Pathways contributing to childhood weight development and overweight in Norway

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Oslo 2012
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1. PREFACE

The epidemiology of obesity includes a complex interaction between genetics, embryology, sociology, nutrition and environment. It has been a privilege for me to explore a part of this enormous research field in a dedicated research environment.

1.1 Acknowledgements

This work was carried out at the Department of Pediatrics and Research Department, Sørlandet Hospital, Kristiansand and at the Division of Epidemiology, Norwegian Institute of Public Health, during the years 2008-2012.

Many people have assisted me in the process of this study.

First, I want to thank the MoBa participants for their donation of questionnaire data, and the Norwegian Institute of Public Health for their extensive work with data registration, excellent support and assistance, and for offering me an inspiring academic milieu.

I also thank my main supervisor Knut Dahl-Jørgensen for giving me the opportunity to work in this fascinating field and considering me competent for this work. I highly appreciate him for his never-ending positive and encouraging support, and his inspiring enthusiasm for research.

My most sincere thanks go to my second supervisor Wenche Nystad for initiating this study, and introducing me to the fascinating and important research field of epidemiology. You have contributed enormously to this process with your reflections and constructive advice. You have sharpened me and given me confidence in presenting my work. Thank you for thorough scientific guidance and support in interpretations and manuscript writing.

I am grateful to Lene Frost Andersen, a committed and important co-supervisor, who has been an excellent and empathic teacher in academic thinking and in the difficult discipline of scientific writing.

Hein Stigum, has been a very skilled statistician of great value to this project. His analytic guidance and supervision in the complexity of the field have been invaluable. Thank you for devoting your time and your repeated efforts in teaching me the principles of DAGs
and new methods in epidemiology and for your wise comments throughout the preparation of the manuscript.

Many thanks to Øyvind Næss, an invaluable co-author in all three papers with broad knowledge in social inequalities.

I am grateful for the financial support provided by a research grant from South-Eastern Norway Regional Health Authority and Sørlandet Hospital HF. Special thanks to Svein Gunnar Gundersen and Sissel Ledang who have managed to build up the research department at SSHF, and to my chief Kåre Danielsen, head of the Department of Pediatrics for the practical arrangements during my study.

Warm regards to all my colleges and friends in the Department of Pediatrics, to the research group in “Kolonien” and especially to Morten Mattingsdal for the meticulous support with figures and computer problems.

Thanks to my very best friends for their comfort and non-academic support in life, not mentioned by name but never forgotten. A special thank you to my friend Hanne, always present with a lot of warmth and genuine care during my stay in Oslo.

Mostly, I am greatly indebted to my former true friend and open-minded mentor and supervisor throughout my career, Per Vesterhus. He created a unique collegial and intellectually stimulating environment in the Department of Pediatrics until he left us earlier this year. I know that he would have liked to share these moments with me.

I wish to show my love and appreciation towards my mother Aase for her endless encouragement, and for always believing in me and teaching me to chase my dreams. Thanks to my younger brother Trond Arve for everlasting friendship and tolerance.

Last, but not least, I want to thank my husband Ulf, my love and friend. Thank you for your continuous support and belief in me and all my projects. Our lovely children Eirik, Marte and Stine also deserve gratitude for filling my life with so much more value than work alone and for being who they are.

Kristiansand, November 2012

Unni Mette Stamnes Köpp
1.2 Summary of Thesis

Background

Obesity is currently one of the world’s largest threats to health. Non-communicable
diseases such as obesity, diabetes and hypertension - all leading to early cardiovascular
death - are increasing all over the world, and the World Health Organization (WHO) and
United Nations (UN) point to the importance of fighting the obesity epidemic. If this
epidemic continues to increase, major problems will arise both for people’s health and for
society as a whole, as the burden of treating its complications will eventually ruin state
and country budgets. Obesity is a leading public health problem also facing children
today. The obesity epidemic affects all age groups, and children with a higher body mass
index (BMI) are more likely to become obese later on in life. The intrauterine
environment is thought to affect many aspects of health, but there is only limited evidence
for the involvement of uterine risk factors in childhood obesity. A growing body of
epidemiological and experimental evidence indicates that the prenatal period may be
critical for the development of childhood obesity. Body weight is regulated by
numerous physiological mechanisms, and short sleep duration can associate with a
hormonal imbalance caused by hunger and appetite. Therefore, identifying factors
during critical periods in early life that are predictive of obesity later on in life could
guide public health interventions in childhood obesity, and hopefully contribute to future
research that will give us a better understanding of the complex aetiology of childhood
weight gain and obesity.

Aims

The overall aim of this thesis was to use a causal model for childhood weight
development / overweight to explore pathways contributing to childhood weight gain and
obesity.

The purpose of Paper I was to estimate the association between maternal pre-pregnancy
BMI, maternal weight change during pregnancy and offspring birth weight using a BMI
classification developed by WHO and adopted by the Institute of Medicine (IOM) in
2009.
The purpose of Paper II was to estimate the association between maternal pre-pregnancy BMI or gestational weight change (GWC) during pregnancy and offspring BMI at 3 years of age, while taking several pre-and postnatal factors into account.

Lastly, in Paper III, we estimated the association between sleep duration in infancy and BMI of the child at 3 years of age to test the proposed hypothesis that impaired sleep during early childhood might increase the weight of the child.

**Material and methods**

This thesis relies on data from the Norwegian Mother and Child Cohort Study (MoBa), a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.9,10 Participants were recruited from all over Norway from 1999-2008, and 38.5% of invited women consented to participate in this study. The cohort now includes 108,000 children, 90,700 mothers and 71,500 fathers. Blood samples were obtained from both parents during pregnancy and from the mother and child (umbilical cord) at birth. Follow up was conducted by questionnaires distributed at regular intervals and by linkage to national health registries. Several sub-studies also collected additional data and biological materials for analysis. Different approaches were used to describe the causal pathways leading to weight gain and obesity, and before analysing data, we drew causal diagrams to evaluate possible associations.

**Main results**

Offspring birth weight increased with increasing maternal pre-pregnancy BMI and with maternal weight gain during pregnancy in all six categories of maternal pre-pregnancy BMI. We also found a positive association between maternal pre-pregnancy BMI and GWC and mean offspring BMI at 3 years of age. Pre-pregnancy BMI and GWC also interacted, and the strength of this interaction associated with the increase in offspring BMI among mothers who gained the most weight during pregnancy and had the highest pre-pregnancy BMI. Furthermore, we have estimated the association between sleep duration in infancy and BMI of the child at 3 years of age. This study indicated that sleep duration in infancy does not associate with BMI at 3 years of age.
Conclusions and future perspectives

Results from the first two studies support the theory that the prenatal period associates with offspring weight and BMI. In the first study we showed offspring birth weight to increase with increasing maternal pre-pregnancy BMI and with maternal weight gain during pregnancy in all six categories of maternal pre-pregnancy BMI. In the second study we showed that both maternal pre-pregnancy BMI and GWC were positively associated with mean offspring BMI at 3 years of age. In the third study, sleep duration in infancy did not associate with BMI at 3 years of age, and thus did not support the hypothesis that less sleep during infancy increases BMI at 3 years of age. Preventing maternal overweight and obesity before pregnancy and encouraging woman to maintain a healthy weight during pregnancy should be made a public health priority.
### 1.3 Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>NIPH</td>
<td>National Institute of Public Health</td>
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<tr>
<td>MoBa</td>
<td>The Norwegian Mother and Child Cohort</td>
</tr>
<tr>
<td>MBNR</td>
<td>The Medical Birth Registry of Norway</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>IOTF</td>
<td>International Obesity Task Force</td>
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<tr>
<td>IOM</td>
<td>American Institute of Medicine</td>
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<tr>
<td>GWC</td>
<td>Gestational Weight Change</td>
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<tr>
<td>Q</td>
<td>Questionnaires</td>
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<tr>
<td>DAG</td>
<td>Directed Acyclic Graph</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>BMI</td>
<td>Body mass index (kg/m²)</td>
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<tr>
<td>SES</td>
<td>Socioeconomic status</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<tr>
<td>LGA</td>
<td>Large for gestational age</td>
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<tr>
<td>SGA</td>
<td>Small for gestational age</td>
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1.4 List of Papers

Paper I


Paper II


Paper III

2. INTRODUCTION

2.1 A historical and social perspective of the project

Obesity derives from the Latin word *obesitas*, which means “stout, fat or plump.” *Esus*, the past particle of *edere* (to eat) with *ob* (over) added onto the word (Wikipedia.org), is today defined as an excess of body adiposity. The Greeks were the first to describe obesity as a medical disorder and Hippocrates described in his writings sudden deaths were more common among obese men than lean ones \(^1\). Historically obesity was viewed as a sign of wealth and prosperity \(^1\). With the onset of the industrial revolution, it was soon realised that the military and economic strength of nations was dependent on both body size and vigour of their soldiers and workers. Studies of poor children indicated that energy supplementation (adding sugar and fat to the daily diet) improved growth \(^12\). The transition of BMI distribution from the underweight range towards the normal range had important consequences on survival and productivity \(^12\). Throughout the 19\(^{th}\) century both height and weight increased in general, and the prevalence of and views on obesity changed in the Western world \(^12,13\). In the 1940s, insurance companies published charts of ideal weights for various heights, and identified an association between excess weight and premature death. Moreover, the government and different medical agencies increased their involvement with the issue of obesity by initiating a campaign that studied the risks of cardiovascular diseases \(^14\).

