Maternal weight, weight change and perinatal outcomes:

Can physical activity and gestational weight gain modify the risk?

Linn Marie Sørbye

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2019

UNIVERSITY OF BERGEN

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Date of defence: 08.02 2019

Year: 2019

Title: Maternal weight, weight change and perinatal outcomes:

Name: Linn Marie Sørbye

Print: Skipnes Kommunikasjon / University of Bergen

Contents

Scientific environment

The work in this thesis has been carried out in the Research Group for Reproductive Epidemiology with a Lifecourse Perspective at the Department of Global Public Health and Primary Care, and at the Department of Clinical Science at the Medical Faculty, University of Bergen.

The work was founded by a three year scholarship from the Norwegian National Advisory Unit on Women's health at Rikshospitalet, Oslo University Hospital.

Main supervisor has been Professor Nils-Halvdan Morken at the Department of Clinical Science, University of Bergen and the Department of Obstetrics and Gynaecology, Haukeland University Hospital.

Professor Kari Klungsøyr and Professor Rolv Skjærven at the Department of Global Public Health and Primary Care have been co-supervisors.

During this PhD work I have been affiliated to the Western Norway University of Applied Sciences, and an affiliate member of the National Research School in Population Based Epidemiology (EPINOR).

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Oslo University Hospital

Western Norway University of Applied Sciences

EPINOR

Acknowledgements

Many people have made valuable contributions to this work. I would like to express my gratitude to each and every one of you. I would like to thank Oslo University Hospital and the Norwegian National Advisory Unit on Women's Health, for financing this project with a three year fellowship.

The greatest thanks goes to my main supervisor Nils-Halvdan Morken for inviting me in the first time I knocked at his door and for having trust in me from the start. I highly appreciate your enthusiasm, solution oriented thinking, your interest in discussing research and for the time you have invested in me. I am grateful to my supervisors Kari Klungsøyr and Rolv Skjærven. To Kari for her guidance and support, through her sharing of experience and advanced knowledge in perinatal epidemiology, medical birth registry data and methodology. To Rolv Skjærven for bringing in his wealth of research experience in registry based epidemiology and family-data, knowledge in advanced statistics, enthusiasm and creativity. The contributions of the three of you have been extremely valuable.

I am grateful to my co-author Oddrun Samdal for sharing her knowledge in health promotion. To Sven Cnattingius and Anna-Karin Wikström for making my dream of analysing Scandinavian data come true and for their valuable contributions to paper III. A great thanks to Katrine Owe for sharing her expertise on physical activity, and I highly appreciate the energy, laughter and sharing of enthusiasm in women's health. I am grateful to Jannicke Igland for her statistical support in STATA and for helping me with the magical syntaxes.

Participating in our weekly research group meetings has enriched me and I would like to express my gratitude to Lorentz Irgens, Kjell Haug, Frode Halland, Hilde Engjom, Tor-Arne Hegvik, Lisa deRoo, Aleksandra Pirnat, Sjur Lehmann and Johanne Instanes. I am indebted to my close colleague and room mate Liv Grimstvedt Kvalvik for her enthusiasm in research, generosity, care, and for her contributions to paper III. I highly appreciate Berit Skretting Solberg for her valuable friendship, encouragement and understanding.

I feel priveliged to having been surrounded by the skilled scientific staff at the Department of Global Public Health and Primary Care and would like to express my gratitude to all professors, post docs and to the research community of PhD candidates. Thanks to Trond Riise and Guri Rørtvedt for their visibility, interest and caring for PhD candidates. Thanks to Mette Tollånes for her help, inspiration and encouragement in research. Being a part of the EPINOR research group has been inspiring and I have appreciated all discussions and friendships with the other PhD candidates. Especially I would like to thank Ingeborg Forthun for her friendship and for sharing her research and thoughts with me.

Thank you to Siri Vangen, Pernille Frese and my other colleagues at the Norwegian National Advisory Unit on Women's health at Rikshospitalet, for your priority on women's health and for inviting me to be a part of your research environment.

I am grateful for all flexibility and support from the Western Norway University of Applied Sciences, and especially to my colleagues at the Midwifery Education: Vigdis Aasheim, Katrine Aasekjær, Anne-Britt Vika Nilsen, Erica Schütt, Bodil Molander Dale, Anne Brunstad, Gunn Terese Haukeland and Eline Skirnisdotter Vik. I would like to thank Roy Modini Nielsen for valuable research discussions and for sharing his enthusiasm in reproductive health.

To my colleagues at Kvinneklinikken in Bergen for their support and for facilitating my research, especially to Ingrid Johanne Garnes and Kristin Boge. Thanks to Ragnhild Johanne Sekse, Sissel Thunes, Jorunn Thunestvedt and Bente Langeland. I am grateful to the Clinical Research Unit at Helse-Bergen for their initial funding, to the research community of PhD candidates, and to Tone Norekvål for providing me with advice and inspiration. Thanks to statistician Karl Ove Hufthammer for his contributions to paper I.

I would like to express my gratitude to the Scandinavian midwives Ellen Nøhr, Ellen Blix and Ulla Waldenström, who clearly have inspired me through their research. I highly admire their work and the courage they have shown. Especially thanks to Ellen Nøhr for being my mentor through these years.

A special thanks to my dearest family and friends. To my parents Kerstin and Trond for always believing in me. To my sister in law Ingvil for all the interesting research discussions we have had.

Finally, I would like to thank Halfdan, the love of my life, for his endless love, support, patience, and for always believing in me. To my gracious daughters Sunniva and Aurora who are my joy and inspiration. Because you are always in my mind, you have been present during the elaboration and writing of this work.

For me this is the end of an incredible journey. Inspired by knowledge and experience I would like to think of a woman's labour as a metaphor for this fantastic and overwhelming, but at the same time strainful and exhausting work. It is all about accepting that you do not know where you are going, to withstand the pressure, dispair and pain of no managing, to surrender, show your vulnerability, to empower, mobilising strength, and most of all patience. Parallel to these feelings, you have the beautiful and overwhelming feeling of an adrenalin kick, flying, and coping. I can still recall the feeling an early morning 17th of May 2017 when submitting my second paper at 5.40 in the morning after working all night long. Easy walking up Kalfaret to the beat of drums from the boys' brigade with a sense of relief, hope and the feeling of coping. Fulfilling this thesis fills me with the same feelings and I know that now I am able to do anything.

Thesis at a glance

Photo: Colourbox.com

Paper I

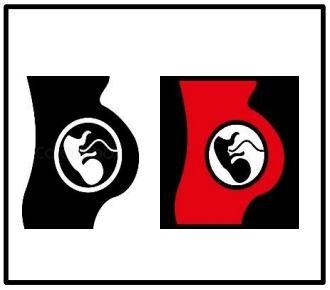
Question: Is there an association between prepregnant body mass index (BMI) and perinatal mortality? Does physical activity modify the association?

Period: 1999-2008

Study population: 77,246 singleton pregnancies in the Norwegian Mother and Child Cohort Study

Exposure: Prepregnant BMI, physical activity

Outcome: Perinatal mortality



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Paper II

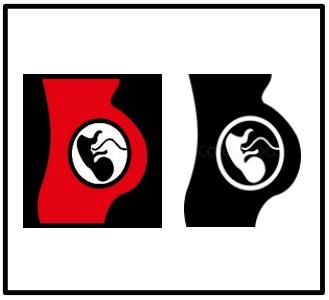
Question: Is there an association between interpregnancy weight change and gestational diabetes mellitus? Does prepregnant BMI in first pregnancy and gestational weight gain in second pregnancy modify the association?

Period: 2006-2014

Study population: 24,198 mothers with their first and second pregnancy in the Medical Birth Registry of Norway

Exposure: Interpregnancy weight change, gestational weight gain

Outcome: Gestational diabetes mellitus



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Paper III

Question: Does weight loss from first to second pregnancy reduce recurrence of gestational diabetes mellitus?

Period: 1992-2010 (Sweden) and 2006-2014 (Norway)

Study population: 614,432 women with their first and second pregnancy in the Medical Birth Registry of Sweden and Norway

Exposure: Interpregnancy weight change

Outcome: Recurrence of gestational diabetes mellitus

Abstract

Background: Maternal overweight and obesity increase the risk of complications during pregnancy and childbirth and are a threath to reproduction. It is of major importance to identify factors that have the potential to reduce the risk of perinatal complications associated with maternal overweight and obesity.

Aims: (I) To investigate the association between maternal prepregnant body mass index (BMI) and perinatal mortality, and further to evaluate if physical activity during pregnancy modifies the association. (II) To investigate the risk of gestational diabetes mellitus (GDM) in second pregnancy by change in prepregnant BMI from first to second pregnancy, and whether BMI in first pregnancy and gestational weight gain (GWG) in second pregnancy modify the risk. (III) To estimate the association between weight change from first to second pregnancy and recurrence of GDM.

Material and Methods: (I) We analyzed 77,246 singleton pregnancies in the Norwegian Mother and Child Cohort study (1999-2008), with linked data from the Medical Birth Registry of Norway (MBRN). (II) In data from the MBRN we investigated 24,198 mothers with first and second pregnancies during 2006-2014, without GDM in first pregnancy. (III) Recurrence risk of GDM was analysed in 2,763 women with GDM in their first pregnancy, and who delivered their first and second child during 2006-2014 in the MBRN and 1992-2010 in the Medical Birth Registry of Sweden.

Results: (I) An increased risk of perinatal death was seen in obese (odds ratio (OR) 2.4, 95% CI (confidence interval) 1.7–3.4) and morbidly obese (OR 3.3, 95% CI 2.1–5.1), as compared to normal weight women. In the group participating in physical activity during pregnancy, obese women had an OR of 3.2 (95% CI 2.2–4.7) for perinatal death relative to non-obese women. In the non-active group the corresponding OR was 1.8 (95% CI 1.1–2.8) for obese women, compared with non-obese women. (II) Compared to women with stable BMI (-1 to 1 BMI units' change), women who gained weight between pregnancies had higher risk of GDM: Gaining 1 to 2 BMI units: relative risk (RR) 2.0 (95% CI 1.5-2.7), 2 to 4 units: RR 2.6 (95% CI 2.0-3.5), and ≥4 units: RR 5.4 (4.0-7.4). Risk increased both for women with BMI <25 and ≥ 25 in first pregnancy, although more strongly for the former group.

