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SLEEP AND OBESITY IN CHILDREN AT DIFFERENT OBESITY RISKS: PATTERNS, ASSOCIATIONS AND EARLY INTERVENTION

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Sleep and obesity in children at different obesity risks: patterns, associations and early intervention

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May we all proceed with wisdom and grace.

Lawrence S. Bacow

ABSTRACT

Background: Childhood obesity is a global health concern with a range of adverse outcomes. Short sleep has been consistently linked to childhood obesity. However, associations between other sleep characteristics and obesity are less studied in children. Some multi-component obesity intervention studies har started included sleep as a target. Nevertheless, whether sleep can be improved and further benefit obesity prevention are still uncertain. Moreover, parental obesity is one of the major risk factors for child obesity, which probably due to both shared genetic factors and obesity-related environment and behaviours within families. Understanding whether and how sleep is involved in the obesity transfer within families has important implications for developing better interventions.

Aims: The overall aim of this thesis was to explore the role of sleep in the development of obesity among children at high and low obesity risks, determined by their parental weight, as well as to assess the effect of a long-term, low-intensive, family-based multi-component intervention on both preventing obesity and promoting sleep.

Materials: All studies included in this thesis are embedded in the Early Stockholm Obesity Prevention Project (Early STOPP), which was a long-term (5-year), low-intensive, family-based obesity prevention project conducted in Stockholm County. In Early STOPP, 181 children with two overweight or at least one obese parent (defined as at high obesity risk) were recruited and randomly allocated to the intervention (n=66) and control (n=115) groups. Meanwhile, a group of children (n=57) with normal-weight parents were recruited randomly as a reference group (defined as at low obesity risk). The baseline data was collected when the child was 1-year-old and an annual follow-up was conducted until the child was 6-year-old.

Methods: Study I is a cross-sectional study of Early STOPP baseline data, where child and parental sleep patterns were compared between high and low obesity risk groups, respectively. In Study II, an explorative study, changes of child sleep patterns from age 1 to 2 years were compared between risk groups. Furthermore, child weekday-weekend sleep variations at age 2 years and associated family factors were explored. Study III is a longitudinal study, where the development of child sleep patterns from age 2 to 6 years were studied and the association between child sleep and obesity was explored. Study IV is a randomised controlled trial (RCT) examining the effect of a long-term, low-intensive, family-based intervention on preventing obesity in children at high obesity risk, as well as effects on secondary behaviour outcomes, including child sleep, physical activity and eating behaviour.

Results: In Study I and II, some differences were observed in sleep patterns between children at different obesity risks. Compared to children at low obesity risk, children at high obesity risk had slightly longer sleep onset latency at both age 1 and 2 years, as well as greater weekday-weekend sleep variations in sleep schedules at age 2 years. Moreover, children in the high obesity risk group were more likely to experience unfavourable sleep characteristics than their peers in the low-risk group during the first two years of life, including more

transient prolonged sleep onset latency and low sleep efficiency. In Study III, when child sleep was assessed using actigraphy, no difference was observed in either child sleep variables or the prevalence of unfavourable sleep characteristics from age 2 to 6 years.

In Study III, from child 2 to 6 years, higher short sleep duration score was associated with a greater increase in BMI z-score (0.12, 95% confidence interval [CI]: 0.01-0.25) across ages. Independent of sleep duration, higher late sleep score was associated with greater increases in both BMI z-score (0.16, 95% CI: 0.05-0.27) and waist circumference (0.60 cm, 95% CI: 0.23-0.98) across ages. Moreover, a significant combined effect was detected between late sleep and family obesity risk on child weight gain, as children at high obesity risk and having habitual late sleep had the greatest increase in both BMI z-score (0.93, 95% CI: 0.40-1.45) and waist circumference (3.45 cm, 95% CI: 1.78-5.12) from age 2 to 6 years.

In Study IV, during the follow-up period, no main intervention effect was identified on either primary outcome (BMI z-score) or other weight-related outcomes (weight and BMI) across ages. At age 6 years, there were 36 children with overweight and obesity, with 12 (23%) in the intervention group and 24 (26%) in the control group. The intervention was not significantly effective for reducing the risk of developing overweight and obesity. For the secondary outcomes, no significant intervention effect was detected in child eating behaviour, total sleep duration or average physical activity across ages.

Conclusion: Frequent exposures to short sleep and late sleep were independently associated with more increases in weight measures in children from age 2 to 6 years. Although the development of sleep was similar in children at different obesity risks, determined by parental weight, a combined effect between child late sleep and high family obesity risk on more weight gain was observed. Moreover, a five-year, low-intensive, family-based, multicomponent obesity intervention was not more effective than routine health care in either promoting behaviours or preventing obesity among children with overweight and obese parents.

LIST OF SCIENTIFIC PAPERS

I. **Sleep differences in one-year-old children were related to obesity risks based on their parents' weight according to baseline longitudinal study data.**
M. Ekstedt, MHSE. Darkeh, LJ. XIU, M. Forssén, E. Johansson, A. Ek, V. Svensson, K. Ekbom, C. Marcus
Acta Paed, 2017, 106: 304-311.

II. **Development of sleep patterns in children with obese and normal-weight parents.**
LJ. XIU, M. Hagströmer, L. Bergqvist-Norén, E. Johansson, K. Ekbom, V. Svensson, C. Marcus*, M. Ekstedt*
J Paediatr Child Health, 2019,55 (7): 809-818.

III. **Sleep and adiposity in children from 2 to 6 years old: a longitudinal study.**
LJ. XIU, M. Ekstedt, M. Hagströmer, O. Bruni, L. Bergqvist-Norén, C. Marcus
Pediatrics, 2020, 145 (3): e20191420.

IV. **Effect of a low-intensive, long-term trial for overweight and obese parents to prevent childhood obesity from 1 to 6 years of age - Early STOPP (Stockholm Obesity Prevention Project)**
C. Marcus, L. Bergqvist-Norén[†], M. Bottai[†], P. Danielsson-Liljeqvist[†], A. Ek[†], M. Ekstedt[†], M. Forssén[†], E. Hagman[†], M. Hagströmer[†], E. Johansson[†], P. Nowicka[†], V. Svensson[†], LJ. XIU[†]
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CONTENTS

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
ASDA	American Academy of Sleep Medicine
BISQ	Brief Infant Sleep Questionnaire
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CHCC	Child health care centre
CI	Confidence interval
CPM	Counts per minute
CSHQ	Children's Sleep Habits Questionnaire
Early STOPP	Early Stockholm Obesity Prevention Project
IOFT	International Obesity Task Force
KSQ	Karolinska Sleep Questionnaire
MCAR	Missing Completely at Random
OR	Odds ratio
PSG	Polysomnography
RCT	Randomized controlled trial
SD	Standard deviation
SES	Socioeconomic status
SPSQ	Swedish Parental Stress Questionnaire
VM	Vector magnitude
WASO	Wake after sleep onset
WHO	World Health Organization
W/H	Weight-for-height

1 INTRODUCTION

Research has been a part of my life ever since I graduated from medical school in China. During working as a resident physician and under paediatrician training, I was continuously engaged part time in research work in the field of child health and development. After I moved to Sweden, I am therefore grateful that I have was given the opportunity to conduct my PhD study at Karolinska Institutet.

Childhood obesity is one of the most severe public health challenges in our time. Much research has been devoted to understanding the etiologies and finding effective prevention approaches. During the last two decades, short sleep has attracted research attention as a risk factor for obesity, and the evidence seems more consistent in children than in other age groups. Yet, much uncertainty still exists about the role of sleep in unhealthy weight gain. Besides sleep duration, how are other sleep characteristics associated with obesity? Is sleep a modifiable behaviour for obesity prevention? Moreover, when trying to understand associations between sleep and obesity in children, family context factors could not be ignored, as the family plays an essential role in both child weight gain and sleep development. The research work in this thesis aims to address these issues to some extent by presenting results based on data from a long-term obesity prevention project in Stockholm County; the Early STOPP study.

In 2009, when the Early STOPP commenced, I was still in China and engaged in a birth cohort study in Southern China, coordinating the processes of study design, piloting, participants recruitment and data collection. When working in the early phase of a longitudinal study, I had always wondered how these large amounts of data would be handled to answer our research questions. Thanks to joining the Early STOPP research group, I got the opportunity to build experience of longitudinal data management and analysis, as well as to improve my ability to review long-term studies more critically.

At present, I am on my way to finishing the PhD study journey, which is a path to more academic adventures. Child health and development is a topic I always want to work with, and I will keep on developing as a researcher in this field.

2 BACKGROUND

2.1 CHILDHOOD OBESITY

2.1.1 Definitions

Obesity is defined as a condition of excess body fat accumulation that may impair health[1]. Body mass index (BMI, weight (kg)/height^2 (m^2)) provides the most practical and low-cost measure for obesity definition in current clinic work and research fields[2]. In adults, international thresholds of BMI are commonly used to define normal weight (18-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obesity ($\geq$ 30 kg/m^2)[2]. Defining obesity in children present challenges, because children's bodies change as they grow. Reference growth curves, based on nationally or internationally representative data, are widely used to monitor growth and to define different weight status in children, such as growth standards developed by World Health Organization (WHO) for children under or over 5 years of age[3,4], and growth charts developed by US Centers for Disease Control and Prevention (CDC) for children over 2 years of age[5]. Cut-offs to define overweight and obesity vary according to the reference used. For example, sex and age-specific standard deviation scores (SDS) /z-scores based on BMI distributions are used in the WHO reference, and in the CDC reference, sex and age-specific centiles are used. In addition, the International Obesity Task Force (IOTF) developed BMI cut-offs for overweight and obesity in children from 2-18 years, corresponding to BMI 25 kg/m^2 and 30 kg/m^2 at age 18 years[6]. These references produce similar but not identical estimates of the prevalence of child overweight and obesity, and significant differences appear under the age of 5 years[7,8]. This may be due to different populations and different statistical approaches to constructing the curves[9]. For children under 5 years of age, standards based on weight-for-height (W/H), rather than BMI, are recommended by WHO for overweight and obesity definitions. US CDC also suggests using WHO's definitions for children under 2 years of age.

Waist circumference is another body measure commonly used as an indirect marker of obesity, particularly abdominal obesity. Waist circumference and waist-to-height ratio have been found as being superior to BMI in predicting cardiometabolic outcomes in adults[10], as increased visceral adipose tissue is more associated with a range of metabolic abnormalities. In children, waist circumference seems to provide similar metabolic risk estimates to BMI[11]. Thus, it is widely accepted that waist circumference is an important complement of BMI to identify individuals at increased cardiometabolic risk[12,13]. Ethnic and gender-specific waist circumference cut-offs for abdominal obesity is available in adults[14]. A waist-to-height ratio of 0.5 has also been commonly used as a cut-off for abdominal obesity, irrespective of age, gender and ethnicity background[13]. In children, since the distribution of body fat sites varies with age, waist circumference percentile curves, as well as cut-offs for abdominal obesity, were established in some countries based on nationally representative population[15,16].

2.1.2 Prevalence

According to WHO, an estimated 40 million children under the age of 5 years were overweight or obesity in 2018[17]. In European countries, during 2006 – 2017, the prevalence estimate of overweight and obesity in children aged 2 to 7 years was 17.9% and the prevalence estimate of obesity was 5.3%[18]. A similar prevalence has been observed in Sweden. In 2008, a nationally representative data reported that 16.6% of children aged 7 to 9 years were overweight and obese and 3.0% were obese[19]. Moreover, a review of Swedish studies reported that no significant increases in overweight or obesity have been observed in school-aged children since 2013[20]. The reasons for the stable tendency are not fully understood, but it may reflect the related health strategies in Sweden has a general benefit in slowing down the prevalence[20].

The uneven distribution of obesity prevalence has been observed across countries, regions and populations[21]. From 1990 to 2010, generally, greater increases in childhood obesity were observed in developing countries (65%) than in developed countries (48%)[22]. The region disparities in obesity prevalence were also apparent in Europe, with the highest level in southern European countries and the lowest level in northern European countries[18]. Reasons for these uneven distributions between countries are complicated, such as genetic background, cultural context, economic level and development level of country[23,24]. In Sweden, although the general trend was stable, strong area gradients were also noted, with a higher prevalence of obesity and overweight were observed in children from less advantaged socioeconomic areas[25,26]. This indicates that more efforts are needed to bring the obesity prevalence down among children who are at higher risk of developing obesity.

2.1.3 Health consequences

Childhood overweight and obesity have been linked to a variety of short-term and long-term health problems. In the short term, studies showed that children with overweight and obesity are more likely to suffer from physical health issues, such as obstructive sleep apnea, musculoskeletal problems and pain, and liver complications[27,28]. They also have more cardiovascular and metabolic risk factors, such as high blood pressure, insulin resistance and dyslipidaemia[28,29]. Also, compared to normal-weight children, children with overweight and obesity are susceptible to a series of psychological problems, such as lower self-esteem, poorer quality of life, depression, eating disorders and other emotional and behavioural problems[30]. They are more likely to experience bullying, teasing and peer rejection, which are probably stressors associated with negative psychological outcomes[30]. In the long term, obesity tracks from early life into adulthood. Previous studies showed that although the predictive accuracy of childhood BMI for adult obesity is only moderate, once obesity establishes during early life and continues through adolescence, it tends to persist to adulthood[31,32]. Moreover, overweight and obesity during childhood increases the risk of developing cardiovascular diseases, diabetes, some cancers, and musculoskeletal disorders in adulthood, which can lead to disability and premature death[33]. Because of these negative health outcomes, childhood obesity increases the burdens on health systems[34].

2.1.4 Development of obesity in childhood

Obesity is a result of long term positive energy balance – the energy intake is more than the expenditure[2]. During childhood, positive energy balance is necessary for growth and development, and the energy imbalance required for unhealthy weight gain is unclear[35]. In epidemiological studies, the understanding of obesity development is mainly based on BMI dynamics across ages. Generally, individual BMI reaches a peak during the first year of life and then declines to the lowest point at around 5 to 6 years of age. After that, BMI gradually increases again, which is known as an obesity rebound. Evidence shows that the delay and higher magnitude of the BMI infant peak, as well as an early and exaggerated obesity rebound, were associated with a higher risk of obesity[1]. A population-based study tracking individual BMI of over 50,000 children from birth to adolescence indicated that 2 to 6 years of age was the critical age for developing sustained obesity, with most children who were obese at this age were obese in adolescence[31]. Studies of adipose tissue during childhood, to some extent, support the BMI dynamics observed in population studies[1]. For example, a significant increase in adipose tissue in obese children compared to lean children from aged 2 years onward was observed in both cross-sectional and longitudinal studies[1]. Based on these evidence, the progression of obesity starts from a very early age, suggesting early childhood is an essential phase for obesity prevention.

2.1.5 High risk determined by parental obesity

Parental obesity has been identified as a predominant risk factor of offspring obesity[36-38], with children of overweight or obese parents having 3–10 times higher risk of developing obesity than children of normal-weight parents[36]. Parental obesity also seems to contribute to the obesity persistence in their offspring[39]. Evidence from twin studies indicates that bodyweight is highly heritable[40], with heritability estimates in BMI and waist circumference ranging from 45% to 87%[41]. However, genetic contribution only partly explains the generational transfer of obesity, as there is substantial variation in heritability estimates[41]. This variation has been attributed to individual characteristics and social-environmental factors, such as age, ethnicity, and country-level gross domestic product[40]. Among children, the influence of family environment on the heritability of weight status has been observed. One twin study showed that heritability of BMI was higher among children in more obesogenic home environments, characterized by food, physical activity and media environment[42]. A large European study also reported that the effect of the obesity-related genotype on BMI was stronger among children with parents of low socioeconomic status (SES)[43]. These findings suggest that the heritability of child obesity varies by home environment and understanding potential risk behaviours within families can further inform home-based obesity prevention efforts. For example, several behaviours, such as higher consumption of sugar-sweetened beverages[44] and a preference for sedentary activities[45], have been observed in children with obese parents even before the obesity occurrence. Short sleep has also been identified as a risk factor for childhood obesity. However, less is known about how child sleep is in families at high obesity risk and how it impacts on weight development in children with a stronger predisposition to obesity.