The prevalence of obesity in general has risen significantly over the past three decades \(^1,15,16\). The rise in obesity reflects a global phenomenon that affects both high-and low-income countries alike. In developing countries, for instance, the transition from rural agrarian to urban economies has accelerated the incidence of obesity by shifting the overall health burden from infectious diseases and malnutrition to Western chronic diseases such as cardiovascular disease, cancer and diabetes \(^17,18\).

The relationship between socio-economic status (SES) and obesity differs between developed and developing societies \(^19\). Studies prior to 1990 concluded that high SES associated positively with obesity in developed societies. Obesity among men, women and children was rare in developing societies, presumably because of the lack of food and high levels of energy expenditure. However, recent analyses of a country’s level of economic development have now shown it to be a modifier of the effects of SES on obesity. Today, obesity has shifted towards poor societies as a result of the Gross
National Product per capita reaching the mid-point value for lower to middle-income economies\textsuperscript{19}.

In developed societies, there is an inverse relationship between SES and obesity among women (increasing SES is associated with a decreasing prevalence of obesity among women). This relationship is less consistent between men and children\textsuperscript{20}. Thus, a complex interaction of social, environmental and policy factors has influenced both the eating habits and the levels of physical activity, making it difficult for many children to maintain healthy body weight\textsuperscript{1}.

\subsection*{2.2 Background}

The prevalence of obesity, defined as body mass index based on gender- and age-specific standards established for children\textsuperscript{21,22}, has been increasing worldwide over the past 30 years in both rich and poor countries as well as in all segments of society\textsuperscript{23}. National data on the prevalence of obesity have indicated the same trend\textsuperscript{24-29}. Additionally, Juliusson et al. have shown a significant increase in the ratio of weight-to-height in Norwegian children during the last 30 years, stating that an increase in fat tissue is responsible for these changes\textsuperscript{26}. In this study, the overall prevalence of being overweight and obese at 3 years of age was 13.8\% and 2.3\% respectively. The risk of obesity can be established during childhood and adulthood, and the risk of an overweight child becoming an obese adult rises with age\textsuperscript{5,18,30}. A variety of childhood factors can contribute to an individual’s risk of becoming overweight and obese, including infant birth weight (high and low), maternal and paternal obesity, increased gestational weight gain, gestational diabetes, breastfeeding, rapid early infant weight gain and SES\textsuperscript{2,21-33}. Additionally, infants born to obese mothers are more likely to be large for gestational age (i.e., macrosomia)\textsuperscript{34}, require neonatal intensive care or be diagnosed with a congenital anomaly\textsuperscript{35}. An increase in the prevalence of overweight and obese children has important public health consequences. As childhood obesity is a rapidly growing problem worldwide, it has become increasingly clear that early life exposure can contribute directly to its prevalence. Early life exposure may be due to different environmental and social impacts that arise during early embryogenesis, pregnancy, birth and even childhood\textsuperscript{4}. Therefore, identifying factors during critical periods in early life that are predictive of obesity later on in life could help reduce the incidence of obesity in the general population. The intrauterine environment is
thought to affect many aspects of health, but there is only limited evidence for the involvement of uterine risk factors in childhood obesity\textsuperscript{36}. To examine how different early contexts interact in the complex multi-factorial aetiology of childhood overweight would add important knowledge to our understanding of childhood obesity and hopefully contribute to a better understanding of childhood weight gain and social disparities in health status\textsuperscript{16,19,37}.

Figure 1.

IOTF/IASO - Causal web of societal influences on obesity (www.iaso.org/www.iotf.org). Reprinted with permission\textsuperscript{38}. [A text description of this figure is also available.]

2.3 The definition of body mass index outcome

Childhood overweight and obesity have both epidemiological and clinical relevance. Ideally, they should be defined by an increase in the risk of morbidity, but currently there is insufficient evidence to establish cutoff points for the relationship between increased paediatric BMI and short and long term health outcomes of BMI\textsuperscript{39}. Children and adolescents are still growing, and there is not one cutoff value to demarcate healthy
weight from overweight or obesity. In general, overweight refers to an individual weighing more than a standard level when height and age are taken into account. However, the definitions of overweight and obese have changed over time. In the United States, the term obesity was not used until the last decade; instead, terms like at-risk of being overweight (between 85th and 95th percentile of BMI) and overweight (above the 95th percentile) were frequently used to define an excessive weight40. In other countries, however, these two groups are referred to as overweight and obese, respectively, by the use of different national references (85th and 95th percentiles, 90th and 97th percentiles or 91st and 98th percentiles) that can be found in relevant national reference charts41 42.

Body composition can be accurately assessed by several methods. Standardised methods are currently available to measure weight, height and other anthropometric variables. Age- and gender-specific percentiles of BMI (kg/m²) are commonly used in epidemiological studies to evaluate a child’s weight status. However, BMI in children changes substantially with age, and the components of BMI include both fat mass and lean mass. The International Obesity Task Force (IOTF) constructed and published in year 2000 international definitions of paediatric overweight and obesity based on data from six countries. They consistently included age- and gender- specific BMI cutoff values to pass through a BMI of 25 kg/m² (overweight) and 30 kg/m² (obese) at age 18 as the threshold from 2 to 18 years of age41.

2.4 The prenatal period and its association with BMI in offspring
The prevalence of overweight and obesity in young women has increased worldwide over the past 20 years16 as well as among childbearing women in Norway43,44. Obesity during pregnancy is associated with an increased risk of gestational diabetes, hypertensive disorders, thromboembolic complications, stillbirths, caesarean section, macrosomia and delivery complications45-47. Moreover, pregnancy outcome is correlated with both pre-pregnancy BMI and gestational weight gain34,45. Pregnancy is also considered to be an important risk factor for new or persistent obesity among women of childbearing years48, and exposure to maternal obesity or high birth weight also represents an increased risk for childhood and adult obesity47,49,50.

A growing body of epidemiological and experimental evidence indicates that the prenatal period may be critical for the development of childhood obesity4,6,36. Seminal work by
Barker and colleagues on birth weight in the late 1980s showed that an unfavourable in utero environment can predispose the foetus to a higher risk of disease acquisition later on in life\textsuperscript{51,52}. In their cohort, they showed cardiovascular disease and metabolic syndrome to be inversely correlated with birth weight\textsuperscript{52}. In Dutch famine and Leningrad famine studies, where cohorts underwent different durations of malnutrition during development, it was proposed that adult disease occurs when the foetal and postnatal environments are inconsistent\textsuperscript{53,54}. Recent research now links the Barker hypothesis to the concept of “Developmental Origins of Health and Disease (DOHaD)”\textsuperscript{55}. The DOHaD hypothesis also emphasises that foetal adaptation is developmentally regulated, and recent epidemiological studies have suggested a U-shaped relationship between birth weight and adult obesity\textsuperscript{56,57}. Childhood obesity may even originate during embryonic and foetal development through in utero programming of appetite and metabolism\textsuperscript{4,58,59}. Early nutrition may affect the regulation of food intake, influence adipose tissue cellularity\textsuperscript{60} and predispose individuals to obesity.

Maternal adiposity may lead to greater placental transfer of nutrients (glucose, free fatty acids and amino acids) during embryonic and foetal development\textsuperscript{61}. Obesity itself associates with insulin resistance, glucose intolerance and therefore higher plasma concentrations of glucose and free fatty acids. In offspring, this may give rise to permanent changes in the hypothalamus, pancreatic islet cells and adipose tissue, and affect neuro-endocrinological and biological systems that regulate bodyweight\textsuperscript{62}. A ‘foetal overnutrition hypothesis’ has important public health implications as it may propel the obesity epidemic to span several generations without any additional environmental or genetic influences\textsuperscript{61-63}. The prevalence of overweight women in Norway is a public health challenge with intergenerational implications\textsuperscript{43}.