Overweight/obese women with an interpregnancy weight loss above 2 units had a 60% lower risk of GDM (RR 0.4, 95% CI: 0.2-0.8). GWG in second pregnancy did not modify the association. (III) Among women with overweight/obesity, recurrence risk of GDM decreased in those who reduced their BMI by 1-2 units (RR 0.80, 95% CI 0.65-0.99) and >2 units (RR 0.72, 95%CI, 0.59-0.89), and increased if their BMI increased by ≥4 units (RR 1.26, 95%CI 1.05-1.51), compared to those with stable BMI. Among women with BMI<25, the risk of GDM recurrence increased if their BMI increased by 2-4 units (RR 1.32, 95%CI 1.08-1.60) and ≥4 units (RR 1.61, 95%CI 1.28-2.02).

Conclusions: (I) Prepregnant obesity was associated with a two- to three-fold increased risk of perinatal death when compared with normal weight. For women with BMI below 30, the lowest perinatal mortality was found in those performing physical activity, however, for obese women the lowest risk was found in the non-active group. (II) The risk of GDM in second pregnancy increased by increasing interpregnancy weight gain, and more strongly among women with BMI <25 in first pregnancy. Overweight/obese women with an interpregnancy weight loss, had a 60% lower risk of GDM. (III) Weight loss >1 BMI unit from first to second pregnancy reduced the risk of GDM recurrence by 20-28% in overweight/obese women. Weight gain between pregnancies increased recurrence of GDM in both normal and overweight/obese women.

Implications: Prepregnant BMI and interpregnancy weight change are both important to perinatal outcomes. A population strategy approach should promote healthy weight in the reproductive population from before conception and throughout the interpregnancy window. Overweight/obese women with GDM in first pregnancy, should be systematically followed up to regain a healthy weight prior to their second pregnancy. Further research on physical activity in obese women is warranted, to evaluate if guidelines on physical activity may need to be customised to obese women. In order to evaluate the role of GWG, weight at the time of the GDM diagnosis should be systematically registered in the medical birth registries.

Key words: BMI, overweight, obesity, interpregnancy weight change, gestational weight gain, physical activity, effect modification, perinatal mortality, GDM, recurrence.

List of Publications

This thesis is based on the following original research papers, which will be referred to by their Roman numerals.

I. Sorbye LM, Klungsoyr K, Samdal O, Owe KM, Morken NH. Prepregnant body mass index and recreational physical activity: effects on perinatal mortality in a prospective pregnancy cohort. BJOG. 2015;122(10):1322-30.

II. Sorbye LM, Skjaerven R, Klungsoyr K, Morken NH. Gestational diabetes mellitus and interpregnancy weight change: A population-based cohort study. PLoS Medicine. 2017;14(8): e1002367.

III. Sorbye LM, Cnattingius S, Skjaerven R, Klungsoyr K, Wikström AK, Kvalvik LG, Morken NH. Weight change between pregnancies and recurrence of Gestational diabetes mellitus. (In Manuscript)

Abbreviations

Adj	Adjusted
BMI	Body mass index
CI	Confidence interval
DAG	Directed acyclic graph
GDM	Gestational diabetes mellitus
IOM	Institute of Medicine
MBRN	The Medical Birth Registry of Norway
MBRS	The Medical Birth Registry of Sweden
MoBa	The Norwegian Mother and Child Cohort Study
Kg/m^2	Kilo per meter squared
OGTT	Oral glucose tolerance test
OR	Odds ratio
p	p-value
Ref	Reference
RCT	Randomised controlled trial
RR	Risk ratio
WHO	The World Health Organization

1. INTRODUCTION

Since the 1980's the global prevalence of overweight and obesity has reached epidemic proportions,[1] and in 2001 The Surgeon General issued a *Call to action* recognizing obesity as a major public health concern.[2] In the general population, obesity has been associated with morbidity and mortality[3,4] and according to the Chief Medical Officer in the United Kingdom (UK), the obese epidemic represents the greatest threat to women's health.[5]

Obesity has adverse consequences for reproductive health, as it increases the risk of adverse otcomes in mother and offspring during pregnancy, childbirth, postpartum, and in the newborn child.[6-9] Maternal body mass index (BMI) is found to be a strong risk factor for perinatal mortality[10,11] and for gestational diabetes mellitus (GDM).[9,12] Children born to women with GDM may further have an increased risk of high birthweight,[13] and overweight in adolescence,[13] indicating a possible inter-generational effect due to genetic or persisting social and environmental factors. Both prepregnant BMI and gestational weight gain (GWG) are associated with adverse outcomes, but evidence for an independent or joint effect is inconsistent.[14,15] Recent studies have identified interpregnancy weight change to be associated with adverse outcomes in pregnancy and childbirth, however, evidence is not consistent as to this representing an independent risk factor or is dependent on maternal BMI in first pregnancy.[16-18]

The high prevalence of overweight and obesity imposes a considerable economic burden to society, as women with overweight and obesity make greater use of health care services in connection with childbirth.[19-22] It is a health priority to identify factors that may counteract the negative consequences of overweight and obesity, in order to reduce complications in pregnancy and childbirth. Physical activity during pregnancy is likely to enhance cardiovascular function, mitigate dyslipidemia associated with pregnancy, and have a disease preventive effect.[23] Moderate GWG may reduce maternal and fetal adverse otcomes.[15,24] This thesis investigates the importance of maternal weight and maternal weight change on risk of perinatal

mortality and GDM in population-based cohort studies in Norway and Sweden. It further seeks to explore the potential modifying roles of prepregnant BMI, GWG and physical activity. Knowledge from this thesis will be important in prevention and treatment of overweight and obesity among women of reproductive age.

1.1 Body mass index and interpregnancy weight change

Body Mass Index

BMI describes a person's weight relative his/her height, and is calculated as weight in kilograms (kg) divided by height in meters squared (m^2).[25] BMI is expressed in units BMI (kg/ m^2), and according to the World Health Organization (WHO), there is an international consensus on the categorisation of BMI (see Table 1).

Table 1. Categorization of body mass index (BMI) according to the the World Health Organization (2000).[25]

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Obese class I	30.0-34.9
Obese class II	35.0-39.9
Obese class III	≥40.0

Overweight and obesity can generally be explained by an energy imbalance, where energy input exceeds energy output, and over time may develop into overweight.[26] BMI is an indirect measure of body fat, and is not a perfect measure of adiposity as it does not take into account age, sex, bone structure, fat distribution or muscle mass.[27]

However, BMI is found to be correlated with total body fat for the majority of individuals, and it is regarded a valid measure of body fat at the population level.[28]

The international consensus on a graded classification of overweight and obesity identifies individuals and groups at increased risk of morbidity and mortality.[25] The consensus builds on the evidence of a well known association between overweight/obesity and all-cause mortality.[3,4]

Interpregnancy weight change

Interpregnancy weight change is defined as BMI in second pregnancy minus BMI in first pregnancy.[16,17] Dependent on the time of reporting BMI, BMI may represent prepregnant BMI,[29] or BMI reported at the first antenatal visit.[16] Interpregnancy weight change is expressed in BMI units (kg/m^2). One BMI unit is relative the person's height, and is equivalent to approximately 2.7 kg in a woman who is 1.65 meters tall (see Figure1).

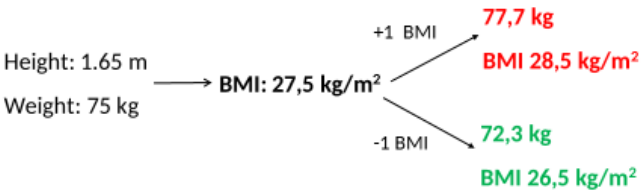

Figure 1. An example of change in 1 body mass index (BMI) unit.

1.2 Prevalence and trend in overweight and obesity

Prevalence

Since the 1980's the worldwide prevalence of overweight and obesity has reached epidemic proportions, causing a major public health concern.[1,30] During 1980-2013, the proportion of women with BMI ≥25 has increased globally from 29.8% to 38.0%.[1] The greatest increase was seen in the years 1992-2002, and was most pronounced for the age group 20-40 years.[1] An annual report from the UK in 2013 revealed that 54% of women aged 34-44 years were classified as overweight or obese.[5] Of 48,553 women who were registered in the Medical Birth Registry of Norway (MBRN) in 2017 and had their prepregnant BMI reported (85.9% reported BMI), 34.3% were overweight or obese (22.1% overweight, 12.2% obese), 61.6% normal weight and 4.1% were underweight.[31] The corresponding proportions reported in the Medical Birth Registry of Sweden (MBRS) in 2016, were 40.1% overweight or obese (26.0% overweight, 14.1% obese), 57.3% normal weight, and 2.6% were underweight.[32]

Trend

Since around year 2000 the trend in mean BMI in children and adolescents has plateaued in many high-income countries, albeit at high levels.[33] In Figure 2 we present mean BMI at the start of first and second pregnancy in our data from the MBRS (1992-2010) and MBRN (2006-2015). The BMI trend seems to reflect the international trend in overweight and obesity.[31,32] The Norwegian data report prepregnant BMI, while the Swedish data report BMI at first antenatal visit which is approximately week 15.