2.1.6 Other family-related factors

The etiological factors for childhood obesity are complex and not fully understood[46]. Besides parental obesity, family SES, often measured using family income, parental education and occupation, is another important family-related risk factor for childhood obesity. Evidence from different areas indicates that associations between family SES and child obesity vary with countries' economic levels, as positive associations were commonly observed in low-income countries[47] and negative associations were often reported in high high-income countries[48,49]. Moreover, among these SES indicators, low parental education seems most strongly associated with child obesity[50], and also related to low recognition of child obesity[51]. Parents with low education level probably are not only characterized by financial disadvantage but also lack of knowledge and skills, which makes healthy lifestyle choices and optimal parenting practices less available[52].

Associations of parental psychological factors with child obesity have been examined, but findings are mixed[53]. The association between maternal general stress and child obesity is more consistent in cross-sectional studies, but less consistent in longitudinal designs[54]. Positive associations between parenting role stress and obesity have been observed in preschool children[53]. Associations between high parenting stress and more obesity risk behaviours have also been observed in children, such as less physical activity and more screen exposure[55,56]. These results indicate that parents who are stressed might engage in more unhealthy parenting practices, which are probably risk factors for child obesity[53]. Moreover, other family factors, such as parenting style, family structure, household chaos, family function, have been linked to child obesity in some, but not all, studies[57].

2.1.7 Preventive intervention

The importance of primary prevention of childhood obesity has been emphasized, since once obesity is established, it is difficult to reverse through interventions and treatments[58]. Preventive intervention programs vary in age groups of targeted children, settings, targeted behaviours, intervention strategies and duration[59]. In 2019, an updated Cochrane review included 153 randomized clinical trials (RCT) of interventions for preventing obesity in children, and among them, 39 RCTs targeting children aged 0 to 5 years[59]. A moderate-certainty evidence was claimed that combined diet and physical activity interventions were more effective than control in reducing BMI (by 0.11 units) and BMI z-score (by 0.07 unit) in this age group[59]. Neither diet nor physical activity interventions alone were more effective than control in preventing obesity, and the significant results were only reported in RCTs at the home level, but not in those at the child-care/preschool level. These results suggest that home-based intervention with targeting multiple obesity-related behaviours are probably most promising in obesity prevention in this age group[60,61]. However, most studies in this review had an intervention duration less than 12 months. The short time frame of these interventions is probably not enough to conclude that child obesity can be prevented in the long term, as previous prevention studies have shown that short-term positive results did not mirror long-term outcomes[62,63]. A more extended intervention period is probably required to

establish a real preventive effect. Moreover, potential adverse events related to intervention were evaluated in several studies[59], such as physical injuries, accidents and insufficient weight gain among young children, and unhealthy eating practices, body satisfaction and self-acceptance among older children. There is no evidence showing that obesity interventions led to more adverse events than the control[59]. However, whether obesity intervention harms parents and family are less studied. Since parents are involved in home-based interventions, the potential adverse effects on them need to be taken into consideration.

Motivational interviewing (MI) is recommended and widely used for obesity prevention in the paediatrics population[64]. As a person-centred strategy, MI is used to elicit patient motivation to promote specific positive behaviours and change specific negative behaviours[65]. However, studies evaluating the effect of MI on preventing obesity showed inconsistent results[66,67], which may be due to different intervention designs and varying proficiency among those who perform MI[67].

2.2 CHILD SLEEP

Sleep is essential for child's growth, development and well-being. At the behavioural level, sleep is defined as a reversible behavioural state of decreased responsiveness and interaction to external surroundings and stimuli[68]. Sleep can also be defined based on electrophysiological criteria, such as different sleep stages and sleep cycle[68]. In this section, we focus on child sleep patterns, which are assessed at the behavioural level.

2.2.1 Sleep patterns

Sleep patterns are generally used in the description of sleep at a behavioural level, in which duration, timing/schedules and quality are key dimensions[69]. Duration is frequently described as the total amount of time spent in sleep over a 24-hour period, including nocturnal sleep and daytime naps[70]. Sleep schedules are often used to describe clock times related to individuals' sleep episodes, such as bedtime, sleep onset, sleep offset and wake-up time. The sleep schedules not only reflect individuals' sleep habits, but are also regulated by sleep homeostatic and circadian systems[68]. The term of sleep quality, reflecting "how good or bad sleep is", can be described using measures of sleep continuity, including wake after sleep onset (WASO) and sleep efficiency[71]. It can also be defined at the subjective level and reflect individuals' satisfaction with their sleep[71,72].

The average sleep pattern, quantified as the mean over a period of days, is often used to describe the overall level of an individual's sleep. In addition, intraindividual sleep variation is another integral part, reflecting the regularity of an individual's sleep[73]. For example, day-to-day sleep variation is quantified as daily variation around the mean level, and weekday-weekend variation is measured as the difference in sleep patterns between weekdays (workdays) and weekends (free days). Great sleep shift between weekdays and weekends, known as "social jetlag", as well as great sleep variations in shift workers, are important sleep health issues among adolescents and adults, as misalignment between an individual's circadian clock and social clock has been linked to adverse health outcomes[74].

2.2.2 Development of sleep patterns in childhood

The development of sleep patterns in children starts with a rapid mature process during the first year of life and continues with more gradual changes in later ages[69]. Sleep duration decreases from an average of 16 hours/day as a new-born to about 12 hours/day at the end of the first year of life and significantly consolidates to the night. During the toddler and pre-school ages, total sleep duration gradually decreases with age, mainly due to the reduction in daytime naps, while the nocturnal sleep duration is relatively stable across ages[75,76]. Sleep quality overnight tends to become better across ages in this age group, as the number of night-time awakenings decreased and the longest sleep period increased with ages[77,78]. Findings of development trends in bedtime or sleep onset time are mixed in toddler and pre-school ages. Some studies reported that child sleep onset time steadily progress later with ages[78,79], while others reported that no age effect was observed[75]. Most studies found that child sleep onset latency was relatively consistent in this age group, around 20 minutes (min) [77], while one study observed that child sleep latency significantly became shorter with ages[75]. These inconsistent results in child sleep timing are probably due to different sleep assessment methods, as well as diverse cultural backgrounds of sleep practices.

The development trends of intraindividual sleep variation in toddlers and pre-schoolers are less studied, as their sleep is supposed to be less influenced by social demands. However, several studies reported that weekday-weekend sleep variations were already observed in this age group and progressed prominent with ages. For example, child bedtimes shifted to later during weekends than in weekdays, from around 12 min at 1-year old to 40 min at 5-year-old[80,81]. Although the variations are not comparable to the observed level in later ages, these results suggest that the misalignment of weekday and weekend sleep might start in early childhood[82].

2.2.3 Unfavourable sleep characteristics

Unfavourable sleep characteristics, often addressed as sleep problems, are common in children. According to parents' reports, around 20% to 45% of children experienced some kinds of sleep problems throughout early childhood[83,84]. Unfavourable sleep characteristics vary across children ages. During infancy and toddler-age, difficulty in falling asleep and frequent nocturnal awakenings are prevalent and are parents' major complains of the child sleep[69,85]. Among pre-school aged children, the frequent nocturnal awakenings declines, whereas difficulty in falling asleep seems to remain prominent[84]. While, a previous study using actigraphy reported that nocturnal awakenings in pre-schoolers were as prevalent as in toddlers, but pre-schoolers signalled less to parents and resumed sleep themselves[83]. Moreover, other types of sleep problems, such as night fears, nightmares and sleep terrors, become common in pre-school age[86]. Although most unfavourable sleep characteristics are mild, transient and developmentally normal, some persist and become chronic problems or disorders that need intervention[87].

2.2.4 Sleep and health

Sleep plays an important role in neuroendocrine function, immune function, cognitive function and memory[88] and is essential for body restoration and daily performance. Short sleep duration has been linked to cardiovascular and metabolic risk factors in school-aged children and adolescents, such as high blood pressure, poor lipid profile and blood glucose regulation[89]. However, the evidence is still limited and it is not well known in toddler ages[90]. Optimal sleep has been generally linked to child development in early childhood, while studies that examined the relationships between sleep and cognition, behaviour and emotional regulation provided mixed findings, and the effect size was relatively small in those studies reported positive associations[91]. In school-aged children, associations of sleep with cognitive scores, school performance and behaviour problems have been studied extensively. However, again, results are inconsistent, with most studies detecting favourable associations or null association[92]. To determine associations between sleep and health is probably a challenge, as great variation in individual sleep needs and tolerance of lack of sleep[88]. Moreover, as mentioned before, most unfavourable sleep characteristics are only transient and developmentally normal, which might not affect health. More attention is probably needed to understand the associations between chronic or persistent poor sleep with health outcomes in children[93].

Sleep is also sensitive to health status. Nearly all physical discomfort and medical issues can disrupt sleep, and sleep disturbances are also symptoms of a range of psychological problems and behavioural disorders, such as stress, general anxiety and depression[94].

2.2.5 Possible associated factors in families

The development of sleep is influenced by complex and dynamic interactions between individual biological factors and various socio-environmental factors[95]. Although genetic effects are important, evidence from twin studies indicates that shared environment have a stronger influence on sleep during early childhood, particularly on sleep duration and bedtime[96,97], emphasizing the critical role of family and parents in child sleep.

Associations between family SES level and child sleep has been studied extensively. A positive association between family SES level and child sleep was reported in some studies, but an equal number of studies failed to identify such association[75,85,98,99]. It is probably due to that different indicators of SES were adopted across studies, as well as diverse cultural backgrounds. Ethnic variations in child sleep have been reported consistently[100], with irregular and short sleep seem more prevalent among children with some racial backgrounds (e.g., Asian, Hispanic and Black) than those with other racial backgrounds (e.g., White/Caucasian)[98,100]. Household chaos, characterized by the lack of structured family routines and high level of marital conflict, has also been found to be associated with low sleep quality and great sleep variation in children[101,102], as well as predict poor sleep during later childhood[103].

Parenting practices have a direct influence on child sleep[104]. For example, lack of bedtime routine and excessive parental involvement have been consistently associated with more sleep problems in children[105]. It is assumed that children with parents who are actively involved in their sleep are less likely to develop their own self-regulation and soothing skills that are necessary for sleep consolidation[104]. Parental emotional status, particularly maternal emotion, has also been linked to child sleep. Maternal depression has been identified as a correlator and predictor of short sleep and sleep problems among young children[106,107]. Maternal high level of anxiety and stress have also been found to have a negative impact on child sleep[108]. It is hypothesised that emotional distress may affect mothers' responsiveness to children's needs, as well as parenting practices related to child sleep, and, in turn, may interfere with child sleep[109,110]. Importantly, most of these associations can also be interpreted alternatively. For example, children with more sleep problems probably require more parental attention and involvement during sleep[104]. Child sleep problems can also be experienced as a major stressor by some parents and further affect their sleep, emotion, and parenting practices[111]. One previous intervention study of infant sleep problem showed that when infant sleep problems reduced, mothers' symptoms of depression also significantly decreased[112].

2.2.6 Sleep assessment

Different methods have been developed to assess sleep at different levels. Among these methods, polysomnography (PSG) is considered the gold standard and provides the most detailed information on sleep architecture and clinical diagnoses. PSG is not commonly used in population studies, due to the required laboratory setting and qualified evaluator and high cost[113]. In the section below, we focus on the most common sleep assessments methods used in population studies of children.

2.2.6.1 Sleep diary

Sleep diary is commonly used in sleep research in children, since it is easy to use and cost-effective[70]. Diaries are often completed by parents or children themselves to document sleep patterns over a time period, usually one week. Diaries can provide information on sleep schedules, night-time awakenings and events that may disturb sleep. Diaries are quite reliable in the assessment of schedules-related variables. Therefore, they are also frequently used to assist to identify sleep periods and artefacts in actigraphy data[114] . However, the validity drops when it comes to sleep quality variables, e.g., night-time awakenings and sleep efficiency, which is probably due to recall biases and parents' limited awareness of children's night-time sleep[70].

2.2.6.2 Actigraphy

Actigraphy is a watch-like device that continuously monitors body movements for extended periods. The use of actigraphy for recording sleep patterns in healthy children and in some paediatric population has been recommended by the American Academy of Sleep Medicine (ASDA)[115]. Actigraphy measures body movements and the collected raw activity data (general in 1-min epochs) are scored as "awake" or "asleep" based on sleep-wake scoring

algorithms. Several algorithms (e.g., Sadeh algorithm and Cole-Kripke algorithm) have been developed, validated and commonly used across ages[116-118]. Among children, when compared to PSG, high sensitivity (ranging from 82.2-90.1) and relatively low specificity (ranging from 50.9-72.8) of actigraphy have been well documented[114]. More specifically, actigraphy is generally good in identifying sleep, but less accurate in identifying awake during sleep periods. This is because actigraphy assesses sleep through measuring the movement of a limb. The amounts of awakenings are easily overestimated in individuals who change position more frequently during sleep (e.g., young children) and underestimated in individuals lying quietly but without sleep (e.g., adults)[119]. Thus, in practical work, actigraphy is suggested to be worn on non-dominant hand[120], and to be worn at least one week to obtain reliable measures of sleep[121]. Moreover, some validated smoothing algorithms have been suggested to secondarily use to reduce the number of awakenings when using actigraphy in young children[122].

Actigraphy gained popularity in sleep research due to its ability to objectively measure sleep in the natural environment, with acceptable accuracy and cost. However, some issues have been repeatedly raised[114]. For example, there is a lack of consistency in the applications of actigraphy, including standard procedures, epoch length, scoring rules and definitions of sleep variables, which makes the comparisons across studies difficult[114]. In addition, different commercial devices are available in the market and each device has its own measurement characteristics. Therefore, scoring algorithms and validation studies are required for specific device[70,123].

2.2.6.3 *Sleep questionnaire*

Sleep questionnaires are critical in assessing behavioural and physiological aspects of sleep. Several paediatric sleep questionnaires were well-established and standardized in different countries[124]. For young children, sleep questionnaires usually address problems of sleep initiation and maintenance, as well as related parental practices. For example, the Brief Infant Sleep Questionnaire (BISQ)[125] is a commonly used screening tool for sleep problems in young children (aged 0 to 29 months). Another popular questionnaire is the Children's Sleep Habits Questionnaire (CSHQ)[126], which is designed for children aged 4 to 10 years. It provides a total score as well as eight subscale scores reflecting possible sleep problems in children. A revised version of CSHQ has also been validated for younger children (aged 2 to 5 years)[127]. There are also questionnaires used to evaluate sleep hygiene, daytime sleepiness, as well as sleep-related beliefs and cognitions in children[124]. There subjective questionnaires offer a cost-effective way to assess aspects of sleep that cannot be measured using diary or actigraphy, although their validity is easily affected by response biases.

