birth weight below the 10th percentile for gestational age on the basis of gender- and parity-specific standards from the PRN. We defined preterm birth as gestational age <37 weeks. We created a binary variable for artificial delivery (secondary section; vacuum delivery; or forceps delivery (yes/no)).

Infancy

The following child characteristics were included: sex of the child; accelerated growth between age 2 and 12 months (measured as change in SDS score of weight for

length); and excessive crying at infant age three months (modified Wessel's criteria: more than 3 hours a day, more than 3 days a week) (38, 39). Feeding practices were investigated with: breastfeeding (none, 1-6 months, >6 months); method of feeding (scheduled vs. on demand, other); number of feedings per day (≤8 feedings a day vs. > 8 feedings a day); number of feedings per night (≤1 feeding a night vs. >1 feeding a night); and start of additional feeding (solid foods) (<4 months, 4-6 months, >6 months, unknown).

Parental nighttime behaviors at infant age three months were: sleeping place (in parents bed vs. elsewhere); swaddling at night (no, yes); pacifier when falling asleep at night (no, yes); and bottle feeding when falling asleep at night (no, yes). Infant sleep disturbances are assessed as potential long-term causes of sleep problems (i.e. waking up by shortness of breath; cough; or itching rash during the last 3 months).

Maternal wellbeing was assessed with the CES-D, the STAI and the MFI again. Maternal sleep/resting duration in hours/day) three months after birth was part of the MFI. Experience of parenthood was assessed with the Dutch questionnaire about the upbringing (Nederlandse vragenlijst voor de opvoedingsituatie) and the care list (Verzorgingslijst). The higher the score of the upbringing list, the more burden parents experienced in the upbringing (40). The higher the score of the care list the more pleasure parents experienced in taking care of their baby (24).

Age at start daycare (0-6 months, 6-12 months, 12-48 months, >48 months) was self-reported by the parents in the seven-year questionnaire.

Context: demographic factors

Information on maternal and childhood demographics included: maternal age (years); single parent household; ethnicity (Dutch, African descent, Turkish, Moroccan, other based on country of birth of mother and grandmother) (41); maternal education (0-6 years, 6-10 years, >10 years after primary education) (42); and ≥1 older sibling in the household (no, yes). Maternal education was used to give an indication about the social economic position of the household (43).

Controlling factors for the outcome measurement.

We added two controlling variables to all models as these might influence the outcome measurement of sleep problems: age of the child and depressive symptoms of the mother. The age of the child at the measurement of sleep problems was obtained from the seven-year questionnaire. Mothers with depressive symptoms might have filled out the questionnaires differently (44-46). Therefore we additionally controlled

for depressive symptoms assessed at the closest time point before the CSHQ questionnaire: at offspring age five years. We assessed depressive symptoms of the mother at this age with the Depression Anxiety Stress Scale (DASS21) (47), with a higher score indicating more problems. Anxiety symptoms of the mother during pregnancy and infancy are both in the model as a possible determinant.

Statistical analysis

Continuous variables were examined for a normal distribution and outliers. Outliers of maternal sleep or resting hours during pregnancy and infancy were removed and replaced with missing values if mothers reported >20 hours or ≤ 2 hours of sleep and if mothers reported long (>12) hours of sleep-rest and desire to sleep more (0.8%) or <8 hours of sleep-rest and desire to sleep less (0.4%) or <6 hours of sleep-rest and no desire to sleep less-more (0.4%). We tested correlation between variables within each category of potential determinants (i.e. pregnancy, birth outcomes, infancy and demographics) to prevent collinearity in the multivariable model. In case of high correlation ($r>0.6$) we added the potential determinant with the strongest association with the outcome to the model and dropped other potential determinants. We performed multiple imputation on missing data of potential determinants using chained equations with the mi impute command making 20 imputed datasets. We inspected the distribution of the imputed variables and compared them with the original dataset.

Demographic characteristics of the baseline sample (approached for CSHQ questionnaire at age seven years); multiple imputation study sample; and complete cases are described using arithmetic means. Hereby we investigated selection bias due to loss to follow up and compared the multiple imputation means to the complete case means (**Table 5.1**). Means and standard deviations are reported for each sleep problem subscale and total sleep duration to compare children with low to moderate and high sleep problem scores (**Table 5.2**). Means of the potential determinants in the multiple imputations are reported for children with low to moderate versus high sleep problem score (**Table 5.3**). Linear regression models were used to explore the associations between the potential determinants and continuous sleep problem score. The regression model with minimal adjustment included two variables that could influence the outcome (age of the child and maternal depression) and was performed separately for each potential determinant. The main analyses (referred to as complete model) also included all potential determinants of all four categories at once. We performed four sensitivity analysis. At first we repeated the multivariable model for three subscales of the sleep problem score: bedtime resistance, daytime sleepiness and parasomnias. As a second sensitivity analysis we performed a separate multivariable model per category; and as a third sensitivity analysis we selected determinants by backward

selection. In the fourth sensitivity analysis we did not control for maternal depression at the age of five years. We evaluated linearity for the significant associations by assessing the change in coefficients across categories .

All analyses were conducted using STATA version 15 (College Station TX, USA). We show results as unstandardized betas with their 95% confidence interval (CI) and used a threshold of p <0.05 for significance. We did not adjust the threshold for multiple comparisons, as this is an explorative study.

RESULTS

There are 7701 live-born singleton infants in the ABCD-study since phase 1. At phase 3b we approached 5768 parent-child pairs of which 2746 parents filled out the complete CSHQ questionnaire (36% of the 7701 eligible infants, **Figure 5.1**).

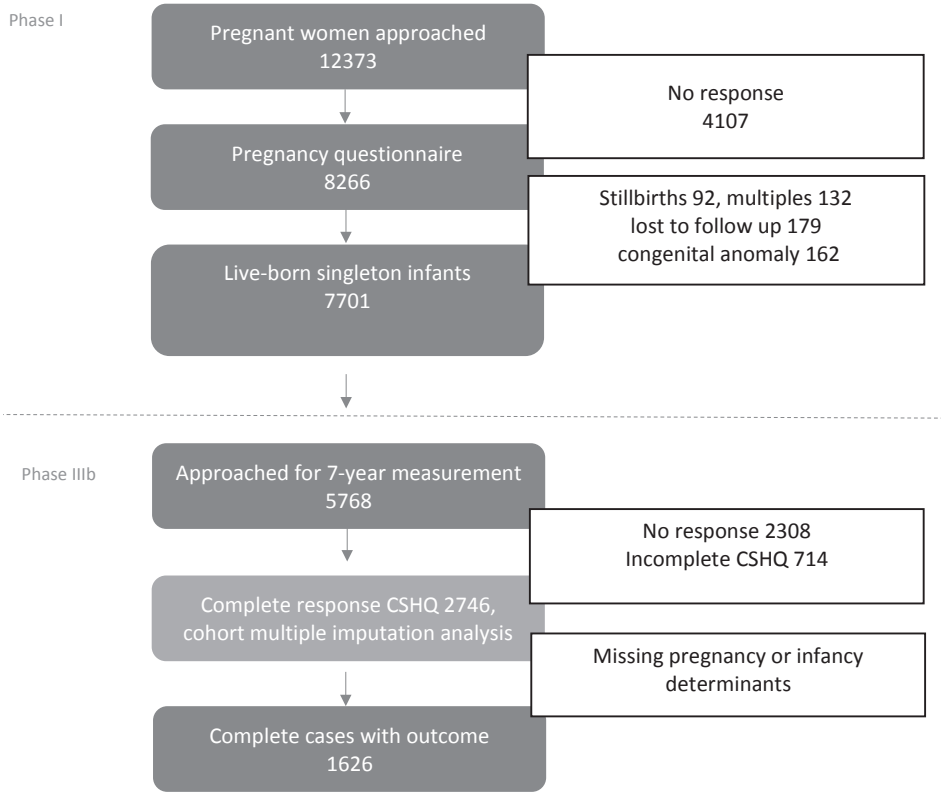

Figure 5.1: ABCD-study cohort profile and selection process for the this study

Table 5.1 shows the comparison between mother-child pairs that were invited for the questionnaire at age 7-8 years (base sample (n=5768) with mother-child pairs that completed the HCSQ questionnaire (n=2746) and complete cases with no missing potential determinants (n=1626). Mother-child pairs with imputed or complete data had slightly lower anxiety scores during pregnancy, were less often from a single parent household, were more often of Dutch origin, had higher maternal education, and more often a higher BMI-SDS delta growth between age 2 and 12 months.

Table 5.1: Demographic characteristics of baseline sample, multiple imputation sample and complete cases, showing selection bias and mean estimations of 20 multiple imputations.

	sample that was approached for questionnaire at age 7 years (n= 5768)	**multiple imputation (n=20) sample that completed CSHQ at age 7-8 years (n=2746)**	**complete cases (no missing values outcome and covariates) (n=1626)**
Pre-pregnancy BMI (kg/m2)	23.0	22.8	22.7
Physical activity during pregnancy			
(%)	15.9 %	10.7 %	8.5 %
None	40.5 %	36.0 %	31.8 %
Low	35.1 %	42.6 %	47.1 %
Moderate	8.5 %	10.7 %	12.7 %
High			
Maternal psychological wellbeing during pregnancy (scoring range)			
Anxiety symptoms score (STAI 20-80)	37.9	36.1	35.4
Sex (male)	49.9 %	51.5 %	51.7 %
BMI-SDS delta growth between age 2 and 12 months (SDS)	0.01	0.06	0.07
Single parent household (% yes)	12.0 %	8.7 %	7.4 %
Ethnicity (%)			
Dutch	60.5 %	72.2 %	78.0 %
African descent	9.9 %	5.6 %	3.4 %
Turkish	4.2 %	1.6 %	1.1 %
Maroccan	7.7 %	3.8 %	1.8 %
Others	17.8 %	16.9 %	15.7 %
Maternal education (%)			
low	19.2 %	11.2 %	7.8 %
middle	37.6 %	33.7 %	32.3 %
high	43.2 %	55.1 %	59.9 %

The mean (SD) sleep problem score in the total sample of 2746 children was 41.3 (4.5). We determined the p90 of sleep problem score within the cohort at a score of 49. Children with a high total CSHQ score scored on average higher on all subscales, most prominently on higher bedtime resistance and daytime sleepiness. Average sleep duration was also shorter in this group (10.3 hours compared to 10.7 hours per day) (**Table 5.2**).

Table 5.2: Child Sleep Habits Questionnaire (CSHQ) subscale scores in children with low to moderate versus high sleep problem score at age 7 years (n=2746)

	low-moderate sleep problem score n= 2460	high sleep problem score (CSHQ ≥ 49) n= 286
Bedtime resistance (6 items, mean (SD))	6.7 (1.2)	9.4 (2.6) *
Sleep onset delay (1 item, mean (SD))	1.4 (0.7)	1.9 (0.9) *
Sleep duration (3 items, mean (SD))	3.5 (0.8)	4.7 (1.4) *
Sleep anxiety (4 items, mean (SD))	4.6 (1.1)	6.6 (1.9) *
Night wakening (3 items, mean (SD))	3.4 (0.8)	4.5 (1.4) *
Parasomnias (7 items, mean (SD))	8.3 (1.3)	9.9 (2.0) *
Sleep disordered breathing (3 items, mean (SD))	3.2 (0.6)	3.7 (1.1) *
Daytime sleepiness (8 items, mean (SD))	10.9 (2.4)	15.7 (3.2) *
Total sleep problem score (CSHQ) (mean (SD))	39.9 (3.9)	53.2 (4.5) *
Sleep duration in hours (mean (SD))	10.7 (0.7) (n=2380)	10.3 (0.8) * (n=259)

*: CSHQ score is significantly different between two groups, Mann-Whitney test p<0.0001. The CSHQ items were rated on a 3-point scale; usually (5-7 times a week), sometimes (2-4 times a week), and rarely (0-1 time a week). A higher CSHQ score indicates more sleep problems on a continuous scale.

Table 5.3 presents information on potential determinants among children with a low to moderate sleep problem score versus a high sleep problem score. All variables were normally distributed. In the pregnancy category STAI and CES-D were highly correlated (r = 0.86) and CES-D was correlated with MFI (r = 0.61). STAI had the strongest correlation with total CSHQ score, so CES-D and MFI sum scores during pregnancy and infancy period were omitted from the analysis.

Results of the regression with minimal adjustment and multivariable regression analyses on the association between potential determinants and both total and high sleep problem score are shown in **Table 5.4**. We only describe the results on total sleep problem score in this results section (first and second column **Table 5.4**), giving a change in total sleep problem score for each potential determinant.

Pregnancy

There were two health indicators of the mother during pregnancy associated with a higher sleep problem score during childhood: pre-pregnancy BMI (β 0.12 (95% CI 0.05, 0.18); and symptoms of anxiety (β 0.06 (95% CI 0.03, 0.09)). Sleep of the mother during early pregnancy was not associated with sleep problems during childhood, neither was gestational diabetes.

Both alcohol and tobacco use during early pregnancy (gestational week 14) were associated with higher sleep problem scores in the multivariable model. Children of mothers that reported drinking ≥1 glass of alcohol a day around 14 weeks of gestation

Table 5.3: Mean and proportion calculated after multiple imputation of potential determinants in children with a low to moderate versus high CSHQ score at age 7 years (n=2746)

	Low- moderate sleep problem score (n=2460)	High sleep problem score (CSHQ ≥ 49, n=286)
Pregnancy		
Pre-pregnancy BMI (kg/m2)	22.7	23.6
Gestational sleep sleep/resting during pregnancy (hours)	8.8	8.9
Gestational diabetes (% yes)	1.4	2.1
Hypertensive condition during pregnancy (% yes)	14.7	14.2
Physical activity during pregnancy (%)		
None	10.3	14.0
Low	35.5	40.2
Moderate	43.4	36.4
High	10.8	9.4
Maternal psychological wellbeing during pregnancy (scoring range)		
Anxiety symptoms score (STAI 20-80)	35.7	40.2
Amount of caffeine intake a day (mg)	177.5	161.2
≥1 glass of alcohol a day during pregnancy (% yes)	0.7	1.4
≥1 cigarette a day during pregnancy (% yes)	5.2	8.4
Medication use during pregnancy (% yes)		
painkillers	22.5	28.3
sedatives or sleep medication	0.5	2.2
antidepressants	0.7	1.8
Drug use during pregnancy (% yes)		
Cannabis	1.4	0.7
Cocaine	0.2	0.7
XTC or speed	0.4	0
Birth outcomes		
Low birth weight <p10 (% yes)	7.8	10.5
Premature birth <36wk (% yes)	4.6	3.8
Artificial delivery (% yes)	9.5	12.5
Infancy		
Male sex (%)	51.9	48.6
Change in BMI SD score between age 2 and 12 months	0.085	-0.158
Excessive crying at age 3 months (% yes)	1.4	2.9
Breastfeeding (%)		
None	15.0	16.9
1-6 months	50.8	52.1
>6 months (reference)	34.1	31.0
Method of feeding at age 3 months (%)		
Scheduled	23.8	26.4
On demand (reference)	71.7	69.7
Other	4.4	3.9
> 8 feedings a day at age 3 months (% yes)	3.1	6.9

Table 5.3: Mean and proportion calculated after multiple imputation of potential determinants in children with a low to moderate versus high CSHQ score at age 7 years (n=2746) (*continued*)