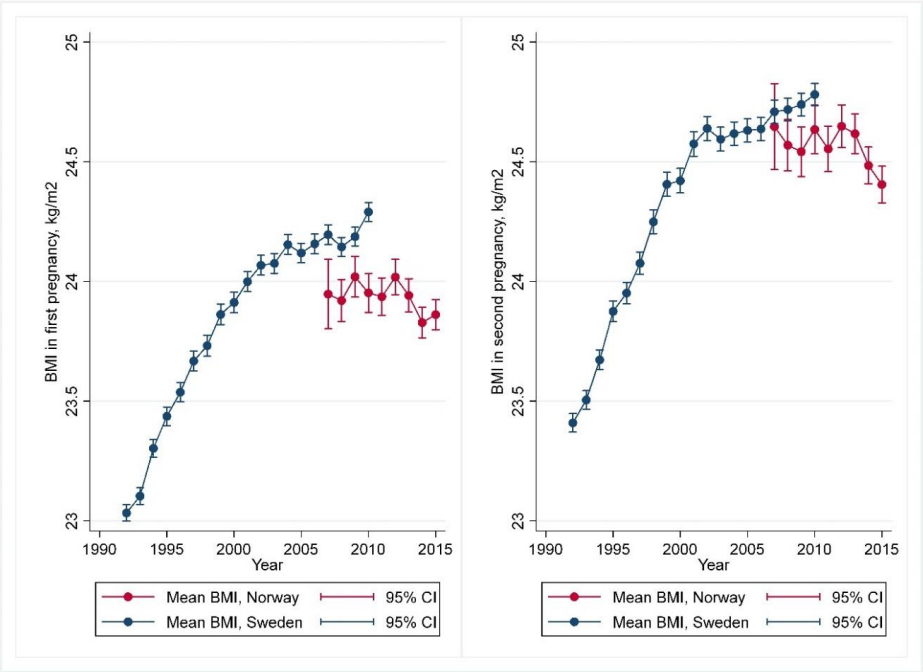

Figure 2. Mean body mass index (BMI) with 95% confidence interval (CI) in first and second pregnancy in data from the Medical Birth Registry of Sweden 1992-2010, and the Medical Birth Registry of Norway 2006-2015.

A longitudinal cohort study from the county of Nord-Trøndelag in Norway, has also revealed an increase in overweight and obesity in women of reproductive age.[34] (see Table 2)

Table 2. Prevalence (%) of overweight (25.0-29.9 kg/m^2) and obesity (≥30 kg/m^2) in women in the HUNT Study of Nord-Trøndelag County, Norway.[34]

Age (years)	HUNT1 (1984-86)		HUNT 2 (1995-97)		HUNT3 2006-08	
	Overweight %	Obese %	Overweight %	Obese %	Overweight %	Obese %
20-29	14.6	3.7	26.7*	10.1*	25.0	13.6**
30-39	19.0	6.0	30.5*	11.7*	31.0	20.3**

*P<0.05 between HUNT1 and HUNT2 **P<0.05 between HUNT2 and HUNT3.

1.3 Risk factors for overweight and obesity

Overweight and obesity are multifactorial and genetic, behavioural, and sociocultural characteristics are likely to explain its development.[25,35] There is a social inequality in overweight/obesity, with a well known inverse association between socioeconomic status (education) and obesity in high-income countries.[36-38] Overweight and obesity are found to be associated with a more sedentary lifestyle,[25,35] seem to increase with increasing age[38] and have a higher prevalence in the Afro-American and non-Hispanic race.[38]

1.4 Overweight and perinatal outcomes

Reviews of observational studies have found strong evidence for prepregnancy BMI to be an independent predictor for many adverse perinatal outcomes,[39,40] and with a strong dose-response association between maternal BMI and outcomes like perinatal mortality[10,11] and GDM.[12] Interpregnancy weight change is found to be associated with several adverse pregnancy outcomes both in women with BMI <25 and ≥25 in first pregnancy.[16,41] Research is not consistent, however, on whether the association between interpregnancy weight change and adverse outcomes is dependent on prepregnant BMI.[16,29,42] As temporal changes in weight are likely to change the risk of adverse perinatal outcomes, authors have suggested a potential causal relationship between overweight/obesity and the risk of adverse pregnancy outcomes.[16]

1.4.1 Perinatal mortality

Definitions

Stillbirth or fetal death is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy;

the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles.[43] (WHO, 2010)

According to the MBRN, a stillbirth is registered at gestational age ≥22 weeks or with birthweight ≥500 grams.[31] The stillbirth rate is calculated as number of stillbirths divided on the number of total births, and reported per 1000 total births. Stillbirths are further categorized as antepartum deaths if death occurs before the onset of labour, intrapartum death if death occurs during labour, and unspecified if timing of death is unknown/missing.[44]

Neonatal death is defined as death among live births during the first 28 completed days of life.[43] Neonatal death is further subdivided into early neonatal death which is death of a live born fetus during the first seven days of life, and late neonatal death after the seventh day but before 28 completed days of life.[43] The neonatal mortality rate is calculated as number of neonatal deaths divided by number of live births and expressed per 1000 live births.

The perinatal period commences at 22 completed weeks of gestation, and ends seven completed days after birth, and perinatal mortality comprises both stillbirths and early neonatal deaths.[43] Perinatal mortality is an indirect public health indicator reflecting women's health, maternity care and neonatal care, and has important implications for public health and clinical practice both at the national and international level.[45]

Despite the WHO definitions, there is no international consensus on the classification of stillbirths,[46] and the most common cut-off values for stillbirths are ≥20 gestational weeks, ≥22 (or birthweight ≥ 500grams), ≥24, and ≥28 gestational weeks.[10,47]

According to the American Academyof Pediatrics, three different classifications of perinatal mortality are used (see Table 3).[45]

Table 3. Definitions of perinatal mortality according to the American Academy of Pediatrics[45]

	Definitions of perinatal mortality	
	Stillbirth	Infant death
1.	≥ 28 weeks	< 7 days
2.	≥ 20 weeks	< 28 days
3.	≥ 20 weeks	< 7 days

In the following we will present results from studies investigating stillbirths, early neonatal deaths and perinatal deaths as the outcome, using several different definitions (see Table 4).

Incidence

Globally there are above 6.3 million perinatal deaths each year, and 98% occur in developing countries.[44] Perinatal mortality has improved remarkably since the 1940's in industrialized countries, and in Europe, USA and Canada perinatal mortality has decreased by 65-80% (particularly since the 1970's).[48] Early neonatal deaths have shown a greater decrease than stillbirths. Compared to other high-income countries, Scandinavian countries have a low perinatal mortality rate.[49] In a study investigating stillbirths over the past 20 years across 12 high-income countries, Norway had the lowest rate with 2.2 and the UK had the highest with 3.8 stillbirths per 1000 births.[50] In Norway perinatal mortality was almost halved, from 23 to 12 per 1000 births in the period 1967 to 1981, both for preterm and full-term births,[51] consistent with other Nordic countries.[52] We evaluated the trend of stillbirth, early neonatal deaths, and perinatal death in Norway from 1967-2015, presented in Figure 3.

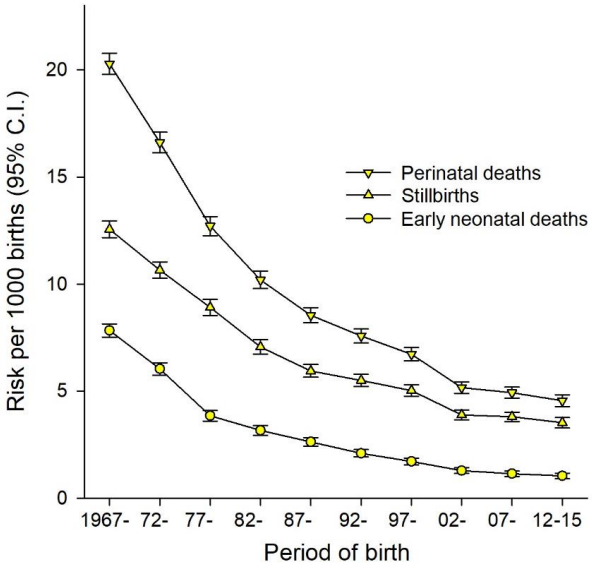

Figure 3. Occurrence of perinatal deaths, stillbirths, and early neonatal deaths in five-year categories, The Medical Birth Registry of Norway 1967-2015.

Risk factors

Stillbirths dominate the proportion of perinatal deaths by representing almost two-thirds.[51] Though stillbirth and early neonatal deaths share many common causes, they differ by congenital anomalies which are more common in early neonatal deaths.[44,48,53] In a review (18 countries), congenital anomalies accounted for a median of 7.4% of stillbirths.[54] The most common causes of stillbirths are fetal malnutrition, abruption placenta, congenital anomalies, infection, diabetes, umbilical cord accidents, and unexplained stilllbirths [46,55] The causes vary by gestational age, and unexplained stillbirth is the most common cause after 28 weeks gestation.[46,56] Unexplained stillbirths comprise 25% and have remained stable in spite of the decrease in stillbirth rate.[57,58] Even though the majority of stillbirths occur preterm, the risk of stillbirth increases with gestational age.[51,56]

The most important contributor to early neonatal death is immaturity followed by congenital anomalies.[59,60] Preterm birth is an important factor, with risk increasing as gestational age decreases with the highest risk for infants delivered before 28 weeks.[61] Obstetric complications before and during delivery, difficulties in adapting to extra-uterine life,[44] hemorrhages, and infections may cause early neonatal deaths.[59]

Maternal obesity is found to be one of the most prevalent risk factors for stillbirths,[46,47,57,62,63] and an important risk factor also for infant and neonatal mortality.[64] Advanced maternal age (≥35 years) increases risk of stillbirth, early neonatal death/ perinatal death,[55,65-67] and nulliparous women have a higer risk compared to multiparous.[47,68] Diabetes and hypertensive disorders (pre-existing and pregnancy induced) are associated with increased risk of stillbirth.[47] There is a social inequality related to stillbirth, demonstrated by an inverse association between maternal education and the risk of stillbirth,[69-71] and a body of evidence links smoking to stillbirth and infant mortality.[72,73] Unmarried,[74] and non-western women[75,76] constitute risk groups for stillbirth, infant death/perinatal mortality.

Maternal BMI and perinatal mortality

A meta-analysis revealed a crude odds ratio (OR) for stillbirth at 1.47 (95% confidence interval (CI) 1.08-1.94) in overweight women and 2.07 (95% CI 1.59-2.74) in obese women, compared to normal weight women[77] Another meta-analysis including more than 4,311 perinatal deaths in eleven cohorts (n=982,236), found that even a modest increase in maternal BMI was associated with increased risk of perinatal death per each 5 BMI unit increase (RR 1.16 (95% CI 1.00-1.35).[10] Findings were also present in strata of stillbirths and neonatal deaths. Table 4 presents the risk of stillbirths and early neonatal deaths by maternal BMI categories in previous studies.