Optimal weight gain for mothers has been periodically questioned and guidelines have been revised, but still there is no general agreement on the recommended weight gain for pregnant women\textsuperscript{34,64-66}. The most widely adopted recommendations concerning weight gain during pregnancy were developed by IOM and published in 1990 and 2009\textsuperscript{67,68}. The recommendations from IOM in 1990 were based on a review of epidemiological studies that associated maternal pregnancy weight gain with birth outcome. The main focus of IOM was the prevention of low birth weight because they noted that low pregnancy weight gain associated with an increased risk of preterm birth and small for gestational age (SGA) infants. Over the next 20 years, the percentage of women that were already
overweight or obese prior to pregnancy increased. The 1990 guidelines did not give an upper limit gain for obese women (BMI >30) as sufficient data were unavailable to establish an optimal range; however, IOM issued a new report in 2009 which included new weight gain guidelines for obese women. These guidelines recommended weight gain ranges during pregnancy on the basis of four pre-pregnancy BMI categories (underweight, normal weight, overweight and obese), with smaller gains recommended for heavier women\textsuperscript{67}. Evidence was insufficient to construct specific guidelines for women with class II (BMI 35.0–39.9) and class III (BMI≥40.0) obesity\textsuperscript{67}.

Relatively little is known about maternal and foetal outcomes along the entire spectrum of BMI in relation to weight change during pregnancy\textsuperscript{34}. Consequently, weight gain during pregnancy gained increasing attention as a critical period for preventing obesity at the population level. Pre-pregnancy weight and GWC during pregnancy gained attention as risk factors for childhood obesity, and high gestational weight gain was a potential risk factor for future obesity\textsuperscript{2,33,69-73}. A previous study has reported a U-shaped association with an increase in adolescent overweight and adult obesity risk in offspring from women with the lowest and highest GWC\textsuperscript{74}. In a recent study, this association became linear after adjustment for maternal pre-pregnancy BMI\textsuperscript{73}, which highlights the importance of considering both GWC and pre-pregnancy BMI.

Unfortunately, little is known about weight development during the earliest years of life. Few studies have addressed the association between maternal pre-pregnancy BMI and GWC during pregnancy and overweight/obesity in children, and their results were conflicting\textsuperscript{2,31,33,70,71,75}.

Parental obesity, especially maternal obesity, appears to be an important risk factor for childhood overweight/obesity\textsuperscript{2,36,72}. Parental obesity may increase the risk of obesity through genetic mechanisms or through shared characteristics within the familial environment such as food preferences and intake.

\textbf{2.5 Sleep duration and its association with BMI in offspring}

Body weight is physiologically regulated. This process involves central and peripheral components that interact with different aspects of the environment, including nutrition, exercise and other critical factors\textsuperscript{12,76}. In light of the alarming increase in the prevalence
of obesity, population studies have proposed a dose-responsive relationship between short sleep duration and high BMI in different age groups\textsuperscript{77-81}. They also found that higher BMI is associated with shorter sleep duration\textsuperscript{82}, and a reduction of sleep time has been proposed to be one of the contributing factors\textsuperscript{83}.

Disruption of the circadian rhythm in the body, including periods of short or partial sleep, exerts a condition of physiological stress and several metabolic hormones are known to be involved\textsuperscript{7}. Previous studies indicated that short sleep duration results in a hormonal imbalance with decreased levels of leptin, glucose intolerance and insulin sensitivity, but with increased levels of ghrelin, hunger and appetite\textsuperscript{7,8}. A study by Spiegel et al. was the first to report that sleep restriction affects appetite hormones and behaviour, showing that two nights of sleep restriction to 4 h instead of 10 h triggered a decrease in the level of leptin, an increase in the level of ghrelin, and an increase in the sensation of hunger and appetite\textsuperscript{84}. Additionally, short periods of sleep have been associated with reduced leptin levels independent of obesity in two separate studies\textsuperscript{82,85}. These hormonal changes may contribute directly to an energy imbalance and lead to overweight or obesity.

Assorted recent cross-sectional\textsuperscript{80,81,86} studies suggest that short sleep duration could be a risk factor for weight gain or obesity, but it has been difficult to establish a causal association\textsuperscript{77,87,88}. Recent prospective studies support a link between sleep duration in childhood and subsequent overweight risk\textsuperscript{36,89-91} which may be stronger in younger children\textsuperscript{92}. Of the longitudinal studies\textsuperscript{36,90-94}, only two small studies\textsuperscript{91,94} have included sleep duration in children aged younger than 2 years as a parameter of investigation. Measurements on sleep in infancy may reflect a greater susceptibility to the biological (changes in the central appetite regulatory system and increased expression of leptin) effects of short or consistently short sleep with impact on weight regulation and body composition in childhood\textsuperscript{7}. 
3. AIMS AND OBJECTIVES

The overall aim of this thesis was to explore factors contributing to childhood overweight and obesity.

1. To estimate the association between maternal pre-pregnancy BMI and maternal weight change during pregnancy and offspring birth weight using the BMI classification developed by WHO and adopted by IOM in 2009.

2. To estimate the associations between maternal pre-pregnancy BMI or gestational weight change during pregnancy and offspring BMI at 3 years of age, while taking several pre-and postnatal factors into account.

3. To assess the association between duration of sleep in infancy and BMI of the child at 3 years of age.
4. SUBJECTS AND METHODS

4.1 Subjects and data collection

This thesis is a sub-study based on the Norwegian Mother and Child Cohort Study (MoBa) that was conducted by the Norwegian Institute of Public Health. Briefly, MoBa is a nation-wide cohort that consists of more than 108 000 pregnancies that occurred between 1999 and 2009. The aim of the cohort study was to elucidate the aetiology of disorders that may originate in early life by following the health of children and their parents over an extended period of time. The majority of pregnant women in Norway were invited to participate, and the participation rate was 44%. Participants were recruited to the study via a postal invitation that was issued in conjunction with an offer to receive a routine ultrasound examination that is offered to all pregnant women in Norway at 17-18 weeks of gestation. The questionnaires can be viewed at the MoBa website (www.fhi.no/morogbarn). Participating women received three questionnaires during pregnancy and additional questionnaires when the child was 6, 18 and 36 months. Furthermore, data from a questionnaire completed by the father during an early phase of this study were also included in the analysis. The first questionnaires (Q1) covered previous pregnancies, medical history before and during pregnancy, medication, occupation, exposure in workplace and at home to potentially harmful substances, lifestyle habits and mental health. The second (Q2) questionnaire is sent to participants at about week 22 and covered food habits. A third questionnaire (Q3) was sent at 30 weeks and covered the women’s health status during pregnancy as well as work situation and habits. The fourth questionnaire (Q4) covered child health and nutrition as well as maternal disorders, wellbeing and mental health when the child was 6 months of age. The fifth questionnaire (Q5) at 18 months and the sixth questionnaire (Q6) at 36 months focused mainly on the child’s developmental status. Records from the Medical Birth Registry of Norway (MBRN) from the present pregnancy were included as part of the data set. The MBRN has recorded standardised information from all deliveries since 1967\textsuperscript{95}. Today, they provide information on health services related to pregnancy characteristics, childbirth and the neonatal period.

The thesis consisted of two study populations:
Paper I

This study was based on version 4 of the quality-verified data files that were released for research in February, 2009. The present material included women recruited from 2000 to 2007 and consisted of 63,491 pregnancies. Records from MBRN from the present pregnancy were included as part of the data set. For the present study we used data from two postal questionnaires. The first (Q1) was responded to around gestational week 17-18, and the second (Q3) around gestational week 30.

The present material was restricted to pregnancies with single, full-term live births at gestational week 37 or beyond. We excluded pairs where the child had Down’s syndrome, and women with weight reduction more than 26 kg and weight gain more than 40 kg up until gestational week 30. We also eliminated data on 170 women that provided unrealistic information (height < 130 cm or > 195 cm, weight < 25 kg), and 27 women with missing information on birth weight. This gave a total number of 58,383 pregnant women and their offspring.

Paper II

This study was based on version 5 of the quality-verified data files that were released for research in February, 2011. Our study population included 105,117 pregnancies recruited from 1999 to 2009. Records from MBRN from the present pregnancy were included as part of the data set. We used data from five postal questionnaires. The first (Q1) was completed around gestational week 17, the second (Q3) was completed around gestational week 30, the third (Q4) was completed when the child was 6 months old, and the fourth (Q6) was completed when the child was 36 months old. Furthermore, data from a questionnaire completed by the father during an early phase of this study were also included in the analysis. The study was restricted to single, full-term live births at gestational week 37 and beyond, and to those without weight reduction more than 26 kg or weight gain more than 40 kg up until gestational week 30. Cases of children with Down’s syndrome were excluded from the analysis. We also excluded 245 and 45 women that provided unrealistic height (< 130 cm or > 196 cm) and weight (< 25kg or > 40 kg) information, respectively. This gave a total number of 90,198. In addition, we excluded 42 children with unrealistic heights (< 83 cm or > 120 cm) and/or weights (< 9 kg or > 38 kg). The entry criteria into our study was restricted to children who reached 3 years of age and for whom the mother had returned Q1 (gestational week 17), Q3 (gestational week
30), Q4 (6 months), and Q6 (36 months) with complete information on offspring height and weight at age 3 (study sample 1: n = 31 169). We analysed a sub-sample with information of paternal BMI (study sample 2: n= 5 898).