2.3   SLEEP AND OBESITY IN CHILDREN

2.3.1   Associations

Sleep is increasingly acknowledged as one of the obesity-related behaviours. An association between short sleep duration and incidence of obesity has been consistently reported in

children and indicated by several reviews, with estimated odds ranging from 1.2 to 1.9[128,129]. Associations of short sleep duration with higher waist circumference and percentage of body fat were also observed in children at different ages[130-132]. Moreover, several studies with relatively large study population found associations between overlong sleep and obesity in preschool-[133] and school-aged[134] children, suggesting the possible U-shaped association between sleep duration and obesity, as well as the existence of optimum length of sleep for healthy weight development. However, the current evidence is heavily based on reported sleep data. Moreover, as mentioned before, child sleep is not stable across ages, but only some studies have performed repeated sleep measures and examined the association of chronic or habitual short sleep with obesity[130,132].

Beyond sleep duration, some other sleep variables and characteristics have also been linked to obesity in children. Late bedtime has been correlated to high BMI in most studies in preschool-aged children[135,136], as well as predicts obesity in later childhood[135,137]. Several studies suggested that associations between late sleep and unhealthy weight in children are probably independent of sleep duration[135]. It has also been reported that late sleep may modify the association between sleep duration and BMI, as the association between short sleep and higher BMI was present only among children with bedtime later than 21:00[138]. No study has been performed to examine association between sleep onset latency and weight status in young children. Only two studies were conducted in school-aged children, and no significant association was reported[139,140]. Evidence of associations between sleep quality and obesity is mostly from school-aged children and adolescents, and findings are mixed, with some reported negative associations, but some reported no association[136]. Very few studies have been performed examining the association between sleep quality and obesity in early childhood, which is surprising, given unfavourable sleep and low sleep quality are common in young children. One longitudinal study in children from age 0 to 7 years reported no association between child sleep problems and obesity[141]. Another longitudinal study indicate that the associations between child sleep problem and obesity in later childhood varied with the definitions of sleep problem adopted[142]. Thus, besides sleep duration, studies with objective measures are needed to understand how other sleep dimensions are associated with weight gain in young children.

2.3.2 Possible mechanisms

The mechanisms underlying the linkage between sleep and obesity are still not clear and several possible mechanisms have been suggested. The impact of sleep loss on appetite control has been observed in experimental studies in adults. Changes of appetite-related hormones, with an increase in ghrelin, an appetite stimulator, and a reduction in leptin, an appetite suppressor, have been observed after acute sleep loss in most, but not all, studies[143-146]. An enhanced brain activity in areas related to food stimulation and reward after sleep restriction has also been observed in neuroimaging experimental studies[147]. These results indicate that insufficient sleep might alter the physiological system of appetite control and lead to more food intake. Meanwhile, observational studies generally reported associations

between short sleep and higher calorie intake across ages[148-150]. The increased activity of the hypothalamic-pituitary-adrenal gland axis has also been seen in individuals with chronic short and late sleep, such as increase secretion of cortisol[151]. This may affect blood glucose control and further contribute to obesity and other metabolic issues[152]. It may also suggest that high stress is the third factor affecting both sleep and weight gain. Moreover, possible genetic factors have been suggested linking disturbed sleep and obesity, such as circadian clock genes[153,154]. At the dietary level, associations between poor sleep and obesity-promoting diet have been observed across ages. Short and late sleep have been associated with greater intake of fat and carbohydrates, more consumption of sweets, higher intake of energy-dense foods, less intake of healthy foods[155-157]. Besides, by nature, short and late sleep may also increase the opportunities for eating, particularly eating during the night.

Studies have also examined associations between short sleep and energy expenditure. Laboratory studies showed that energy expenditure increased around 134 kcal/day during sleep deprivation period than during the period of habitual sleep, when food intake was controlled[158]. While when energy intake was not controlled, energy intake was around 300 kcal/day more during the sleep deprivation period[159]. These indicate that when sleep is restricted, individuals tend to consume more calories than the energy needs for extending wakefulness[160]. In population studies, associations of short sleep with less physical activity and more sedentary behaviour have also been reported[161-163].

Some previous studies examined the possible related mechanisms in young children. Associations between short sleep and greater energy intake, predominantly energy intake at night, have been observed in toddlers[164,165]. An experimental study of a small group of children at 3 years old reported that intakes of total calories, sugar and carbohydrates were increased following sleep restriction[166]. Obesity-related eating behaviours, such as greater food responsiveness[167], greater emotional overeating[168], less favourable dietary[169] and irregular eating[170] have also been reported in preschool-aged children. In addition, given that young children have less autonomy over the food available and environment, family factors probably cannot be ignored when trying to understand the association between sleep and obesity in young population[171]. For example, family income and parental education have been found to be able to modify the relationship between short sleep and obesity in children[172,173]. However, less is known about whether family obesity background, such as parental obesity, has an impact on the association between child sleep and obesity.

2.3.3 Targeting sleep in obesity prevention

Sleep has been included in some obesity interventions as a behavioural target. Around 20% of the family-based obesity preventions in children between 2008 and 2015 included sleep promotion strategies[174]. Most of sleep promotion strategies are educating parents on sleep hygiene, such as normal sleep development in children, age-appropriate sleep duration, bedtime routines and soothing strategies[174]. Moreover, most interventions measured children's sleep by parent report[174]. A one-year intervention study during infancy targeting sleep and feeding practices reported significant intervention effect on weight gain among

infants in the group receiving both sleep and feeding intervention, while no effect on infant sleep was observed[175]. Another obesity prevention including sleep component in children between aged 2 to 5 years reported that children in the intervention group had significantly increased sleep duration (around 40 min/day) and decreased BMI than children in the control group after 6-month intervention[176]. However, most RCTs of multicomponent behavioural obesity intervention including sleep component reported no intervention effect on either child sleep or weight-related outcomes[177]. Thus, the effect of including sleep promotion in multicomponent obesity prevention on both sleep and weight gain is still largely unknown. More high-quality RCTs with objective sleep measure and long-term follow-up are needed to clarify the role of sleep as a modifiable behaviour for obesity prevention in children.

2.4   SUMMARY

Child poor sleep, particularly short sleep duration, has been consistently linked to childhood obesity. However, most evidence relies on parental reports and less is known about the associations of other sleep characteristics with child obesity. There are also knowledge gaps in whether sleep patterns differ between children at different family obesity risks and whether the association between child sleep and obesity differs by family obesity risk. Moreover, whether sleep can be improved in multicomponent obesity intervention and further benefit preventing obesity in children is still uncertain.

3 AIMS

The overall aim is to explore the role of sleep in the development of obesity among children at high and low obesity risks, determined by the parental weight, and whether child sleep can be promoted in a long-term, multicomponent obesity prevention project.

Specific aims:

To describe sleep patterns in 1-year-old children at high and low obesity risks and their parental sleep, and to examine parent-child sleep correlations. *(Study I)*

To study weekday-weekend sleep variations in 2-year-old children at high and low obesity risks, as well as associated factors. *(Study II)*

To compare the development of sleep patterns and sleep characteristics across ages in children at different obesity risks. *(Study II, III)*

To examine the longitudinal associations between sleep and obesity from age 2 to 6 years, and whether the associations differed by family obesity risks. *(Study III)*

To investigate the effect of a long-term, low-intensive, family-based, multicomponent intervention to prevent obesity among children at high obesity risk from age 1 to 6 years, as well as the intervention effect on child eating behaviour, sleep duration and physical activity. *(Study IV)*

4 METHODS

4.1 MATERIAL

All studies included in this thesis are embedded in the Early Stockholm Obesity Prevention Project (Early STOPP). Early STOPP was a cluster RCT conducted from 2009 to 2018 in Stockholm County, Sweden. Early STOPP targeted young children with overweight and or obese parents, who were at high risk of developing obesity. The primary aim was to evaluate whether a low-intensive, long-term, family-based intervention would be superior to routine health care in preventing obesity among young children at high obesity risk. Early STOPP also aimed to explore how obesity-related behaviours, such as dietary, physical activity and sleep, associated with weight increase, as well as whether these behaviours could be modified and contribute to a successful obesity prevention in this age group. A protocol for the Early STOPP trial was published in 2011[178], and the trial was registered at ClinicalTrials.gov (NCT01198847).

4.2 STUDY DESIGN

Study I was designed as a cross-sectional study where both child and parental sleep patterns were examined at the baseline. Study II is an explorative study, where child weekday-weekend sleep variations were explored cross-sectionally at age 2 years, and changes of sleep patterns from age 1 to 2 years were compared between high and low obesity risks. Study III is a longitudinal study, where the development of sleep patterns from age 2 to 6 years was described, and the association between child sleep and adiposity was explored. Study IV is concerned with intervention effects in the RCT Early STOPP on primary weight-related outcomes and secondary behavioural outcomes, including child sleep, physical activity and eating behaviour. An overview of the design and population for each of the studies is presented in Table 1.

Table 1. Overview of the studies included in the thesis.

	Study I	Study II	Study III	Study IV
Aim(s)	To compare sleep patterns in 1-year-old children and their parents' sleep between families at high and low obesity risks. To explore associations between child and parental sleep.	To compare changes in sleep patterns and characteristics between children at different obesity risks from age 1 to 2 years. To explore the weekday–weekend sleep variations in 2-year-old children at different obesity risks, as well as related factors.	To compare the changes in sleep patterns and characteristics in children at different obesity risks from age 2 to 6 years. To examine longitudinal associations of sleep characteristics with adiposity, and whether the associations differed by family obesity risk.	To investigate the effects of a long-term, low-intensity, family-based intervention on preventing obesity in children at high obesity risk, as well as on child eating behaviour, sleep duration and physical activity.
Designs	Cross-sectional	Cross-sectional Longitudinal	Longitudinal	RCT
Participants	Baseline data collected up to May 2012. 167 children at 1-year-old, 166 mothers, 157 fathers	Cross-sectional analysis: 145 children, from age 1 to 2 years. Longitudinal analysis: 142 children, at 2-year-old	107 children, from age 2 to 6 years	181 children, from age 1 to 6 years
Main Variables & Methods	Child sleep patterns (sleep diary) Parental sleep patterns and sleep quality (Karolinska Sleep Questionnaire)	Sleep patterns and sleep characteristics (sleep diary) Weekday-weekend sleep variations (actigraphy)	Sleep patterns and sleep characteristics (actigraphy) BMI z-score, waist circumference	Weight, BMI, BMI z-score, overweight and obesity Sleep duration, physical activity level (actigraphy), Eating behaviours (Child Eating Behaviour Questionnaire)

4.3 RECRUITMENT AND PARTICIPANTS

4.3.1 Setting, randomization and recruitment

In Early STOPP, the child healthcare centre (CHCC) was the unit of randomization. One hundred thirty-two CHCCs in Stockholm County were invited to the study. Of these, 67 CHCCs participated and were randomly assigned to the intervention (32 CHCCs) and control groups (35 CHCCs), by using a computer-generated randomization Excel list that was formulated to stratify by capacity of CHCCs.

Recruitment of families took place at the enrolled CHCCs from May 2009 to May 2013. Parents were invited to the project when they visited a local CHCC for their child's eight-month check-up. Eligibility criteria for the families included: (1) family being at high obesity risk (high-risk), which was defined as having at least one obese parent (BMI $\geq$ 30 kg/m^2) or two overweight parents (BMI 25 – 29.9 kg/m^2), (2) having a full-term birth infant under age 1 year, (3) the infant being without chronic health problems likely to affect growth and development, and (4) parents being able to communicate in Swedish[178]. For twin pairs, the first twin was included. Meanwhile, a group of children with two normal-weight parents (BMI 18 – 24.9 kg/m^2) and meeting other inclusion criteria were also recruited randomly through the enrolled CHCCs as a low obesity risk reference group (low-risk). Therefore, among individuals without intervention, we had the opportunity to investigate obesity-related behaviours in children at high or low obesity risks.

In the study protocol[178], the recruitment of participants to the intervention and control groups was planned at a 1:1 ratio. However, the recruitment of participants to the intervention group did not reach the goal, although the inclusion period was extended. The final enrolment ratio was 2:1 control/intervention. Based on the calculation that a sample size of 186 participants with 62 in the intervention group and 124 in the control group would provide > 80% power (at a significance level of α =0.05) to detect a difference of 50% in the primary weight outcome as planned in the study protocol[178].

4.3.2 Participants

In total, 238 families were recruited in Early STOPP. There were 181 families at high obesity risk, with 66 in the intervention group and 115 in the control group, and 57 families at low obesity risk. The recruitment of randomized participants is displayed in Figure 1.

In Study I, families enrolled up to May 2012 and with sleep diary data at baseline were included (n = 167). In Study II, since no intervention effect was identified at child 2 years old, all children in the Early STOP with sleep dairy data at both age 1 and 2 years were included (n = 145). A flowchart of participants inclusion is presented in Figure 2. In Study III, only children from the observational groups were included (high-risk control group and low-risk group), and they had at least two sets of sleep measures between age 2 to 6 years (n = 107). A flowchart of participants inclusion is presented in Figure 3. In Study IV, all randomized families were included in the analysis of intervention effects (n = 181).
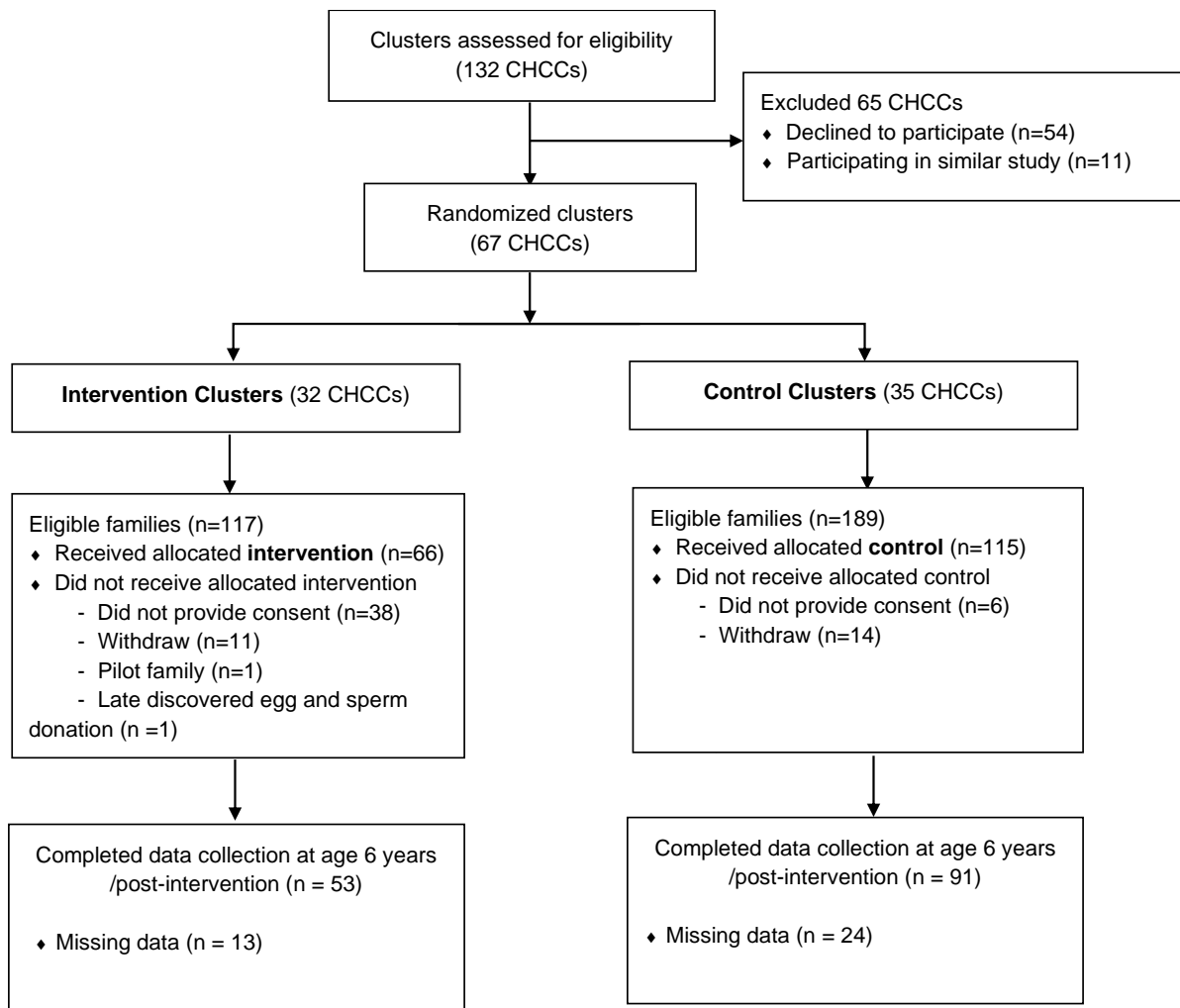
Figure 1. Flowchart of recruitment of randomized participants in Early STOP.
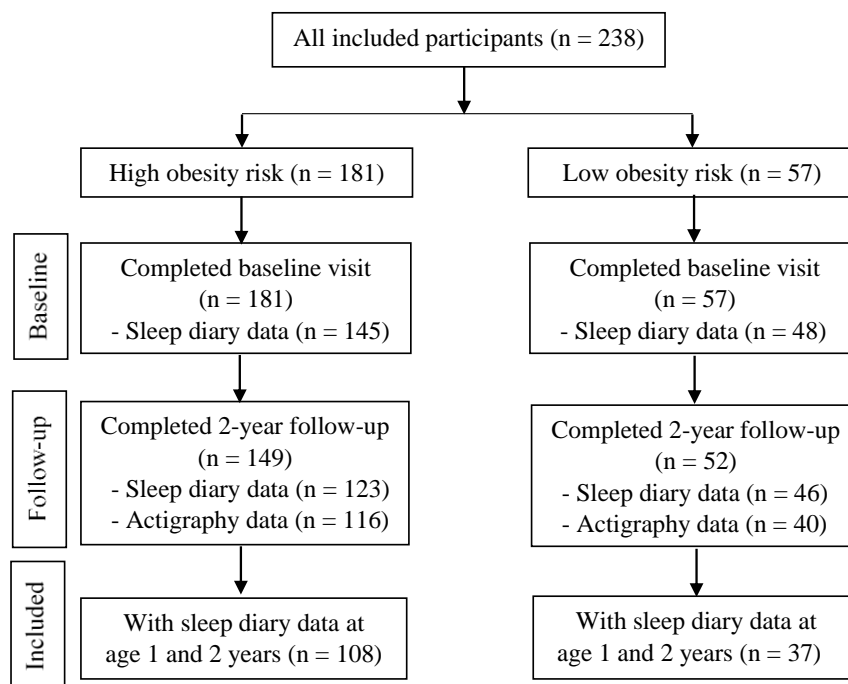