Table 4. Studies examining maternal body mass index (BMI) and risk of stillbirth, early neonatal death, and noonatal death.

Paper	Design	Body mass index		Stillbirth		Neonatal death		Risk estimate
		Categories	Collected	Risk estimates	Defined	Risk estimates	Defined	
Cnattingius 1998[8] Sweden N=167,750	Population-based cohort Prospective	<20 20-24.9 25-29.9 ≥30	<15week	1.0 1.2 (0.9-1.7) **1.6 (1.1-2.3)** **2.6 (1.7-3.8)**	≥28w	1.0 1.1 (0.8-1.6) 1.3 (0.9-1.9) 1.2 (0.7-2.1)	0-7 day	OR (95% CI)
Stephansson 2001[72] Sweden N= 649+690	Population-based Case-control Prospective	≤19.9 20.0-24.9 25.0-29.9 ≥30	<15 week	1.0 1.2 (0.8-1.7) **1.9 (1.2-2.9)** **2.1 (1.2-3.6)**	≥28)			OR (95% CI)
Sebire 2001[78] United Kingdom N=287,213	Large unselected cohort Retrospective	20.0-24.9 25.0-29.9 ≥30	<20 week	1.00 1.10 (0.94-1.28) **1.40 (1.14-1.71**				OR (95% CI)
Cedergren 2004[11] Sweden N=805,275	Prospective Population-based cohort	19.8-26.0 29.1-35.0 35.1-40.0 >40	<15 week	1.00 **1.79 (1.59-2.01)** **1.99 (1.57-2.51)** **2.79 (1.94-4.02)**	≥28w	1.00 **1.59 (1.25-2.01)** **2.09 (1.50-2.91)** **3.41 (2.07-5.63)**	<7 day	OR (95% CI)
Kristensen 2005[79] Denmark N=24,505	Cohort study Aarhus University Hospital	<18.5 18.5-24.9 25.0-29.9 ≥30	Pre-pregnant	1.3 (0.7-2.6) 1.0 1.2 (0.6-2.2) **3.1 (1.6-5.9)**	≥28w	1.3 (0.5-2.9) 1.0 1.0 (0.4-2.2) **2.7 (1.2-6.1)**	1-28 day	OR (95% CI)
Nohr 2005[63] Denmark N=54,505	Danish National Birth Cohort Prospective data	<18.5 18.5-24.9 25.0-29.9 ≥30	Pre-pregnant	0.8 (0.3-2.2) 1.00 **2.0 (1.4-2.9)** **3.2 (2.0-4.9)**	≥28w			OR (95% CI)
Salihu 2008[80] USA N=1,405,698	Population-based Cohort study	18.5-24.9 30.0-34.9 35.0-39.9 ≥40	Pre-pregnant	NB Only in black race		1.0 1.1 (1.0-1.2) **1.2 (1.1-1.4)** **1.3 (1.1-1.5)**	0-6 day	HR (95% CI)
Khasan 2009[81] United Kingdom N=99,403	Population-based Cohort study	<18.5 18.5-24.9 25.0-29.9 30.0-40.0 >40.0	16 week	1.35 (0.83-2.19) 1.00 1.02 (0.82-1.28) 1.04 (0.79-1.37) 1.62 (0.90-2.90)	>24w	1.11 (0.54-2.28) 1.00 0.57 (0.39-0.82) 0.89 (0.61-1.30) 1.54 (0.72-3.31)	<28 days	RR (95% CI)
Tennant 2011[82] United Kingdom N=40,932	Cohort study 5 maternity units	<18.5 18.5-24.9 25.0-29.9 ≥30	Early pregnant	0.98 (0.42-2.25) 1.00 1.34 (0.94-1.89) **2.32 (1.64-3.28)**	≥20w	1.89 (0.73-4.88) 1.00 1.35 (0.79-2.32) **1.97 (1.13-3.45)**	1 year	OR (95% CI)
Ovesen 2011[7] Denmark N=369,347	Population-based Cohort study	<18.5 18.5-24.9 25.0-29.9 30.0-34.9 ≥35	Pre-pregnant	0.75 (0.53-1.06) 1.00 **1.39 (1.18-1.65)** **1.60 (1.27-2.01)** **1.86 (1.39-2.47)**	≥22w			OR (95% CI)
Johansson 2014[64] Sweden N=1,857,822	Population-based Cohort study	<18.5 18.5-24.9 25.0-29.9 30.0-34.9 ≥35	12 week			0.79 (0.51-1.24) 1.00 **1.27 (1.11-1.47)** **1.71 (1.39-2.10)** **2.40 (1.82-3.17)**	28 days N=1,318	OR (95% CI)
Yao 2014[83] USA N=2,868,482	Retrospective Cohort study	18.5-24.9 25.0-29.9 30.0-34.9 35.0-39.9 40.0-49.9 ≥50	At booking	1.00 **1.36 (1.29-1.43)** **1.71 (1.62-1.83)** **2.04 (1.89-2.21)** **2.50 (2.28-2.74)** **3.11 (2.54-3.81)**	N=9,030			HR (95% CI)

1.4.2 Gestational diabetes mellitus

Definition

GDM is defined as glucose intolerance of various degrees that is first detected during pregnancy.[84,85] The definition includes women with unrecognised glucose intolerance that may have antedated the pregnancy, and applies regardless of whether insulin is used for treatment or the condition persists after pregnancy.[85] Women with GDM seem to have a β cell dysfunction as a result of chronic insulin resistance that manifests with hyperglycemia.[86] A normal pregnancy is characterised by a physiological decrease in insulin sensitivity,[87,88] and in women with GDM this adds to the chronic inflammation and induces a greater insulin resistance than in healthy pregnant women.[84]

Prevalence

The prevalence of GDM has increased in most populations, though there is a heterogeneity within and between different populations.[89-91] In Europe the prevalence of GDM is reported to be 2-6 % of pregnancies.[91] The recurrence rate is found to be 30-48%, and varies by populations and study design.[92] Data from the MBRN confirms the increasing trend of GDM from 2006-2014 across all regions in Norway (see Figure 4).[31] This is most probably a result of the increased attention the diagnosis GDM has received, as well as the increasing prevalence of risk factors like overweight/obesity, immigrants, and higher maternal age. Though the prevalence is different across regions of Norway, it is clear that the curves for the different regions follow the same increase (showing that the reporting of GDM is almost the same throughout Norway).

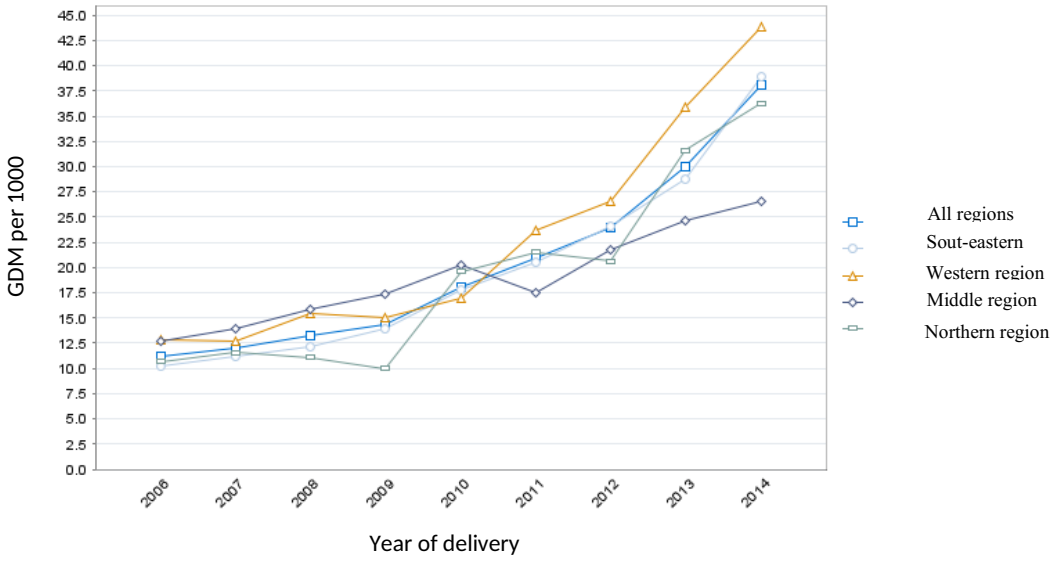

Figure 4. Incidence of gestational diabetes mellitus (GDM) per 1000 births according to year of delivery (2006-2014). Overall and stratified by the four health regions of Norway. Bank of statistics, the Medical Birth Registry of Norway[31]

Since the first introduction of the GDM criteria in the 1960's,[93] GDM has been a subject of considerably controversy,[85,94] as to the clinical importance of the diagnosis and the magnitude of its consequences for mother and offspring.[85] Due to lack of consensus among clinicians regarding testing methods, diagnostic glycaemic thresholds and value of routine screening, screening practice and policy for the GDM diagnosis vary across Europe.[91] There is also a heterogeneity in the reporting of GDM due to a lack of universally accepted diagnostic criteria, resulting in inconsistency in diagnosing and management of GDM in clinical practice.[95]

Short, and long-term consequences of GDM

GDM has both short, and long-term consequences for the woman and her offspring; Women with GDM have increased risk of metabolic syndrome,[96] cardiovascular

disease,[97] and type 2 diabetes mellitus[98] later in life. In a meta-analysis of 20 retrospective and prospective cohort studies (n=675,455), the overall relative risk (RR) of women developing type 2 diabetes after a pregnancy complicated by GDM was 7.43 (95% CI: 4.79-11.51), compared to women without GDM.[98] There has been found a strong, continuous association between maternal glucose levels and birthweight above the 90th percentile, with no obvious glucose threshold.[94] In addition to the increased risk of high birthweight,[13] offspring born to GDM mothers are more prone to be overweight in adolescence,[13] indicating a possible intergenerational effect due to genetic or persisting social and environmental factors. In the short-term, GDM increases the risk of adverse pregnancy and infant outcomes, such as preeclampsia, caesarean section, shoulder dystocia, and giving birth to a macrosomic neonate (>4500 grams).[99]