**Paper III**

This study was also based on version 5 of the quality-verified data files. For the present study, we used data from four postal questionnaires. The first (Q1) was completed around gestational week 17, the second (Q4) was completed when the child was 6 months old, the third (Q5) was completed when the child was 18 months old and the fourth (Q6) was completed when the child was 36 months old. The study was restricted to single, full-term live births at gestational week 37 and beyond (≥ 259 days). In addition, 124 children with unrealistic heights (< 83 cm or > 120 cm) and/or weights (< 9 kg or > 38 kg) were excluded. Moreover, only children who had reached 3 years of age and for whom the mother had returned Q1 (gestational week 17), Q4 (6 months), Q5 (18 months) and Q6 (36 months) with complete information on offspring height and weight at age 3 (n = 28 306) were included.

### 4.2 Outcome and main exposure

**Outcome**

**Paper I**

*Birth weight*

As a measure of foetal growth, we used birth weight (g) as a continuous variable from MBRN. The expected birth weight was adjusted for gestational age based on ultrasound data. If these were unavailable, expected birth weight was estimated from last menstrual period at > 37 weeks (≥ 259 days) provided by MBRN.

**Papers II and III**

*Body mass index*

The main outcome variable was offspring BMI (kg/m²), which was calculated by dividing the parent reported weight by the square height when the child was 36 months old (Q6). This value was treated as a continuous variable. Our study sample conformed to a normal
distribution of the population axis and was comprised mostly of normal weight children. Additionally, we excluded children with unrealistic heights (< 83 cm or > 120 cm) and/or weights (<9 kg or >38 kg) based on the Norwegian growth charts and IOTF.

Main exposure

Papers I and II

Maternal pre-pregnancy body mass index

Maternal pre-pregnancy BMI was based on self-reported weight and height prior to conception and as documented in the first questionnaire (Q1). BMI was treated as a continuous or categorical variable divided into six categories based on the WHO recommendations as follows: underweight (BMI < 18.5 kg/m²), normal range (BMI 18.5-24.9 kg/m²), overweight (BMI 25.0-29.9 kg/m²), obese class I (BMI 30.0-34.9 kg/m²), obese class II (BMI 35.0-39.9 kg/m²), obese class III (BMI ≥ 40.0 kg/m²)\textsuperscript{16}. Additionally, we eliminated data on women that provided unrealistic information on height (< 130 cm or > 195 cm) and/or weight (< 25 kg).

Weight change

Women were asked in the first questionnaire (Q1): What was your total weight (kg) before pregnancy, and what is your total weight now? Each women`s response from the total weight before pregnancy question was used as the pre-pregnancy weight. In the third questionnaire (Q3), women were asked: What was your total weight in the last control, and what was the date of the last control? Weight change was calculated from maternal self-reported weight at gestational week 30 reported in the third questionnaire (Q3) and pre-pregnancy weight reported in the first questionnaire (Q1). Weight change was treated as a continuous variable or coded into five categories as follows: 1 = weight loss until 26 kg, 2 = > 0 but ≤ 5 kg weight gain, 3 = > 5 kg but ≤ 13 kg weight gain, 4 = > 13 kg but ≤ 20 kg weight gain or 5 = > 20 kg weight gain. Weight gain in pregnancy is formerly expressed as maternal weight change (MWC) and used in paper I. In paper II it was expressed as gestational weight change (GWC).
Paper III

Sleep duration

The main exposure variables were parental report of infant sleep duration at 6 and 18 months of age. The question on sleep duration at 6 months was as follows: How long does your baby sleep in a 24 h period: <8 h, 8-10 h, 11-12 h, 13-14 h, or >14 h? The question on sleep duration at 18 months was as follows: How long does your child sleep in a 24 h period: ≤ 10 h, 11-12 h, 13-14 h, or ≥ 15 h? Since sleep duration habits can change between 6 to 18 months, sleep habits at 6 and 18 months were classified into four categories as follows: ≤ 12 h at both 6 and 18 months, ≤ 12 h at 6 months and > 12 h at 18 months, > 12 h at 6 months and ≤ 12 h at 18 months, and > 12 h at both 6 and 18 months.

4.3 Statistical methods

Based on a review of previous studies, a pre-analytical approach was used to decide which underlying causal mechanisms and plausible confounding factors would be included in the statistical models. Causal diagrams in the shape of directed acyclic graphs (DAG) were used as tools in drawing causal models between exposure, potential confounders and outcome.

Paper I

The association between maternal pre-pregnancy BMI and maternal weight change during pregnancy and offspring birth weight was based on Figure 2. Three linear regression models were used: 1) maternal pre-pregnancy BMI on birth weight, 2) pre-pregnancy BMI on maternal weight change and 3) maternal pre-pregnancy BMI on birth weight mediated through maternal weight change. From these models, we estimated the total effect of pre-pregnancy BMI on offspring birth weight, the direct effect of maternal pre-pregnancy BMI on maternal weight change, and the indirect effect of pre-pregnant BMI on offspring birth weight passing through maternal weight change during pregnancy. In all models, we adjusted for confounders (maternal education, age, parity and smoking). For each regression model, we checked assumptions (linearity and constant variance) and looked for points with large influences (plotting delta-beta) to see if the results were robust against outliers.
Figure 2. An assumed causal relationship between maternal pre-pregnancy BMI, maternal weight change during pregnancy and offspring birth weight.

**Paper II**

The DAG included maternal BMI as the main exposure and offspring BMI as the outcome, as well as other important cofactors (Figure 3). According to our DAG, the variables age, parity, maternal education, smoke, exercise and paternal BMI were part of confounding paths for the maternal-offspring association, and we adjusted for these in all models. Sex was a confounder for the birth weight-BMI association and was also adjusted for. Gestational age and the presence of complications during pregnancy had already been adjusted for by eliminating these samples from our data set. The variables we adjusted for are shown framed, the closed confounder pathways are shown as dashed lines in the DAG. After adjustment, four paths were open: one direct path from mother to offspring BMI and three paths with GWC, birth weight, and breast feeding-media-day care as intermediate variables. To estimate associations, we applied four different models from the study sample. In model 1, we studied the total effect of maternal pre-pregnancy BMI on offspring BMI at 3 years of age after adjusting only for the confounders mentioned above. We then added intermediate variables one by one into the model. In model 2, we added GWC. In model 3, we added birth weight, and in model 4, we added several postnatal factors such as breastfeeding, day care and media consumption at 3 years of age. Differences in estimates between two consecutive models provide the indirect effect passing through the intermediate variables involved. We also tested the interaction between maternal pre-pregnancy BMI and GWC. For each regression model, we checked assumptions (linearity and constant variance) and looked for points with large influences (plotting delta-beta) to ensure that results were robust towards outliers.
Figure 3. An assumed causal relationship between maternal pre-pregnancy BMI, gestational weight change during pregnancy, and offspring BMI at 3 years of age.

Paper III

To estimate the association between duration of sleep in infancy and BMI of the child at 3 years of age, we applied five different models based on figure 4. According to our DAG, the variables age, parity, education and smoke were part of the confounding paths for the maternal-offspring association. In model 1, the unadjusted association between sleep duration at 6 months of age and offspring BMI at 3 years of age was assessed. In model 2, the same association tested by model 1 was examined except that adjustments were made for the aforementioned maternal confounders and child gender. In model 3, the unadjusted association between sleep duration at 18 months of age and offspring BMI at 3 years of age was assessed. In model 4, the same association tested by model 3 was examined, except that adjustments were made for maternal confounders and gender. In model 5, several combinations of sleep duration at 6 and 18 months served as the exposure (categorised as described above), and adjustments for maternal confounders and gender were made.
Figure 4. An assumed causal relationship between sleep duration in children aged 6 and 18 months with offspring BMI at 3 years of age.

SPSS version 18.0 (SPSS Inc. Chicago, USA) was used to conduct all analyses in this thesis.