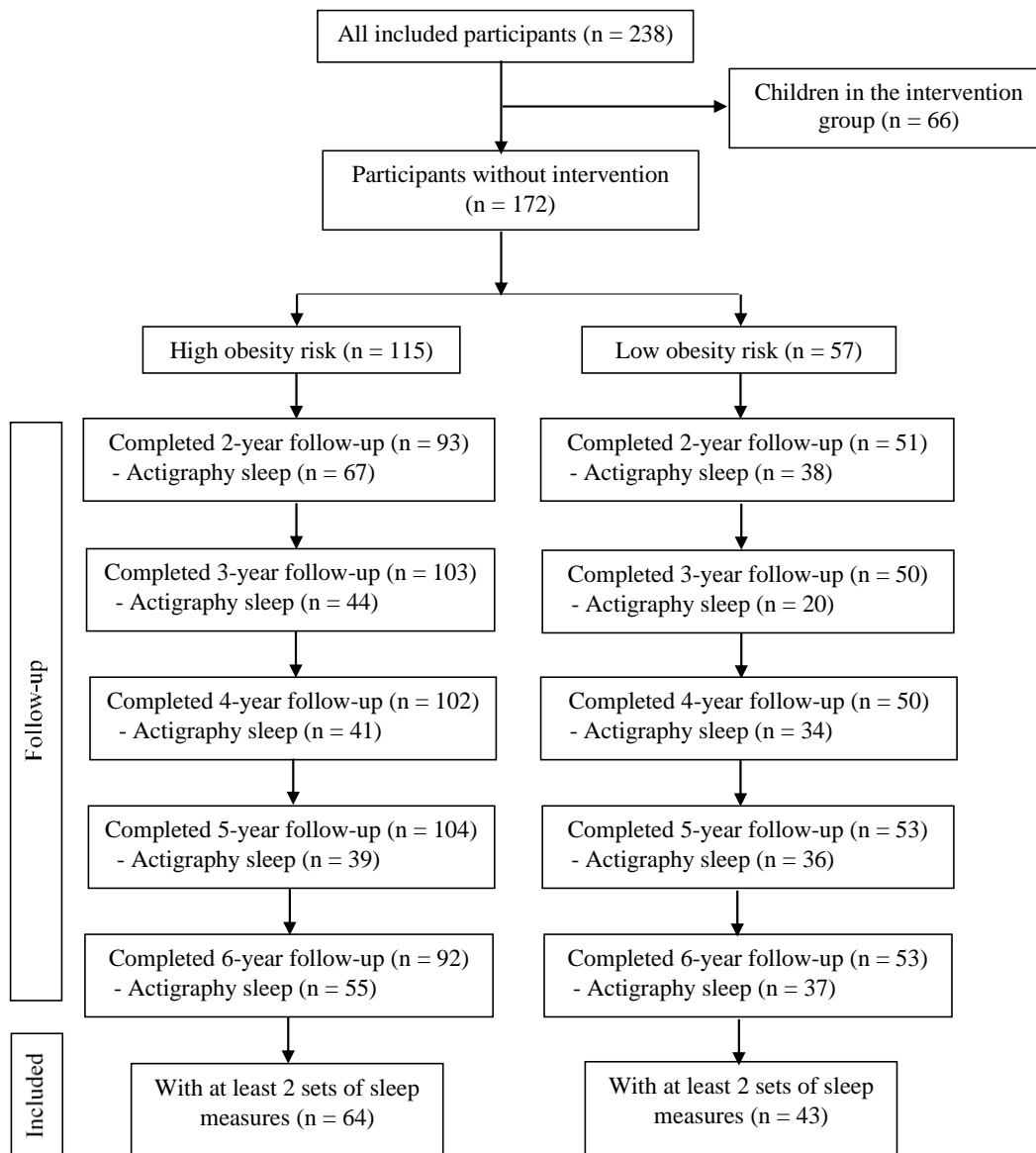**Figure 2.** Flowchart of participants included in Study II.

Figure 3. Flowchart of participants included in Study III.

4.4 DATA COLLECTION

In Early STOPP, baseline data and measures were collected when the child was one year old. Family follow-ups, including anthropometric measurements, parents filling questionnaires, food diary and sleep diary, and child wearing actigraphy for collecting sleep and physical activity data, were conducted within two months of the child's birthday every year until the child was six years old.

4.5 INTERVENTION

The family-based intervention consisted of two components: individually targeted coaching and written materials on health promotion. The coaching sessions were provided by trained coaches and based on MI techniques. The coaching sessions aimed at increasing parental awareness and skills to promote parenting behaviours related to child diet, sleep, and physical activity. For child sleep, the educational material was adapted for the child age and based on

evidence and recommendations, including knowledge of sleep development during the first years of life, ideal environments for promoting sleep, keeping consistent sleep schedules, regular bedtime routines and strategies of handling night-time awakenings. The basic structure of the coaching session included a report on the current situation, identifying problems, assistance in problem-solving, and providing positive encouragement for further development as well as goal-setting. A coach manual contained detailed information specific to each focus area, including educational material, duration of each session, and suggestions and tips to the families. Coaches attended meetings with the project manager every six months to ensure protocol adherence and held supervision sessions with an expert in MI during the first years of the study. Given that the coaches had a curriculum to follow, the MI concept could not be fully adhered to.

The coaching sessions were conducted four times during the first study year, at child age 12, 15, 18, and 21 months, and twice a year during the rest of the study period (12 sessions in all). Each session took around one hour. Moreover, during the intervention period, families could request intensified coaching due to a child gaining weight or sudden changes in the family, such as divorce. In these cases, families were offered two extra sessions that year. On average, each family received 9 coaching sessions during the intervention period. In total, 22 families (33%) received at least 12 coaching sessions; among them, 12 families (18%) received more than 12 sessions. In addition to the coaching, the families were provided with written materials on health promotion tailored to the current age of the child. Advice in the materials was based on the latest evidence-based recommendations about diet, physical activity, and sleep.

The families in control and low-risk groups received only routine health care from CHCCs.

4.6 MEASUREMENTS AND DEFINITIONS

4.6.1 Anthropometrics

Anthropometric measurements were collected on both children and parents by trained research staff, using standard procedures and calibrated instruments[178]. Weight was measured with portable scales (Tanita HD-316, Tanita Corp.; Tokyo, Japan) to the nearest 0.1 kg, with shoes and heavy clothing removed. Height was measured to the nearest 0.1cm using a portable stadiometer. Waist circumference was measured to the nearest 0.1 cm measured right between the lower costal (rib) border and the iliac crest using a nonextensible tape. All measures were taken three times and mean values were calculated. The BMI was calculated based on height and weight.

Parental weight status was categorised based on the WHO standards as normal weight (BMI $= 18 - 24.9 kg/m^2$), overweight (BMI $= 25 - 29.9 kg/m2$) and obese (BMI $\geq 30 kg/m2$) at baseline. For children, BMI z-scores were derived from both the Swedish age- and sex-specific reference values[179] (Study I and III) and the WHO child growth standards[3,4] (Study IV). In Study II, child weight status was defined based on WHO child growth standards for

children aged younger than 5 years[2]: normal weight (W/H between -2 z-scores to 2 z-scores), overweight (W/H above 2 z-scores) or obesity (W/H above 3 z-scores). In Study IV, for child age 2 to 6 years, overweight and obesity were defined based on cut-offs from the IOTF[6].

4.6.2 Child sleep

4.6.2.1 Sleep diary (Study I & II)

Child sleep patterns were recorded by parents using a seven-day consecutive sleep diary. In sleep diaries, parents were instructed to record the clock times of nocturnal sleep period and daytime nap period, as well as clock times and duration of each night-time awake episode after sleep onset. Based on parental reports, child nocturnal sleep duration, sleep efficiency, nap duration and total sleep duration were calculated, respectively. The definitions of sleep variables are presented in Table 2. The mean values were calculated across the whole week.

4.6.2.2 Actigraphy (Study II-IV)

From age 2 years, child sleep was measured yearly for seven consecutive days using a wrist-worn actigraphy, ActiGraph GT3X+ (ActiGraph LLC, Pensacola, FL, USA), a tri-axial accelerometer with sensitivity 0.05 g and a sampling rate of 30–100 Hz. Activity counts were collected at a 30-Hz sampling rate and integrated to 1-minute epochs using the manufacturer's software. Each epoch was scored as either "awake" or "asleep" based on Sadeh's sleep algorithm[116], which has been validated in children using PSG[116,180]. To reduce the overestimation of night-time awakenings, a secondary algorithm, developed and validated by Sitnick et al[122,181], was adopted. Specifically, when 2 consecutive epochs with activity counts $\geq$ 100 and the third epoch with an activity count above 0, the first epoch was considered as the start of an awakening. An awakening was scored as ending, signifying a return to sleep, at the first of 3 consecutive epochs with counts of 0[122,181]. Smoothing was automated using an Excel formula (Microsoft, Redmond, WA, USA). Individual nights were not usable if the actigraphy was off, the diary was not completed properly, or the actigraphy sleep did not correspond to the sleep period recorded in the diary. At least four usable nights of sleep recordings were required for one valid sleep measure.

Definitions of sleep variables assessed using actigraphy are also presented in Table 2. Average values were calculated across the whole week. Weekday-weekend sleep variations were calculated as weekend values minus weekday values and day-to-day variations were calculated as the means of standard deviations across the entire week.

Table 2. Definitions of sleep variables measured using sleep diary and actigraphy, respectively.

Sleep Diary		Actigraphy	
Variables	**Definition**	**Variables**	**Definition**
Bedtime (h:min)	Parents recorded the clock time when their child was put to bed at night.	Sleep onset (h:min)	The clock time for the first of 5 consecutive minutes scored as asleep between 19:00 and 24:00.
Sleep onset latency (min)	Parents recorded how long time it took for the child to fall asleep.	Sleep onset latency (min)	Number of minutes between sleep onset and parental reported bedtime.
Wake-up time (h:min)	Parents recorded the clock time when their child woke up in the morning.	Sleep offset (h:min)	The clock time for the first of 10 consecutive minutes scored as awake between 04:00 and 10:00.
Nocturnal sleep duration (h)	Number of minutes between the wake-up time and bedtime minus the recorded sleep onset latency and wake during sleep period / 60.	Nocturnal sleep duration (h)	Number of minutes scored as sleep between nocturnal sleep onset and sleep offset / 60.
Sleep efficiency (%)	(Nocturnal sleep duration) / (wake-up time ─ bedtime) *100.	Sleep efficiency (%)	(Nocturnal sleep duration) / (sleep offset ─ sleep onset) *100.
Nap time (h:min)	Parents recorded the clock time when their child had a nap during the daytime (08:00-19:00).	Onset of nap (h:min)	The clock time for the first of 5 consecutive minutes scored as asleep during daytime (08:00-19:00).
Nap duration (h)	Parents recorded how many hours the child slept during the daytime (08:00-19:00).	Nap duration (h)	Number of minutes scored as asleep during daytime/60.
24-hour total sleep duration (h)	The total sleep hours during the entire day, including nocturnal sleep duration and daytime naps.	24-hour total sleep duration (h)	The total sleep hours during the entire day, including nocturnal sleep duration and daytime naps.
		Midpoint of sleep (h:min)	Mean clock time between nocturnal sleep onset and sleep offset.

h - hour, min – minute. h:min represents clock time.

4.6.2.3 Unfavourable sleep characteristics (Study II & III)

Several sleep characteristics reflecting sleep schedule, quantity and quality were defined in Study II and III, respectively (Table 3).

In Study II, based on sleep diary data, four unfavourable sleep characteristics were classified, in terms of late sleep, prolonged sleep onset latency, short nocturnal sleep and low sleep efficiency. The upper or lower quantiles of sleep measures generated based on both age 1 and 2 years were used as cut-offs. Three trajectories of each characteristic were defined across two ages: (1) 'never' (no unfavourable sleep characteristic at any age), (2) 'transient' (unfavourable sleep characteristic at either age 1 or age 2 years) and (3) 'persistent' (unfavourable sleep characteristic at both age 1 and 2 years).

In Study III, based on actigraphy data, five unfavourable sleep characteristics, including late sleep, long sleep latency, low sleep efficiency, short sleep duration and irregular sleep onset, were classified and scored as 1 at each age from age 2 to 6 years. Cut-offs were from either published recommendation[71,182] or lower/upper quartiles. For each characteristic, the total score range was 0 to 5: 0 indicated never having the characteristic and 5 indicated the maximum prevalence of the characteristic across ages. Moreover, to analyse the interactive effect between sleep characteristics and family obesity risks, categorical variables of "habitual characteristics" were further defined, as a child having a specific habitual characteristic (total score $\geq$ 3) or not (total score < 3).