Risk factors

The underlying genetic, physiological, and environmental factors behind the development of GDM are not fully understood.[84,88] Risk factors for GDM are advanced maternal age, high prepregnant BMI, family history of diabetes mellitus, weight gain in early adulthood, non-white ethnicity, and smoking.[100,101] History of impaired glucose intolerance and GDM in a previous pregnancy, weight gain in early adulthood, weight gain between pregnancies, excessive GWG during the first 18-24 weeks are also associated with GDM.[101] Prepregnant BMI is found to be an important risk factor for GDM.[12,102] Results from a meta-analysis revealed a crude pooled OR for GDM in underweight, overweight moderately obese and morbidly obese women of 0.75 (95% CI 0.69-0.82), 1.97 (95% CI 1.77-2.19), 3.01 (95% CI 2.34-3.87), and 5.55 (95% CI 4.27-7-21), respectively (when compared to normal weight women).[12] A combination of healthy lifestyle characteristics may reduce the risk of first time GDM; women with BMI<25, who did not smoke, who participated in moderate physical activity≥150 min/week, and with a healthy eating pattern had a 83% lower risk of GDM (RR 0.17, 95%CI 0.12-0.25), compared to women who did not adhere to a healthy lifestyle.[102]

Screening for GDM in Norway and Sweden

Screening practice and policy concerning GDM have been inconsistent across Europe,[91] and screening according to traditional risk factors is a poor method to predict which women will be diagnosed with GDM.[103] It is suggested that a simple approach that offers an oral glucose tolerance test (OGTT) to women >25 years and/or with a BMI ≥25 is as good.[103]

Until 2017, the diagnostic criteria of GDM in Norway were fasting plasma glucose levels at <7.0 mmol/l and serum blood glucose 2 hours following a 75 grams OGTT of ≥7.8 but <11.1 mmol/l.[104] These criteria were defined according to National Guidelines for antenatal care, made by the Norwegian Society of Gynecology and Obstetrics in 1998 and updated in 2008 and 2014.[104] As the traditional risk factor screening seemed to miss 30-50% of GDM cases, new Norwegian national guidelines for screening GDM were introduced in 2017.[105] The diagnostic criteria for GDM according to the new guidelines are fasting plasma glucose levels from 5.3 to 6.9 mmol/l and 2 hours level from 9.0 to 11.0 mmol/l.[105] Screening (OGTT) will be offered in week 24-28 to women with the following risk factors: primiparous women >25 years (multiparous >40), Asian/African ethnicity, close relatives with gestational diabetes, and prepregnant BMI >25 kg/m^2. Multiparous women with birthweight >4500 grams, glucoseintolerance, preeclampsia, shoulderdystosia, or GDM in a prior pregnancy will also be offered screening.[105] Women with prepregnant BMI 30 kg/m^2 (or other risk factors) will also be offered a blood test (HbA1c) before week 16, in order to identify women with undiagnosed diabetes/hyperglycemia.[105]

The main diagnostic criterion for GDM in Sweden are based on a 75 g OGTT with a fasting capillary blood glucose level ≥6.1 mmol/L (plasma≥7.0 mmol/L) and/or a 2 hours capillary blood glucose ≥9.0 mmol/L (plasma glucose ≥10.0 mmol/L).[90,106] One region in Sweden (around 25 % of the pregnant population) has since 1998 only diagnosed manifest diabetes and not impaired glucose tolerance during pregnancy, based on a fasting capillary blood glucose ≥6.1 mmol/L (plasma glucose ≥7.0 mmol/L) and/or a 2 hours blood glucose ≥11.1 mmol/L (plasma glucose ≥12.2

mmol/L). Like Norway, selective glucose tolerance tests are performed based on risk factors.[90,106]

1.4.3 Pathophysiological mechanisms and obesity

Adipose tissue is not a passive organ of energy storage, but plays an important role in the regulation of insulin resistance both in pregnant and non-pregnant women.[107,108] Adipocytokines are adipose tissue-derived hormones, also secreted by the placenta, that contribute acheaving adequate metabolic control and energy hemostase in the maternal metabolism.[107] Cytokines secreted by the adipose tissue modulate the immune system causing chronic systemic inflammation and insulin resistance, known as the metabolic syndrome.[109] Obese women may present with a pertubed metabolic state with dyslipidemia, characterised by higher triclyceride, lower HDL concentration, hyperinsulinemia, elevated leptin concentrations, and low-grade inflammatory response.[110] The altered maternal vascular function and dyslipidemia may dysregulate blood and nutrition flow to the developing fetus,[110] affecting fetoplacental growth and metabolism in-utero.[88] This metabolic compromise also seems to be apparent in the fetus at birth.[111] (See suggested model Figure 5)

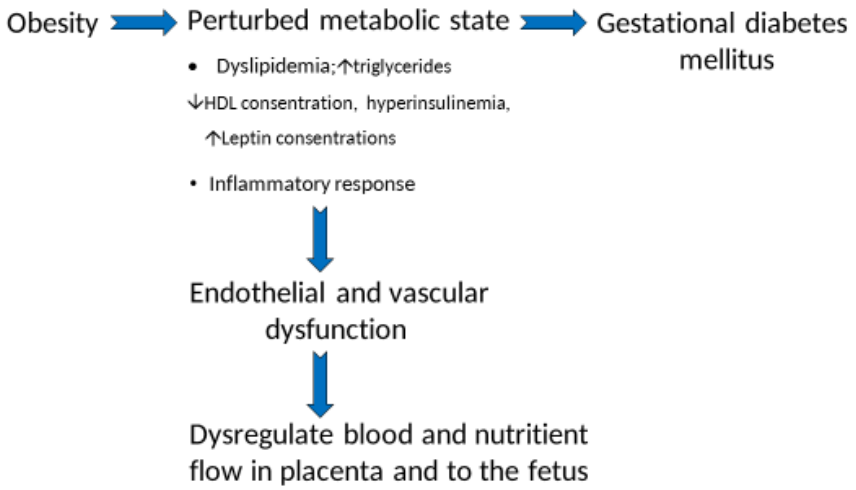

Figure 5. Obesity and suggested pathophysiological alterations in pregnancy

This is well demonstrated in a Canadian randomised controlled trial (RCT) that revealed how maternal life-long high fat diet is associated with obesity and adverse fetal and neonatal outcomes in a rat animal model.[112] Female rats fed on high fat diet early in life, had increased body fat, serum leptin and triclycerides prior to pregnancy and a more than 3-fold increase in fetal death, as well as decreased neonatal survival. The adverse outcomes were associated with poor development of the placenta vasculature with reduced blood flow, lower oxygenation of fetal tissue, which may cause hypoxia, poor fetal growth and neonatal survival.[112]

The underlying metabolic defects related to the development of GDM are decreased insulin sensitivity together with an inadequate insulin response.[84] A normal pregnancy induces metabolic alterations characterized by a physiological 50-60% decrease in insulin sensitivity during pregnancy.[87,88] Obese women are likely to have a decreased insulin sensitivity already at the start of pregnancy,[113] and are at an increased risk of developing GDM and fetal overgrowth during pregnancy.[114] The lack of insulin response in obese women during pregnancy may be explained by β cell dysfunction due to chronic decreased insulin sensitivity and compensatory hyperinsulinemia relative to lean women.[113]

1.5 Risk/effect modification

When the magnitude of the effect of the primary exposure on an outcome differs depending on the level of a third variable, we have effect modification.[115] In case of effect modification, the association between a risk factor and an outcome will differ in subgroups of the population.[116] Effect modification variables enhance or reduce the risk of an outcome associated with exposure, by affecting the influence of an exposure on risk of outcome.[116] When effect modification is present, it will be misleading to present the overall estimate of the association. Stratified analyses will reveal a heterogeneity in risk according to the third variable.[116] In *Paper I*, physical activity is evaluated as an effect modifier. We investigate if the risk of perinatal death

associated with prepregnant BMI shows a heterogeneity by level of physical activity. By identifying groups across which the association between exposure and outcome differs, interventions can be targeted to the groups that will benefit the most from intervention, and preventive actions can be more effective.[117]

1.5.1 Physical activity

Definitions of physical activity

Physical activity is broadly defined as any bodily movement produced by skeletal muscles that result in energy expenditure.[118] Physical activity can be categorised according to when the physical activity occurs during daily life such as occupational, household, sports, conditioning and other activities. Intensity of physical activity is commonly categorised into light, moderate and vigorous intensity.[118]

Leisure-time physical activity is undertaken in the individual's spare time that leads to any substantial increase in total energy expenditure.[119] Recreational physical activity includes sport, exercise, and hobbies.

Exercise is a subcategory of physical activity that is planned, structured, repetitive, with the intention to improve or maintain physical fitness (rather than to achieve or maintain established level).[118]

Physical fitness is a set of attributes that people have or achieve and can be measured by specific tests. Physical fitness consists of a health-related (e.g. cardiorespiratory endurance, muscular endurance, muscular strength, body composition, flexibility), and a skill-related (e.g. agility, balance, coordination, speed, power, reaction time) component.

There seems to be a lack of standardized terminology in the use of physical activity, and physical activity and exercise may be used interchangibly.[118,120] Consequently, it is challenging to compare epidemiologic studies evaluating physical activity, as

studies vary according to definitions, intensity, duration, frequency and mode[121,122] In the following, we have defined physical activity as recreational physical activity of moderate intensity according to the different activities reported in the MoBa questionnaire. When reviewing the literature, we have focused on recreational physical activity, leisure-time physical activity and exercise.