	Low- moderate sleep problem score (n=2460)	High sleep problem score (CSHQ ≥ 49, n=286)
> 1 feeding during the night at age 3 months (% yes)	16.5	24.0
Start of additional (solids) feeding (%)		
<4 months	5.5	6.0
4-6 months	93.5	92.1
>6 months	1.0	1.9
Parental nighttime behaviors at age 3 months (% yes)		
Sleeping in parent's bed	7.9	14.1
Swaddling at night	20.1	24.8
Pacifier when falling asleep at night	54.9	58.9
Bottle feeding when falling asleep	3.9	8.3
Waking up during the first 3 months by (% yes)		
Shortness of breath	3.6	4.9
Dry cough	2.0	3.6
Itching rash	7.0	9.8
Maternal psychological wellbeing 3 months after birth (scoring range)		
Anxiety symptoms score (STAI 20-80)	33.6	37.2
Perceived burden of upbringing (NVOS 5-20)	5.9	6.1
Perceived pleasure of baby care (VL 5-20))	16.7	16.2
Maternal sleep/resting duration at 3 months (hours)	7.5	7.6
Start daycare before age 12 months (%)	37.5	46.7
Context		
Maternal age (years)	32.1	31.6
Single parent household (% yes)	8.0	14.7
Ethnicity (%)		
Dutch	73.5	60.8
African descent	5.0	10.5
Turkish	1.5	2.4
Moroccan	3.4	7.3
Others	16.6	18.9
Maternal education (%)		
low	10.4	18.4
middle	33.3	37.1
high (reference)	56.3	44.6
≥1 older sibling(s) in household (% yes)	40.6	41.6
Controlling variables		
Maternal depression, anxiety stress score (DASS) at 5 years of age (SD)	7.8	11.0

CES-D: Center for Epidemiologic Studies Depression; STAI: State-Trait Anxiety Inventory ; NVOS; Dutch questionnaire about the upbringing; VL, Dutch care list; CSHQ (Child Sleep Habit Questionnaire); DASS (Depression, Anxiety and Stress scales)

Table 5.4: Associations between potential determinants and the total sleep problem score (n=2746)

	Minimally adjusted	Multivariable (complete)
	ß (95% CI)	**ß (95% CI)**
Pregnancy		
Pre-pregnancy BMI (kg/m2)	**0.16 (0.10, 0.22)**	**0.10 (0.04, 0.17)**
Gestational sleep sleep/resting (hours)	0.10 (-0.04, 0.23)	-0.04 (-0.18, 0.11)
Gestational diabetes (yes)	0.65 (-1.10, 2.39)	-0.64 (-2.39, 1.11)
Maternal psychological wellbeing during pregnancy (scoring range)		
Anxiety symptoms score (STAI 20-80)	**0.11 (0.08, 0.13)**	**0.06 (0.03, 0.09)**
Caffeine intake a day (mg)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)
≥1 glass of alcohol per day during pregnancy (yes)	**2.38 (0.01, 4.75)**	**2.55 (0.21, 4.89)**
≥1 cigarette per day during pregnancy (yes)	**1.46 (0.54, 2.39)**	**1.08 (0.11, 2.04)**
Medication use during pregnancy (yes)		
painkillers	**0.55 (0.04, 1.05)**	0.46 (-0.04, 0.96)
sedatives or sleep medication	2.48 (-0.10, 5.05)	1.49 (-1.11, 4.09)
antidepressants	1.83 (-0.52, 4.17)	1.17 (-1.17, 3.51)
Drug use during pregnancy (yes)		
Cannabis	-1.10 (-2.95, 0.76)	-1.72 (-3.59, 0.16)
*Cocaine **	0.69 (-3.25, 4.62)	0.42 (-3.57, 4.41)
XTC or speed	-0.20 (-3.71, 3.30)	0.14 (-3.44, 3.72)
Birth outcomes		
Low birth weight <p10 (yes)	**0.90 (0.12, 1.67)**	0.24 (-0.54, 1.02)
Premature birth <36wk (yes)	0.03 (-0.98, 1.05)	-0.18 (-1.19, 0.84)
Artificial delivery (yes)	0.51 (-0.28, 1.31)	0.26 (-0.53, 1.04)
Infancy		
Male sex (yes)	-0.31 (-0.73, 0.11)	-0.35 (-0.77, 0.07)
Change in BMI SD score between age 2 and 12 months	**-0.32 (-0.58, -0.05)**	**-0.32 (-0.60, -0.04)**
Breastfeeding		
None	0.26 (-0.39, 0.92)	0.08 (-0.61, 0.77)
1-6 months	-0.06 (-0.53, 0.42)	-0.06 (-0.56, 0.45)
>6 months (reference	reference	reference
Excessive crying at age 3 months (yes)	0.47 (-1.81, 2.75)	-0.39 (-2.71, 1.93)
Method of feeding at age 3 months		
Scheduled	-0.05 (-0.60, 0.50)	-0.13 (-0.70, 0.45)
On demand (reference)	reference	reference
Other	-0.28 (-1.52, 0.96)	-0.41 (-1.65, 0.82)
> 8 feedings a day at age 3 months (yes)	**1.92 (0.52, 3.32)**	0.92 (-0.45, 2.29)
> 1 feeding during the night at age 3 months (yes)	**1.36 (0.75, 1.98)**	0.44 (-0.24, 1.13)

Table 5.4: Associations between potential determinants and the total sleep problem score (n=2746) (*continued*)

	Minimally adjusted	Multivariable (complete)
Start of additional (solids) feeding		
<4 months		
4-6 months (reference)	0.66 (-0.31, 1.63)	0.01 (-0.96, 0.98)
>6 months	reference	reference
	0.47 (-2.19, 3.12)	-0.08 (-2.80, 2.64)
Parental nighttime behaviors at age 3 months		
(yes)	**1.62 (0.71, 2.53)**	0.82 (-0.15, 1.80)
Sleeping in parent's bed	**0.62 (0.06, 1.19)**	0.28 (-0.30, 0.85)
Swaddling at night	0.30 (-0.14, 0.74)	0.40 (-0.06, 0.85)
Pacifier when falling asleep at night	**1.43 (0.19, 2.68)**	0.62 (-0.69, 1.92)
Bottle feeding when falling asleep		
Waking up during the first 3 months by (yes)		
Shortness of breath	0.60 (-0.74, 1.93)	-0.32 (-1.68, 1.04)
Dry cough	1.51 (-0.44, 3.45)	0.54 (-1.46, 2.53)
Itching rash	0.46 (-0.50, 1.43)	0.01 (-1.01, 1.03)
Maternal psychological wellbeing 3 months after birth (scoring range)		
Anxiety symptoms score (STAI 20-80)	**0.09 (0.06, 0.12)**	**0.04 (0.00, 0.07)**
Perceived burden of upbringing (NVOS 5-20)	**0.16 (0.00, 0.31)**	-0.11 (-0.30, 0.08)
Perceived pleasure of baby care (VL 5-20)	**-0.18 (-0.28, -0.09)**	-0.09 (-0.22, 0.03)
Maternal sleep/resting duration (hours)	0.07 (-0.10, 0.25)	0.12 (-0.07, 0.30)
Start daycare before age 12 months (yes)	**0.77 (0.33, 1.20)**	0.02 (-0.46, 0.50)
Context		
Maternal age (years)	-0.04 (-0.09, 0.01)	-0.00 (-0.06, 0.05)
Single parent household (yes)	**1.73 (0.98, 2.48)**	0.71 (-0.10, 1.52)
Ethnicity		
Dutch (reference)	reference	reference
African descent	**2.48 (1.55, 3.40)**	0.88 (-0.13, 1.90)
Turkish	1.35 (-0.36, 3.05)	-0.55 (-2.34, 1.25)
Moroccan	**2.00 (0.89, 3.11)**	0.52 (-0.73, 1.77)
Others	**0.72 (0.15, 1.29)**	0.33 (-0.25, 0.91)
Maternal education		
low	**2.12 (1.43, 2.81)**	0.54 (-0.29, 1.38)
middle	**0.81 (0.35, 1.27)**	0.34 (-0.14, 0.82)
high (reference)	reference	reference
≥1 older sibling(s) in household (yes)	0.37 (-0.06, 0.80)	0.13 (-0.34, 0.60)

Regression model with minimal adjustment: adjusting for the maternal depression, anxiety and stress score (DASS21) at the 5-year questionnaire and the age of the child at the time of the outcome measurements. Multivariable regression model: also adjusted for all other factors added at once. **Bold:** statistically significant ($p < 0.05$), STAI: State-Trait Anxiety Inventory; NVOS: Dutch questionnaire about the upbringing situation; VL: Dutch caregiving list. *: wider 95% CI due to a low incidence of cocaine use.

had more than two points higher sleep problems scores (ß 2.55 (95% CI 0.21, 4.89)) and children of mothers that reported smoking ≥1 cigarette per day in that period had approximately one point higher sleep problem scores (ß 1.07 (95% CI 0.10, 2.03)). In the regression model with minimal adjustment, medication use during pregnancy was associated with more sleep problems. Associations for painkillers; sedatives or sleep medication; and antidepressants were in the same direction, but all associations were attenuated and non-significant in the multivariable analysis. Caffeine; cannabis; cocaine and XTC or speed intake during pregnancy were not associated with sleep problems.

Birth outcomes

Having a low birth weight was associated with a higher sleep problem score (ß 0.90 (95% CI 0.12, 1.67)) in regression model with minimal adjustment only. Premature birth and artificial delivery were not associated with sleep problems.

Infancy

Being a mother with more symptoms of anxiety three months after delivery, independent of anxiety symptoms during pregnancy and all other potential determinants, was again associated with a higher sleep problem score for the child at age seven years, only for the continuous outcome (ß 0.04 (95% CI 0.00, 0.07)). A higher perceived burden of the upbringing by the mother and lower pleasure in taking care of the baby three months after delivery were both associated with the more sleep problems in the regression model with minimal adjustment, but effects disappeared after adjustment for the other potential determinants. Children who had a relative larger increase in BMI SD score compared to their peers had a lower sleep problem score at age seven years (ß -0.32 (95% CI -0.58, -0.05)).

Some infancy factors (e.g. feeding and sleeping practices; and start of daycare) were associated with more sleep problems in the regression model with minimal adjustment, but after adjustment for all other potential determinants associations disappeared or were much smaller and non-significant. Gender, breastfeeding; on demand feeding; start of additional (solid) feeding; maternal sleep duration during infancy, excessive crying; and waking up by shortness of breath; dry cough; or itching rash were not associated with childhood sleep problems.

Context

Ethnicity, maternal education and single parenting were only associated with childhood sleep in the regression model with minimal adjustment, and associations were much smaller after adjustment for other variables in the complete model. The sen-

sitivity analysis showed that single parent household; ethnicity; and maternal education level were significantly associated in the model with contextual factors only. Maternal age and older siblings in the household were not associated with childhood sleep problems.

Sensitivity analyses

Regression analysis for subscales of the CSHQ sleep problem score showed that the associations were in essence in the same direction compared to the total sleep problem score and often also significant on CSHQ subscales (**Table S5.1**). Bedtime resistance was more often significant than the other subscales and often without significance on the total sum score. Multivariable models ran separately for each category showed similar results than the complete model (**Table S5.2**). The beta's in these models are larger and more often significant. After backward selection of the potential determinants we identified the same factors, as well as single parent household and ethnicity to be significantly associated (**Table S5.2**). Analysis without controlling for maternal depression did not change the results (data not shown).

DISCUSSION

This study explores potential determinants during the first 1000 days of sleep problems at school age in an urban sample born in 2003-2004. Pregnancy factors positively associated with a higher sleep problem score at age 7-8 years were pre-pregnancy BMI; drinking ≥1 glass of alcohol or smoking ≥1 cigarette per day; and having more symptoms of anxiety during pregnancy. Maternal symptoms of anxiety and relative infant weight loss during infancy were also positively associated with more sleep problems.

We are the second study to report an association between pre-pregnancy BMI and a higher sleep problem score during childhood. Mina et al studied the same association, with sleep problems measured at offspring age 3-5 years. They report that the average CSHQ sleep problem score was 6 points higher in children of mothers with extreme obesity (BMI>40 kg/m^2) compared to lean mothers (BMI 18.5-25 kg/m^2) and that the found association was independent of demographic factors, prenatal factors and maternal concurrent symptoms of anxiety and depression (48). We calculated simple adjusted beta coefficients for problems scores of children of mothers with pre-pregnancy overweight, obesity and extreme obesity to compare our results and found similar effect sizes. Compared to children of lean mothers, we found a 1.26 point higher sleep problem score (95% CI 0.63, 1.89) in children of mothers with

overweight; 1.99 for obesity (95% CI 0.81, 3.17); and 5.02 for extreme obesity (1.69, 8.35). The found association between maternal BMI and sleep problems is although small, in line with epidemiologic studies with other neurodevelopmental adverse outcomes. (48-52). A study in mice revealed an epigenetic biological pathway that could explain this association: maternal obesity disrupted epigenetic regulation of brain development in the offspring (53).

We explored associations for several medications and substances used during early pregnancy. We found that smoking ≥1 cigarette per day during pregnancy was associated with a higher sleep problem score, hereby confirming the findings of an earlier study in children up to age 12 years (21). Both animal and human studies have shown abnormal cardiorespiratory response during sleep, less sleep and more fragmented sleep in newborns after prenatal nicotine exposure (54-57). Also, nicotine in breastmilk has been shown to decrease sleep length in infants (58). Unknown is if these associations are still present during later childhood. The underlying mechanism for the association might be the interaction between nicotine with its nicotinic acetylcholine receptors (59). Activation of these receptors alters the development of the fetal nervous system during the early prenatal stage. This may lead to a delayed neurodevelopment in the first few years of life; decreased cognitive functioning; and negative behavioral outcomes during childhood, which could all lead to sleep problems (59). Next to smoking, we also found an association with alcohol use. Drinking ≥1 glass of alcohol a day during pregnancy was associated with a higher sleep problem score in our sample. In prior studies, maternal alcohol use during pregnancy has been associated with night terrors but not with other sleep problems at age four to nine years (20) and to shorter sleep and lower sleep efficiency at age eight years (19). A possible mechanism is that prenatal alcohol exposure alters the function of the hypothalamic-pituitary-adrenocortical axis, which causes higher blood cortisol levels and influences sleep infrastructure in the child (60, 61). We found no significant association with drug use or medication use, probably due to the low prevalence. We therefore recommend further investigation of these associations in larger cohorts with more variation in medication use.

Both maternal psychological wellbeing during pregnancy and infancy were associated with a higher sleep problem score at age 7-8 years. Although the coefficients seem small, they reflect the change in sleep problem score per 1 point difference on the STAI, which has a range of 20-80. For a child of a mother with >2 SD higher STAI score, this means a two-and-a-half point higher sleep problem score (ß2.49 (95% CI 1.36, 3.62)). Two other studies found an association between postnatal maternal mental health and childhood sleep problems (20, 22), but the association with prenatal ma-

ternal mental health has not been assessed to our knowledge. The potential mechanism explaining pre- and postnatal effects of maternal mental health problems on the child's sleep is through dysregulation of the hypothalamic-pituitary-adrenal axis and higher levels of cortisol in mother and child (61-63). A higher cortisol exposure effects the fetal programming of the nervous system and leads to an increased risk for behavioral problems (64). Sleep problems might be associated through similar pathways as behavioral problems.