Table 3. Definitions of unfavourable sleep characteristics in Study II and III.

Sleep characteristics	Definitions and cut-offs
Study II (sleep diary)	
Late sleep	Average bedtime > 20:30[1].
Prolonged sleep onset latency	Average sleep onset latency > 30 min[1].
Short nocturnal sleep	Average nocturnal sleep duration < 10 h[2].
Low sleep efficiency	Average sleep efficiency was < 90%[2].
Study III (actigraphy)	
Late sleep	Average sleep onset > 21:00[3].
Long sleep latency	Average sleep onset latency > 45 min[3].
Low sleep efficiency	Average sleep efficiency < 90%[3].
Short sleep duration	Average total sleep duration < 10 h/day (at age 2 years), < 9.7 h/day (at age 3 years), 9.5 h/day = 1 (at age 4 and 5 years) and < 9.2 h/day (at age 6 years)[4].
Irregular sleep onset	Day-to-day sleep onset variation > 52 min[5].

h – hour, min – minutes
Sources of cut-offs: [1]upper quantiles of sleep measures at both age 1 and 2 years; [2]lower quantiles of sleep measures at both age 1 and 2 years; [3]published sleep recommendations[71,182]; [4]lower quantiles of total sleep duration at each age; [5]mean value of upper quantiles of sleep onset variation at each age.

4.6.3 Parental sleep

In Study I, parental sleep habits were assessed using the Karolinska Sleep Questionnaire (KSQ). The KSQ was developed to record regular sleep patterns, as well as to evaluate subjective sleep quality in adults[183]. It has been validated against polysomnography and has shown good correlations with objective sleep measurements[183]. Three indices of sleep quality were used in Study I, including the sleep quality index (4 items), non-restorative sleep index (3 items) and daytime sleepiness index (5 items). Each item is rated on a 6-point Likert scale, from 1 (5 times or more per week) to 6 (never). Higher index scores indicate better sleep quality, less non-restorative sleep and less daytime sleepiness.

4.6.4 Child eating behaviour

In Study IV, child eating behaviour was assessed using the Swedish version of Child Eating Behaviour Questionnaire (CEBQ) at all follow-up ages, except age 4 years. The CEBQ includes 35 items on child eating style and behaviors[184]. Parents rate each behaviour on a five-point Likert scale, from "never" to "always." These items cluster into eight factors divided into two main dimensions: Food approach, including the factors: Food responsiveness, Emotional overeating, Enjoyment of food and Desire to drink; and Food avoidance, including the factors: Satiety responsiveness, Slowness in eating, Emotional undereating and Food fussiness. The Swedish version of the CEBQ was validated using confirmatory factor analysis and one item on snacking in the factor of Satiety responsiveness was excluded for an optimal fit[185]. The Cronbach's alpha for each factor ranged from 0.58 to 0.92 across ages.

4.6.5 Parental stress

In Study IV, the Swedish Parental Stress Questionnaire (SPSQ) was used to evaluate the potential adverse effects of the intervention on parents. The SPSQ is a revised version of the Parenting Stress Index, consisting of 34 items, which has shown good validity and stability for measuring perceived parental stress[186]. Each item is scored on a five-point Likert-type scale, from "strongly disagree" to "strongly agree." Different aspects of parental stress were assessed: sense of incompetence (11 items), role restriction (7 items), social isolation (7 items), relationship with spouse (5 items), and parental health (4 items). The total scores indicate general parental stress, with higher scores for higher stress levels. The Cronbach's alpha on the total score across ages ranged from 0.70 to 0.88 for mothers and from 0.67 to 0.84 for fathers.

4.6.6 Other child and family-related factors

Other child and family-related factors were collected using questionnaires.

Family education level (Study I-IV). Parents reported their highest educational levels at baseline, as compulsory education (nine years), high school (twelve years), or postsecondary education (college/university). Family education level was defined as low if both parents had

attended school for twelve years or less and as high if at least one parent had postsecondary education.

Family ethnic background (Study II-IV). Parents reported their national origin at baseline. Family ethnic background was categorized as Nordic if both parents were born in Nordic countries and non-Nordic if one parent was not born in Nordic countries.

Family living conditions (Study I-III). Family living conditions were reported as apartment/terraced house or detached house. This information was collected annually.

Having siblings (Study I-III). Parents reported whether the child having older or younger siblings (yes/no). This information was collected annually.

Care centre attendance (Study I-III). Parents reported the care centre attendance of the child, as a child attended a day-care centre, full-time (spending ≥ 30 hours/week in day-care centres) or part-time/at home (spending < 30 hours/week in day-care centres). This information was collected annually.

Primary caregiver (Study I). Parents reported who was the primary caregiver of the child at baseline, as mother, father or both parents.

Feeding practices (Study I). Parents reported if the child still was breastfed (yes/no) and if the child usually had night meals between 22:00-05:00 (yes/no) at baseline.

Parental marital status (Study III). Parental reported their marital status as married/cohabiting or separated. This information was collected annually.

Child screen time (Study III). Parental reported how many hours per day the child spent in watching TV, video and other media devices. Child screen time was defined as ≥ 2 hours/day or not. This information was collected annually.

Physical activity level (Study III). Based on questionnaire data, a child was classified as having a high physical activity level if he/she spent at least 2 hours/day outdoors playing and was perceived as having a high level physical activity by the parents, otherwise, a child was classified as having a low physical activity level. This information was collected annually.

Season (Study II-III). The date when sleep was assessed using actigraphy was categorized as the summer period (from April to September) or winter period (from October to March).

4.7 STATISTICAL METHODS

Statistical methods used in this thesis are summarized in Table 4. Statistical analysis was performed in SPSS, versions 21 and 26 (IBM, Armonk, NY, USA). All tests were two-sided, and p values of < 0.05 were considered statistically significant.

In Study III, multiple data imputation using 100 imputed datasets was performed, since the missing data were missing completely at random (Little's MCAR test, $p = 0.14$). Moreover,

the Bonferroni correction for multiple testing was adopted when multiple comparisons were made.

Table 4. Statistical methods used in this thesis.

	Study I	Study II	Study III	Study IV
Descriptive statistics	×	×	×	×
Independent t-test	×	×	×	×
Chi-square test	×	×	×	×
Mann-Whitney U-test	×			
Pearson correlation	×			
Linear regression	×			
Analysis of variance (ANOVA)		×		
Logistic regression		×		×
Analysis of variance for repeated measures		×		
Linear mixed model			×	×
Generalized linear model			×	×
Missing data analysis (Little's MCAR test)			×	

MCAR – Missing Completely at Random

4.8 ETHICAL APPROVALS

The Early STOPP was conducted following the guidelines of the Declaration of Helsinki. The Stockholm Regional Ethical Review Board approved this project, files no. 2009/217-31, 2009/754-32 and 2010/756-32. Written informed consent was obtained from all families.

5 RESULTS

5.1 STUDY POPULATION

The baseline characteristics of children and parents in Early STOPP are presented in Table 5. Children in the high and low-risk groups had comparable characteristics and weight measures at baseline. As study designed, parents in the high-risk group had higher weight, BMI and greater waist circumference than parents in the low-risk group. Apart from these, more families in the high-risk group had a low education level than in the low-risk group. Moreover, parents recruited to Early STOPP had slightly higher education level than the general population within the same age ranges (from age 25 to 44 years) in Stockholm County during the recruitment period (less than 12 years education: 41% vs. 47%).

In Study I, 167 one-year-old children and their parents were included for analysis after the exclusion of 40 children without a completed sleep diary. Among these 167 children, 121 were in the high-risk group and 46 were in the low-risk group. There was no difference in baseline characteristics or body measures between the included and excluded children.

In Study II, 145 children, with 108 in the high-risk group and 37 in the low-risk group, having completed sleep diary at both age 1 and 2 years were included for analysis of changes of sleep patterns across ages. There was no difference in baseline characteristics between children included and not included (n = 91) in the study. Moreover, among the 145 children, 142 children with actigraphy data at age 2 years were included in the analysis of the weekday-weekend sleep variations.

Out of 172 children in the non-intervention groups, Study III consisted of 107 children with at least two sets of actigraphy sleep data during the study period, with 64 in the high-risk group and 43 in the low-risk group. Compared to those excluded (n = 65), included children were more often from low-risk families, had a mother with lower BMI, lived in a detached house, and had low BMI z-score and waist circumference at age 6 years.

In Study IV, 181 children, with 66 in the intervention group and 115 in the control group, were included for analysis of the intervention effect. At baseline, compared to the intervention group, children in the control group had higher BMI (mean difference [*diff*] = 0.52, p = 0.04), higher W/H z-score (mean *diff* = 0.32, p = 0.04), and were more often from families with low education level (38% vs. 23 %, p = 0.04).

Table 5. Baseline characteristics of participants in Early STOPP.

	High-risk			Low-risk
	Total (n = 181)	Intervention (n = 66)	Control (n = 115)	Reference (n = 57)
Child				
Age, months	11.9 (1.1)	11.9 (1.3)	12.0 (1.1)	12.2 (0.7)
Gender				
Boy	91 (51)	33 (50)	59 (51)	22 (39)
Having siblings				
Yes	83 (46)	26 (39)	57 (50)	34 (60)
Attending daycare				
Yes, full-time	5 (3)	1 (2)	4 (4)	2 (4)
Birth weight, kg	3.69 (0.6)	3.65 (0.6)	3.72 (0.6)	3.64 (0.5)
Weight, kg	10.3 (1.3)	10.1 (1.3)	10.4 (1.3)	10.0 (0.9)
Length, cm	76.4 (3.0)	76.3 (3.6)	76.4 (2.7)	76.1 (3.0)
Waist circumference, cm	46.0 (3.2)	45.3 (3.4)	46.4 (3.1)	46.4 (2.5)
BMI, kg/m^2	17.6 (1.6)	17.3 (1.5)	17.8 (1.7)	17.4 (1.2)
BMI z score[a]	0.63 (1.0)	0.41 (1.0)	0.75 (1.0)	0.55 (0.8)
W/H z-score[a]	0.73 (1.0)	0.52 (1.0)	0.84 (1.0)	0.62 (0.8)
Mother				
Age, years	34.0 (4.4)	34.3 (4.4)	33.7 (4.4)	34.3 (4.6)
BMI, kg/m^2	31.9 (6.2)	32.0 (6.6)	31.8 (5.9)	22.4 (2.1)
Education level				
< 12 years	72 (42)	25 (40)	47 (44)	13 (23)
Nordic background				
No	15 (9)	5 (8)	10 (9)	6 (10)
Father				
Age	39.4 (15.7)	38.4 (14.4)	40.0 (16.4)	36.6 (5.6)
BMI, kg/m^2	30.1 (4.7)	29.3 (4.7)	30.5 (4.7)	23.1 (1.5)
Education level				
< 12 years	81 (52)	26 (47)	55 (55)	13 (24)
Nordic background				
No	24 (15)	7 (12)	17 (17)	2 (4)
Family				
Education level[b]				
Low	55 (32)	14 (23)	41 (38)	6 (11)
Nordic background[c]				
Non-Nordic	35 (21)	12 (19)	23 (22)	7 (12)
Living condition				
Apartment/terraced house	89 (53)	38 (60)	51 (48)	27 (47)

The mean (SD) and number (%) are presented for continuous data and categorical data, respectively.
BMI – body mass index. W/H – weight-for-height. [a]Calculated from WHO growth reference for children under age 5. [b]Family education level: low level = neither parent's education was >12 years; high level = at least 1 parent's education was > 12 years. [c]Family Nordic background: non-Nordic = at least 1 parent was non-Nordic background; Nordic = both parents were Nordic background.
Missing data: child birth weight (n=18), waist circumference (n=8); maternal weight measures (n=1), Nordic background (n=14) and education level (n=11); paternal age (n=7), weight measures (n=16), Nordic background (n=26) and education level (n=29); family education level (n=11), Nordic background (n=13), living condition (n=11).

5.2 WEIGHT DEVELOPMENT IN CHILDREN

Anthropometric measurements among children in three groups from age 1 to 6 years are presented in Figure 4. At age 6 years, compared with children in the low-risk group, children in the high-risk group had significantly higher weight (mean *diff* = 2.20 kg, p < 0.001), BMI (mean *diff* = 1.29 kg/m2, p < 0.001) and BMI z-score (mean *diff* = 0.73, p < 0.001). There were 36 children with overweight and obesity at age 6 years; none of them was in the low-risk group.
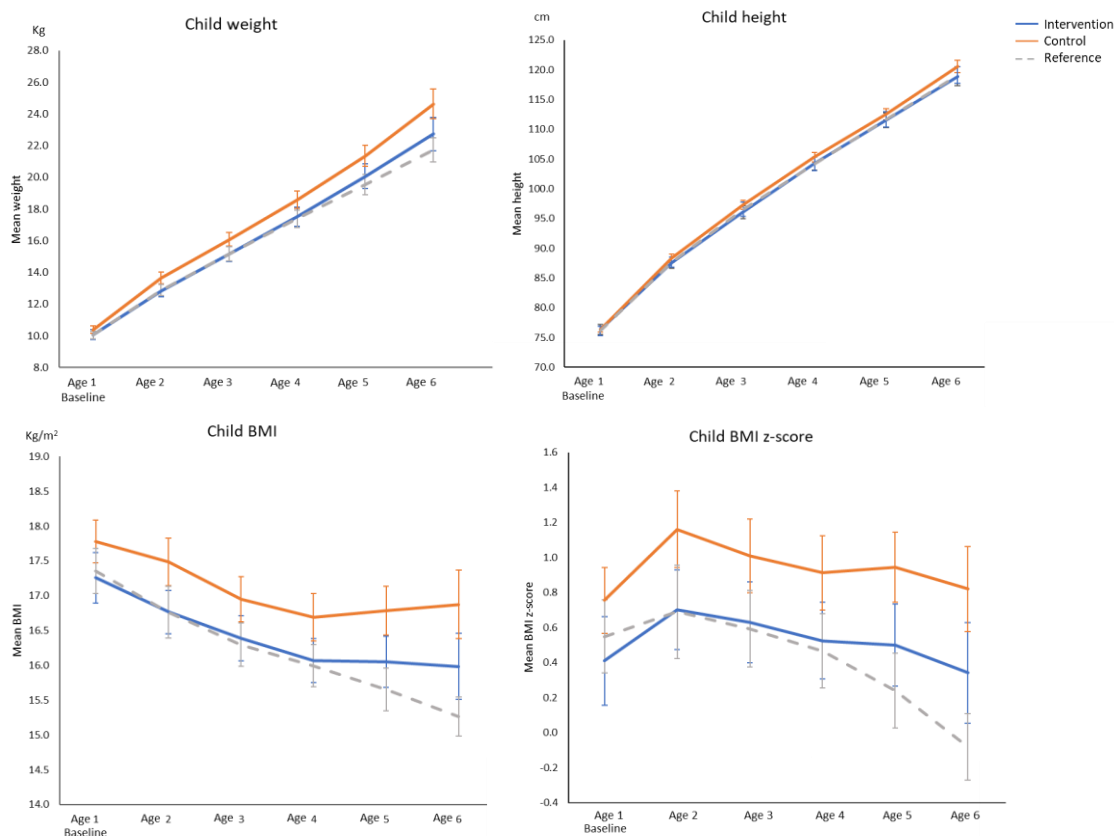

Figure 4. Anthropometric measures of children across ages by group (Error Bars: 95% CI). *(Study IV)*