Benefits of physical activity

Physical activity lowers the risk of cardiovascular disease and premature mortality in a dose-response manner in the general population.[123,124] Observational studies of pregnant women have found that physical activity or exercise before or during pregnancy may reduce the risk of abnormal glucose intolerance,[125] GDM,[121,125,126] preeclampsia,[121,127,128] and stillbirth.[129] A meta-analysis of clinical intervention studies found a 28% (RR 0.72; 95% CI: 0.58-0.91) protective effect of GDM in the physical activity intervention group, compared to the control group.[130] However, some studies have revealed a heterogeneity in the benefits of physical activity according to maternal BMI.[125,127,129]

In non-pregnant individuals, physical activity is likely to improve insulin sensitivity and plasma lipid and lipoprotein concentrations, lower blood pressure and proinflammatory cytokines consentrations in peripheral circulation, as well as reduce oxidative stress.[23] Physical activity during pregnancy is likely to enhance cardiovascular function, mitigate dyslipidemia associated with pregnancy and have a disease preventive effect.[23] During pregnancy exercise is found to cause a brief transient reduction in oxygen and nutritient delivery to the placental site, followed by a compensatory increase in maternal blood volume, intervillous space blood volume, cardiac output and placental function.[131] According to Clapp and co-workers, moderate intensity exercise during the hyperplastic phase of placental growth early in pregnancy (8-9 week), is likely to improve placenta functional capacity with less non-functional tissue and greater volume of villous tissue in the placenta later in

pregnancy. This is likely to enhance nutritient delivery and increase the overall growth rate of the fetus in later gestation.[132,133]

Guidelines for physical activity during pregnancy

Guidelines for recommended physical activity during pregnancy show variations across countries, and few pregnant women seem to meet these recommendations.[120,134] Norwegian guidelines advise pregnant women with uncomplicated pregnancies to perform moderate-intensity exercise for at leat 150 minutes per week (20-30 minutes per day on most or preferably all days of the week).[135] An upper level of safe exercise intensity has not been established, but women should be able to carry on a conversation while exercising. The guidelines differentiate between women according to their prepregnant physical activity habits; women with uncomplicated pregnancies who have been regular exercisers prior to pregnancy, may continue with high-intensity activities. Pregnant women who have been physically inactive prior to pregnancy, should start with light intensity activities and follow a gradual progression of exercise.Women with medical or obstetric complications must be evaluated and physical activity individualized.[135,136] According to the American College of Sports Medicine, obese women who are medically pre-screened for contraindications may engage in physical activity three to four times per week, using a target HR range of 102–124 bpm for women 20–29 years of age and a range of 101–120 bpm for women 30–39 years of age while maintaining the ability to carry on a conversation, starting with 25 min per session and adding 2 minutes per week until sessions reach 40 minutes, and continuing until delivery.[137]

1.5.2 Gestational weight gain

GWG is defined as the amount of weight that a pregnant woman gains between the time of conception and the onset of labour,[39] and is the sum of products of conception, expansion of plasma volume, extra cellular fluid and maternal fat

deposition.[138] Until 1990, guidelines suggested a GWG of 9-11 kg for all women, independent of BMI category.[139] In order to minimize the negative consequences of inadequate or excessive weight gain for mother and fetus, the Institute of Medicine (IOM) provided recommendations for GWG according to prepregnant BMI categories in 1990[139] and 2009.[39] (see Table 5) The recommended ranges for gestational weight gain are for singleton births, however, until now there has been insufficient evidence to construct specific guidelines for women with BMI obesity grade II or III.[39]

Table 5. Institute of Medicine (IOM) guidelines for total gestational weight gain in singleton pregnancies, based on prepregnant body mass index.[39,139]

IOM guidelines 1990[139]		**IOM guidelines 2009[39]**		
Prepregnant BMI*	**Weight gain kg**	**Prepregnant BMI***	**kg/m^2**	**weight gain kg**
<19.8	12.7-18.1	**Underweight**	<18.5	12.5-18.0
19.8-26.0	11.3-15.9	**Normal weight**	18.5-24.9	11.5-16.0
>26 – 29.0	6.8-11.3	**Overweight**	25.0-29.9	7.0-11.5
>29.0	At least 6.8**	**Obese class I**	30.0-34.9	5.0-9.0
		Obese class II	35.0-39.9	5.0-9.0
		Obese class III	≥40	5.0-9.0

*In 1990 prepregnant BMI is categorized according to Metropolitan Life Insurance Company ideal weight-for-height standards, while 2009 recommendations are based on WHO.[25]

**Upper recommended range for adolescents and black people, lower end for women <157 cm.

A recent report from the Norwegian Institute of Public Health systematically reviewed whether a GWG below the recommended 5-9 kg in obese women could be beneficial.[140] They concluded that data from four RCT studies were too little information to conclude that a GWG below 5 kg or a weight loss in women with BMI ≥30 changed the risk of miscarriage, preterm birth, stillbirth and low birthweight.

Prepregnant BMI seems to be associated with GWG.[14,141,142] In a Danish cohort study, mean GWG was 10.5 (±8.3) kg in obese women, 14,7 (±6.4) kg in overweight, 15.8

(±5.2) in normal weight, and 15.3 (±5.1) kg in underweight women.[14] GWG has increased across all subgroups, and more women tend to gain weight below or above the recommended ranges.[39] In a recent review and meta-analysis of pooled data on more than one million women, 47% of women had a weight gain greater than and 23% less than the IOM recommendation,[141] which is consistent with a cross-sectional population-based study that found an overall 32% compliance to the guidelines; 47 % of women had excessive, and 21% inadequate GWG.[142] Overweight and obese women were more likely to have excessive weight gain.[142] (20% in underweight, 37% in normal weight, 64% in overweight and 55% in obese women). Adequate weight gain was 41% in underweight, 38% in normal weight, 25% in overweight and 23% in obese women.[142]

Post partum weight retention seems to increase with increasing BMI category,[24] and excessive GWG may result in excessive postpartum weight retention which is likely to move the women into a higher BMI category at the time of subsequent pregnancy.[39,40,143] Reviews investigating the association between GWG and GDM, have not been able to conclude due to unsufficient evidence,[40,141] which could be explained by the inconsistent definitions of GWG or the nature of the variable.

1.6 Epidemiology as conceptual framework

Epidemiology is the science and practice which describes and explains disease patterns in populations, and uses this knowledge to prevent and control disease and improve health.[116] (Bhopal 2008, page 3)

Epidemiology is used as a theoretical framework throughout this thesis. The key strategy in epidemiology is to seek differences and similarities in the disease patterns of groups and populations.[116] This is possible as illness and disease are not randomly distributed, but follow certain patterns. These patterns are a product of the determinants of health, which is the range of personal, social, economic, and

environmental factors that influence health.[144] The population's health is determined by the interrelationship among these factors.[144]

In epidemiology we study the association between postulated causal factors and disease, and much emphasize is placed on empirical data.[116] Though experimental studies are considered the gold standard when investigating causal associations, non-experimental studies in epidemiology contribute with a new way of thinking about causality when experimental studies are not possible.[116] Causal thinking draws upon the theories and principles of other disciplines, and causation is established by judgement on the basis of this knowledge.[116,145] In Bradford Hill`s criteria of causality cause must precede effect,[145] but criteria for causality should be used more as a framework for thoughts about the evidence, rather than a checklist.[116,146] Epidemiologic understanding of cause and effect does not have to be 100 % complete and accurate to permit useful application,[146] wchich has been well demonstrated in previous studies[147-149] Even though we are not able to draw conclusions about causal inference from observational studies, we may generate hypothesis of causal inference between variables. Knowledge from epidemiologic studies is directly applicable to the groups and populations studied, but only indirectly to individuals, and only to those who are reasonably typical of the population studied.[116]

Litterature review completed 31 August 2018.

2. AIMS OF THE STUDY

Reproductive health is challenged by the rise in maternal overweight and obesity. We aimed to investigate the association between BMI and change in BMI from first to second pregnancy, and perinatal outcomes. We further evaluated potential effect modifying variables in order to be able to target preventive strategies to reduce the risk of perinatal complications associated with maternal overweight and obesity.

The specific aims were:

To examine the association between maternal prepregnant BMI and perinatal mortality, and further to evaluate if physical activity during pregnancy modified the association (*Paper I*).

To investigate the risk for GDM in second pregnancy by change in BMI from first to second pregnancy, and whether BMI in first pregnancy and GWG in second pregnancy modified the risk (*Paper II*).

To estimate the association between weight change from first to second pregnancy and risk of GDM recurrence (*Paper III*).

3. MATERIAL AND METHODS

3.1 Study design

All three studies are defined as nationwide population-based historical cohort studies, as the cohorts were identified from information recorded in the past.[150] Data were prospectively collected and the recording of exposure information was performed before the occurrence of disease.

In *Paper I* we used data from the Norwegian Mother and Child Cohort study (MoBa), with linked data from the MBRN. The pregnancy was the unit of analysis, and each woman contributed with her first registered pregnancy.

In *Paper II* we used data from the MBRN. By the unique national identification number, each child was linked to his/her mother, so that each record consisted of the mother and her successive two first births (Family design).

In *Paper III* we utilized pooled data from the Medical Birth Registries of Norway and Sweden, with the same family design as in *Paper II*.

3.2 Data sources

3.2.1 The Norwegian Mother and Child Cohort Study

MoBa is a nationwide prospective population-based cohort study, conducted by the Norwegian Institute of Public Health.[151,152] The main aim of the MoBa study was to detect causes of disease by the estimation of exposure-outcome associations among the children and their parents.[153] All pregnant women in Norway during 1999-2008 were invited to participate through a postal invitation three weeks before attending the routine ultrasound examination in 17-20 weeks of pregnancy. As the ultrasound

screening is provided free of charge, 98% of pregnant women attend.[154] Inclusion was restricted to women who were able to read Norwegian as all information material and questionnaires were in Norwegian only. Women were recruited from nearly all Norwegian hospitals and maternity units exceeding 100 annual deliveries, with 50 of 52 maternity units participating. MoBa has collected data through questionnaires and biological material. Self-reported data on general health, diet and environmental exposure were collected during pregnancy week 13-17, week 22 and week 30. The participation rate was 41%, and the cohort includes approximately 114,000 children, 95,000 mothers and 75,000 fathers.[153]

In *Paper I* we have used Questionnaire 1 (Q1), completed in week 13-20 in pregnancy. Focus in this questionnaire is previous pregnancy and outcome, medical history before and during pregnancy, medications, occupation, exposures at work and at home, lifestyle and mental health. The 5th version of the MoBa quality-assured file was used.