We found an association between relative infant weight loss (negative BMI SD change between infant age of two and twelve months) and sleep problems score during childhood. In clinical practice, attention is raised when the weight of a child changes with more than 0.67 SD between two measurements. For this reason we repeated the analysis with a categorical variable (delta BMI < -0.67; -0.67 to 0.67; and > 0.67 SD) and noticed that the association with delta-BMI was mostly driven by a higher sleep problem score (>p90) in children with a large decrease in BMI (delta-BMI SD < -0.67), although associations were not significant (data not shown). Possible pathways for an association or common mechanism of relative weight loss and sleep problems would be self-regulation disturbance or neurodevelopmental problems causing both growth and sleep disorders. We are unaware of earlier studies that investigated relative weight loss during infancy and sleep problems during childhood.

Previous research is inconclusive on the effects of ethnicity on childhood sleep (25, 65-67). We did see a significant association between ethnicity and sleep problems in the regression model with minimal adjustment and in the contextual model, but not in the multivariable model. With backward selection however, ethnicity and also single parent household were significantly associated. A possible explanation is that differences between ethnicities and single versus double parenthood are due to cultural and environmental differences in upbringing and sleeping habits which were also included in the complete model (3). It would be interesting to explore which factors contribute to the ethnic and socioeconomic differences in sleep problems observed in the regression models with minimal adjustment and previous studies.

Strengths and limitations

A strength of this study is the large sample size, followed from early pregnancy onwards. We explored potential early life determinants during pregnancy and infancy and measurements of parental wellbeing. Use of tobacco; alcohol; drugs; and medication was assessed during early pregnancy, which is the most important period of fetal neurodevelopment. Many potential determinants have not been studied before and there are many other contextual factors that have not been measured in the

ABCD-study. Therefore we cannot rule out residual confounding. Another limitation is that we could have introduced colliders by adding all potential determinants at once. As previously suggested we have added backward selection as a sensitivity analysis which provided similar results overall. Additionally we provided possible explanations for the associations we found. This is an explorative study, we therefore recommend confirmation of our findings in future studies including mediation analysis and selection of relevant confounders based on causal models (also known as directed acyclic graphs (DAGs)). Due to multiple testing there is a higher chance of finding a positive association. This is however an explorative study, for which reason we do not want to tighten the threshold to a lower p-value.. The findings need to be replicated in other populations, preferably combined with assessment of the mechanical pathways. A limitation was information bias as information on sleep problems and most potential determinants were based on self-report, which could suffer from socially desirable answers and recall bias. In the comparison with other studies, we noticed that there is a large variation in the assessment method of sleep problems, which limited the comparison with other studies. The mean CSHQ score in our sample was comparable to other studies, but close to the cut-off score used in a prior study (5). For this reason, we used the 90th percentile as a cut-off for sleep problems in descriptive statistics. We used the total sum score and subscale scores and found comparable results. Bedtime resistance problems were more prevalent than other sleep problems and could influence sleep duration and sleep efficacy. As shown in **Table 5.1** selection bias plays a role in our study as the mothers in the analyzed sample were more often of Dutch origin and had higher maternal education and less often living as a single parent. We minimized selection bias by performing multiple imputation for missing covariates. As this is an observational study, the results only show an association between potential determinants and sleep outcomes and do not assess causation.

Future recommendations

We recommend further research to reproduce our findings of potential determinants in the first 1000 days of life. Future studies may explore possible mechanisms of causality by conducting mediation analysis and selection of confounders could be done with the help of causal models (also known as directed acyclic graphs (DAGs)). Environmental factors during infancy that we could not include, but are recommended for future studies, are: screen time in the first two years of life; ambient noise (background noise from music or television; street sounds); and parenting practices (including bedtime routine and sleep initiation method) (25, 68). Uniform measurement of sleep problems can enhance comparability between studies.

Conclusions

We found the following factors as potential determinants of sleep problems among children aged 7-8 years as: pre-pregnancy BMI; alcohol and tobacco use during pregnancy; relative infant weight loss; and maternal mental health during pregnancy and infancy. If confirmed by other studies, these potential determinants may be used for early identification of children with increased risk of sleep problems. Early identification is the first step to early intervention and promotion of healthy sleep during the child's lifetime.

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SUPPLEMENTAL INFORMATION

Table S5.1: Multivariable associations between potential determinants and the subscales and total sleep problem score (n=2746)

	subscale bedtime resistance	subscale daytime sleepiness	subscale parasomnias	CSHQ total
	ß (95% CI)	**ß (95% CI)**	**ß (95% CI)**	**ß (95% CI)**
Pregnancy				
Pre-pregnancy BMI (kg/m2)	**0.03 (0.01, 0.05)**	0.03 (-0.00, 0.06)	**0.03 (0.01, 0.04)**	**0.10 (0.04, 0.17)**
Gestational sleep sleep/resting (hours)	0.03 (-0.01, 0.08)	-0.05 (-0.12, 0.02)	0.02 (-0.02, 0.05)	-0.04 (-0.18, 0.11)
Gestational diabetes (yes)	0.06 (-0.46, 0.57)	-0.50 (-1.38, 0.39)	-0.11 (-0.58, 0.37)	-0.64 (-2.39, 1.11)
Maternal psychological wellbeing during pregnancy (scoring range) *Anxiety symptoms score (STAI 20-80)*	**0.01 (0.00, 0.02)**	**0.02 (0.00, 0.03)**	**0.01(0.00, 0.02)**	**0.06 (0.03, 0.09)**
Caffeine intake a day (mg)	0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)
≥1 glass of alcohol per day during pregnancy (yes)	0.26 (-0.43, 0.95)	**1.27 (0.08, 2.45)**	**0.36 (-0.27, 0.99)**	**2.55 (0.21, 4.89)**
≥1 cigarette per day during pregnancy (yes)	0.14 (-0.14, 0.42)	**0.51 (0.03, 1.00)**	0.23 (-0.03, 0.49)	**1.08 (0.11, 2.04)**
Medication use during pregnancy (yes) *Painkillers* *sedatives or sleep medication* *antidepressants*	 -0.04 (-0.19, 0.11) 0.47 (-0.30, 1.24) **0.75 (0.05, 1.44)**	 0.16 (-0.09, 0.42) 0.18 (-1.12, 1.48) 0.01 (-1.16, 1.18)	 **0.19 (0.05, 0.32)** 0.46 (-0.23, 1.15) -0.02 (-0.65, 0.61)	 0.46 (-0.04, 0.96) 1.49 (-1.11, 4.09) 1.17 (-1.17, 3.51)
Drug use during pregnancy (yes) *Cannabis* *Cocaine ** *XTC or speed*	 **-0.69 (-1.25,-0.14)** **1.28 (0.10, 2.46)** 0.11 (-0.94, 1.17)	 -0.62 (-1.57, 0.33) -0.89 (-2.91, 1.14) 0.22 (-1.60, 2.03)	 -0.03 (-0.54, 0.47) 0.24 (-0.83, 1.32) 0.50 (-0.47, 1.48)	 -1.72 (-3.59, 0.16) 0.42 (-3.57, 4.41) 0.14 (-3.44, 3.72)
Birth outcomes				
Low birth weight <p10 (yes)	0.10 (-0.13, 0.33)	-0.05 (-0.45, 0.34)	0.11 (-0.10, 0.32)	0.24 (-0.54, 1.02)
Premature birth <36wk (yes)	-0.19 (-0.49, 0.11)	0.04 (-0.47, 0.56)	0.15 (-0.13, 0.42)	-0.18 (-1.19, 0.84)
Artificial delivery (yes)	-0.04 (-0.26, 0.19)	0.11 (-0.27, 0.50)	**0.21 (0.00, 0.42)**	0.26 (-0.53, 1.04)
Infancy				

Table S5.1: Multivariable associations between potential determinants and the subscales and total sleep problem score (n=2746) (*continued*)

	subscale bedtime resistance	subscale daytime sleepiness	subscale parasomnias	CSHQ total
Male sex (yes)	0.12 (-0.00, 0.24)	**-0.64(-0.85 -0.43)**	0.09 (-0.03, 0.20)	-0.35 (-0.77, 0.07)
Change in BMI SD score between age 2 and 12 months	**-0.09(-0.17,-0.01)**	-0.10(-0.23, 0.04)	-0.03 (-0.10, 0.03)	**-0.32 (-0.60, -0.04)**
Breastfeeding				
None	-0.05 (-0.26, 0.15)	-0.07 (-0.42, 0.28)	0.13 (-0.06, 0.31)	0.08 (-0.61, 0.77)
1-6 months	-0.01 (-0.15, 0.14)	-0.17 (-0.43, 0.08)	0.11 (-0.03, 0.24)	-0.06 (-0.56, 0.45)
>6 months (reference	reference	reference	reference	reference
Excessive crying at age 3 months (yes)	-0.25 (-0.83, 0.33)	-0.69 (-1.82, 0.44)	0.13 (-0.49, 0.74)	-0.39 (-2.71, 1.93)
Method of feeding at age 3 months				
Scheduled	-0.02 (-0.18, 0.14)	-0.15 (-0.43, 0.13)	0.10 (-0.05, 0.25)	-0.13 (-0.70, 0.45)
On demand (reference)	reference	reference	reference	reference
Other	-0.07 (-0.43, 0.28)	0.05 (-0.54, 0.63)	-0.14 (-0.46, 0.17)	-0.41 (-1.65, 0.82)
> 8 feedings a day at age 3 months (yes)	0.31 (-0.09, 0.71)	0.61 (-0.07, 1.29)	**-0.38(-0.74,-0.01)**	0.92 (-0.45, 2.29)
> 1 feeding during the night at age 3 months (yes)	0.18 (-0.02, 0.38)	-0.07 (-0.41, 0.27)	0.20 (-0.00, 0.40)	0.44 (-0.24, 1.13)
Start of additional (solids) feeding				
<4 months	0.10 (-0.18, 0.38)	-0.10 (-0.61, 0.41)	-0.03 (-0.30, 0.23)	
4-6 months (reference)	reference	reference	reference	0.01 (-0.96, 0.98)
>6 months	-0.19 (-1.03, 0.66)	-0.20 (-1.52, 1.12)	0.22 (-0.50, 0.93)	reference
				-0.08 (-2.80, 2.64)
Parental nighttime behaviors at age 3 months (yes)				
Sleeping in parent's bed				
Swaddling at night	**0.37 (0.10, 0.64)**	0.30 (-0.15, 0.74)	-0.07 (-0.32, 0.17)	0.82 (-0.15, 1.80)
Pacifier when falling asleep at night	0.06 (-0.11. 0.23)	0.02 (-0.27, 0.31)	0.07 (-0.08, 0.23)	0.28 (-0.30, 0.85)
Bottle feeding when falling asleep	0.03 (-0.11, 0.16)	**0.25 (0.02, 0.48)**	-0.02 (-0.14, 0.11)	0.40 (-0.06, 0.85)
	0.20 (-0.18, 0.57)	0.42 (-0.21, 1.05)	-0.04 (-0.38, 0.30)	0.62 (-0.69, 1.92)

Table S5.1: Multivariable associations between potential determinants and the subscales and total sleep problem score (n=2746) (*continued*)

	subscale bedtime resistance	subscale daytime sleepiness	subscale parasomnias	CSHQ total
Waking up during the first 3 months by (yes)				
Shortness of breath	-0.08 (-0.52, 0.36)	0.06 (-0.60, 0.72)	-0.24 (-0.59, 0.11)	-0.32 (-1.68, 1.04)
Dry cough	0.02 (-0.53, 0.57)	0.09 (-0.89, 1.07)	0.30 (-0.20, 0.80)	0.54 (-1.46, 2.53)
Itching rash	-0.02 (-0.31, 0.27)	0.17 (-0.32, 0.66)	-0.10 (-0.37, 0.16)	0.01 (-1.01, 1.03)
Maternal psychological wellbeing 3 months after birth (scoring range)				
Anxiety symptoms score (STAI 20-80)	0.01 (-0.00, 0.02)	0.02 (-0.00, 0.03)	0.01 (-0.00, 0.02)	**0.04 (0.00, 0.07)**
Perceived burden of upbringing (NVOS 5-20)	0.02 (-0.04, 0.07)	-0.07 (-0.16, 0.03)	-0.04 (-0.09, 0.01)	-0.11 (-0.30, 0.08)
Perceived pleasure of baby care (VL 5-20)	-0.01 (-0.05, 0.02)	-0.02 (-0.09, 0.04)	-0.01 (-0.04, 0.03)	-0.09 (-0.22, 0.03)
Maternal sleep/resting duration (hours)	**0.06 (0.01, 0.12)**	0.05 (-0.04, 0.15)	-0.02 (-0.07, 0.03)	0.12 (-0.07, 0.30)
Start daycare before age 12 months (yes)	-0.04 (-0.18, 0.10)	-0.14 (-0.38, 0.11)	-0.01 (-0.14, 0.12)	0.02 (-0.46, 0.50)
Context				
Maternal age (years)	**0.03 (0.01, 0.04)**	**-0.04(-0.07,-0.01)**	0.00 (-0.01, 0.02)	-0.00 (-0.06, 0.05)
Single parent household (yes)	**0.35 (0.11, 0.58)**	0.27 (-0.14, 0.67)	0.02 (-0.20, 0.23)	0.71 (-0.10, 1.52)
Ethnicity				
Dutch (reference)	reference	reference	reference	reference
African descent	0.14 (-0.16, 0.44)	**0.82 (0.31, 1.33)**	0.10 (-0.18, 0.37)	0.88 (-0.13, 1.90)
Turkish	0.51 (-0.01, 1.04)	0.11 (-0.80, 1.02)	**-0.77(-1.26,-0.29)**	-0.55 (-2.34, 1.25)
Moroccan	0.31 (-0.06, 0.68)	0.56 (-0.07, 1.20)	-0.09 (-0.42, 0.24)	0.52 (-0.73, 1.77)
Others	0.16 (-0.01, 0.33)	0.29 (-0.00, 0.58)	-0.03 (-0.18, 0.13)	0.33 (-0.25, 0.91)
Maternal education				
low	**0.34 (0.09, 0.58)**	-0.19 (-0.60, 0.23)	0.18 (-0.05,0.40)	0.54 (-0.29, 1.38)
middle	**0.18 (0.04, 0.32)**	0.04 (-0.20, 0.29)	**0.14(0.01, 0.27)**	0.34 (-0.14, 0.82)
high (reference)	reference	reference	reference	reference
≥1 older sibling(s) in household (yes)	-0.04 (-0.18, 0.09)	**0.35 (0.11, 0.59)**	-0.09 (-0.22, 0.04)	0.13 (-0.34, 0.60)

Multivariable regression model: adjusted for the maternal depression, anxiety and stress score (DASS21) at the 5-year questionnaire and the age of the child at the time of the outcome measurements and for all potential determinants added at once. **Bold:** statistically significant ($p < 0.05$)

STAI: State-Trait Anxiety Inventory; NVOS: Dutch questionnaire about the upbringing situation; VL: Dutch caregiving list; *: wider 95% CI due to a low incidence of cocaine use.