5.3 CHILD SLEEP ACROSS AGES

5.3.1 Sleep variables (Study I-III)

At 1-year-old, based on sleep diaries, children's mean (SD) bedtime was 19:49 (48min), wake-up time was 06:57 (44min), and it took them around 17min (10, 26min) to fall asleep. From age 1 to 2 years, children's nocturnal sleep duration decreased from an average of 10.5h (0.7) to 10.3h (0.7) and total sleep duration decreased from 12.4h (0.8) to 11.6h (0.7), whereas the sleep efficiency was relatively constant. *(Study I and II)*

Actigraphy sleep patterns from age 2 to 6 years are presented in Table6. Age effects were observed in most sleep variables. Children tended to get later sleep onset (7 min/year, p < 0.001), longer nocturnal sleep duration (4 min/year, p < 0.001), better sleep efficiency (1.4% per year, p < 0.001) and shorter total sleep duration (14 min/year, p < 0.001) from age 2 to 6 years. The sleep onset latency and sleep offset were relatively stable across ages. Weekday-

weekend variation in sleep onset increased with age (8 min/year, p < 0.001), while day-to-day sleep onset variation was relatively stable. The day-to-day variation in total sleep duration slightly decreased with ages (3min/year, p < 0.001). *(Study III)*

Table 6. Actigraphy assessed sleep patterns from age 2 to 6 years. *(Study III)*

	Age 2	Age 3	Age 4	Age 5	Age 6
Average sleep patterns					
Sleep onset (h:min)*	20:30 (42)	20:36 (48)	20:36 (42)	20:48 (48)	21:00 (42)
Sleep onset latency (min)	39 (19)	40 (22)	33 (16)	33 (16)	34 (19)
Sleep offset (h:min)	06:30 (42)	06:48 (36)	06:48 (42)	06:54 (42)	06:48 (36)
Nocturnal sleep period (h)*	10.03 (0.6)	10.13 (0.6)	10.25 (0.5)	10.05 (0.5)	9.80 (0.4)
Nocturnal sleep duration (h)*	9.13 (0.6)	9.55 (0.6)	9.78 (0.5)	9.65 (0.5)	9.50 (0.4)
WASO (min)*	54 (24)	35 (20)	28 (14)	24 (13)	18 (9)
Sleep efficiency (%)*	86 (4)	88 (5)	91 (3)	91 (3)	92 (3)
24-hour sleep duration (h)*	10.50 (0.5)	10.02 (0.5)	9.78 (0.5)	9.65 (0.5)	9.51 (0.4)
Weekday-weekend variation[&]					
Sleep onset (min)*	12 (36)	24 (36)	36 (54)	36 (42)	42 (48)
24-hour sleep duration (min)	8 (41)	-4 (48)	-8 (44)	-4 (43)	-10 (47)
Day-to-day variation[§]					
Sleep onset (min)	38 (19)	44 (24)	43 (28)	39 (23)	41 (20)
24-hour sleep duration (min)*	52 (22)	56 (27)	42 (20)	43 (17)	40 (16)

WASO = wake after sleep onset. h - hour, min - minute
[&]Weekday-weekend sleep variations were calculated as weekend values minus weekday values. The minus value indicated that children had longer sleep duration during weekdays than weekends.
[§]Day-to-day variations were calculated as the means of the standard deviations across full weeks.
*Age effect can be identified in the sleep measures at the Bonferroni-corrected alpha level P < 0.004.

5.3.2 Unfavourable sleep characteristics (Study II-III)

From age 1 to 2 years, according to sleep diary data, most children did not experience or only experienced transient unfavourable sleep characteristics (Figure 5). Around 14% of children had persistent late sleep at both age 1 and 2 years, and around 10% of children had persistent other unfavourable sleep characteristics, respectively. *(Study II)*

From age 2 to 6 years, based on the actigraphy data, age effects were identified in the prevalence of late sleep onset and low sleep efficiency, respectively. The prevalence of late sleep onset increased with age, from 21.8% to 40.1%; and the prevalence of low sleep efficiency decreased with age, from 31.6% to 5%. While the prevalence of short sleep, long sleep latency and irregular sleep onset were relatively stable across ages (Table 7). *(Study III)*

5.3.3 Associated factors to child sleep (Study I-III)

Gender differences in child sleep were identified. At 1-year-old, girls showed higher sleep efficiency (mean *diff* = 12 min, p = 0.006) and longer nocturnal sleep (mean *diff* = 16.8 min, p < 0.001) than boys. In the longitudinal data from age 2 to 6 years, girls also showed longer nocturnal sleep duration than boys (mean *diff* = 10 min, p = 0.02). *(Study I and III)*

Family education level was associated with child sleep variations. At 2-year-old, compared to children from families with high education, those from families with low education level

showed more delayed sleep offset (mean *diff* = 11min; 95% confidence index [CI]:5-27) and the midpoint of sleep (mean *diff* = 7min; 95% CI: 6-20) on weekends than during weekdays. From age 2 to 6 years, we also observed that children from low educated families showed greater variation in sleep onset, as regards both weekday-weekend variation (mean *diff* = 16 min, p = 0.009) and day-to-day variation (mean *diff* = 7 min, p = 0.02). *(Study II-III)*

Children with siblings showed shorter sleep onset latency (β = 14.4 min, p = 0.002) and higher sleep efficiency (β = 0.25, p = 0.001) than those without siblings at 1-year-old, as well as more weekday–weekend variation in sleep onset at 2-year-old (mean *diff* = 16 min, p < 0.05). *(Study I-II)*

Seasonal differences were observed in child sleep, as children had slightly later sleep onset (mean *diff* = 12 min, p = 0.006) and shorter nocturnal sleep duration (mean *diff* = 7 min, p = 0.04) during the summer period than during the winter period *(Study III)*.

5.4 SLEEP AND FAMILY OBESITY RISKS (STUDY I-III)

5.4.1 Sleep in children at different obesity risks (Study I-III)

5.4.1.1 Sleep patterns (Study I-III)

At age 1 year, based on sleep diary data, children in the high-risk group had later bedtime, later wake-up time, longer sleep onset latency and lower sleep efficiency than children in the low-risk group. After adjustments for other factors, only the difference in sleep onset latency between groups was significant (β = 15 min, p = 0.001). From age 1 to 2 years, the trend of child sleep onset latency was still significantly different between groups (p = 0.01). However, the sleep onset latency at age 2 years differed by only one minute between groups and the effect size of the difference was relatively small (Cohen's effect size 0.12). *(Study I-II)*

At age 2 years, based on actigraphy data, differences in weekday-weekend sleep variations were identified between groups. Compared to children in the low-risk group, those in the high-risk group had greater weekday-weekend variations in sleep schedules, in terms of more delayed sleep offset (adjusted mean *diff* = 18min; 95% CI: 4-33), midpoint of sleep (adjusted mean *diff* = 14min; 95% CI: 3-25) and nap onset (adjusted mean *diff* = 42 min; 95% CI: 10-74) during weekends than weekdays. *(Study II)*

When the longitudinal changes of sleep patterns in children from age 2 to 6 years were examined using actigraphy data, no group difference in either average sleep variables or sleep variations could be identified, indicating that the development of sleep patterns in children at high and low obesity risk was similar. *(Study III)*

5.4.1.2 Sleep characteristics (Study II and III)

From age 1 to 2 years, based on sleep diary data, more children in the high-risk group experienced transient unfavourable sleep characteristics than in the low-risk group, in terms of prolonged sleep onset latency and low sleep efficiency (Figrue 5). After further

adjustments for other child and family factors, these differences were still significant, indicating that children in the high-risk group had increased odds of transient prolonged sleep onset latency (odds ratio [OR] = 3.8, 95% CI: 1.4-11.1, P = 0.008) and transient lower sleep efficiency (OR = 4.0, 95% CI: 1.3-12.5, P = 0.01) than children in the low-risk group during ages 1 to 2 years. *(Study II)*
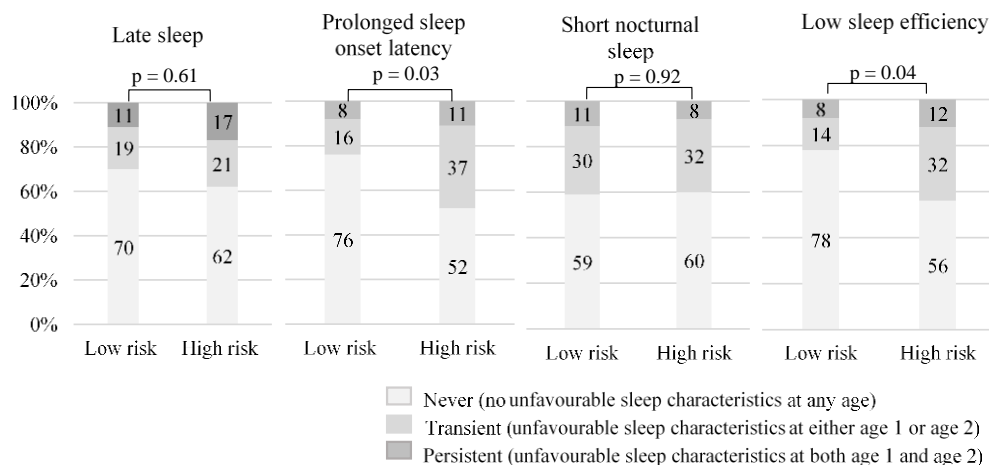

Figure 5. Proportions of unfavourable sleep characteristics trajectories in children at different obesity risks from age 1 to 2 years (%). *(Study II)*

From age 2 to 6 years, based on actigraphy data, the prevalence of unfavourable sleep characteristics at each age and the prevalence of habitual characteristics in children at different obesity risk are presented in Table 7. After adjustment for other child and family factors, the family obesity risk was not associated with any unfavourable sleep characteristic. *(Study III)*

Table 7. Unfavourable sleep characteristics in children at different obesity risks from age 2 to 6 years, including the prevalence at each age (%), the total scores (mean (SD)) and the prevalence of habitual characteristics (%). *(Study III)*

Sleep characteristic	Risk group	Age 2	Age 3	Age 4	Age 5	Age 6	Total scores	Habitual characteristic[§]
		%	%	%	%	%	Mean (SD)	%
Late sleep	High risk	20.3	31.3	28.1	37.5	45.3	1.63 (1.1)	21.9
	Low risk	23.3	34.9	30.2	37.2	34.9	1.58 (1.3)	25.6
Short sleep duration	High risk	19.1	23.4	25.0	21.9	31.3	1.17 (1.1)	13.2
	Low risk	38.6	18.6	27.9	23.3	13.9	1.16 (1.1)	13.2
Long sleep latency	High risk	23.4	31.2	28.1	21.9	29.7	1.22 (1.1)	14.1
	Low risk	27.9	30.2	25.6	20.9	16.3	1.23 (1.1)	14.0
Low sleep efficiency	High risk	37.5	15.6	5.0	2.0	7.8	0.69 (0.8)	2.0
	Low risk	25.6	7.0	5.0	7.0	2.3	0.53 (0.7)	2.5
Irregular sleep onset	High risk	26.2	30.9	33.4	25.0	30.3	1.41 (1.3)	21.7
	Low risk	24.1	34.4	25.6	22.0	16.7	1.23 (1.4)	17.4

Results are pooled results from all imputation datasets.
[§]Habitual characteristics, the total score of the characteristic was greater than 3.

5.4.2 Sleep in parents at different obesity risks (Study I)

Parental sleep was compared between groups when the child was 1-year-old. After adjustment for parental age and education level, mothers in the high-risk group tended to have later bedtime and longer sleep onset latency than mothers in the low-risk group, over both weekdays and weekends. Nocturnal sleep duration was shorter for both mothers and fathers in the high-risk group during weekdays. Group differences in subjective-rated sleep quality were only seen in mothers, with mothers in the high-risk group experiencing more non-restorative sleep (mean index score: 3.7 vs. 4.2) and more daytime sleepiness (mean index score: 4.4 vs. 4.7) than mothers in the high-risk group. After adjustments for both child and parental factors, children's bedtime was positively associated with both parents' bedtimes, and the correlation was stronger between mother and child ($r = 0.35$, $p < 0.01$) than between father and child ($r = 0.19$, $p < 0.05$). Children's sleep efficiency was only associated with mothers' sleep quality index ($r = 0.20$, $p < 0.01$).

5.5 SLEEP AND OBESITY (STUDY I-III)

5.5.1 Associations between sleep and weight gain (study I-III)

In Study I, after adjustments for other covariates, child bedtime at 1-year-old was positively related to their BMI ($\beta = 0.17$, $p < 0.05$). In Study II, no association between any unfavourable sleep characteristic and child weight gain from age 1 to 2 years was detected.

Table 8. Associations of five sleep characteristic scores with weight gain in children from age 2 to 6 years. *(Study III)*

Sleep characteristic scores§	Adiposity	
	BMI z-score	Waist circumference
Late sleep		
Model 1	0.12 (0.02 to 0.23)*	0.45 (0.10 to 0.80)**
Model 2	0.16 (0.05 to 0.27)*	0.60 (0.23 to 0.98)**
Short sleep duration		
Model 1	0.12 (0.01 to 0.24)*	0.47 (0.10 to 0.84)*
Model 2	0.12 (0.01 to 0.25)*	0.39 (-0.01 to 0.80)
Long sleep latency		
Model 1	0.11 (-0.03 to 0.25)	0.25 (-0.17 to 0.67)
Model 2	0.12 (-0.06 to 0.18)	0.23 (-0.25 to 0.71)
Low sleep efficiency		
Model 1	0.10 (-0.08 to 0.29)	0.20 (-0.38 to 0.77)
Model 2	0.16 (-0.03 to 0.34)	0.20 (-0.42 to 0.82)
Irregular sleep onset		
Model 1	0.01 (-0.14 to 0.89)	0.14 (-0.23 to 0.51)
Model 2	0.04 (-0.08 to 0.15)	0.26 (-0.13 to 0.64)

Results are pooled for all imputation datasets. The application of the Bonferroni correction for multiple comparisons indicates statistical significance at $p < 0.005$. Values are estimated parameters for fixed effects of sleep characteristics total scores (95% CI). Model 1: adjusted for age, gender, obesity risk group and baseline BMI z-score or waist circumference. Model 2: model 1 additionally adjusted for other confounders, including maternal ethnicity, family education level, parental marital status, living condition, having siblings or not, screen time and physical activity level.
§Total score ranged from 0 to 5, with higher scores indicating a higher prevalence of five sleep characteristics, respectively, across ages.
*$p < 0.05$, ** $p < 0.005$.

In Study III, associations of five unfavourable sleep characteristics scores with obesity are presented in Table 8. Higher scores indicated more exposures to certain unfavourable sleep characteristics from age 2 to 6 years. When only adjustment for child age, gender and family obesity risk (Model 1), late sleep score and short sleep duration score were both positively associated with changes in BMI z-score and waist circumference across ages (at the alpha level $P < 0.05$). After adjustment for other factors (Model 2) and at the Bonferroni-corrected alpha level $P < 0.005$, only association between the late sleep score and waist circumference was significant, and this association was independent of sleep duration. No relationship could be detected between other sleep characteristic scores and child weight gain.

5.5.2 Associations between late sleep and obesity by family obesity risks (Study III)

In Study III, a significant combined effect between child habitual late sleep and family risk on child weight gain was observed (Table 9). More specifically, for children at low obesity risk, having habitual late sleep did not significantly increase their risk of gaining more weight across ages. While, for children at high obesity risk, having habitual late sleep was significantly associated with greater increases in both BMI z-score and waist circumference across ages.