3.2.2 The Medical Birth Registry of Norway

The MBRN is a nationwide population-based registry being the first of its kind in the world.[155] It was established in 1967 by the Directorate of Health aiming at conducting epidemiological surveillance and research on perinatal health.[156] The MBRN is based on compulsory notification of all live- and stillbirths from 16 weeks of gestation (12 weeks from 2001) and close to 100% of births are reported to MBRN.[156] The MBRN is routinely linked with the Population Registry in order to ensure data quality and complete notification.

Information from a standard antenatal form completed at visits to a midwife or a doctor during pregnancy, is brought by the mother upon admission to the labour ward.[156] Midwives and doctors attending the birth complete a standardized notification form with prospectively collected data on demographics, maternal health

before and during pregnancy, previous reproductive history, complications during pregnancy and delivery and pregnancy outcomes.[156] In 1999, a new and more detailed form based on check boxes was introduced, and information on smoking and ultrasound based estimation of gestational age was included. The collection of maternal height and weight was initiated in 2006 together with the implementation of a revised electronic birth notification system, however, electronic notification of births from all delivery units in the country was not complete before 2014. Both mothers and children are registered in the MBRN by their unique national identification numbers, enabling all births to be linked to their mothers in maternally linked sibling files.

3.2.3 The Medical Birth Registry of Sweden

The MBRS is a nationwide population-based registry established in 1973 by an act of the Swedish parliament, in order to study ante- and perinatal factors and their importance for the health of the infant.[157] Information from standardized medical record forms used at all antenatal care clinics, all delivery units and upon all pediatric examination of the newborn infants are sent to the National Board of Health for computerization.[157] Data in the MBRS has been prospectively collected by the staff responsible for patient care, from the first antenatal visit and onwards.[157] The most frequent initial visit to an antenatal clinic is after ten full weeks of pregnancy, and 90% of women have made an initial visit after twelve full weeks.[157] Close to 100% of all births in Sweden are reported to the registry, and the quality of the registry has been regularly evaluated.[157,158] Information on BMI at the start of pregnancy was available from 1992 and maternal smoking from 1983.[157]

As in Norway, it is possible to link information from other registries as well as link all births to their mothers by using the unique personal identification number assigned to all legal residents in Sweden.[159] Information on maternal country of birth and

education level were retrieved from the Immigration Registry and Education Registry, respectively.

3.2.4 Statistics Norway and Statistics Sweden

Statistics Norway and Statistics Sweden are national statistical institutes responsible for official statistics related to economy, population and society at national regional and local levels.[160,161] The National Education Database located at Statistics Norway, and the Education Registry located at Statistics Sweden have systematically collected individually based statistics on ongoing and completed education.[160,161] The National Population Registry is also located at Statistics Norway, keeping information on maternal country of birth.

3.2.5 The National Registry

The National Registries are population registries that contain information on everyone that resides or have resided in the two countries.[159,162] Everyone in the National Registry has been assigned an 11-digit personal identification number. The Tax Administration issues each child with this identification number once they have received a notification of birth from the hospital. The National Registry in Norway is maintained by the Norwegian Tax Administration.[162] The National Registry in Sweden is administered by the Swedish Tax Agency.[159]

3.3 Study Populations

Paper I

Women who contributed with their first registered pregnancy in the MoBa study during 1999-2008 were included. The unit of analysis was the pregnancy. Singleton pregnancies without major congenital anomalies, with gestational age ≥22 weeks, and where women did not have pregestational diabetes mellitus were included. Pregnancies resulting in offspring with major congenital malformations (according to the European Surveillance of Congenital Anomalies),[163] were excluded. Women had to have their prepregnant height and weight reported and women with a BMI below 15 or above 60 or height below 1.40 meters, were excluded in order to ensure biologically plausible data. A final study population of 77,246 pregnancies was included to study the association between prepregnant BMI and perinatal mortality. When evaluating the effect modifying role of recreational physical activity, 72,306 pregnancies were analysed, since. Women who had not answered both questions about recreational physical activity *in the last three months before pregnancy* and *until week 17 in the actual pregnancy* in the Q1 questionnaire (see Appendix 1), were excluded (n=4,940). Within this excluded group are women who answered the questionnaire on physical activity from the first version of Q1(1A), as the questions differed from those in the latter version (n=2,567 in the total MoBa cohort).

Paper II and *Paper III*

Unit of analysis was the mother with her first and second pregnancy. In *Paper II*, the study population consisted of 24,198 women who delivered their first and second child in Norway during 2006-2014. To be included women had to have their pre-pregnancy height and weight reported for both pregnancies, and women with a diabetes mellitus diagnosis prior to first or second pregnancy or GDM in first pregnancy were excluded. Women with prepregnancy BMI below 15 (n=11) or interpregnancy weight change above 30 or below -30 BMI units (n=3) were considered implausible and were excluded. In the analysis exploring the potential

effect modifying role of GWG in second pregnancy, women had to have their weight registered both before and at the end of second pregnancy, giving a study population of 11,972 women.We excluded women with a weight loss during pregnancy (n=100) as there is no international consensus supporting weight loss in pregnancy.[39] Women with GWG above 70 kg were considered implausible and women were excluded.

In *paper III*, 614,432 women had their first and second singleton pregnancy in Sweden during 1992-2010 and Norway during 2006-2014. Of these, 512,217 were Swedish and 102,215 were Norwegian. Women with diabetes mellitus prior to first pregnancy or second pregnancy were excluded, giving 432,045 (70%) women with available information on BMI in both pregnancies. In this population, 2,763 women had GDM during their first pregnancy.

3.4 Variables and methods

Definitions and general variables used in this thesis

Body mass index

BMI was categorized according to WHO[25] (see Table 6). In P*aper I* we used the woman's prepregnant height and weight collected from MoBa Q1 in pregnancy week 17-20. In *Paper II* we calculated BMI from height and prepregnant weight reported at the first antenatal visit in data from the MBRN (see Appendix 2). The reporting of maternal height and prepregnant weight to the MBRN increased steadily from 0.1% in 2006 to 71.6% of births in 2014.[164] During this period, the distribution of women across the different BMI categories was stable over time (see Figure 6).

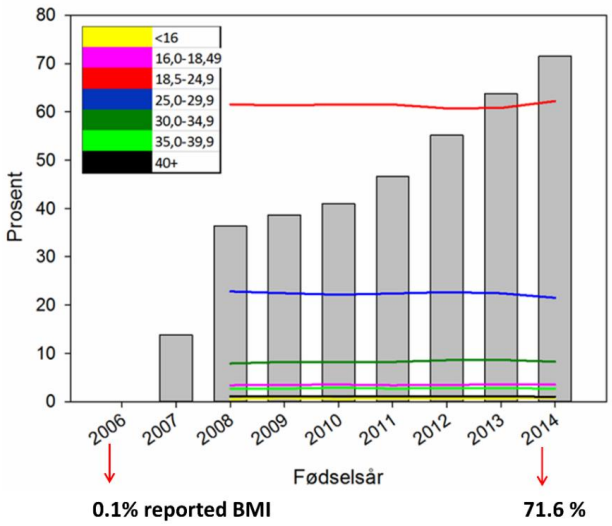

Figure 6. Percent reported body mass index (BMI) from 2006-2014 (grey columns) and proportions of women in the different BMI categories (coloured lines). Statistics from the Medical Birth Registry of Norway at the Norwegian Institute of Public Health.[164] (Modified from https://www.fhi.no/nyheter/2015/fodselsstatistikk-for-2014-publiser/)

In *Paper III* we calculated BMI from height and prepregnant weight from the MBRN, and from height and weight reported in first trimester in the MBRS. BMI in *Paper III* therefore represents both prepregnant and early pregnancy BMI.

Interpregnancy weight change

In *Paper II* and *Paper III* we defined interpregnancy weight change as BMI in second pregnancy minus BMI in first pregnancy, expressed continuously as BMI units (kg/m^2) (see Figure 7). Interpregnancy weight change was grouped into six categories[17,18] (see Table 6).

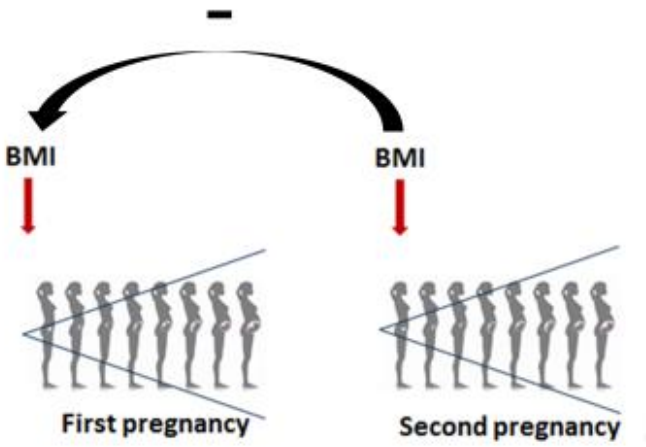

Figure 7. Interpregnancy weight change

Table 6. The categorisation of outcome, exposure and covariates used in the three papers.