Table S5.2: Multivariable associations between different selections of potential determinants and sleep problems: in a separate model per category; selected with backward selection; and a complete model as in Table 4 (n=2746)

	pregnancy	birth outcome	infancy	context	backward selection	complete model
	ß (95% CI)	**ß (95% CI)**	**ß (95% CI)**	**ß (95% CI)**	**ß (95% CI)**	**ß (95% CI)**
Pregnancy						
Pre-pregnancy BMI (kg/m2)	**0.13 (0.07, 0.19)**				**0.12 (0.05, 0.18)**	**0.10 (0.04, 0.17)**
Gestational sleep sleep/resting (hours)	0.02 (-0.11, 0.16)					-0.04 (-0.18, 0.11)
Gestational diabetes (yes)	-0.11 (-1.84, 1.62)					-0.64 (-2.39, 1.11)
Maternal anxiety symptoms score during pregnancy (STAI range 20-80)	**0.09 (0.07, 0.12)**				**0.07 (0.04, 0.09)**	**0.06 (0.03, 0.09)**
Caffeine intake a day (mg)	**-0.00 (-0.00,-0.00)**					-0.00 (-0.00, 0.00)
≥1 glass of alcohol per day during pregnancy (yes)	**2.47 (0.14, 4.80)**				**2.59 (0.28, 4.91)**	**2.55 (0.21, 4.89)**
≥1 cigarette per day during pregnancy (yes)	**1.17 (0.23, 2.10)**				**1.01 (0.09, 1.92)**	**1.08 (0.11, 2.04)**
Medication use during pregnancy (yes)						
Painkillers	0.37 (-0.13, 0.87)					0.46 (-0.04, 0.96)
sedatives or sleep medication	1.59 (-099, 4.18)					1.49 (-1.11, 4.09)
antidepressants	1.17 (-1.14, 3.49)					1.17 (-1.17, 3.51)
Drug use during pregnancy (yes)						
Cannabis	-1.39 (-3.26, 0.48)					-1.72 (-3.59, 0.16)
Cocaine *	0.63 (-3.35, 4.61)					0.42 (-3.57, 4.41)
XTC or speed	-0.01 (-3.57, 3.55)					0.14 (-3.44, 3.72)
Birth outcomes						
Low birth weight <p10 (yes)		**0.88 (0.10, 1.65)**				0.24 (-0.54, 1.02)
Premature birth <36wk (yes)		0.07 (-0.95, 1.09)				-0.18 (-1.19, 0.84)
Artificial delivery (yes)		0.47 (-0.33, 1.27)				0.26 (-0.53, 1.04)
Infancy						

Male sex (yes)		-0.36 (-0.78, 0.06)		-0.35 (-0.77, 0.07)
Change in BMI SD score between age 2 and 12 months		**-0.31 (-0.58, -0.04)**	**-0.33 (-0.59, -0.07)**	**-0.32 (-0.60, -0.04)**
Breastfeeding				
None		0.35 (-0.34, 1.04)		0.08 (-0.61, 0.77)
1-6 months		0.06 (-0.44, 0.56)		-0.06 (-0.56, 0.45)
>6 months (reference		reference		reference
Excessive crying at age 3 months (yes)		-0.40 (-2.70, 1.90)		-0.39 (-2.71, 1.93)
Method of feeding at age 3 months				
Scheduled		-0.03 (-0.60, 0.54)		-0.13 (-0.70, 0.45)
On demand (reference)		reference		reference
Other		-0.36 (-1.61, 0.88)		-0.41 (-1.65, 0.82)
> 8 feedings a day at age 3 months (yes)		1.14 (-0.24, 2.53)		0.92 (-0.45, 2.29)
> 1 feeding during the night at age 3 months (yes)		0.64 (-0.04, 1.32)		0.44 (-0.24, 1.13)
Start of additional (solids) feeding				
<4 months		0.40 (-0.58, 1.37)		
4-6 months (reference)		reference		0.01 (-0.96, 0.98)
>6 months		0.16 (-0.51, 0.82)		reference
				-0.08 (-2.80, 2.64)
Parental nighttime behaviors at age 3 months (yes)		**1.09 (0.15, 2.03)**		0.82 (-0.15, 1.80)
Sleeping in parent's bed		0.29 (-0.29, 0.86)		0.28 (-0.30, 0.85)
Swaddling at night		0.41 (-0.04, 0.87)		0.40 (-0.06, 0.85)
Pacifier when falling asleep at night		1.07 (-0.21, 2.34)		0.62 (-0.69, 1.92)
Bottle feeding when falling asleep				
Waking up during the first 3 months by (yes)		-0.15 (-1.52, 1.23)		-0.32 (-1.68, 1.04)
Shortness of breath		0.68 (-1.37, 2.73)		0.54 (-1.46, 2.53)
Dry cough		0.14 (-0.87, 1.16)		0.01 (-1.01, 1.03)
Itching rash				

Maternal psychological wellbeing 3 months after birth (scoring range)			
Anxiety symptoms score (STAI 20-80)	**0.08 (0.05, 0.11)**	**0.04 (0.01, 0.07)**	**0.04 (0.00, 0.07)**
Perceived burden of upbringing (NVOS 5-20)	-0.09 (-0.28, 0.10)		-0.11 (-0.30, 0.08)
Perceived pleasure of baby care (VL 5-20)	-0.06 (-0.18, 0.07)		-0.09 (-0.22, 0.03)
Maternal sleep/resting duration (hours)	0.12 (-0.05, 0.30)		0.12 (-0.07, 0.30)
Start daycare before age 12 months (yes)	0.39 (-0.06, 0.84)		0.02 (-0.46, 0.50)
Context			
Maternal age (years)	-0.00 (-0.06, 0.05)		-0.00 (-0.06, 0.05)
Single parent household (yes)	**1.23 (0.45, 2.01)**	**0.85 (0.07, 1.62)**	0.71 (-0.10, 1.52)
Ethnicity			
Dutch (reference)	reference	reference	reference
African descent	**1.68 (0.71, 2.65)**	**1.29 (0.33, 2.24)**	0.88 (-0.13, 1.90)
Turkish	0.58 (-1.19, 2.35)	0.19 (-1.50, 1.88)	-0.55 (-2.34, 1.25)
Moroccan	**1.36 (0.19, 2.53)**	**1.21 (0.09, 2.33)**	0.52 (-0.73, 1.77)
Others	**0.59 (0.02, 1.16)**	0.49 (-0.07, 1.05)	0.33 (-0.25, 0.91)
Maternal education			
low	**1.31 (0.53, 2.08)**		0.54 (-0.29, 1.38)
middle	**0.61 (0.14, 1.07)**		0.34 (-0.14, 0.82)
high (reference)	**reference**		reference
≥1 older sibling(s) in household (yes)	0.32 (-0.13, 0.77)		0.13 (-0.34, 0.60)

Multivariable regression model: adjusted for the maternal depression, anxiety and stress score (DASS21) at the 5-year questionnaire and the age of the child at the time of the outcome measurements, and for all potential determinants selected per category, by backward selection or all added at once (complete model). **Bold:** statistically significant ($p < 0.05$), STAI: State-Trait Anxiety Inventory; NVOS: Dutch questionnaire about the upbringing situation; VL: Dutch caregiving list. *: wider 95% CI due to a low incidence of cocaine use.

6

The need of having a plan in excessive infant crying – a qualitative study of parents' experiences of healthcare support

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ABSTRACT

Aim: Excessive infant crying increases parents' concerns regarding their infant's health and the burden of parenting. We aimed to gain insight in the healthcare support needs of parents with excessively crying infants.

Methods: An exploratory qualitative study was conducted in the Netherlands. We performed semi-structured interviews with parents of 12 infants between June and December 2020, followed by inductive and deductive thematic analysis.

Results: Parents described what their needs were with regard to the assessment of infant crying and support by professionals. Long-lasting crying made parents feel that there must be a somatic cause. If they could soothe their infant, they gained more confidence that their infant was healthy. We identified four interrelated themes: (i) confidence in the professional; (ii) seeking a somatic cause for the crying; (iii) seeking acknowledgment; and (iv) exhaustion of parents and feelings of failure.

Conclusion: Parental support needs were best fulfilled by professionals who took them seriously, demonstrated medical expertise, and offered a practical plan. Perinatal parental education on normal infant behavior and infant soothing techniques might improve parental self-efficacy at an early stage and prevent medicalization of excessive crying.

1. INTRODUCTION

Infant crying and sleeping problems are periodically prevalent in many newborns, but when it is more severe and persistent, it is called excessive infant crying or infant colic. The prevalence of excessive infant crying lies between 5 and 25%, depending on the definition and research design. [1, 2] Crying can last for multiple hours per day, but does not have a somatic cause in > 95% of infants. [3, 4] Definitions of excessive crying contain either the prolongation or excesses of crying, or the inability to soothe, and are limited to somatically healthy infants. [2, 5, 6] Despite the lack of a somatic cause, evidence and practice acknowledge that excessive crying can have long-term consequences for the development, health, and attachment of the infant. [5, 7, 8]

Parents looking for medical care for their excessive crying infants often expect medical advice and solutions, such as pharmacological or nutritional interventions. But such interventions are only evidence-based for excessive crying due to cow's milk protein allergy or gastroesophageal reflux disease. [5, 9, 10] Even if a trial treatment is started for excessive crying without somatic cause, parents will not find their needs fulfilled. [9] Cornerstones in the management of excessive infant crying are parental reassurance and education. [5] However, there is little literature on how to reassure parents and when to provide interventions or education on dealing with (excessive) crying infants.

Colic management practices and perspectives of mothers and health professionals are explored by Abreu-D'Agostini et al. in a qualitative study. [9] They interviewed professionals and parents and concluded that health professionals focus on investigating somatic causes and solutions, with insufficient attention being paid to the parental perspectives, especially the maternal anguish of not seeing the pain of their child being resolved. They conclude that professionals should seek partnership with parents and promote parental education for safe infant crying management [9]. A recent study in the Netherlands investigated maternal satisfaction with professional healthcare for excessive infant crying with a questionnaire in an online recruited sample [11]. They found high rates of dissatisfaction with the provided healthcare (55%) in a population of mothers expressing a higher average need for information (84-93% needed information related to the crying of their infant and 77-85% needed information related to their own well-being). They conclude that offering effective reassurance to parents without downplaying the seriousness of the situation is essential and that it is important to be sensitive to the specific needs of each family. To our knowledge, there is only one intervention study on family-centered medical support of excessive crying. Salisbury et al. [12] performed a randomized control trial examining integrated care

for the treatment of infant colic. Parents in the intervention group had three treatment sessions with a pediatrician and a mental health clinician together within 1, 2, and 6 weeks of baseline. During these sessions, parents received individualized treatment plans addressing infant sleep, feeding, routine, and family mental health. The control group received standard pediatric care from their own care provider. The intervention had a significant beneficial effect on infant crying and sleep, but the specific mechanisms could not be determined due to personalized treatment plans. The treatment model and intervention were based on the local multidisciplinary pediatric and mental health approach of the study site." [12] Concluding that there is not enough evidence on how to best support families dealing with excessive crying from an early stage, we aimed to gain insight in the healthcare support needs of parents with excessively crying infants. To fulfill this aim, we performed a qualitative study in which we interviewed parents with excessively crying infants.

2. METHODS

2.1 Population and setting

An exploratory qualitative study was conducted with parents who had visited a pediatrician for excessive crying. In the Netherlands, well-being child visits are performed by preventive care physicians and nurses, and a pediatrician can be consulted only after referral by preventive or primary care physicians. We included families that received care in three Dutch pediatric departments (St. Antonius, Meander MC, Tergooi MC). We were aware that some of the professionals in these pediatric departments used the Happiest Baby Method for parental education and soothing, but we did not select parents based on usage of this method. Parents were recruited between June and December 2020 through pediatric departments and preventive Public Health Services.

Families had to meet all inclusion criteria: (i) referral to a pediatrician for excessive crying before the age of five months and one or more appointments with a pediatrician; (ii) infant age up to three months at the start of crying; (iii) ending of excessive crying at the time of the interview; and (iv) infant age below seven months at the time of inclusion. Families from the Public Health Service of the interviewer were excluded from the study to prevent shyness on the part of the participants to share their experiences in the interview. Participants were recruited until data reached saturation for all topics on the topic list.

2.2 Procedures

We described the study protocol to the Medical Ethical board of Amsterdam University Medical Centers and it was assessed and waived for full ethical approval [W20_238 # 20.274, May 28 2020]. The information letter included: the character of the study, anonymity, and being able to end their participation when desired. Parents signed informed consent before the start of the interview (supplemental information on procedures and author contributions are provided in **Table S6.1**) . [13]

2.3 Data collection

Four researchers with medical, psychological, and anthropological expertise, and personal experiences, prepared a topic list based on clinical practice and literature. [5, 8, 9, 12] This list was further supplemented after a trial interview (the trial interview was not used in the analysis). **Table S6.2** shows the topic list including themes that may possibly impact families and support needs during a period of excessive crying.

12 out of the 15 families that had been referred to our study agreed to participate (demographics and reasons for refusal to participate in the study are listed in **Table S6.3**). One interviewer performed semi-structured in-depth interviews lasting 60-90 minutes at the family's home or by using Microsoft Teams video conferencing, depending on personal preferences and COVID-19 precaution guidelines for clinical research. Interviews were audio-recorded with permission of participants.

2.4 Data analysis

We thematically analyzed transcribed interviews using MAXQDA software. [14] We conducted the six phases of thematic analysis according to Braun & Clarke [15] Within the research team, data were coded and analyzed simultaneously as well as independently. Discrepancies within the research team were discussed and proceeded with another round of analyzing, dissecting, and working with thematic analysis. [15] More detailed information on the thematic analysis and author contributions is available in **Table S6.1**. Names in quotes are pseudonymized.

3. Results

3.1 Participants

Detailed demographics of participants are displayed in **Table S6.3**. We interviewed parents of 12 infants: nine mothers, one father, and two couples. Seven of the twelve infants were firstborn, parents were all medium to highly educated, and all parents worked three or more days per week. Infant age at the time of interview was between two and six months, meaning that some parents were still on parental leave. A large portion of the families had received several interventions from different medical

professionals, including: (i) feeding changes; (ii) medication; (iii) mentioning or practicing the soothing methods of the Happiest Baby Method; and (iv) hospitalization.

3.2 Main results

In the thematic analysis, we identified four themes that depict the care needs of families that deal with excessive crying infants (**Figure 6.1**):

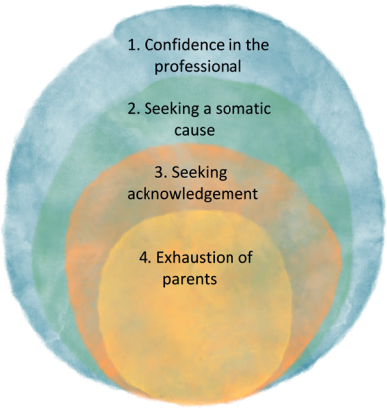

Figure 6.1: Four interrelated themes that depict the care needs of families that are dealing with excessive crying infants

3.3 Theme 1: Parental need to feel confidence in the healthcare professionals

Confidence in the professional was discussed in all interviews and consisted of the following three sub-themes:

3.3.1 "Taken seriously"

If parents felt that they were taken seriously and acknowledged, this boosted their confidence in the professional. They had to feel that the professional wanted to work together with them and had no doubts about the crying being excessive (quotes 1 and 2, **Table 6.1**). Physical examination and further diagnostics, prescription of special formula or medication or referral to pedagogical support or specialized medical care were also perceived as part of being taken seriously.