4.4 Ethical considerations

MoBa has been approved by the Norwegian Regional Committee for Ethics in Medical Research and the Data Inspectorate in Norway. Informed consent was obtained from each participant before inclusion. Invitations for participation were sent to pregnant women in collaboration with individual participating hospitals. Important information on the purpose of the study, the protection of privacy and other practical details were also included. It was emphasised that participation was voluntary and that consent from children would be sought when they were older. Informed consent was obtained from each participant before inclusion in the MoBa study. Women were informed of their right to withdraw from the study at any time. The individual identities were unknown. This study did not in any way influence the environment negatively and did not introduce any environmental hazards.

Throughout history, many cultures have viewed obesity as the result of a character flaw. During early Christianity times food was viewed as a gateway to the sins of sloth and lust\textsuperscript{13}. In modern Western culture, excess weight is often regarded as unattractive, and is associated with various negative stereotypes and social stigmas and thus could be a reason for discrimination\textsuperscript{97}. The principal goal in general though should be to decrease discrimination\textsuperscript{98}.
The relationship between social determinants and BMI varies globally, and different explanations have been put forth\textsuperscript{19}. Low prevalence of obesity in less developed countries may be due to the lack of food. Individuals within higher SES appear to have access to a greater food supply, which correlates with the increasing prevalence of obesity and may be coupled with the tendency to reach fat body shapes. By contrast, in developed society, where SES is less clearly defined, increasing SES is associated with a decreasing prevalence of obesity, especially among women. Attitudes toward obesity in developed societies among women could be one explanation, but dietary restraint, increased physical activity, social mobility and inheritance may also play important roles.

In this present public health context, the main actors under consideration are the state and the doctors in their roles as agents of the state, and on the other hand, the individual. The main principles or ethical values to consider are respect for self-determination, the pursuit of a good life, the promotion of a common good, the obligation between parents and children and justice\textsuperscript{99}. This project raises different ethical problems as follows:

First, it a challenge to promote one body shape as good, without implying that others body shapes are bad. At the same time, it is difficult to prevent people from linking this to personal and moral issues.

A second ethical dilemma is that our results may create potential problems of social stigmatisation for both obesity and education. Changes in self-perception may become evident as individuals identify themselves as belonging to one of two groups.

A third dilemma is that parents already have an ethical and legal obligation to promote the “best interest of the child.” Part of this is achieved through proper nutrition during prenatal and childhood periods of life, and this may require the entire family to eat differently. Because no dietary advice is constant and not all overweight children become obese, our results may not be beneficial for everyone.

Our goal was to follow ethical guidelines as prescribed by the International Epidemiological Association (IEA) and to adhere to principles of good conduct when dealing with epidemiological practices and scientific research (i.e., to conduct practices and research in accordance with defined protocols, methods, procedures and proper documentation).

The author’s work is independent of the funders. There are no conflicts of interest.
5. SUMMARY OF PAPERS

5.1 Paper I
Maternal pre-pregnant Body Mass Index, maternal weight change and offspring birthweight

Unni Mette Stamnes Köpp, Lene Frost Andersen, Knut Dahl-Jørgensen, Hein Stigum, Øyvind Næss, Wenche Nystad.

Epidemiological evidence indicates that higher or excessive birth weight is associated with increased risk of adiposity during child- and adulthood. Maternal adiposity may lead to greater placental transfer of nutrients (glucose, free fatty acids and amino acids) during embryonic and foetal development. In offspring, this may give rise to permanent changes in the hypothalamus, pancreatic islet cells and adipose tissue, and affect the neuro-endocrinological and biological systems that regulate bodyweight. A ‘foetal overnutrition hypothesis’ has important public health implications as it may propel the obesity epidemic to span several generations without any additional environmental or genetic influences.

We aimed to estimate the association between maternal pre-pregnancy BMI and maternal weight change during pregnancy and offspring birth weight using a BMI classification developed by WHO and adopted by IOM in 2009. The study included 58 383 pregnant women.

Conclusion: Offspring birth weight increased with both increasing maternal pre-pregnancy BMI and maternal weight gain during pregnancy in all six categories of maternal pre-pregnancy BMI. Women with the highest level of education had the highest offspring birth weight.

5.2 Paper II
The associations between maternal pre-pregnancy body mass index or gestational weight change during pregnancy, and body mass index of the child at 3 years of age

Unni Mette Stamnes Köpp, Knut Dahl-Jørgensen, Hein Stigum, Lene Frost Andersen, Øyvind Næss, Wenche Nystad.

The intrauterine environment is thought to affect many aspects of health, but there is only limited evidence for the involvement of uterine risk factors in childhood obesity. Pre-
pregnancy weight and GWC during pregnancy have gained attention as risk factors for childhood obesity at the population level, and high gestational weight gain is a potential risk factor for future obesity. Furthermore, paternal BMI may also be important. In this study, we aimed to estimate the association between maternal pre-pregnancy BMI or GWC during pregnancy and offspring BMI at 3 years of age, while taking several pre-and postnatal factors into account. This study showed that both maternal pre-pregnancy BMI and GWC were positively associated with mean offspring BMI at 3 years of age. Pre-pregnancy BMI and GWC also interacted, and the strength of this interaction associated with the increase in offspring BMI among mothers who gained the most weight during pregnancy and had the highest pre-pregnancy BMI. Our findings show that results could be biased by not including pre-pregnancy paternal BMI.

Conclusion: This large population-based study showed that both maternal pre-pregnancy BMI and GWC were positively associated with mean offspring BMI at 3 years of age.

5.3 Paper III
The association between duration of sleep in infancy and body mass index of the child: The Norwegian Mother and Child Cohort Study.

Unni Mette Stamnes Köpp, Hein Stigum, Knut Dahl-Jørgensen, Lene Frost Andersen, Øyvind Næss, Wenche Nystad.

Short sleep duration is related to a hormonal imbalance with decreased levels of leptin, glucose intolerance and insulin sensitivity, but increased levels of ghrelin, hunger and appetite. Moreover, several studies have found that short sleep duration is a risk factor for obesity, but it has been difficult to establish a causal association. Of the longitudinal studies, only two small studies have included sleep duration in children aged younger than 2 years as a parameter of investigation. In this study, the association between duration of sleep in infancy and BMI of the child at 3 years of age was assessed. The study included 28 306 children and exposure variables were sleep duration at 6 and 18 months of age.

Conclusion: This large population-based study indicated that the duration of sleep in infancy does not associate with BMI at 3 years of age.
6. DISCUSSION

6.1 General discussion

Presently, there is a substantial amount of research on factors associated with childhood overweight and obesity. An increase in childhood overweight and obesity has important public health consequences.

The obesity epidemic is escalating, and estimates on the number of overweight infants and children rose steadily from 1990 to 2008\textsuperscript{100}. The overall global prevalence of overweight and obesity defined by IOTF criteria is approximately 10% and 2- 3\% respectively\textsuperscript{101}. The current study demonstrated that approximately 12\% of the offspring were overweight, and 2\% were obese at 3 years of age. A woman’s pre-pregnancy weight and adiposity, and weight gain during pregnancy are related to offspring weight through a complex multi-factorial aetiology. Epigenetic modifications may represent one mechanism by which exposure to an altered milieu may influence phenotype later on in life. However, the prevalence of overweight and obesity in young women has increased worldwide over the past 20 years, and in our study, 22.3\% of mothers were overweight and 9.1\% were obese. While it would be optimal to have every women achieve her ideal body weight prior to conception, healthy and sustained weight loss is extremely difficult. Pre-conception weight loss is also challenging as approximately 40\% of all pregnancies are unplanned\textsuperscript{102}. Gestational weight gain may be modifiable and be an excellent opportunity for women to make healthy lifestyle changes\textsuperscript{103}. This effort may help prevent obesity in the next generation as well as long term weight gain in the mother.

The results of the two first papers support evidence for the importance of early life exposure.

6.1.1 Maternal pre-pregnancy BMI, maternal weight change and birthweight (Paper I).  
This study showed that offspring birth weight increased with both increasing maternal pre-pregnancy BMI and maternal weight gain during pregnancy in all six categories of pre-pregnancy BMI.

No large population-based pregnancy cohort has previously investigated the effects of different patterns of weight gain based on the most recent BMI classification from WHO\textsuperscript{16}. Earlier and more recent studies have demonstrated a relationship between high
maternal BMI and large offspring\textsuperscript{68,104,105} as well as consistent association between maternal weight gain and birth weight\textsuperscript{62,64,106,107}. The IOM recommended gestational weight gain\textsuperscript{67,68} within each pre-pregnancy BMI category associates with more favourable birth outcomes\textsuperscript{67,108} than if weight gain is above or below the suggested range\textsuperscript{67,109}. Unfortunately, similar weight gain recommendations do not exist in the Nordic countries yet\textsuperscript{110}. The optimal weight gain among obese women remains unclear\textsuperscript{68,108}. A recent large study demonstrated that the 2009 IOM recommendation include weight gain ranges that influenced the risk of large-for-gestational-age (LGA) and small-for-gestational-age (SGA) in opposite directions\textsuperscript{111}. Additionally, the IOM report called for more research on severely obese women in order to establish gestational weight gain guidelines and recent studies suggest the importance of balancing the potential risks of LGA, SGA, spontaneous preterm births, and medically indicated preterm births, as these risks may differ by degree of obesity\textsuperscript{107,111-115}. There is also a concern that attempts diet induced maternal ketosis which has been associated with a risk of neurocognitive disorders\textsuperscript{116-118}.