Table 9. Adjusted associations of habitual late sleep with obesity measures by family obesity risks. *(Study III)*

	Low obesity risk		High obesity risk	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
BMI z-score				
No habitual late sleep	Reference	—	0.39 (0.05 to 0.73)	0.023
Habitual late sleep	0.15 (-0.41 to 0.70)	0.60	0.93 (0.40 to 1.45)	< 0.001
Waist circumference				
No habitual late sleep	Reference	—	1.64 (0.56 to 2.71)	0.003
Habitual late sleep	0.91 (-0.79 to 2.61)	0.29	3.45 (1.78 to 5.12)	< 0.001

Habitual late sleep: total score of late sleep ≥ 3. No habitual late sleep: total score of late sleep < 3.
All models were adjusted for child age, gender, maternal ethnicity, family education level, parental marital status, living condition, having siblings or not, screen time, physical activity level, total sleep duration, and baseline BMI z-score or waist circumference.

5.6 EFFECTS OF INTERVENTION (STUDY IV)

5.6.1 On primary weight outcomes

No main intervention effect could be identified in the primary outcome (BMI z-score) or other weight-related outcomes (weight and BMI) across ages during the follow-up period, after adjustments for baseline measures, as well as child gender, family education level, and Nordic background (Table 10). Only an intervention-by-time effect was observed on child weight, as children in the intervention group had less weight increase per year than children in the control group. After exclusion of the 4 children with W/H greater than +3 SDs above the WHO Child Growth Standards at baseline, the intervention results were similar.

Table 10. Intervention effect of weight-related outcomes. *(Study IV)*

| | Intervention Mean (SD) | Control Mean (SD) | Between-group adjusted mean difference[b] (95 % CI) | Adjusted models[c] | | | | | |
| | | | | Intervention effect | | Age effect | | Intervention × age interactive | |
				Estimated effect (95 % CI)	p	Estimated effect (95 % CI)	p	Estimated effect (95 % CI)	p
BMI z-score[a]				-0.11 (-0.49, 0.26)	0.53	-0.08 (-0.13, -0.04)	**<0.001**	-0.005 (-0.08, 0.07)	0.89
Age 1	0.41(1.0)	0.75(1.0)	—						
Age 2	0.70(0.9)	1.16(1.1)	-0.16 (-0.4, 0.1)						
Age 3	0.63(0.9)	1.01(1.1)	-0.10 (-0.4, 0.2)						
Age 4	0.53(0.8)	0.91(1.1)	-0.07 (-0.3, 0.2)						
Age 5	0.50(0.9)	0.94(1.0)	-0.14 (-0.4, 0.1)						
Age 6	0.34(1.0)	0.82(1.2)	- 0.14 (-0.4, 0.1)						
Weight				0.44 (-0.53, 1.41)	0.38	2.65 (2.54, 2.76)	**<0.001**	-0.24 (-0.41, -0.06)	**0.008**
Age 1	10.08(1.3)	10.39(1.3)	—						
Age 2	12.84(1.5)	13.65(1.8)	-0.20 (-0.9, 0.6)						
Age 3	15.17(1.9)	16.09(2.1)	-0.37 (-1.1, 0.4)						
Age 4	17.52(2.2)	18.58(2.7)	-0.44 (-1.2, 0.3)						
Age 5	20.06(3.0)	21.34(3.4)	-0.75 (-1.5, 0.0)						
Age 6	22.73(3.8)	24.63(4.5)	-1.33 (-2.1, -0.5)						
BMI				-0.01 (-0.65, 0.62)	0.97	-0.15 (-0.22, -0.07)	**<0.001**	-0.05 (-0.18, 0.07)	0.40
Age 1	17.26(1.5)	17.78(1.7)	—						
Age 2	16.76(1.2)	17.48(1.7)	-0.24 (-0.7, 0.2)						
Age 3	16.39(1.2)	16.95(1.6)	-0.11 (-0.6, 0.3)						
Age 4	16.07(1.2)	16.69(1.7)	-0.09 (-0.5, 0.4)						
Age 5	16.05(1.4)	16.79(1.8)	-0.23 (-0.7, 0.2)						
Age 6	15.98(1.7)	16.88(2.4)	-0.33 (-0.8, 0.1)						

[a] Calculated from the WHO growth reference for children under age 5 years and for children 5-19 years[187].

[b] Group mean differences at age 2 to 6 years were adjusted for group differences in measures at baseline, respectively.

[c] The outcomes were analyzed using mixed linear models, with adjustments for child gender, family education level, Nordic background and the respective baseline weight measure.

At age 6 years, there were 36 children with overweight and obesity, with 12 (23%) in the intervention group and 24 (26%) in the control group. In the adjusted longitudinal generalized estimating equation models, the intervention was not significantly effective for reducing the odds of developing overweight and obesity (OR = 1.02, 95% CI: 0.45-2.31, p = 0.96) during the entire follow-up period. The prevalence of overweight and obesity were also compared between groups at each follow-up age. At age 4 years, after adjustment for baseline BMI and other factors, the risk of overweight and obesity was lower in the intervention group than in the control group (OR 0.3, 95% CI: 0.09-0.96). However, this favourable effect of the intervention was not detected later during the follow-up period.

5.6.2 On secondary behavioural outcomes

In the intention-to-treat analysis, after adjustment for child gender, family education level, and Nordic background, no main intervention effect could be identified on any secondary behavioural outcome during the follow-up period, including child eating behaviour, total sleep duration (Figure 6a) and average physical activity level. We also conducted additional analysis to explore the possible intervention effects on child sleep schedules, including actigraphy assessed average sleep onset and day-to-day sleep onset variation (Figure 6b, 6c). After adjustment for child gender, family education level and Nordic background, there was no intervention effect on either average sleep onset (mean *diff* = -7min, p = 0.49) or day-to-day sleep onset variation (mean *diff* = -9min, p = 0.07) from age 2 to 6 years.
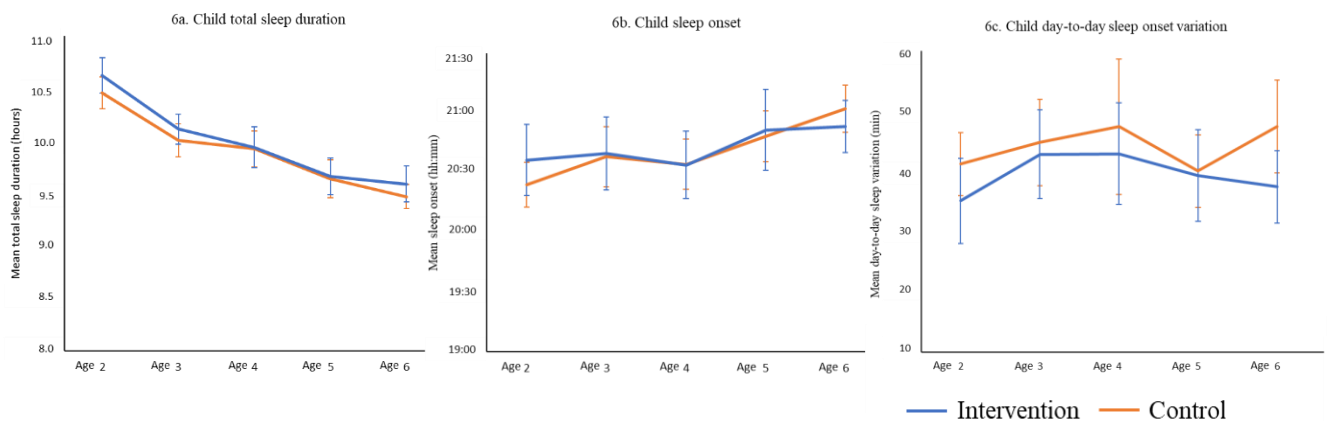
Figure 6. Actigraphy assessed sleep of children in the intervention and control groups from age 2 to 6 years. (Error Bars: 95% CI)

5.7 ACTIGRAPHY VERSUS SLEEP DIARY

Among children with both sleep diary and actigraphy data, we performed additional analysis to compare sleep variables assessed using sleep diary and actigraphy (Table 11). The correlations between actigraphy-assessed and diary-reported sleep revealed relatively high agreement for sleep schedule measurements: correlations for the sleep onset and offset times were both 0.87 (p < 0.001). Correlations between actigraphy-assessed and parental-reported nocturnal and 24-hour total sleep duration were both over 0.60 (p < 0.001). While correlations in sleep quality between two methods, concerning WASO and sleep efficiency,

were relatively low, particularly the correlation in WASO was only 0.36 (p < 0.001). Pair t-tests revealed significant differences in all sleep measures between two methods (all p < 0.001). The actigraphy-assessed sleep onset was 12 min later than parental-reported sleep onset, and sleep offset was 6 min earlier than the reported wake-up time. WASO assessed using actigraphy was 24 min more than parental reported, and sleep duration were around 40 min shorter than the reported values.

Table 11. Comparisons and correlations of sleep assessed using actigraphy and diary

| Sleep variable | Actigraphy vs. Sleep diary | |
| | Comparison | Correlation |
	Mean difference (95% CI)	Coefficient (r)
Sleep onset (min)	12 (10, 14)	0.92
Sleep onset latency (min)	14 (12, 15)	0.66
Sleep offset (min)	-6 (-8, -5)	0.92
WASO (min)	24 (22, 25)	0.36
Sleep efficiency (%)	-6.4 (-6.7, -6.0)	0.54
Nocturnal sleep duration (min)	-47 (-49, -44)	0.63
24-hour total sleep duration (min)	-46 (-48, -43)	0.72

WASO, wake after sleep onset. All p < 0.001

6 DISCUSSION

6.1 MAIN FINDINGS

Family obesity risk, determined by parental weight, does not seem to be related to child sleep patterns. Although some differences in sleep were observed among children at different obesity risks at age 1 and 2 years, the development of sleep patterns from age 2 to 6 years was similar between two risk groups.

Frequent exposures to short sleep and late sleep from age 2 to 6 years were independently associated with greater increases in child weight gain across ages. Moreover, a significant combined effect between habitual late sleep and high family obesity risk on child weight was observed.

At the end of this long-term, low-intensive, family-based, multicomponent obesity intervention, no significant intervention effect was identified on either primary weight outcome or secondary behaviour outcomes such as sleep, eating behaviour and physical activity.

6.2 DEVELOPMENT OF CHILD SLEEP PATTERNS

6.2.1 Average sleep patterns

In this thesis, the development of sleep patterns from age 1 to 6 years in a group of Swedish children was described. Age effects can be identified in most sleep variables. Generally, as children grew older, they tended to get later sleep onset, slightly longer nocturnal sleep and better sleep efficiency. The 24-hour total sleep duration decreased with ages through the great reduction in daytime nap. These changes, in line with most previous studies, reflect the gradual maturation of sleep during toddler- and pre-school ages, as a decrease of sleep need, a consolidation of night-time sleep and reduced night-time awakenings[75,83,88]. In this study, child sleep onset latency was relatively constant across ages, fluctuating between 33 to 40 min. One meta-analysis of child sleep measured using actigraphy supports our data, showing that sleep latencies across studies ranged from 8 to 35 min in the pre-school age group and there was no significant age difference[188]. While, another longitudinal study reported that child sleep onset latency decreased with ages, from around 13 min at 3-year-old to 6 min at 7-year-old[75]. Discrepancies in sleep onset latency values might be due to various methodologies used across different studies. For example, different criteria have been used for actigraphy defined sleep onset; e.g., 3 min, 5 min or 10 min of inactivity[114,119]. Moreover, these differences may also reflect the great inter-individual variations in the ability to fall asleep.

Overall, child sleep patterns in this study are comparable to most, but not all, previous studies in the same age group. The reported total sleep duration in children at age 1 and 2 years are in correspondence to the reference values established in the same age group of children in Finland[189] and the US[190]. At pre-school ages, children in this study have slightly longer actigraphy assessed nocturnal sleep duration than children from the US and Switzerland[188].

Child's bedtime or sleep onset time is similar to the reports from other Nordic countries, but much earlier than bedtime in children from southern European countries, e.g., Italy, and most Asian countries[191,192]. For example, the average bedtime for toddlers in Hong Kong was around 22:00[193]. These discrepancies suggest that several considerations need to be made when comparing child sleep patterns across studies, which include the sleep assessment methods, child age and different social-cultural backgrounds.

6.2.2 Intraindividual sleep variation

Another aspect of sleep pattern that has so far not been addressed enough among young children is the intraindividual variation. Significant day-to-day variations in both child sleep onset (38 to 44 min) and sleep duration (40 to 52 min) were observed in Study III. Similar results were found in one previous study on a group of 4 years old children, with around 42 min for bedtime variation and 1 hour for sleep duration variation[194]. The development of daily sleep variations among young children is poorly understood and mixed findings were reported in school-aged children[195]. In our longitudinal dataset, there was no age effect on daily variation in sleep onset, while the daily variation in total sleep duration slightly decreased with ages.

It is known that weekday-weekend sleep variations are prominent in school-aged children and tend to peak during adolescence and early adulthood, with delayed sleep schedule and catch-up sleep during weekend[82]. This trend might be due to biological changes in circadian rhythm during these ages, e.g., an increase in evening chronotype, that do not match school or social schedules[196]. In our data, the delayed sleep onset on weekends compared to weekdays occurred already at child 2-year-old and became greater with ages. Similar findings were also reported in studies from other countries[80,81], indicating that a shift of sleep schedules to later hours during the weekend already occurred in early childhood. These changes suggest that the family environment might already have an impact on the sleep regularity during early childhood. For example, parents could be less strict with bedtime on the weekend. In contrast to catch-up sleep during weekend commonly reported in adolescents[197], children tended to have a slightly shorter sleep duration on weekends than weekdays in this age group. The reduced sleep duration during weekends than weekdays was also seen in the same age group children from other countries[81,198], suggesting that the sleep compensation during weekend probably becomes apparent during later ages.

6.2.3 Prevalence of unfavourable sleep characteristics

Unfavourable sleep characteristics are common in children at this age group, with the prevalence ranging from 10% to 45% across different types and ages (Study II and III). Although the prevalence rates are high, it appears that relatively few children having persistent unfavourable sleep characteristics, for example, around 10% during the first two years of life (Study II). Similar figures have been reported in other longitudinal studies[199], indicating that unfavourable sleep characteristics are probably normative features for most of the children during early childhood. Moreover, as children grew older, we observed that the

prevalence of late sleep increased, and the prevalence of low sleep efficiency decreased with ages. This is in line with the development changes reported in previous studies[83,199,200], as night awakenings become less frequent in the late preschool years compared to earlier years, whereas bedtime resistance becomes more prominent.

6.3 SLEEP IN CHILDREN AT DIFFERENT OBESITY RISKS

To my knowledge, this thesis is the first study to compare sleep in children at different obesity risks, to try to characterise this obesity-risk behaviour before obesity occurrence. In Study I and II, we observed some differences in sleep patterns among children at high and low obesity risks. Children at high obesity risk tended to have longer sleep onset latency, lower sleep efficiency and greater weekday-weekend variations than children at low obesity risk at age 1 to 2 years. However, in the follow-up data from child age 2 to 6 in Study III, no difference was seen in either sleep measures or sleep characteristics across ages. One possible explanation of the inconsistent results is the use of different sleep measurements. Sleep diary, used in Study I and II, has relatively low validation in assessing sleep quality variables, such as sleep efficiency and sleep onset latency[201]. In the high-risk group, mothers' lower sleep quality as we observed in Study I might also affect their reports of the child's sleep, as a previous study showed that parents who suffered poor sleep tended to report low sleep quality in children[202]. Another explanation is that the differences in child sleep between different obesity risks probably only occur in the first years of life. The relatively small effect size indicates that the clinical relevance of these differences is probably low and does not last to the later childhood.