3.3.2 "Expertise"

Confidence in the professional increased when parents felt reassured that the professional had expertise to investigate potential somatic causes of the crying (quote 3). Looking back at the newborn period, parents mentioned that the referral from preventive or general medicine to a pediatrician should be done as soon as possible.

3.3.3 "A plan to hold on to"

Several parents indicated that a clear plan for infant care and a follow-up appointment to monitor improvement increased their confidence in the professional (quotes 1, 15 and 16). Several parents had received information on the soothing techniques (5 S-es) of the Happiest Baby Method.

3.4 Theme 2: Parental need to investigate somatic causes

Wanting to investigate somatic causes is the second theme, and of importance because parents experience an inability to soothe their infant. Parents felt that there had to be something wrong with their infant. Several mothers described it as "*motherly instinct*". Parents explained that this doubt remained for several weeks: even though the crying mostly resolved, they started doubting again on 'off-days' when the crying increased again (quote 4). Some parents had also forgotten that a medical examination had been carried out (quote 3).

3.5 Theme 3: Parents seeking acknowledgment of crying

Parents told us that relatives and friends confirmed that their infant cried excessively, and often supported and motivated them to seek medical care. At their clinic visit with a professional, they expected to also be acknowledged and receive confirmation that the crying was excessive. A professional could accomplish this by listening carefully to the parents and addressing the crying as it happened during the clinic visit or during a clinical admission, but also by asking the parents to keep a diary of the crying or making home videos to show in the clinic (quotes 5 and 6).

> *"You see all these mothers shopping in town, with their babies asleep in the stroller. But the excessive crying infants are all at home and you don't see those."*

The expectations of parents regarding sleeping and crying before giving birth were very different from real (average) crying and sleep durations, and actually being parents of a newborn infant. Several parents declared during the interviews that their expectations about spending time with their infant were too positive. Parents suggested that it would be best to inform future parents about normal infant behavior and sleep before birth.

3.6 Theme 4: Parental need for support to break the negative spiral of feelings of exhaustion and failure

Parental well-being was not explicitly verbalized by parents as a healthcare need when they visited a pediatrician, but some parents declared that their own stress and exhaustion were the reason to not further postpone seeking extra (medical) care.

Parents expressed their exhaustion during the period of excessive crying in the interviews and described the negative spiral as: "*on days that the baby did not feel well, I would feel worse*". The crying itself did evoke intense emotions, described with words like: "*despair, all-time low, if this is it… , wanting to give up, and survival mode*". Feelings of exhaustion were often combined with feelings of failure as they

could not comfort their own baby (quote 7). From that perspective, parents actually hoped for a somatic reason for the crying, to excuse themselves from any blame for the constant crying of their baby.

> *"I remember that Sunday when I was walking around our neighborhood at six in the morning and talking to my mom on the phone, crying. I didn't know what to do and was so tired and didn't know how to help Pheline."*

Parents appreciated professionals who actively verbalized how hard the infant care must be for the family (quotes 1 and 9). The timing of in-depth questions or remarks on parental well-being (steps 4 and 5) was essential, as some parents did not expect or appreciate them, even though they had feelings of insecurity (quote 8).

3.7 Analytic narrative: data extracts

We identified relationships between the four themes. Parental reflection on provided care was most frequently discussed by how parents experienced the care in terms of 'confidence in a professional' (theme 1 **Figure 6.1**). This confidence was partly determined by the medical expertise to rule out somatic causes (theme 2). Independent of the wish to exclude somatic causes, parents were hoping to find acknowledgment that the crying was indeed excessive (theme 3). While parents had already been worried about the crying for a while, a motive to seek medical care was their own exhaustion, due to the burden of taking care of their infant and feelings of despair that they could not bear the excessive crying any longer (theme 4). "Parental need for support to break the negative spiral of feelings of exhaustion and failure" is therefore a distinct theme and visualized as the inner circle in **Figure 6.1**.

We observed that parents perceived care as sub-optimal, when the themes were not addressed in sequence during medical support. For example, parents did not listen to explanations as to why a somatic cause was unlikely, if they felt that the professional did not acknowledge the severity of the crying (quote 12). Further, they did not feel confident with the care plan if they were not convinced that their child was healthy (quote 14). Parents even subconsciously hoped to find a somatic cause, so they would not feel guilty about their inability to soothe their infant (quote 10). Support was better received after a professional gained their trust by verbalizing the difficulties of infant care during a period of excessive crying (quote 1).

Parents explained that once they realized the crying was able to be soothed using the techniques of the Happiest Baby Method, this reassured them that the judgment of the professional was right: a somatic cause then became less likely (quote 13). Prac-

Table 6.1: Extracted sequential steps in medical assessment and support for families dealing with excessive crying including illustrative quotes from parents

Steps in assessment and support by professionals	Citations of positive parental experiences	Citations of parental experiences that did not meet their care needs
1: Gaining parents' trust	Quote 1:The first thing she said was: "How are you holding up?" And then, yes, I started crying, because I was just so exhausted. But she gave me hope: "You are not leaving here without us making a plan that you can use and hold on to." (interview 2)	Quote 2: After four weeks with my crying infant I went to the Public Health Service for her regular check-up, to finally tell my story… But I got called in with "the four-week-old-infant can come in" instead of her name. Well, the tone was set… (interview 13)
2: Physical examination	Quote 3: I told my husband: "I guess no one actually checked him from top to bottom." After which he responded: "I believe that is what the pediatrician did when we first came in." And I said: "Well, I guess it all happened so quickly and in a natural way for her that I didn't actively notice the physical examination of the pediatrician." (interview 11)	Quote 4: I still sometimes wonder if this is all normal and not reflux. Because when I lay him down he still spits up thick milk and he can be very restless while nursing or even start screaming, spitting up and so on. (interview 11)
3: Listening, diary and video taking	Quote 5: What made that we had different feelings about this second pediatrician? Well, he really listened. And asked me to indicate with green, orange and red how much she cried per hour. And everything was red, illustrating perfectly how dramatic the crying was. (interview 13)	Quote 6: I really had the feeling: are we being taken seriously? Because the moment you actually speak to someone and you have your child with you, he is in his car seat and nothing happens at all. And when you get home, all hell breaks loose. But the professionals aren't there, so they don't see what we see. (interview 6)
4: Addressing well-being and confidence of parents first	Quote 7: We called the pedagogical worker to arrange a hospital stay, as it was not normal how long it took us to finally get him to fall asleep. And I think that she sensed that I didn't dare to take this step, because she told me on the phone that this was not a sign of failure. (interview 7)	Quote 8: So all of a sudden he said: "Well, you know, I will talk to the pediatrician, so you can leave Evi here for three days and get some rest." And I said: "Sorry, but are you crazy? I am not here for myself! I am sitting here for my daughter: I have a feeling that something is wrong with her and I want you to investigate what's wrong with her, as she is just crying all day." And he said: "Yes, but there is nothing wrong. Some babies just have a higher temperament." And I really thought "Well, if this is my future, for real, I wish I had never had a baby". (interview 4)

Table 6.1: Extracted sequential steps in medical assessment and support for families dealing with excessive crying including illustrative quotes from parents (*continued*)

Steps in assessment and support by professionals	Citations of positive parental experiences	Citations of parental experiences that did not meet their care needs
5: Confirm burden of care, absolve parents from any blame, seek help	Quote 9: He was a very nice pediatrician and when he held her he said: "Now you are really very sweet, but your mother is here for a reason. I know you cry all day long." That left me completely in tears. I really wanted to hug that man; he knew what I was feeling (interview 8)	Quote 10: For a long time I thought… It can't be just the crying, there has to be something wrong with my child. Somehow I even wanted it to be cow's milk intolerance, so I knew that I wasn't doing anything wrong. I felt like I was failing as a mother because I couldn't help him. (interview 3)
6: Diagnose excessive crying	Quote 11: Yes, so we came to the hospital and he was crying out loud while changing for his examination. The doctor immediately said: "It's a screamer and I can imagine that it drives you crazy. You've come just in time, because if you wait a few more weeks you'll really want to throw him in the bin. So." (interview 11)	Quote 12: And the family physician kind of reassured me like: "Well, he might have reflux, but to me this is a healthy infant." But I just kept thinking: "I notice this with my child, why don't they acknowledge the crying? Why won't they confirm my feeling that this isn't normal?" (interview 10)
7: Explain absence of alarm symptoms and unlikelihood of somatic causes	Quote 13: It was only after five days that it appeared to me that there was nothing wrong with Julia. The pedagogical worker explained everything that she did and why she did it. If we were soothing, she came to see us and provided tips on how we could improve. It was really hard work, but she was able to be soothed and that became more and more apparent to me. So she was crying, but she was able to be soothed during the clinical admission and that was very positive. With that conviction, we took her home that Monday. (interview 4)	Quote 14: If she could have explained why she didn't think of an allergy, it would have been fine, or anything, if she could just explain, then we wouldn't need a referral. (interview 7)
8: A clear plan to hold on to	Quote 15: "If you try this for two weeks, we will get in contact with you." This is when you feel taken seriously and makes you want to try for two more weeks." (interview 13)	Quote 16: You miss a coordinating person. Actually you just want someone to say: "Just do this and we will discuss this further in a week's time, but just try this." (interview 9)

ticing the techniques with a professional gave more confidence than written material or a simple comment that parents should look up the soothing techniques online.

4. DISCUSSION

We explored needs for healthcare support in families dealing with excessive infant crying. Parents explained how the excessive crying impacted their parenthood and family well-being and how they experienced medical help. We identified four themes that depict the care needs of these families (theme definition summarized in **Figure 6.1**). The themes are interconnected, with the most 'visible' outer layer being 'confidence in the professional', and 'exhaustion of the parents' as the deepest and most hidden layer of family care needs. While excessive crying is how the problem started, if and when parents seek help for excessive crying can be triggered by parental exhaustion and feelings of failure (parental perspective) more than the severity of crying.

Analyzing how the four identified themes address the research question, we extracted sequential steps in medical assessment and support for families dealing with excessive crying, visualized in **Figure 6.2**.

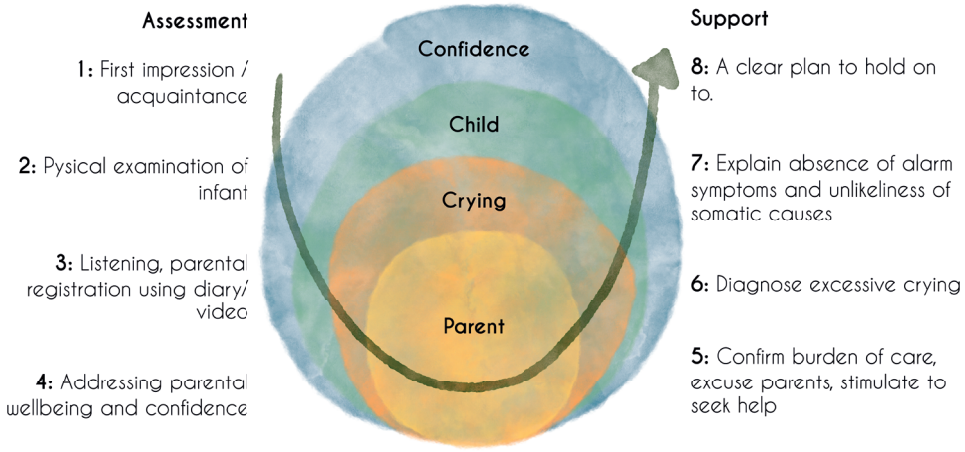

Figure 6.2: Extracted sequential steps in medical assessment and support for families dealing with excessive crying related to the four themes. For example: the outer circle, theme 1, is addressed in steps 1 and 8.

The pathway starts with the assessment of the situation by the professional. Parents get a first impression of the genuine interest of the professional during the initial meeting (step 1). Next, is investigating somatic causes (step 2) and giving parents the

opportunity to share their experiences and deliberate on the severity of crying (step 3), including how the crying is affecting their own well-being and coping with the crying in their current situation (step 4).

After the assessment of care needs, the support by the professional could start by addressing parental well-being. This could be done by confirming the burden of care, absolving the parents from any blame and advising them to seek help for their well-being, if needed (step 5). Parents appreciated getting confirmation that the crying was excessive (step 6); an explanation of the unlikelihood of somatic causes (step 7); and involvement in making a clear plan for infant care and soothing with follow-up appointments (step 8).

Our finding that the parental perspective seems leading in determining the care needs for excessive crying is in line with the parenting theory of van der Pas. [16] According to her definition, a parent is 'a person who has an unconditional and timeless awareness of being responsible for a child' (page 40 reference [16]). Parenthood makes a person vulnerable. They need 'good parent' experiences, enabling them to grow as a parent and buffering their child rearing from possible adverse effects. [16] Our findings illustrate this. The parental exhaustion and feelings of insecurity caused parents to fail to meet their own expectations of parenthood, which they (unconsciously) wished to discuss with a professional. Exhaustion and feelings of insecurity can also complicate the treatment of excessive crying, a finding that is in line with existing literature. [5, 9, 12] Abreu-D'Agostini et al. found that, due to their inability to stop the crying, parents can feel distressed, insecure, and helpless. [9] A recent Dutch study found that both fathers and mothers of infants with excessive crying scored significantly higher on parental stress, depression, anxiety, and bonding problems. [8] Parental depression, with a global prevalence of 11.9%, can complicate infant soothing and bonding with parents. [17, 18] During the support phase, professionals can advise parents to seek help for their own psychological well-being or to seek guidance in parenthood or expertise from an Infant Mental Health specialist (step 5 **Figure 6.2**). It is a novel approach to make the parental perspective leading during the support phase of excessive crying. It implies that the goal of support is not exclusively to alleviate infant crying through pharmacological and behavioral interventions (step 8), but also to address parental well-being (step 5), to acknowledge the excessive crying (step 6), and to explain the unlikelihood of somatic causes (step 7). Very recently, van der Veek et al. reported topics similar to steps 5 to 7 to be of importance in supporting parents that deal with excessive crying. [11]

Most parents expected a somatic cause for the excessive crying, but they adjusted their expectations when they noticed that the infant was able to be soothed by others and, later, by themselves. Parents described the soothing techniques they learned as effective, similar to Brazilian parents in a previous study. [9] Although the soothing techniques of the Happiest Baby Method itself were not evaluated, we found that the ability of parents to soothe their child, positively affected parental self-efficacy in families that were dealing with excessive infant crying. This confirms findings of a preventive intervention study that taught mothers in a postpartum hospital unit the theoretical background and calming techniques of the Happiest Baby Method , leading to improvements in parenting self-efficacy. [19] The soothing techniques of the Happiest Baby Method have also shown to be effective in soothing pain in infants after vaccination and in calming a crying or fussing infant. [20-22]

A strength of our study is that our sample was heterogeneous in terms of age of the baby, and family composition. Crying started at different ages during the first three months of life and parents mentioned various care pathways, leading to very rich data. The themes concerning the need for care and support were identified repetitively during and across different interviews and data saturation was reached, indicating robustness of the findings. Quotes 2, 4, 6, 8 and 10 illustrate that each theme is essential and if one step is left out, underlying parental experiences and emotions would perpetuate the worries about the crying. The four themes were related to each other in several ways, but each theme is distinct and essential in describing our findings on parental healthcare needs, indicating rigorousness of the analysis. All interviewed parents were able to reflect on events surrounding excessive crying and express their feelings on provided care. Many parents were able to clearly describe their care needs retrospectively and by analyzing the interviews we discovered mutual connections between the themes.