This study also indicated that both BMI and weight gain (\(\leq 20 \text{ kg}\)) up until gestational week 30 can influence birth weight even among women within obesity classes II or III.

Previous results from smaller studies suggest that weight gain influences birth weight more in underweight and normal weight mothers\textsuperscript{119-122}, but is less apparent in overweight and obese women. Our results are more in agreement with Shapiro et al.\textsuperscript{122}, who showed that maternal weight gain >35 lbs/15.9 kg resulted in higher birth weight in all categories on the basis of four pre-pregnancy BMI groups as well as among obese women.

Educational attainment represents the social variable that have been shown to have the largest socioeconomic differential at least in the Nordic countries\textsuperscript{123}. For example, education can represent the dimension of knowledge and the ability to understand public health messages. The determinants of birth weight are likely to be socially patterned\textsuperscript{20,37,124} and birth weight is an indicator of health that has been associated with a host of diseases in adulthood\textsuperscript{125}. A Norwegian study among schoolchildren has shown that obesity had increased greatly from 1992 to 2000, and that obesity was related to social class\textsuperscript{24}. However, in our study women with the highest level of education had higher offspring birth weight compared to those with the lowest level of education, but there was no statistically significant effect of education on offspring birth weight. In previous studies, high birth weight, low socio-economic position and parental overweight
were independent risk factors of overweight in children. These attributes gave the highest risk of overweight in 5-7 year old children\textsuperscript{126}. In a recent review of cross-sectional studies in the past 15 years, associations between SES and adiposity in school-age children from Western developed countries were predominately inverse, and very few positive associations were found\textsuperscript{127}. In the future, individual level risk factors for childhood obesity need to be studied in conjunction with different aspects of social environment and gender\textsuperscript{128}.

The implication of this study is that pre-pregnancy BMI alone is an important predictor of birth weight. Furthermore, weight gain during pregnancy has an effect on offspring birth weight independent of maternal pre-pregnancy BMI.

6.1.2 Maternal pre-pregnancy BMI, gestational weight change and BMI of the child at 3 years of age (Paper II).

This study showed that both maternal pre-pregnancy BMI and GWC were positively associated with mean offspring BMI at 3 years of age. Pre-pregnancy BMI and GWC also interacted, and the strength of the interaction between these two factors was associated with the increase in offspring BMI among mothers who gained the most weight during pregnancy and had the highest pre-pregnancy BMI. Our findings show that results could be biased by not including pre-pregnant paternal BMI.

According to country estimates in the WHO European Region, more than 50\% of men and women were overweight, and approximately 23\% of women were obese\textsuperscript{100}. In this study, 22.3\% of mothers were overweight, and 9.1\% were obese. Furthermore, 14\% of children were overweight. Obese mothers are more likely to have obese children\textsuperscript{2,36,59,72}. From a public health perspective, it is important to address the effects of pre-pregnancy BMI and GWC during pregnancy on offspring BMI in childhood\textsuperscript{129}.

Our work extends previous studies in several ways. First, it is one of few prospective studies\textsuperscript{33,73} on the current epidemic of obesity to examine the associations between maternal pre-pregnancy BMI and offspring BMI, and between GWC and offspring BMI. Second, former studies have used the frequency of overweight and obese children as outcome variables, whereas to the best of our knowledge, there is no published study
using mean offspring BMI at 3 years of age. Third, we include paternal pre-pregnancy BMI in our analysis.

Earlier studies found an association between a higher GWC, maternal BMI and overweight/obese children and adolescents at 3, 7, 6-12 and 9-14 years of age. Branum et al. found associations between pre-pregnancy BMI or GWC and the child BMI z score at 4 years of age, but their study resulted in a null association in the fixed effect models for shared family-level environmental, genetic and behavioural characteristics. Another previous study found no association between GWC and offspring BMI, but in this study weight gain was not the primary predictor of interest. In a recent retrospective cohort, a strong association was found between GWC and offspring overweight at 7 years of age for women who were underweight before pregnancy71. Consistent with former studies, we have confirmed the finding that GWC during pregnancy is positively associated with offspring BMI and that there is a linear and positive association between maternal pre-pregnancy BMI and GWC and mean offspring BMI at 3 years of age.

Additionally, each unit increase in maternal BMI increased offspring BMI at 3 years of age by 0.034 BMI units. This implies that mothers with a BMI of 35 (obese) would have offspring with a BMI that is 0.5 units higher than of offspring born to mothers with a BMI of 20 (normal). To illustrate this point, shifting the offspring BMI curve by 0.5 BMI units to the right on the population axis results in an increase in the proportion of overweight offspring (BMI > 17.7) from 13 to 21% (data not shown).

Pre-pregnancy BMI and GWC also interacted with an effect of 0.012 for maternal BMI and an effect of 0.003 for the interaction. The strength of this interaction associated with the increase in offspring BMI among mothers who gained the most weight during pregnancy and had the highest pre-pregnancy BMI. From this last model, we can calculate the contribution maternal BMI makes to low and high GWC, for example when the GWC= 5 or the weight gain is 20 kg. If we focused on the effect of an obese mother versus that of a mother with normal pre-pregnancy BMI on offspring BMI, the effect of an increase in pre-pregnancy maternal BMI (from 20 to 35) of 15 units if the weight gain is 5 kg results in an increase of 0.41 BMI units\((0.012*15+0.003*15*5= 0.41)\) in the offspring, and the effect of an increase in pre-pregnancy maternal BMI from (20 to 35) of
15 units if the mother’s weight gain is 20 kg results in an increase of 1.08 BMI units 
(0.012*15+0.003*15*20 = 1.08).

Parental obesity may increase the risk of obesity through genetic mechanisms or through 
shared characteristics in the family environment such as food preferences and intake. The 
foetal over-nutrition hypothesis is relevant to the effect of maternal BMI and weight 
change during pregnancy on offspring BMI. One way to investigate if the association 
between pre-pregnancy maternal BMI is due to the intrauterine environment is by 
comparing the parental-offspring association of BMI, using pre-pregnant parental BMI. 
Such comparisons have been carried out in a few studies but with mixed results indicating 
a greater maternal-offspring association of BMI in some studies, whereas other 
studies did not support these differences. A study from MoBa by Fleten et al. showed a 
similar association in the parental-offspring association of BMI at 3 years of age, indicating that the association is likely to be explained by shared family risk factors. 
Our DAG (Figure 3) suggests that paternal BMI may be a confounder for the maternal- 
offspring BMI association. This was confirmed by the detection of a strong confounding 
effect for parental BMI and shows that results could be biased by not including pre- 
pregnant paternal BMI (Table 3).

**Table 3.**
Comparing the effect of maternal pre-pregnancy BMI on child BMI at 3 years in study sample 1 
and in study sample 2. Also shown is the effect of adjusting for pre-pregnancy paternal BMI in sample 2. 
The missing data in column 1 is due to no data available for paternal BMI in sample 1. 
Other cofactors are as in model 1 in table 2.

<table>
<thead>
<tr>
<th>Pre-pregnant maternal BMI (kg/m²)</th>
<th>Study sample 1</th>
<th>Study sample 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=31 169</td>
<td>N=5898</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.037</td>
<td>0.041</td>
</tr>
</tbody>
</table>

In studies that specifically addressed the effects of maternal pre-pregnancy BMI and/or 
GWC during pregnancy on offspring overweight/obesity in children, only Oken et al. included pre-pregnancy paternal BMI data, which was divided into > 25 and 
< 25 BMI units. Our results support the conclusions of the Oken et al. and show that
offspring BMI at 3 years of age increases by 0.13 BMI z score units for every 5 kg increase in GWC after adjusting for parental BMI.

In addition, adjusting for several potential postnatal explanatory variables (breastfeeding, media, daycare) appeared to have little or no impact on the strength of the associations.

As obesity rates among childbearing women continue to rise, the findings that both maternal pre-pregnancy BMI and GWC are positively associated with offspring BMI acquire importance.

Preventing maternal overweight and obesity before pregnancy and encouraging woman to maintain a healthy weight during pregnancy should be made a public health priority. Although we still have not found the best way to prevent childhood obesity, the data in this study suggest that antenatal healthcare should be directed towards encouraging a healthy lifestyle within the context of the whole family.