One important hypothesis in Early STOPP is that children in families at high obesity risk might develop obesity-related behaviours earlier than those children at low obesity risk. Children at high obesity risk might be exposed to more obesogenic home environment shaped by their heavier parents, incorporating food, physical activity and sleep. They might also have more genetic tendencies to obesity-related behaviours, as recent genetic studies indicated that some circadian-related gene variants associated with both obesity and poor sleep[203]. No difference in child sleep between high and low risk group was detected. In addition, during early childhood, no difference in child energy intake or physical activity between risk groups was detected either in other sub-studies of Early STOPP[204,205]. Taking these results together, we cannot conclude that young children at high obesity risk present more obesogenic behaviours than their peers at low obesity risk. Overweight and obese parents might create more obesogenic home environment than those normal-weight parents, such as the availability of unhealthy foods, less opportunities for physical activity and lack of sleep routine, but these differences might not have an impact on child behaviours yet. Another possible reason is that obese parents might care more about their children's weight and tend to choose a healthier lifestyle for them. Thus, for future studies, it might be interesting to compare parenting behaviours between families at different obesity risks.

6.4 ASSOCIATION BETWEEM SLEEP AND OBESITY

In Study III, frequent short sleep exposure was associated with greater increases in child BMI z-score and this finding is in line with previous studies showing that chronic sleep curtailment increase the risk of obesity[130,132]. Besides sleep duration, this study indicates that frequent late sleep, later than 21:00, is an independent and important risk factor for more weight gain in children from 2 to 6 years old. The associations between late sleep and higher BMI have been observed previously in preschool- and school-aged children[135,137]. Late bedtime has also been related to larger waist circumference in school-aged children[152,206]. Different pathways have been examined to explain the association between late sleep and obesity. Late sleep has been associated with more energy intake in children, particularly more energy intake after 20:00[207], as well as associated with poorer diet quality and eating habits, characterized as more intake of energy-dense food and less intake of vegetables and fruits[208,209]. One previous study also noticed that a higher glucose level mediated the association between late bedtime and waist circumference in children[152], indicating the possible impact of late sleep on insulin regulation. However, no study has examined these associations in young children.

Most previous studies exploring the associations between sleep and obesity were cross-sectional designs or longitudinal designs with only once or twice sleep observations at some ages[210]. The current study, using repeated measures of sleep, provides important evidence of the association between habitual unfavourable sleep and weight gain during childhood. Compared to transient late sleep, habitual late sleep are more likely to be a marker of unhealthy family environment or lifestyle behaviours in general. These children may not only frequently expose to late sleep, but also to other obesity-related behaviours, which together result in more weight gain in the long term.

We know of no study investigating the association between sleep and obesity by taking family obesity risk into account. A previous study found that the association between poor sleep and higher BMI was more pronounced in under unfavourable family context, characterized by low parental education, poverty and more stressful life events[172]. In this study, we observed a combined effect between family high obesity risk and habitual late sleep on significantly more weight gain in children. This result may support the findings from twin studies, that the heritability of body weight could be modified by environmental and behavioural factors[42,43]. It may also indicate the shared genetic impact on both preference of late sleep and gaining more weight[203].

In this study, no association of either sleep onset latency or sleep efficiency with child weight gain was observed. Although studies in adolescents and young adults tended to report associations between poor sleep quality and obesity[211], this association in young children is still largely uncertain. Most studies using reported data did not identify the association between sleep quality and BMI in this age group[212,213]. One study noticed that the associations between infant sleep problem and obesity at school ages varied across definitions of sleep problem[142], suggesting more objective evidence is needed to clarify the association between sleep quality and obesity during early childhood. Moreover, no association between

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irregular sleep and more weight gain was found in young children in the current study either. In contrast, numerous studies observed associations between great sleep variations and obesity in school-aged children and adolescents[214,215]. This might indicate that the association between sleep variations and obesity become prominent when children grow older, as the great sleep variations become more common.

6.5 INTERVENTION EFFECT ON WEIGHT OUTCOMES

It is widely accepted that obesity prevention should start from early childhood. The most recent Cochrane review of RCT for preventing obesity in children reported moderate-certainty evidence that interventions combining diet and physical activity can reduce the risk of obesity in young children aged 0 to 5 years[59]. However, the effect size was relatively small and most RCTs had the intervention duration no more than 12 months. There is still a lack of evidence in establishing a long-term preventive effect, as there are data indicating that short-term results do not mirror long-term outcomes[216-220].

Childhood obesity should be able to be prevented, even in individuals at high obesity risk, as evidence shows that environmental and behavioural factors can modify the genotype of obesity to phenotype[42]. Parents play vital role in child weight development[221,222]and parental involvement and responsibilities are identified as important and effective techniques in the obesity intervention in children[223,224]. However, despite promising short-term results[59,225-227] long-term follow-up studies often, but not always[228], fail to detect any persisting effects on weight[216-220]. Most likely the education process has been successful, and the parents received information through intervention and have understood what was required. This presumption is based on child improved behaviours have been regularly reported after intervention[229-231] and the short-term intervention outcomes are generally good[59]. Thus, the education is probably successfully delivered and received, but it has no effect on childhood obesity. In the current study, no intervention effect was identified on child obesity-related behaviours. In contrast to most other RCTs targeting the general population, this study targeted children with overweight and obese parents. For these obese parents, education might not be enough to change their behaviours. Instead, long-term behavioural support together with education is probably necessary for promoting healthy behaviours.

In the current study, children in the intervention group gained less weight every year compared to those in the control group, but there was no overall intervention effect. It is possible that the present study was underpowered to be able identify a small positive effect. Moreover, although we had a long intervention period (five years), the frequency and total intervention duration were relatively low. It is likely that a more intense intervention may be need for these children who are at higher risk of developing obesity to result in a better outcome. However, it is questionable whether more frequent preventive sessions are affordable for the families and the society. Furthermore, even if such a small effect as observed in this study can be confirmed statistically in a larger study, it can still be

questioned if the cost-effectiveness is acceptable. Therefore, other types of long-term intervention with reasonable cost might be required to obtain a substantial reduction of childhood obesity, for example, through digital support systems.

6.6 INTERVENTION EFFECT ON CHILD SLEEP

After short sleep has been associated with obesity, sleep promotion has been included in some, but not all, family-based obesity interventions[174]. Two multicomponent trials during early childhood, including sleep promotions, reported significant effects on BMI after intervention[176,232]. Another 4-arm intervention study reported that the effect on BMI among children who received sleep intervention were retained during follow-up after the intervention. However, most other interventions did not detect effect on either child sleep or weight gain[233]. Moreover, previous studies heavily focused on examining the intervention effect on child sleep duration. The possible intervention effect on child sleep timing should also be evaluated, as bedtime routines and regular sleep schedule were included in nearly all sleep promotion materials, and late sleep is significantly associated with child obesity. However, in the present study, no intervention effect on child sleep was observed, in terms of child sleep duration, sleep onset time and daily sleep variation.

As most previous studies, our intervention targeted not only sleep, but also diet and physical activity. In one coaching session, the sleep component might have been too short and not intense enough to address the issues that parents had about their child's sleep. Whether exclusively targeting sleep will be better than multicomponent intervention is still uncertain, since very few studies had an exclusive intervention arm only focused on sleep. An intervention study during infancy reported that infants in the "sleep" arm had longer nocturnal sleep than infants in other groups, although there was no group difference in infant growth[175]. In another intervention project, also starting from infancy, children in the exclusive sleep intervention arm did not have longer or better sleep than the control group, but they had lower BMI z-score during the follow-up period than the control[228]. Moreover, in the current intervention, sleep hygiene education was focused. Sleep education might improve parental practice of child sleep, but the long-term effect on child sleep is still lack of evidence. One European obesity prevention study showed that when sleep intervention was performed through the different levels with different strategies, child sleep might be improved in a multilevel obesity prevention project[234].

6.7 METHODOLOGICAL CONSIDERATIONS

This thesis focuses on clarifying the role of sleep in childhood obesity, with taking family obesity risk into consideration. Repeated sleep assessment using actigraphy provides longitudinal and objective evidence of the association between sleep and obesity in young children. Moreover, the effectiveness analysis in Early STOPP provides important evidence regarding whether sleep is modifiable in a low-intensive, long-term and family-based obesity

prevention. However, a number of methodological issues and limitations need to be addressed when interpreting results in this study.

6.7.1 Sleep and obesity

The associations of interest in observational studies need to be interpreted carefully by taking possible confounding factors into account. The causality is difficult to establish when not all possible confounding variables are collected, and the sample size is relatively small. In the association between child sleep and obesity, there are a number of unmeasured factors that may explain or mediate the associations observed in this study. Some factors might be on the causal pathway. For example, increased energy intake and unhealthy dietary patterns are known to be important behavioural mechanisms linking poor sleep with weight gain. Other factors may confound the associations by affecting both the dependent and the independent variables. For example, poor family function and parents' conflicts might have an impact on both child sleep and eating behaviours, which result in more weight gain in the long term. Moreover, some factors may moderate the association of interest. In the current study, we identified that the association between late sleep and more weight gain could be amplified by high family obesity risk. We also tried to address other possible factors that might moderate the associations by including them as covariates in the statistical analysis, such as parental education level. However, not all possible factors can be included in the analysis.

Another common issue with longitudinal cohort studies is bias due to differential non-response or drop-out. As it is so often the case that non-responders are more often from some high-risk group and exhibit more unfavourable characteristics than those responders in surveys. In Study III, children without enough actigraphy sleep data were excluded. We observed that the excluded children were more often from high obesity risk families and exhibited higher BMI z-score and waist circumference at age 6 years than included children. The response pattern seems to be related to family obesity risks, with families at high risk being less likely to respond to follow-ups than families at low obesity risk. We assumed that families in the high-risk group probably were less motivated to cooperate during the follow-up, as they were allocated to the control group and only provided with routine child health care. Moreover, parents in the high-risk group had slightly higher general stress than parents in the low-risk group (data not published), indirectly showing that families at high obesity risk might have experienced more stressful life, which probably had a negative impact on the study participation.

6.7.2 Early STOPP

The RCT design is considered as the gold standard to evaluate treatment and intervention effects. Therefore, external validity and internal validity are always concerned. External validity is the extent to which the study results can be generalized outside the context of the study. Early STOPP was performed in Stockholm County, which is a high-income city. Moreover, nearly 60% of parents recruited in Early STOPP had more than 12 years education, in contrast to around 50% in the general population within the same age group in Stockholm

during the recruitment period[235]. Thus, the Early STOPP population may not be representative of the general Swedish population, and the results should be generalized with caution to other population with lower SES level. Moreover, more parents with high education level participation in the study probably also reflects the fact that more health-conscious people tend to participate in these preventive trials than those who are less health-conscious. Such self-selection into studies can also threat the internal validity, which refers to the extent to which the study result is trustworthy.

In Early STOPP, differences in weight-related outcomes were observed at baseline, with children in the control group already being heavier than children in the intervention group. There were four children had W/H greater than +3 SDs according to WHO Child Growth Standards versus no one in the intervention group. Moreover, children in the control group were more often from families with low education level. These baseline differences might suggest the possible selection bias during randomization and family recruitment. In Early STOPP, the CHCC, instead of an individual family, was the unit of randomization. The differences in recruitment performance between different CHCCs has been noticed. Moreover, the difficulty in recruitment of the intervention group has been documented in Early STOPP. Although the recruitment period was extended, the enrolment ratio turned out to become 2:1 control/intervention, instead of planed 1:1 ratio. These issues might introduce selection bias and results in unbalanced baseline between groups. Even though these baseline differences were adjusted in the analysis of the intervention effect, they might decrease the precision of the effect estimates.

Another limitation of Early STOPP concerns intervention delivery. As described earlier in the method, although the coaching sessions were designed based on MI techniques, the MI concept could not be fully adhered to in the project[236]. Coaches received limited training in MI during the first years of the project. This means the coaches' MI skills have not been further evaluated. Also, the level of MI adherence, which has not been evaluated, probably varied among coaches and across time. Thus, due to a possible lack of MI proficiency or adherence, we probably did not successfully deliver the intervention as it was planned.

6.7.3 Sleep assessments

Comparisons of child sleep patterns in Study I and II are mainly based on sleep diary data. The sleep assessment using a sleep diary is known to be susceptible to reporting bias[83]. When comparing sleep variables assessed using diary and actigraphy in our study, relatively low agreements in sleep quality measurements were detected, which might be due to parental recall bias and their low awareness of children's nocturnal awakenings. If this measurement issue is systematic and is the same for both risk groups, it will only have marginally influence on our results of group comparisons. However, some other factors that were different between groups might also affect the sleep diary data and further affect the estimates of group comparisons. For example, we found in our study that mothers in the high-risk group had lower sleep quality than mothers in the low-risk group, and one previous study showed that parental own poor sleep can affect their reports of the child's sleep[202].

The assessment of sleep using actigraphy has some limitations too. What actigraphy measures is not sleep itself, but body movements. Sleep-wake scoring algorithms were developed for detecting sleep and wake in the movement data[116,118]. There are always concerns about the reliability and validity of the scoring algorithm. High sensitivity and relatively low specificity were documented in nearly all validation studies, particularly in young children[181], with a sensitivity range = 82 – 91 and a specificity range = 50 – 72. In other words, actigraphy was consistently good at accurately identifying sleep periods, but less accurate in identifying WASO in paediatric population[114]. In the current study, overestimation of WASO was also observed in our data, when only using Sadeh's scoring algorithms through the manufacturer's software. We further performed a secondary smoothing algorithm to reduce the overestimation of night-time awakenings. However, the smoothing algorithm was developed and validated in another actigraphy device and there is no validation study of using this smoothing algorithm on the device used in the current study. This measurement bias might affect the accurate estimates of child sleep, as well as the association between sleep quality to obesity. Moreover, the comparisons between our sleep measurements to other actigraphy studies should be used with caution, as definitions of sleep variables vary between studies[114]. For example, when defining "sleep onset", three rules are most frequently used in actigraphy data, as 3, 10 or 15 consecutive minutes scored as sleep[114].

Another limitation of sleep assessment in the current study is the use of quartiles as the cut-off values for classifying some unfavourable sleep characteristics. This is because of a lack of well-established cut-offs for some sleep characteristics. For example, the commonly used recommendations for optimal sleep duration are based on reported sleep data[237,238], and most practice recommendations for paediatric sleep are lack of or only with limited evidence support[182]. However, using quartiles to classify data naturally generates a group of individuals (25% or 75%) with specific characteristics, which might increase the chance of positive findings. Also, quartiles might not have any clinical value. Given the popularity of actigraphy in sleep research, there is a need to establish normal values for child sleep measured using actigraphy.

6.7.4 Statistical considerations

First, as in other longitudinal studies, missing data is common in our dataset. In Study III, from child age 2 to 6 years, only 18% of included children had complete actigraphy sleep data at all five measuring points. We conducted multiple data imputation, and also performed mixed linear models in the analysis of longitudinal associations, which have a high tolerance for missing data. However, the great missing data might introduce potential bias in the associations analysis[239]. Second, the relatively small sample size in this study might not have enough power to detect small differences in the comparisons or to detect associations between low prevalence exposures and outcomes, for example, the association between low sleep efficiency and weight gain.

7 CONCLUSIONS

Frequent exposures to short sleep and late sleep were independently associated with more increases in obesity measures in children from age 2 to 6 years. Although the development of sleep was similar in children at different obesity risks, determined by parental weight, a combined effect between child late sleep and high family obesity risk on more weight gain was observed. Moreover, a five-year, low-intensive, family-based, multicomponent obesity intervention was not more effective than routine health care in either promoting behaviours or preventing obesity among children with overweight and obese parents.

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