A limitation is that we did not include parents with excessive crying infants who were not referred to a pediatrician. This may have biased our results as these parents might be more concerned about somatic causes or experience more stress than parents who received care from preventive or primary care physicians. Our sample did not include low-educated parents, who might differ in healthcare needs. Further, our sample may be selective since some of the professionals in the three hospitals that recruited families for this study provided the Happiest Baby Method for excessive infant crying. As a result, the majority of our study participants received the same treatment at different phases of infancy and by different professionals.

Based on our results, we invite professionals providing medical care to families with excessive crying infants to include the steps in **Figure 6.2** in their care plan. Steps might have to be repeated by various professionals and over time (e.g. steps 2 and 7 if parents keep seeking a somatic cause). We propose more parental education on normal sleeping and crying behavior of infants and infant soothing techniques to improve parental self-efficacy at an early stage. Concluding from our study, parents with excessive crying infants wished that they had been better informed before the crying started. Other studies confirm that soothing techniques can easily be taught to parents in short guidance sessions, preferably not by written or video instruction alone, and can be integrated in existing pre- and postpartum care. [19, 20, 23]

Further implementation research is needed to investigate whether the proposed steps in care for excessive crying are indeed effective and suitable for families with different backgrounds.

5. CONCLUSION

Parental support needs were best fulfilled by professionals who took parents seriously, demonstrated medical expertise, and offered a practical plan. Perinatal parental education on normal infant behavior and infant soothing techniques might improve parental self-efficacy at an early stage and prevent medicalization of excessive crying.

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SUPPLEMENTAL INFORMATION

Table S6.1: Supplemental information on procedures and authors' contributions.

Protocol development, research question, topic list	WK (MD), MHa (MD, MPH), MHo (PhD), LvH (PhD)
Interviews (in Dutch) [1]	WK (Medical Doctor in Preventive Public Health Services with both professional and personal experience with excessive crying infants, no prior professional relation to participants)
Transcribing (in Dutch)	WK and trusted third party, transcripts were not returned to participants for comments and/or corrections.
Fragmentation (step 1 thematic analysis)	WK
Code tree preparation (in Dutch)	WK, MHo, MHa
Coding of transcripts (step 2 thematic analysis)	WK, MHa
Theming (steps 3-4 thematic analysis)[2]	WK, MHa, LvH, MHo
Structuring of the themes (step 5 thematic analysis)	All, participant checking planned in future study.

1: Parents were orally informed by their referring professional and orally by phone and in text by the researcher. Parents received the information letter and consent form by e-mail.

2: Theming. After all interviews had been coded, four authors searched for patterns in the raw data. We identified four key themes from the interview data. After the findings were analyzed for these four themes, all authors reviewed the four themes, discussed the robustness of the findings, and named and structured the themes as shown in **Figures 6.1 and 6.2**.

Table S6.2: Topic list for interviews.

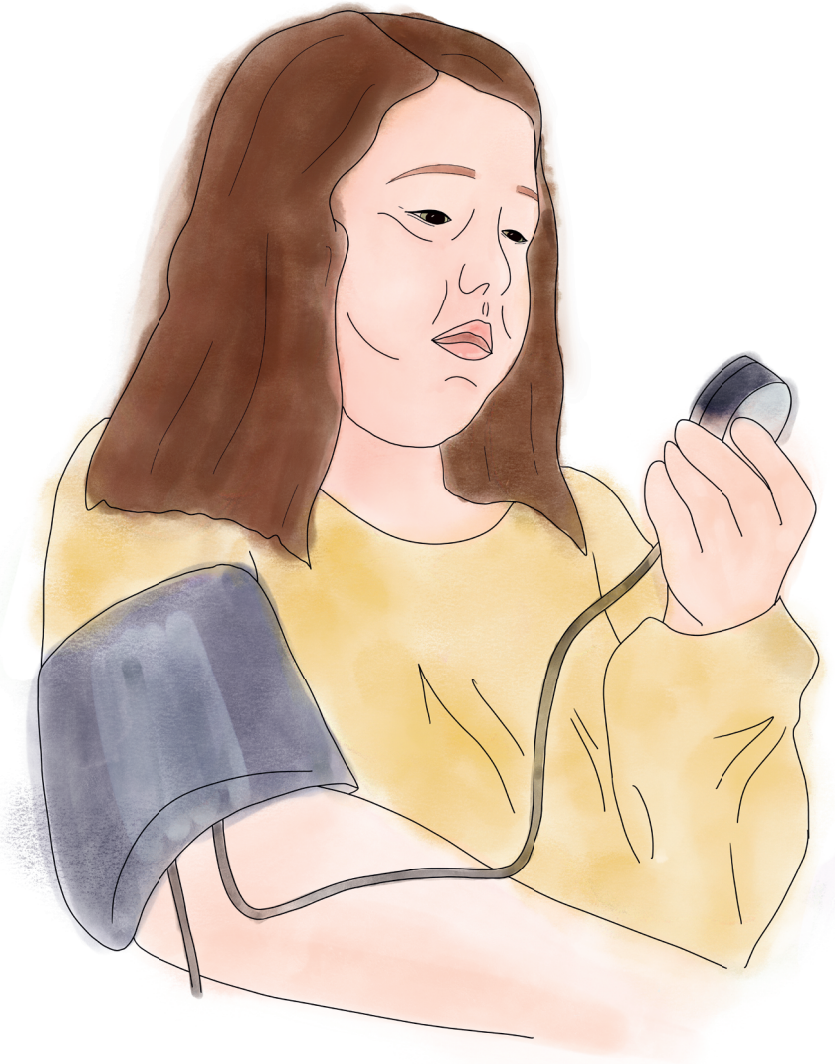
Background information	Infant age, household characteristics, parental education, work situation.*
General satisfaction/opening questions	Important things that parents would like to say before describing in chronological order:
	Pregnancy, expectations regarding parenthood.*
	Start of the crying after the baby was born.*
Crying and infant care	Parental concerns regarding infant crying, timing of concerns, number of hours per day, duration over weeks
	Who did you discuss your concerns with? Acknowledgment, circumstances of influence
	What advice did you receive? How did you feel about the given advice?
	When did you seek help from a pediatrician?*
Prompts on crying and infant care	Looking for a somatic cause. Parental knowledge and education on normal infant crying.* Risk of shaken baby syndrome.
	How did you perceive the given care?
	Happiest Baby Method.
Family situation	Family situation, complicating factors.* Attention to family situation by professionals.
Prompts on family situation	How was the family situation and parental wellbeing discussed with professionals?
	Was the family situation of importance to support needs?
	How did the family situation effect the parental ability to deal with excessive crying?
Coordination between healthcare providers	Consistency of given care and advice between disciplines.
Parental control on care demand	Experienced control and role in healthcare support. Experienced acknowledgment and personal attention.
Prompts on parental control	What would be the best moment to discuss parental wellbeing?
	Pregnancy and parenthood circumstance.*
Ideal care	Looking back, what would have been the ideal healthcare support for your family?
Wrapping up	Summary, what was the most important topic of this interview for you?

*: The topic list included the course of the excessive crying and received care, and did not contain questions about their healthcare needs. The aim of the questions was to let parents explain their situation to the interviewer and let them reflect on their healthcare needs by describing how they experienced healthcare. We coded their response to describe provided care for the whole study sample and performed thematic analysis to seek patterns in the data regarding healthcare needs.

Table S6.3: Demographics of 12 participants*.

Interviewed parents	mother	9
	father	1
	father and mother	2
Family situation	Firstborn infant with parents	7
	Sibling(s), infant and parents	5
Infant age at the time of interview	2-4 months	3
	4-5 months	5
	5-6 months	4
Educational level parents (ISCED) #	High (tertiary education)	15
	Medium (upper or post-secondary education)	5
	Unknown	4
Working hours parents	Both parents working 3 or more days/week	11
	Unknown	1

* Of the three couples that did not participate, one mother did not perceive the crying as excessive; one family did not respond to our invitation, and one family still perceived the crying as excessive at the time of inclusion.
# High: tertiary education (International Standard Classification of Education 2011 (ISCED11) 5-8); Medium: upper or post-secondary education (ISCED11 3-4)



7

General discussion

1 INTRODUCTION

In this chapter, we will reflect on the findings of this thesis and discuss methodological considerations. Subsequent sections will provide recommendations for future research, health practice, and policy, and the chapter ends with a general conclusion and take-home message to all current and future parents.

2 GENERAL DISCUSSION

The overall theme of this thesis is a public health perspective on sleep during the early stages of life – the period from conception until the second birthday. The key assumption is that developing good sleep habits early on in life results in life-long benefits, not only for sleeping habits themselves, but also for cognitive and behavioral development, and cardio-metabolic health. There is public awareness of the importance of good sleep, also among the young. However, the consideration of what is good sleep varies widely. As a result, existing and future parents often have questions related to sleep health and turn to health care providers for advice.

The main findings in this thesis are:

A. Sleep and health of mother and child have a bi-directional relationship and are affected by multiple environmental factors during the first 1000 nights;
B. Infant problematic sleep is common and often coincides with excessive infant crying as well as mental complaints in parents;
C. Problematic sleep seems persistent from infancy to childhood.

A) Sleep and health of mother and child have a bi-directional relationship and are affected by multiple environmental factors during the first 1000 nights

The theoretical frameworks for this thesis are: (i) the developmental origins of health and disease (DOHaD) hypothesis; and (ii) the current knowledge on infant sleep development (1, 2). **Table 7.1** displays the findings in this thesis related to the developmental milestones in sleep patterns during the first 1000 nights. Our findings suggest a bi-directional relationship, although causality cannot be confirmed based on our studies. Our findings support the hypothesis of fetal programming of brain structures and hormonal settings involving sleep that are affected by the in-utero and early-life environment (3-6).

Table 7.1: Thesis findings related to milestones in sleep development during the first 1000 nights.

	Milestones in sleep development		Thesis findings
Pregnancy	Melatonin-receiving brain structures developed by the 18th week of pregnancy and fetal synchronization to the maternal rhythm by melatonin		*Chapters 2 and 5:* Sleep and health of mother and child have a bi-directional relationship and are affected by multiple environmental factors during the first 1000 nights, an association between gestational sleep deprivation and childhood sleep problems was not assessed.
Infancy	0-1 months: day-night differences stimulated by light-dark cycles and feeding schemes 3 months: a decrease in daytime sleep and increase of infant self-soothing 6-48 months: change in sleep cycles		Chapter 3: inconsistent evidence for an association between infant sleep duration and childhood body composition. *Chapter 4:* Parental discontent with infant sleep was associated with later problematic sleep . *Chapters 5 and 6:* several contextual determinants during pregnancy and infancy were associated with childhood sleep problems.

Early-life environmental factors associated with sleep problems were: maternal overweight during pregnancy, maternal anxiety during pregnancy and infancy, and alcohol and tobacco use during pregnancy. This suggests that maternal health and lifestyle are associated with childhood sleep. These findings on in-utero and early-life environmental factors that are modifiable are of great public health relevance as they could be targets for universal promotion of sleep health during the first 1000 nights.

B) Infant problematic sleep is common and often coincides with excessive infant crying as well as mental complaints in parents.

With 1 out of 4 infants having problematic sleep, consistent with the current literature, we found that infant sleep problems were a common complaint (7). We investigated parental perspectives of early sleep problems to understand parental health care needs and to find targets for universal and indicated prevention of sleep problems. In our qualitative analysis, we found that parental concerns about somatic causes of infant crying were associated with parental perceptions on the severity of infant crying and sleep problems. Parental wellbeing and feelings of incompetence also influenced parental perceptions of infant crying, which is in line with the observations that parental wellbeing is a potential confounder for parent-perceived sleep problems (8-10). Parental wellbeing might attenuate tolerance for infant crying or fussing. Kahn et al. showed bi-directional links between parental intolerance for

infant crying and infant sleep, which is consistent with the transactional model of infant sleep (11). Their longitudinal findings suggest that increasing parental tolerance for crying may lead to better infant sleep if targeted after the age of three months, but not at an earlier age. This idea is consistent with findings demonstrating that parental responsiveness in the early months promotes early self-regulation, including sleep regulation and physiological regulation (12, 13). Decreased parental responsiveness and intolerance for infant crying could both be affected by parental emotional wellbeing. During the first months of life, the biological mechanisms of sleep timing are developed and misalignment of these processes may determine sleep problems coinciding with excessive infant crying (14). Infant crying affects parental wellbeing and induces parental stress and concerns about somatic causes for the crying, resulting in more medical consultations than sleep problems alone (15, 16).

We investigated parental needs during the first stages of infant sleep development in the case of excessive infant crying. While excessive crying is how the problem started, it is not the severity of crying that determines when parents seek help. They seek health care support, after a longer period of infant crying, due to exhaustion and feelings of failure (the parental perspective). Our finding that the parental perspective seems leading in determining the care needs for excessive crying is in line with the parenting theory of van der Pas (17). Making the parental perspective leading during the support phase of excessive crying is a novel approach. It implies that the goal of support is, in addition to alleviating infant crying or sleep problems, also to address parental wellbeing.

C) Problematic sleep seems persistent from infancy to childhood.

Infants whose parents expressed concerns about sleep at early health check-ups were also more likely to develop problematic sleep in the second year of life. Our findings are in line with three previous studies examining persistence of problematic sleep during infancy and toddlerhood (18-20). Sleep problems seem persistent from infancy to later childhood and adulthood (18-20). Adopting healthy sleep habits might be easier during early infancy than in later infancy and childhood (21, 22). The development of self-regulation and self-soothing skills are influenced by parental and environmental factors, such as parental soothing and bedtime behaviors, which are bi-directionally related to child bedtime behavior (19, 23-27).

Interventions based on modifying parental behaviors and cognition can improve parental sleep-related behaviors and ultimately infant self-regulation and sleep (28). In the Netherlands and internationally, several evidence-based care programs - promoting healthy parental behavior and cognition - are available: ‘VoorZorg’ (nurse home

visitation intervention), 'Stevig Ouderschap' (Supportive Parenting Intervention), and 'Video Interactie Begeleiding' (video-feedback intervention to promote positive parenting (VIPP)) (29-31). While these programs proved effective in improving environmental factors and parental self-efficacy, municipalities are not required to contract these programs by law, and the programs are therefore not available in all Dutch municipalities (32).

The two laws - the 'Jeugdwet' and 'Wet Publieke Gezondheid' - together with the political agenda, determine the appointment and activities of Dutch Youth Health Care professionals. Dutch Youth Health Care professionals see ~ 95% of families with newborn children for periodic wellbeing visits and are appointed by municipalities to support families at an individual or group level. However, parents are not always satisfied with the care provided or do not always turn to Youth Health Care in the case of infant sleeping difficulties (16, 33, 34). Where parents look for medical and pedagogical support in the case of sleep problems is influenced by their trust in various disciplines and their personal connection to professionals. We provide recommendations for further research and clinical practice in paragraphs 7.4.2 and 7.5.