6.1.3 Duration of sleep in infancy and BMI of the child at 3 years of age (Paper III).

This large population-based study indicated that the duration of sleep in infancy does not associate with BMI at 3 years of age.

This is one of the first population-based studies that estimated the associations between sleep duration in 6- to 18- month-old children and offspring BMI later on life. The size of the study enabled us to separately assess the association between duration of sleep in children aged 6 and 18 months and offspring BMI.

Prospective studies have tested the hypothesis that short sleep duration at baseline predicted weight gain or incidence of obesity over the follow up period36,89-93,139,140, but it has been difficult to establish a causal association77,87,88. However, only a few studies have addressed the effect of sleep duration in early childhood on overweight or obesity later in life36,91,94,139. One concern is that publication bias may have precluded negative longitudinal associations from being published. Of the longitudinal studies36,90-94, only two small studies91,94 have included sleep duration in children aged younger than 2 years as an exposure. The study of Taveras et al.91 of 915 infants found that compared to infants sleeping more than 12 hours, those with less than 12 h sleep at age 6 months, 1 year and 2 years had approximately 5% higher sums of subscapular and triceps skinfold thickness at
3 years of age. This is a smaller effect size than the one described by Diethelm et al.\textsuperscript{94} whose study of 481 participants revealed a 14% difference in the sum of these skinfold thicknesses at age 7 between children who had consistently long (> 13 h) and consistently short (<13 h) sleep durations at 1.5 and 2 years of age. However, in the study of Diethelm et al. the effect of short sleep duration was not statistically noticeable for the trajectories of BMI. However, in our study the group with the shortest sleep duration tended to have a lower variance and hence fewer children with very high BMIs. Additionally, no linear associations were found in studies involving younger children\textsuperscript{36,90,92}, similar to our study.

The reason for the differences between our findings and those reported by others are not clear.

The review from Horne et al.\textsuperscript{88} raises many questions. For instance, prevalence of overweight/obesity varies between studies reporting < 10 hours sleep\textsuperscript{79,80}, showing the prevalence to be about double\textsuperscript{79} in children reporting < 10 hours sleep compared to those reporting > 10 hours of sleep. Furthermore by dichotomy of sleep duration both of these factors could lead to over-generalisations in the link between short sleep and obesity. It is also possible that the mixed results seen in observational studies are secondary to the well known methodological challenges of activity and dietary assessment or other age dependent confounding effects on obesity.

Our study sample also featured a normal distribution on the population axis and consisted of mostly normal weight children; however, when only the overweight/obese children were analysed for an association between sleep duration and BMI at 3 years of age, the findings remained essentially unchanged (data not shown).

Currently, a decrease in the sleeping hours of children and adults concords with the high incidence of obesity today\textsuperscript{8}. The review of Montasa et al.\textsuperscript{87} concluded that short sleep duration was a factor in obesity. Additionally, Nilsen et al.\textsuperscript{77} noted that it was difficult to establish a causal association because the association between sleep duration and the development of obesity appears to be weak and slowly emerging; consequently, reliable estimation requires that large groups of people are followed up over long time periods.

This large population-based study does not support the hypothesis that less sleep during infancy increases BMI at 3 years of age.
6.2 Methodological strengths and limitations

Considering of methodology

The validity of a study is usually separated into two components: internal validity refers to the accuracy of the estimates for the study sample while the external validity refers to the accuracy of the estimates for the people outside the study sample (also named generalizability)\textsuperscript{141,142}. In studies of causation it corresponds to accurate measurement of effects apart from random variation, and internal validity is a prerequisite for the external validity. Errors in the estimation of prevalence and associations in epidemiological studies are traditionally classified as random or systematic\textsuperscript{141,142}. Random error leads to loss of precision whereas systematic errors represent a threat to the validity of the results. Selection bias, information bias and confounding are the main sources of systematic errors. Lack of precision in measurement and inadequate sample size are the main sources of random error\textsuperscript{142}.

Strengths

The MoBa cohort is a large population-based study with a prospective design. The majority of pregnant women in Norway were invited to participate through a postal invitation in connection with a routine ultrasound examination that is offered to all pregnant women in Norway at 17-18 weeks of gestation (www.fhi.no/morogbarn). A cohort study can provide a comprehensive picture of health effects emanating from a given exposure, and the large sample size can provide sufficient power to estimate associations, even for small effects. In addition, MoBa contains extensive questionnaire data with detailed information on maternal, paternal and child health, socio-economic factors, child development, nutrition and environmental exposures before, during and after pregnancy, and made it possible to control for confounding. The prospective design and broad recruitment decrease the risk of recall bias. The study is linkable to MBRN. The size of the study enabled us to assess separately the effects of maternal pre-pregnancy BMI and weight change during pregnancy on birth weight and offspring BMI at 3 years of age for different categories of pre-pregnancy BMI, including obesity class I–III. Another major strength of this study were repeated measurements on sleep duration at age 6 and 18 months, a period covering a vulnerable window where short or consistently short sleep duration in early life may reflect a greater susceptibility to the biological effects.
Limitations

Selection bias and loss to follow up

Selection bias is distortions that result from procedures used to select subjects and from factors that influence study population. Selection bias may affect prevalence rates by showing rates which are not representative for the entire population\textsuperscript{142}.

The target population of the MoBa cohort was all pregnant women in Norway, and the participation rate was 44\% in version 4 and 42\% in version 5. There is a skewed self selection of women regarding several characteristics as participating women tend to have a slightly different age distribution a higher level of education, lower parity and smoke less compared with the Norwegian source population of pregnant women\textsuperscript{9}. This may result in selection bias and therefore our results may underestimate the effect of education. This may indicate that participants in MoBa are more health oriented than non-participants, although not all characteristics or exposure levels differ. Breastfeeding practices between MoBa participants and other children do not show apparent differences\textsuperscript{143}. Although it is likely that there is a socioeconomic gradient that influences prevalence estimates, also reflected in the lower rates of preterm birth and lower birth weight, the estimates of association can still be valid\textsuperscript{10}.

The questionnaires in MoBa are extensive. While not all mothers returned questionnaires, those returning follow up questionnaires may have differed from those who choose not to return questionnaires. In Paper I, the response rate among participating women who received questionnaires during pregnancy was approximately 93\%. However, in Papers II and III, the response rate among participating women was 94\% to the first questionnaire at gestational age 17 (Q1) and to the third questionnaire at gestational week 30 (Q3) during pregnancy. The response rate for the questionnaire sent out when offspring were 3 years of age (Q6) was 61\%. In Papers II and III, any selection at inclusion and loss of participants until 3 years of age could have influenced the composition of the study population. Loss to follow up seemed to increase as children got older. The distribution of women who responded to all questions could be different in each BMI category and alter the results. In the first paper we excluded approximately 5.4\% of the participants due to incomplete information; however, the distribution of missing values was approximately the same (about 5\%) in each BMI category for maternal weight and height, and for education it was only 0.4\%.
**Information bias**

Information bias can occur by measurement errors in the needed information of study variables and caused by errors in the collecting, recording, coding or processing of data\textsuperscript{142}. For discrete variables measurement errors is usually called classification error or misclassification. Classification error of measurement which depends on the value of other variable is called differential misclassification. Additionally, if classification error does not depend on other variables is called non differential misclassification\textsuperscript{142}.

Pregnant women may be unwilling to answer stigmatising questions or underreport levels of unwanted exposure. Likewise, some may over-report more publicity desirable exposure.

Information about pre-pregnancy BMI for mother, father, weight change in pregnancy, and child reported weight and height at 3 years of age was self-reported. Inevitably, it was prone to some misclassification due to under- or over-reporting of weight and height. Self-reported measurement of weight varies with socio-demographic characteristics and BMI. Overweight women tend to underestimate, whereas underweight women tend to overestimate it\textsuperscript{144}. Additionally, the validity of self-reported weight and height shows that women tend to underestimate weight and to overestimate height\textsuperscript{68}, although the overall validity of these reports in reproductive women is found to be good\textsuperscript{145}. When calculating BMI the tendency to underestimate weight increases with weight, and is greatest among obese women\textsuperscript{145}.

This could lead to a negative bias with a systematic misclassification of increased BMI into lower BMI categories. However, most studies on maternal pre-pregnancy weight and maternal weight change are based on self-reported weight, and validation studies have showed that self-reported weight may be adequate to use in large population-based epidemiological studies\textsuperscript{144}.