3 METHODOLOGICAL CONSIDERATIONS

Before drawing a final conclusion, we discuss the general strengths and limitations of the studies described in this thesis. We used observational data from three cohort studies: the Greek Rhea cohort in *chapter 2*, the Dutch ABCD-study in *chapters 2 and 5*, and the Sarphati Cohort in *chapter 4*. Both Dutch cohorts include children born (ABCD-study) or living (Sarphati Cohort) in Amsterdam and therefore our studies are most representative of urban Dutch populations. The cohort studies are subject to selection bias due to selective inclusion and attrition rates of the cohorts. A strength of both birth cohorts is their low attrition rate during the first year after birth (78% of recruited mothers participated in Rhea and 53% in the ABCD-study (35, 36)). All three cohorts made strong efforts to include minority populations and families with lower (health) literacy. Selection bias could influence the associations found between maternal and infant health and sleep. Sleep habits, sleep problems, and sleep duration are known to differ across cultures, but it is unknown whether these differences also affect health (37-39).

The studies in this thesis include measurements of sleep and health during different periods of gestation, infancy, and later childhood. In a narrative synthesis of available literature, we found inconsistent evidence for an association between infant sleep

duration during the first two years of life and body composition during later childhood. Perhaps infant sleep duration itself may not be of relevance, but other metrics, such as sleep quality, should be further looked into with regard to cardio-metabolic outcomes. We used longitudinal data to minimize the chance of reversed causality. Mediation analysis enabled us to explore potential underlying mechanisms of the observed associations.

We used both quantitative and qualitative methods in this thesis, which increased our understanding of the complexity of sleep during the first 1000 nights of life. Quantitative analyses enabled us to test hypotheses on the bi-directional association between sleep and health during this period. The qualitative analyses provided rich data on the health care needs of parents with excessive infant crying. It showed simultaneous occurrence of poor parental and infant sleep and perceived health problems. These findings align with the potential determinants of childhood sleep problems identified in *chapter 5,* in which maternal mental health was associated with childhood sleep problems. We perceive the use of mixed methods as a strength of this thesis, as it provides both insights in the prevalence and the perceived burden and needs of parents.

Our studies were able to include data from both mothers and fathers in quantitative and qualitative analysis, which provides valuable information on family characteristics, potential determinants and parental perspectives. Especially the perspective of fathers is relatively understudied.

4 RECOMMENDATIONS FOR FUTURE STUDIES

We recommend studies directed at improving sleep health, both during pregnancy and infancy. Interventions that could be implemented in local health care systems are described in systematic reviews (40-42). Implementation studies are needed to evaluate long-term effectiveness and the suitability of these interventions in different health care settings, including Youth Health Care, and for parents in vulnerable situations. Implementation studies can study how interventions stimulate parental and infant behavioral changes. An example is that parental responsiveness in the early months is positively associated with infant self-regulation, including sleep regulation (12, 13).

4.1 Measurement of infant sleep health

For future studies we recommend adequate measurement of sleep duration and sleep quality during infancy (starting between age one and six months), preferably with a

combination of direct and parent-reported measures (55-57). For the assessment of problematic sleep behavior, number of night awakenings by parent-report is considered superior to direct measures such as actigraphy or videosomnography, since direct measures cannot determine if an infant self-soothed after a night awakening (58, 59). At all ages, nighttime sleep duration is the most commonly assessed variable of sleep health. Using nighttime sleep duration therefore enables comparability across studies.

The most commonly used measurement instrument of sleep health during infancy is the standardized Brief Infant Sleep Questionnaire (BISQ), which includes questions on both (nighttime) sleep duration and sleep quality. However, we found that parents qualify their infants' sleep as problematic for other reasons than those investigated by the BISQ questions, as the group of infants with BISQ-defined problematic sleep only partly overlapped with the group of infants with parent-defined problematic sleep (*chapter 4*). The acceptability and interpretation of sleep complaints - as well as the need for, and content of, interventions - are shaped by cultural values, norms, and beliefs (60). We are curious to see if the revised BISQ questionnaire (BISQ-R) is superior in capturing parental perspectives, as it includes a wider array of sleep behaviors and outcomes and has an age-based norm-referenced scoring system (57). Participatory research methods could be used to further incorporate parental perspectives on the screening of sleep problems and relevant outcomes of interventions (61).

4.2 Improving sleep health by modifying determinants of sleep

We recommend future research to reproduce and build on our findings of potential determinants of sleep in the first 1000 nights of life. Environmental factors during infancy that were not included in this thesis, but are recommended to be explored in future studies, are for example: screen time in the first two years of life (television, touchscreens) (43); ambient noise (background noise from music or television; street sounds); (19, 27, 44); parental emotional availability (13); parenting practices (including bedtime routine and sleep initiation method) (45); maternal mental health during pregnancy and infancy (non-)sensitive parenting style (46-48), and circadian rhythm of parents (49).

While preventive programs like 'Video Interactie Begeleiding', 'Voorzorg', and 'Stevig Ouderschap' are acknowledged interventions, their efficacy in improving environmental factors on the micro level (individual family) and meso level (social network) is not well investigated. More research is needed to evaluate the effects of these interventions on child development and parental self-efficacy and self-confidence, and

to improve and strengthen the interventions and their application in daily practice (29-31).

4.3 The association between sleep health and cardio-metabolic health

Our observed association between gestational sleep deprivation and childhood cardio-metabolic outcomes supports the investments in interventions targeting healthy sleep during pregnancy (50). The mechanisms by which maternal sleep influences health during the first 1000 nights are not fully understood, but multifactorial (51). Causal mechanisms can be tested by mediation analysis in observational and experimental studies. Mediators of the association between gestational sleep deprivation and childhood outcomes could be shorter gestational age and the occurrence of gestational diabetes.

The relationship between infant sleep and later childhood health needs further investigation. Sleep duration has been associated with cardio-metabolic outcomes above the age of two years (52, 53). For sleep quality, the evidence of an association with cardio-metabolic outcomes is inconsistent. Few studies examined dimensions of sleep quality, efficiency and bed/wake times, in relationship with weight status (54).

5 RECOMMENDATIONS TO HEALTH CARE AND POLICY

Based on the thesis findings, we have the following recommendations:

5.1 Recommendations to healthcare organizations and professionals:

- We recommend education on the importance of sleep health for professionals working in Youth Health Care (performing health check-ups and prevention in the Netherlands), general practice, pediatrics, and obstetrics.
- We recommend all professionals to give extra attention to pregnant women with sleep problems and mental health complaints; we refer to effective non-pharmacological interventions described in recent meta-analyses (62, 63).
- We recommend professionals to be alert to sleep problems in the case of parental discontent with infant sleep. The BEARS (Bedtime problems, Excessive daytime sleepiness, Awakenings during the night, Regularity and duration of sleep, and Sleep-disordered breathing) sleep screen is a useful tool that includes questions similar to those used in Youth Health Care centers participating in the Sarphati

Cohort. BEARS can be easily implemented during well-child examinations and in consultations initiated by parents with concerns regarding infant sleep (7, 64).

- We recommend the use of effective behavioral interventions to prevent or treat sleep problems in the early years; we refer to effective interventions described in recent systematic reviews (40-42).
- We propose increasing parental education on normal sleeping and crying behavior of infants and infant soothing techniques to improve parental self-efficacy and responsiveness, and promote infant self-regulation at an early stage (12, 13).
- When implementing interventions, it is important to take into account parental perspectives regarding preferred communication, education, and treatment. Parenthood makes parents vulnerable to feelings of incompetence. They need 'good parent'-experiences, enabling them to grow as a parent and buffering their child rearing from possible adverse effects (17).

5.2 Recommendations to policy makers

- We recommend uniform earmarked financing of preventive programs like 'Voorzorg' and 'Video Interactie Begeleiding' in all municipalities to promote healthy parental behavior and cognition, and to reduce inequalities in health by:
- improving environmental factors (e.g. a decrease in maternal tobacco use has been observed for 'Voorzorg' (29));
- increasing parental self-efficacy regarding infant soothing and parental bedtime behaviors (31).
- Interventions based on modifying parental behaviors and cognition can improve parental sleep-related behaviors and ultimately infant self-regulation and sleep (28). We recommend policies that improve equal access to such interventions, also in families that do not pro-actively seek medical care or (commercial) pedagogical support (32, 65).

6 FINAL CONCLUSIONS

During the first 1000 nights, sleep and health of mother and child have a bi-directional relationship. Sleep problems can originate from various environmental factors during the first 1000 nights and can be persistent from infancy to later childhood. Sleep problems are common during infancy and often coincide with excessive infant crying as well as mental complaints in parents. Health care support should, in addition to alleviating infant crying or sleep problems, also address parental wellbeing. Future studies and public health efforts are needed to develop and implement evidence-based strategies to improve sleep health in all families.

7 TAKE-HOME MESSAGE TO ALL CURRENT AND FUTURE PARENTS

We would like to conclude this thesis with a few words to parents. Almost all parents act from a basis of parental love they feel for the new life developing in their family (17). After birth, parents look for a rhythm and routine to keep their child well-fed and energized to grow, both facilitated by good infant sleep. Good infant sleep is more than sleeping through the night. Our acceptability and interpretation of sleep complaints, as well as the need for treatment interventions, are shaped by cultural values, norms, and beliefs (60).

Good sleep is invaluable for pregnant mothers and families with newborn infants, but is not something that you can simply 'start doing'. Pregnant women and parents with newborns may realize that:

- sleep difficulties during pregnancy and infancy are common,
- optimizing family sleep health might be hard for
    - o pregnant mothers with irregular sleep due to work or older siblings,
    - o parents with excessive crying infants who do not sleep well during the night.

All readers might realize that parents cannot improve family sleep health all by themselves! With this thesis we do not wish to put extra pressure on parents by simply urging them to ensure good sleep. We found that the goal of healthcare support is not just to 'cure' infant crying or sleep problems, but also to be thoughtful of parental wellbeing. We call for more evidence-based support and a healthy environment to improve sleep and health during the first 1000 nights of your and future newborns.

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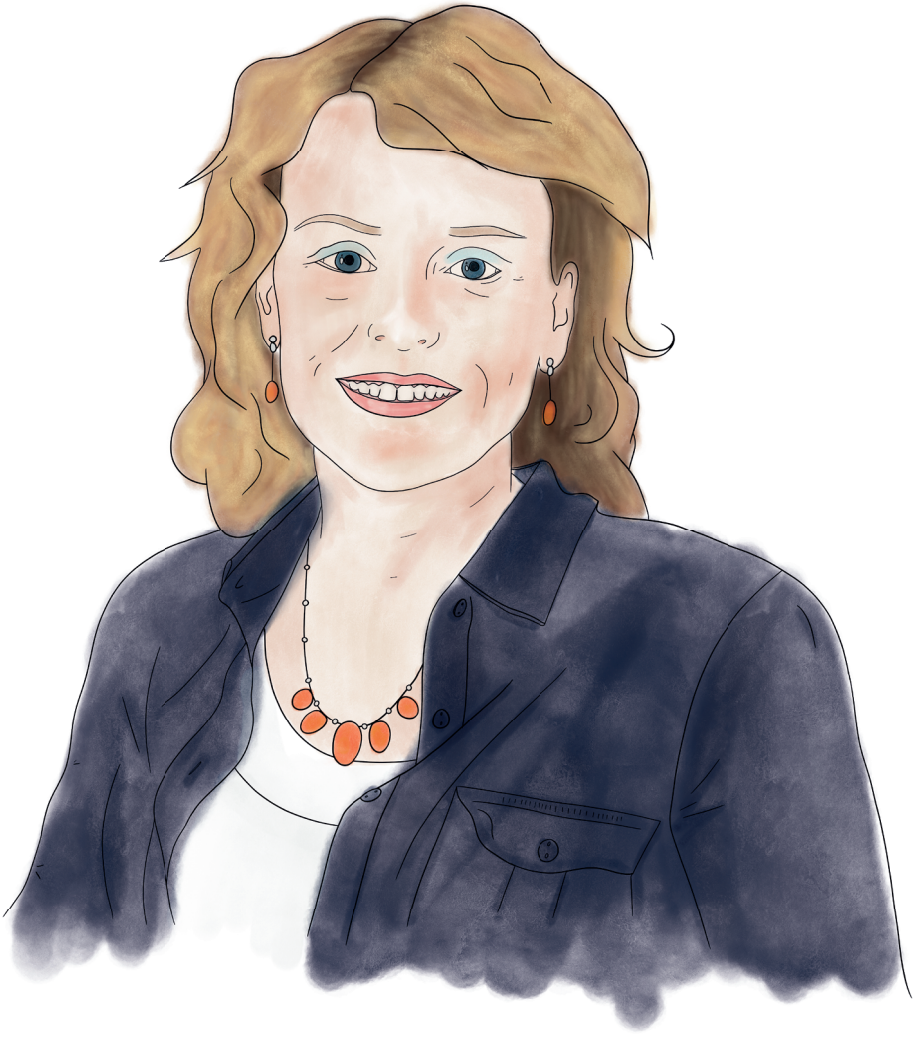

Portfolio

ABOUT THE AUTHOR

Margreet was born as the oldest of three daughters of Conny and Jan van Ginkel. Together with her two sisters, she was raised with the value of caring for nature and the community. Margreet and her sisters spend days and stay-over-weeks at her grandparents' farm. On the farm they observed the full cycle of life, health and behavior in nature. In their family and tight community in Ermelo they loved cuddling with newborns and toddlers. Altogether her upbringing is reflected in her becoming mom and health professional, investigating early development. Margreet found a great partner in Ralf to follow her social and personal dreams.

Margreet met her husband (Ralf) in 2003, during her first year of Medical School and together they followed their social and personal dreams and grew into academic medicine. As medical students, they wrote their first three publications together. During Medical School they learned scientific reasoning and academic thinking from Ralf's father, professor Egbert Harskamp, and mentors at University Medical Centre Groningen, University of Texas Health Science Centre San Antonio, San Antonio Metropolitan Health, and University of Pennsylvania.

Becoming a medical doctor in 2010, Margreet realized that her scientific ambitions could best be reached with a PhD-trajectory. But it wasn't until she found her medical specialty, Public Health, and personally obtained funding from the city of Amsterdam that she did start one. She found a resonance of her scientific ambitions after speaking to professor Marie-Louise Essink Bot and Tanja Vrijkotte and realized that an opportunity was created by Marie-Louise through an academic residency program in Public Health.

In the intervening years Margreet worked at Wilhelmina's Children's Hospital, Utrecht, GGD Zuid-Oost Gelderland and pediatric research at Duke University, USA. At Duke University she had her first experience with Big Data under supervision of professor Danny Benjamins and was given the opportunity to start her Master in Public Health at the University of North Carolina. Moreover, at Duke hospital, her biggest dream was fulfilled as their oldest daughter Caroline was born. Her charm filled their home with love and led to a strong bond with other mothers in their US community. Back in the Netherlands, Emma was born in 2015 and their son Julian completed the family in 2018. Enjoying life and love with her family and community in Weesp is the most important thing to Margreet.

She specialized in Public Health by combining clinical work in Youth Health Care at GGD Amsterdam with academic growth at the department of Public and Occupational Health, Amsterdam UMC and the Netherlands School of Public and Occupational Health. She provides Youth Health Care to newborns, infants, toddlers, school children and teenagers, since 2014 in Amsterdam and recently in Weesp. She educates colleagues in child development and sleep health and mentors medical students and colleagues. She started the second part of her Public Health training at Amsterdam UMC, and obtained additional funding to complete her PhD. She learned to become a full academic; obtained funding for following projects and will become a trainer to future medical specialists in Public Health. As post-doctoral researcher she is project leader of 'Calming and sleeping for all families in Youth Health Care' which combines research and practice in an interventional study in Youth Health Care. Supervising health innovation research at community level with direct benefits to parents and newborns combines the best of her both worlds!