Total weight gain is a common indicator in the literature of pregnant women, determined by subtracting initial gestational weight from the weight in late pregnancy\textsuperscript{144}. It is then crucial to certify that weight gain was calculated from the last measurement during pregnancy, ensuring that women did not gain additional weight after that. If the gestational duration was 37 weeks, and total weight was calculated by week 32, the association could be underestimated. Hence in MoBa weight was reported in
questionnaire three (Q3) around gestational week 30. In the fourth (Q4) questionnaire when the child was 6 months old the mother was asked about weight at delivery of the offspring. The total weight gain during the first trimester is relatively small and non-linear, and increases significantly and reaches a peak in the second trimester. By limiting weight gain to 30 weeks of gestation and including complete data only on full-term births at gestational week 37 and beyond, our findings were not distorted by contributing to preterm delivery or weight of accumulating body fluids such as those leading to edema as frequently happens in the last trimester.

Measurements errors, for example, random measurements inaccuracies of height and weight may also occur in misclassification due to under- or over-reporting in children; however, in a recent prevalence study regarding overweight and obesity in Norwegian children, there were no significant differences in the analyses of self-reported height and weight between participants and non-participants. Including paternal BMI in paper II reduced the study sample from 31 169 to 5 898 and could have introduced some selection bias seen by comparing the two crude estimates. The demographic characteristics in the large study sample 1 differ from those of the smaller study sample 2, including paternal BMI. In study sample 2, the mothers had a slightly lower maternal pre-pregnancy BMI, gestational weight gain and a higher education. They also had a tendency towards nullipara, were older, smoked less, more frequently exercised, breastfed more and more frequently used day care in kindergarten than mothers in study sample 1.

In addition, the fathers seemed to have a slightly decreased BMI distribution of obesity compared with the total Norwegian male population. We demonstrate the importance of including the father in this type of study and suggest that findings could be biased by not including paternal BMI.

Maternal smoking during pregnancy represents a variable particularly prone to misclassification. Underreporting is more plausible than over-reporting; thus, misclassification of smoking status could underestimate the true effect of maternal smoking on birth size (paper I) and this could have biased our results.

Sleep duration in children aged 6 or 18 months may be reported inaccurately and reflect parental perceptions of sleep rather than sleep of the individual child per se. If pattern of
misclassification depend on the exposure status it could either exaggerate or underestimate true effects.

Confounding

The word confounding has a Latin origin meaning to mix together or confuse\textsuperscript{142}. Confounding occurs when all or part of the apparent association between the exposure and outcome is in fact accounted for by a third factor (or set of factors) that affect the outcome and are not themselves affected by exposure\textsuperscript{142}.

An important factor for causal interference is the possibility that the observed association between exposure and the effect is spuriously created, enhanced, reduced or eliminated because of confounding by another factor. In MoBa there is information available on many characteristics potentially linked to exposure and outcome. Based on a review of previous studies and an assumed possible underlying causal mechanism, we assessed covariates including plausible confounding factors using DAG. The possibility of non-measured confounding cannot be excluded. For example, women with lower SES may be prone to return infrequently to prenatal visits and this lack of information and exclusion could confound the results.

However, to decide whether a connected factor should be treated as a confounder or as an intermediate on the causal pathway was sometimes a challenge.

Maternal health problems during pregnancy may influence birth weight, and we attempted to address this by performing separate analyses to adjust for gestational diabetes, diabetes and preeclampsia, but the findings remained essentially unchanged.

Sex was a confounder for the birth weight-BMI association and it was also adjusted for. Gestational age and presence of complications during pregnancy had already been adjusted for by restricting of samples.

Deciding how to treat exercise was not straightforward due to the role with maternal BMI. Results from studies investigating the association between exercise and birth weight of the offspring have been inconsistent\textsuperscript{147-149}. It is though shown that overweight and obese women are less likely to exercise\textsuperscript{150,151}. In a recent study from MoBa, they show that the exercise-birth weight association diminishes by including maternal BMI\textsuperscript{152}, indicating differences in birth weight to be explained by other confounding variables.
rather than exercise. When we did not include exercise in the analyses the results remained unchanged (data not shown).

Energy intake is one part of the energy balance equation and it seems logical that dietary factors are one side of the rise in obesity prevalence. To follow food habits and food trends that may have implications for the later development of overweight or obesity is challenging. Numerous epidemiologic studies and clinical trials have investigated the role of dietary factors; however, the influence of these on body fatness is unclear\(^{153}\). In weighing up the advantages and disadvantages, the authors concluded that methodological issues in the dietary information can complicate the interpretation of results with measurements errors in dietary assessment as well as residual and unmeasured confounding.

The distinction between a confounder and a mediator can be difficult and will often leave the interpretation of the results open. Considering the sleep duration-offspring association, short sleep duration may operate by increased caloric intake because of enhanced appetite (e.g., short sleep duration is related to a hormonal imbalance with decreased levels of leptin, glucose intolerance and insulin sensitivity, but with increased levels of ghrelin, hunger and appetite) and by more opportunities to eat, and/or by reduced energy expenditure because of reduced temperature and increased fatigue, leading to less physical activity. If this is the way short sleep duration works, adjustment for any of these components on the pathway in the analyses will block the opportunity to show that short sleep duration is in fact associated with weight gain and later obesity through that particular pathway. To overcome this, we applied five different models. We studied the unadjusted association between sleep duration at 6 months or 18 months of age and offspring BMI at 3 years of age. We also adjusted for the maternal confounders and gender in both models. In a last model, we added several combinations of sleep duration at 6 and 18 months of age as the exposure and adjusted for maternal confounders and gender. Additionally, adding other potential postnatal confounders such as breastfeeding at 6 months, day care and media consumption at 3 years of age to the models did not alter the results except from sleep habits in infants with < 12 h sleep at 6 months and > 12 h sleep at 18 months, which became non-significant (data not shown).

There is epidemiological evidence that overweight and obese mothers are less likely to breastfeed than normal weight women\(^{154,155}\), and we included maternal pre-pregnancy
BMI in the different models in paper III to detect underlying confounding structures related to early introduction of solids in infants; however, these results remained unchanged (data not shown).

**Generalisations**

The exposures in our thesis are thought to act through biological and environmental effects and to interact with each other with genetic susceptibility. Participants in MoBa may differ from non-participants in some ways; for example, mothers in MoBa smoke less than the general population. Even if the exposure level differs between the participants and non-participants, association between exposure and outcome may have the same size as in the population in general\textsuperscript{10}.
7. CONCLUSIONS AND FUTURE PERSPECTIVES

The main findings in this thesis were:

**Paper I**

Offspring birth weight increased with both increasing maternal pre-pregnancy BMI and maternal weight gain during pregnancy in all six categories of maternal pre-pregnancy BMI. Women with the highest level of education had the highest offspring birth weight.

**Paper II**

This large population-based study showed that both maternal pre-pregnancy BMI and GWC were positively associated with mean offspring BMI at 3 years of age. Pre-pregnancy BMI and GWC also interacted, and the strength of this interaction associated with the increase in offspring BMI among mothers who gained the most weight during pregnancy and had the highest pre-pregnancy BMI. Our findings show that results could be biased by not including pre-pregnancy paternal BMI.

**Paper III**

The results of this large population-based study indicate that there is no association between duration of sleep in infancy and BMI at 3 years of age.

The regulation of body weight and adiposity is a complex process that involves genetic, environmental, behavioural, psychosocial and endocrine/regulatory factors. Both excess and reduced nutrient availability during foetal development can give rise to later development of obesity. However, little is known about weight development across the earliest years of life, and few studies have particularly assessed the association between maternal BMI and weight gained during pregnancy and a future risk of overweight/obesity in children\(^2,33,71\).
It is difficult to draw conclusions; however, the findings in this thesis support the theory that the prenatal period is associated with offspring weight and BMI.

Ultimately a complete understanding of the rising tide of obesity in children and adults will require a careful explication of the complex manner in which genes and environment interact. Further research in this area relating to what extent different maternal BMI and weight change for women in these findings are pertinent to children later in life could potentially reduce the prevalence of obesity.

We want to expand the project to a follow up of the children at 7 and 10 years of age. No large population-based pregnancy cohorts have previously investigated the association between maternal pre-pregnancy BMI and different patterns of GWC and offspring BMI at age 7. Furthermore, there are no previous large population studies that have examined a plausible effect of duration of sleep during early childhood on childhood BMI at age 7, and research is endorsed to study the causal roles in the association between duration of sleep in infancy and BMI in children.

To examine how different contexts (socio-economic factors, family and child characteristics, diet and physical activity and inactivity) interact in the complex multi-factorial aetiology of childhood overweight would add important knowledge to our understanding of the aetiology of childhood obesity.
8. REFERENCES


143. Häggkvist A. Breastfeeding practices and factors influencing breastfeeding in the Norwegian Mother and Child Cohort [Master thesis]. Oslo: The Medical Faculty, University of Oslo; 2006.


9. PAPER I - III