CURRICULUM VITAE

Education

Preparatory scientific education (VWO), Christelijk College Groevenbeek, Ermelo, The Netherlands (1997-2003)

Medical Doctorate, School of Medicine, University Medical Centre Groningen, The Netherlands (2003-2010)

2006 - 2007 Scientific rotation at the University of Texas, San Antonio, USA

2007 - 2010: Internships at the University Medical Centre Groningen, Medical Centre Leeuwarden and University of Pennsylvania, USA

2009 Public Health Rotation at 'San Antonio Metropolitan Health District', USA Master of Public Health (2011-2020)

2011 - 2012 Master of Public Health, Gillings School of Global Public Health, University of North Carolina, Chapel Hill NC, USA.

2017 - 2020 Master of Public Health, NSPOH, Utrecht

Jeugdarts KNMG, Netherlands School of Public Health (NSPOH), Utrecht (2014-2017)

Arts Maatschappij & Gezondheid profiel Jeugd, NSPOH, Utrecht (2017-2020)

Amsterdam UMC Doctoral School (2017-2023)

Work history

2014 - present Youth Health Medical Doctor, GGD Amsterdam.

2013 - present Researcher at the Department of Public and Occupational Health, Amsterdam UMC.

2011 - 2013 Researcher in Pharmaco-epidemiology, Department of Pediatrics, Duke Clinical Research Institute, Duke University, Durham NC, USA.

2012 - 2013 Guest researcher in Perinatal Epidemiology, National Institute of Environmental Health Sciences, Research Triangle NC, USA

2011 Youth Health Medical Doctor, GGD Noord- en Oost Gelderland

2010 - 2011 Medical Doctor (ANIOS), Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center of Utrecht, the Netherlands

2004 - 2006 Part-time job as a nurse in homecare.

Awards and grants

2022 ZonMW grant 7440412210015 'Perinatal intervention 'Calming and sleeping' for father and mother'.

2021 ZonMW grant 744130106 'Calming and sleeping for all families in Youth Health Care'.

2021 KAMG arts M&G Marie-Louise Essink-Bot award

Valorization outside professional and academic world

2020 and 2023	News items regarding publications in Vakblad Vroeg, Scientas, and Captise.
2020- 2023	Workshop leader for parental sessions 'Crying, soothing and sleeping', Rondom de Geboorte.
2021	Chairman and speaker at 'Babycongres', Logacom.
2021	Speaker at 'Sleepproblems in young chilren', Vakblad vroeg.
2021	Elearning module on infant sleep for pedagogical workers in daycares, E-wise.
2019	Babycafé parent session on infant sleep, Food4smiles.

List of Publications

2023 Peters AEJ, Verspeek LB, Nieuwenhuijze M, **Harskamp-van Ginkel MW**, Meertens RM. The relation between sleep quality during pregnancy and health-related quality of life - A systematic review. The Journal of Maternal-Fetal & Neonatal Medicine. DOI: 10.1080/14767058.2023.2212829

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2023 **Harskamp-van Ginkel MW**, Imkamp NLE, van Houtum L, Vrijkotte TGM, Ben Haddi-Toutouh Y, Chinapaw MJM. Parental Discontent with Infant Sleep During the First Two Years of Life. Behavioral Sleep Medicine.10:1-14. 2023. DOI: 10.1080/15402002.2022.2156867

2023 **Harskamp-Van Ginkel, MW**, Klazema, W, Hoogsteder, MHH, Chinapaw, MJM, van Houtum, L. The need of having a plan in excessive infant crying – A qualitative study of parents' experiences of healthcare support. Acta Paediatr. 2023; 112: 434– 441. DOI: 10.1111/apa.16618

2022 Torres Toda M, Avraam D, James Cadman T, **Harskamp-van Ginkel MW,** Vrijkotte T, Dadvand P et al. Exposure to natural environments during pregnancy and birth outcomes in 11 European birth cohorts. Environ Int. 2022 Dec;170:107648. DOI: 10.1016/j.envint.2022.107648. Epub 2022 Nov 19.

2022 Elhakeem A, Taylor AE, Inskip HM, Huang JY, **Harskamp-van Ginkel MW**, Vrijkotte T, Magnus M, Lawlor DA et al.: Assisted Reproductive Technology and Future Health (ART-Health) Cohort Collaboration. Association of Assisted Reproductive Technology With Offspring Growth and Adiposity From Infancy to Early Adulthood. JAMA Netw Open. 2022 Jul 1;5(7):e2222106. DOI: 10.1001/jamanetworkopen.2022.22106.

2022 de Poot S, **Harskamp-van Ginkel MW**, Vrijkotte TGM. [Digital media use and sleep of adolescents: the effect of rules at home]. Ned Tijdschr Geneeskd. 2022 Nov 2:166:D6618.

2020 **Harskamp-van Ginkel MW,** Chinapaw MJM, Harmsen IA, Anujuo KO, Daams JG, Vrijkotte, TGM. Sleep during Infancy and Associations with Childhood Body Composition: A Systematic Review and Narrative Synthesis. Child Obes. 2020. 16(2): 94-116. DOI:10.1089/chi.2019.0123.

2020 **Harskamp-van Ginkel MW,** Kool RE, van Houtum L, Belmon LS, Huss A, Chinapaw MJM, Vrijkotte TGM. Potential determinants during 'the first 1000 days of life' of sleep problems in school-aged children. Sleep Med. 2020. 69: 135-144. DOI:10.1016/j.sleep.2019.12.020.

2020 **Harskamp-van Ginkel MW**, Ierodiakonou D, Margetaki K, Vafeiadi M, Karachaliou, M, Kogevinas M, Vrijkotte TGM, Chatzi L. Gestational sleep deprivation is associated with higher offspring body mass index and blood pressure. Sleep. 2020 Dec 14;43(12):zsaa110. DOI:10.1093/sleep/zsaa110.

2018 Contreras, Z. A., Chen Z, **Harskamp-van Ginkel MW**, Vrijkotte TGM, Chatzi L, et al. "Does early onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts." Eur Respir J. 2018:52(3). DOI:10.1183/13993003.00504-2018.

2017 Lewis KM, Ruiz M, Goldblatt P, Morrison J, **Harskamp-van Ginkel MW**, Vrijkotte TGM, Pikhart H et al. Mother's education and offspring asthma risk

in 10 European cohort studies. Eur J Epidemiol. 2017 Sep:32(9):797-805. DOI:10.1007/s10654-017-0309-0.

2015 **Harskamp-van Ginkel MW**, London SJ, Magnus MC, Gademan MG, Vrijkotte TG. A Study on Mediation by Offspring BMI in the Association Between Maternal Obesity and Child Respiratory Outcomes in the Amsterdam Born and their Development study cohort. PLoS One. 2015. 10(10):e0140641. DOI:10.1371/journal.pone.0140641

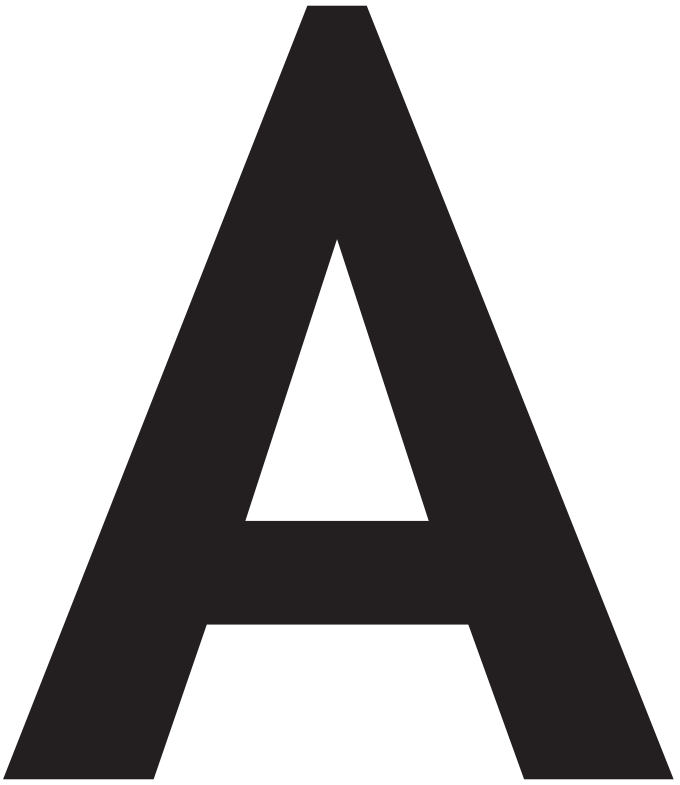
2014 **Harskamp-van Ginkel MW**, Hill KD, Becker K, Cohen-Wolkowiez, Gonzalez D, Barrett JS, Benjamin DK Jr, Siegel DA, Banks P, Watt KM. Drug Dosing and Pharmacokinetics in Children With Obesity: A Systematic Review. JAMA Pediatr. 2015;169:678-85. DOI:10.1001/jamapediatrics.2015.132.

2010 **Van Ginkel MW**, Diepsta A, Dijkstra G, Nieuwenhuijs VB, De Langen ZJ, Rings EHHM. Endoscopic detection of an early manifestation of EBV-related post-transplant lymphoproliferative disorder in a transplanted colon. A case report. Endoscopy. 2010:42 Suppl 2:E101-2.

2008 Harskamp RE, **van Ginkel MW**. Acute respiratory tract infections: a potential trigger for the acute coronary syndrome. Ann Med. 2008:40(2):121-8.

2008 Reddy VS, Harskamp RE, **van Ginkel MW**, Calhoon J, Baisden CE, Kim IS, Valente AJ, Chandrasekar B.Interleukin-18 stimulates fibronectin expression in primary human cardiac fibroblasts via PI3K-Akt-dependent NF-kappaB activation. J Cell Physiol. 2008 Jun:215(3):697-707.

2008 Harskamp RE, McNeil JD, **van Ginkel MW**, Bastos RB, Baisden CE, Calhoon JH. Postoperative internal thoracic artery spasm after coronary artery bypass grafting. Ann Thorac Surg. 2008 Feb:85(2):647-9



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In the following paragraphs, I will specifically mention a number of mentors and colleagues in this regard that all readers should know about.

My interest to academic public health was triggered by prof. Marie-Louise Essink-Bot and it would have been so nice to hand her this thesis. The opportunity to promote child health with research and clinical work in Public Health attracted me and is still what moves me in the two appointments that I fulfill after completing all my training at GGD Amsterdam and Amsterdam UMC. As Marie-Louise is not with us anymore, the role of promotor was with kind interest fulfilled by Tanja Vrijkotte (Associate Professor) and Mai Chin A Paw (Professor). Ines Rupp (MD) became my trainer for the Master of Public Health (arts M&G). Policy and practice based mentoring from the GGD was kindly provided by first Manon van Eijsden, then Irene Harmsen and for the main part Lieke van Houtum (PhD).

Mai, Tanja and Lieke, my promotors and co-promotors, have been very patient, motivational, supporting but leading. There are many things that I learned during my PhD and specialization and I have not always been the easiest to mentor and supervise due to idiosyncrasy and different professional backgrounds. A warm thank you to Mai and Tanja who taught me to slow down in between clinical duties and precisely investigate and interpret data and statistics on sleep and health. Other colleagues of the Department of Public and Occupational Health have been an example for me with their scientific skills and bridges to education and policy. Thank you Ines, for your continuous mentorship. Lieke, but also professor Arnoud Verhoef and arts M&G Marleen Johannes have been a great sounding board for my scientific and clinical interpretations. Thank you! I hope that both my mentors, mentees and colleagues in academic and practice will keep sharpening and improving my current and future projects.

My colleagues at OKT Amsterdam are a constant source of inspiration and support. I want to be part of us ensuring the best opportunities for children in Amsterdam and Weesp. Close colleagues have been very supportive of me splitting time and

focus between both jobs and sharpening my ideas on sleep and soothing support. Both in academic and practice my work has been supported by the 'Amsterdamse Aanpak Gezond Gewicht' and 'Kansrijke Start' (Healthy Start). For this thesis I am very grateful for the specific personal grants that the programs provided me, but also for the general focus shift towards healthy self-regulation, sleep and early life. GGD managers in care; Femke Breman and José Sibon, but also in healthy living; Henriëtte Rombouts and Karen den Hertog, personally inspired me to enhance practical relevance of my projects and to use parental perspectives in our research protocol and interpretations. Thank you!

Scientific research is real teamwork and I had the opportunity to divide the work in all studies of this thesis. Mariette Hoogsteder, Laura Belmon, Anke Huss, Kenneth Anujuo, Joost Daams and Yassmina Ben Haddi were all great co-authors, I enjoyed working with you, thank you! A special collaboration with Despo Ierodiakonou and Katerina Margetaki was made possible after Tanja spoke to Lida Chatzi at DOHAD 2017 about gestational sleep deprivation. Thank you! I enjoyed supervising Ruth Kool, Nicola Imkamp and Willemien Klazema in performing the data gathering, cleaning, coding and first interpretations that lead to the publications that we share authorship on. But also Anneke Ribberink and Karin Sprenkelder ended their scientific rotations with interesting results that we did not (yet) publish. In mentoring others, I find myself forced to underpin my decisions and order my thoughts more logically and together we can do and oversee more aspects of the research project. Thank you for all the time you invested in our research projects and giving me the opportunity to complete the projects to publications in International Scientific journals and this thesis.

Three chapters of this thesis are based on cohort data and as research end-user and reader one does not comprehend how much time and effort this took from project teams and participants. Amsterdam UMC and Public Health Service Amsterdam have done a great job in setting up the ABCD-study and Sarphati cohort. I am very thankful to all the mothers, fathers and children who participated in the Rhea cohort, Amsterdam Born Children and their Development (ABCD)-study and the Sarphati Cohort by consenting for data sharing, filling out questionnaires and participating in on-site measurements. I would also like to thank all the youth health care professionals that performed the data registration at the Public Health Service of Amsterdam and Stichting Amsterdamse Gezondheidscentra Zorgontwikkeling BV for both the ABCD-study and the Sarphati cohort. I would further like to point out that the cohorts are supported by grants from The Netherlands Organisation for Health Research and Development (ZonMW), The Netherlands Heart Foundation, Municipality of Amsterdam and other foundations and that ongoing support is needed. Special thanks to the families who

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About the author and this thesis

Margreet Harskamp provides public health care to infants, toddlers, school children and teenagers. As a Medical Doctor in Youth Health Care at GGD Amsterdam she educates families and colleagues in child development and sleep health and mentors medical students, clinical and academic colleagues.

She obtained her Master in Public Health at Amsterdam UMC and the Netherlands School of Public Health. Her research on healthy growth and development has focused on sleep and growth since 2017. The overall theme of this thesis is a public health perspective on sleep during the first 1000 nights.

Given the importance of sleep for both our physical and mental health, developing good sleep health is pivotal. The environment of the child is known to influence adaptive responses and potential epigenetic mechanisms. Sleep health during this period could be one of the stressors affecting the environment of a fetus and infant.

Interesting outcomes of this thesis are that sleep and health of mother and child have a bi-directional relationship and are affected by multiple environmental factors during the first 1000 nights. The outcomes call for more evidence-based support and a healthy environment to improve sleep and health during the first 1000 nights for all future newborns. But the outcomes also indicate that the goal of healthcare support is not just to ‘cure’ infant crying or sleep problems, but also to be thoughtful of parental wellbeing.