	Paper I			*Paper II*			*Paper III*		
	Categories	**Strata**	**Source**	**Categories**	**Strata**	**Source**	**Categories**	**Strata**	**Source**
BMI (kg/m^2)	<18.5 18.5-24.9* 25.0-29.9 30.0-34.9 ≥35	<30* ≥30	MoBa	<18.5 18.5-24.9* 25.0-29.9 ≥30	<25* ≥25	MBRN	<18.5 18.5-24.9* 25.0-29.9 ≥30	<25* ≥25	MBRN MBRS
Interpregnancy weight change (units kg/m^2)				<-2 -2 to <-1 -1 to <1* 1 to <2 2 to <4 ≥4		MBRN	<-2 -2 to <-1 -1 to <1* 1 to <2 2 to <4 ≥4		MBRN MBRS
GWG (kg)				0-7.9 kg 8.0-15.9 ≥16	<13.9 ≥14	MBRN			
Recreational physical activity	Non-active Active*		MoBa						
Maternal age (years)	<20 20-35* ≥35		MBRN	<25* 25-29 30-34 ≥35		MBRN	<25* 25-29 ≥30		MBRN MBRS
Maternal country of birth				Nordic* Non-nordic			Nordic* Non-Nordic		MBRN MBRS
Maternal education (years)	9-12 13-16 ≥17*		MoBa	<11 11-14 ≥14*			<10 ≥10*	<10 ≥10	
Smoking	No* Sometimes Daily		MBRN MoBa[1]	No* Yes		MBRN[2]	No* Yes	No Yes	MBRN MBRS[3]
Interpregnancy interval (months)				<12 12 to 23* 24 to 35 ≥36	<24 ≥24		<24 ≥24*	<24 ≥24	MBRN MBRS
Year of second delivery				Continuous		MBRN	1992-2001* 2002-2006 2007-2014		MBRN MBRS
Parity	Nullipara Multipara*		MBRN						
Marital status	Cohabitant* Other		MBRN						
Chronic hypertension	No* Yes		MBRN						
Perinatal mortality	No Yes		MBRN						
GDM				No Yes		MBRN	No Yes		MBRN MBRS

* Reference category. [1] Maternal smoking at the beginning of pregnancy. [2] Maternal smoking at the end of second pregnancy. [3] Smoking at the start of second pregnancy.

Perinatal mortality

We defined perinatal mortality as the number of stillbirths and early neonatal deaths per thousand births (livebirth and stillbirths).[44] The MBRN defines stillbirth as death of a fetus at gestational age ≥ 22 week or with birthweight ≥500 grams.[31] Early neonatal death is defined as the death of a live-born infant during the first seven days of life.[31,165]

Gestational diabetes mellitus

In Sweden and Norway the birth registries notify GDM by a check box on the birth notification form, or as diagnostic codes according to the International Classification of Diseases version 9 (648W) and 10 (O244).

Gestational weight gain

We defined GWG as total weight in kg at the end of second pregnancy minus prepregnant weight (see Figure 8). Data was retrieved from the MBRN (Appendix 2). Weight at the end of pregnancy was both self-reported and objectively measured at the time of last antenatal visit, or when women entrered the labour ward. The continuous variable was categorized into three categories,[166] and the overall median level of GWG (14 kg) was used as threshold when dichotomizing (see Table 6).

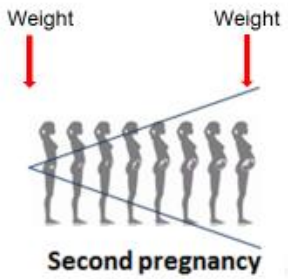

Figure 8. Gestational weight gain in second pregnancy.

Recreational physical activity

We defined physical activity as participating in any combination of recreational physical activities of moderate intensity. We obtained self-reported information from Q1 in MoBa (see Appendix 1) in which participants were asked how often they engaged in 14 different types of activities; walking/strolling, brisk walking, running/jogging/orienteering, bicycling, training studio/weight training, special gymnastics/aerobics for pregnant women, aerobics/gymnastics/dance with running or jumping, dancing, skiing, ball sports, swimming, riding and other). The same question ("How often do you exercise?") was asked for the last 3 months before the current pregnancy and during pregnancy (13-17 week), and the level of each activity was defined as never, 1-3 times per month, 1 time a week, 2 times a week, 3 or more times a week. For activities of at least moderate intensity,[167] the frequency of each activity was transformed into a monthly score that was summed across all activities. Walking (strolling) and other activities were considered low intensity activities and scored as 0.[168,169] Women who performed recreational physical activity at least once a week were categorized as *physically active*, while those who were physically active less than once a week were categorized as *non-active*.

Maternal age

Maternal age represents mother's age in years at the time of delivery, and is registered continuously in data from MBRN and MBRS. We further categorized maternal age in the respective papers (see Table 6).

Maternal country of birth

Maternal country of birth was obtained from Statistics Norway (*Paper II*/*Paper III*), and from the Immigration Registry at Statistics Sweden (*Paper III*) (see Table 6).

Maternal smoking

Maternal smoking in *Paper I* represents smoking at the beginning of pregnancy, reported by women at their first antenatal visit. Maternal smoking habits were notified by check boxes on the standardized antenatal forms; "no", "occasionally", "daily" or women could decline to answer. Information on smoking habits was collected from MBRN, but in cases with missing information we added self-reported data on smoking from MoBa Q1. In questionnaire Q1 women were asked "Do you smoke now (after you became pregnant)?", and checkboxes were similar as described above.

In *Paper II* maternal smoking habits were retrieved from MBRN and represent self-reported smoking at the end of second pregnancy. Women were asked at approximately pregnancy week 36, or at the time they entered the labour ward. Chech-boxes were similar to the description above.

The smoking variable in *Paper III* represents smoking early in pregnancy and was reported at the first antenatal care visit. Data is retrieved from MBRN and MBRS. In the Swedish data the check-boxes were different; "never", "1-9 cigarettes per day", "≥10 cigarettes per day". In harmonizing the pooled data from MBRN and MBRS, smoking habits reported as daily, occasionally, 1-9 cigaretter per day, and ≥10 cigarettes per day were considered "smoking". Evidence from a study validating self-reported tobacco use in the MoBa cohort against measured maternal plasma cotinine, found that 66% of women reporting occasional smoking, had a plasma cotinine cut-off value corresponding to daily smokers.[170] We therefore considered daily and occasional smokers as smokers in *Papers II* and *III*.

Interpregnancy interval

Interpregnancy interval was calculated as the date of the second birth minus the date of first birth, minus the duration of second pregnancy in days. Gestational age of the second pregnancy was based on second trimester ultrasound estimations, or if

missing, on the mother's last menstrual period. Interpregnancy interval was expressed in days, and was categorized into months as shown in Table 6.

Education

In *Paper I* level of education was obtained from MoBa Q1, and represents self-reported maternal fulfilled education at the start of pregnancy. In *Paper II* we obtained data on maternal highest level of education by 2014 through linkage to the National Education Database at Statistics Norway. In *Paper III* both data from Statistics Norway and data on maternal education from the Education Registry at Statistics Sweden were utilized. Maternal education in the respective paper was categorized as presented in Table 6.

Marital status

Marital status was retrieved from the MBRN in *Paper II* and *Paper III*, and also from the MBRS in *Paper III*.

Chronic hypertension

Chronic hypertension was defined as maternal blood pressure ≥140/90 mm Hg prior to pregnancy or before week 20, according to ICD-10. The diagnosis was was obtained from the MBRN where it was notified by means of check boxes or free text on the notification form.

Methods and variables used in each paper

Main exposure in *Paper I* was prepregnant BMI categorized in underweight, normal weight, overweight, obese (30-34.9) and morbidly obese (≥35), with the normal

weight category as reference (see Table 6). Main outcome was perinatal death (yes, no). In the multivariable model we adjusted for potential confounders based on empirical evidence; Maternal age (<20, 20-35 (reference), ≥35 years)), parity (nulliparous, multiparous (reference)), marital status (married/cohabitant (reference), single/other)), chronic hypertension (yes, no (reference)), and smoking at the start of pregnancy (no (reference), sometimes, daily). Preeclampsia, gestational hypertension and GDM were considered to be intermediate variables on the path between BMI and perinatal death, and therefore not adjusted for in the model.[150]

We estimated the odds ratio of perinatal death by recreational physical activity (*active, non-active*) with the *non-active* group as the reference. This was done both for physical activity before and during pregnancy. To explore if recreational physical activity during pregnancy modified the association between prepregnant BMI and perinatal death, we added the interaction term ((BMI <30, ≥30) x (physical activity during pregnancy (*active, non-active*) in the multivariable logistic regression model. Due to limited cases, BMI was used as a dichotome variable with 30 as the threshold, as BMI ≥30 was associated with an increased odds of perinatal mortality. As the interaction analysis was significant, the association between BMI (<30, ≥30) and perinatal death was performed in strata of physical activity during pregnancy.

The described analyses were also performed for recreational physical activity before pregnancy. We also added recreational physical activity (*active, non-active*) before pregnancy and during pregnancy as potential confounders in the logistic regression model, to assess if this changed the association between prepregnant BMI and perinatal mortality. Finally we investigated the odds ratio for perinatal death according to prepregnant BMI (underweight, normal weight, overweight and obese) and physical activity during pregnancy (*active*, *non-active*), combining the variables in 8 categories in one model. The reference category was normal weight women who were *active* during pregnancy. Maternal age, parity, marital status, chronic hypertension and smoking at the start of pregnancy were potential confounders adjusted for in the model.

Main exposure in *Paper II* was interpregnancy BMI change categorized in 6 categories by BMI units (see Table 6). Interpregnancy BMI change of -1 to <1 was defined as stable weight and used as reference category. GDM (yes, no) in second pregnancy was the main outcome, and potential confounders adjusted for in the multivariable model were maternal age at second pregnancy (<25 (reference), 25-29, 30-34, ≥35 years), maternal country of birth (Nordic (reference), non-Nordic), years of education (<11,11-13, ≥14 (reference)), smoking in second pregnancy (no (reference), yes), interpregnancy interval (<12, 12-23 (reference), 24-35, ≥35 months), and year of second birth (continuous).[100] We explored the association between interpregnancy BMI change and GDM in strata of maternal country of birth, maternal age (<30, ≥30 years), smoking and interpregnancy interval (<24, ≥24 months).

To evaluate effect modification by prepregnant BMI in first pregnancy we added the interaction term ((BMI <25, ≥25) x (interpregnancy BMI change (six categories)) in the multivariable logistic regression model. We chose to dichotomize BMI at 25 due to limited cases, and a BMI ≥25 is defined as overweight,[25] and was in our study associated with an increased risk of GDM in second pregnancy. To evaluate effect modification by GWG in second pregnancy, we added the interaction term ((GWG <14, ≥14 kg) x (interpregnancy BMI change (six categories)) in the multivariable model. Due to limited cases we choose to use the the median threshold of GWG which was 14 kg, but a threshold of 16 kg was also investigated. The association between interpregnancy BMI change and GDM was explored in strata of BMI in first pregnancy and GWG during second pregnancy (see Table 6). Finally we investigated the RR of GDM by combining change in BMI (6 categories) between first and second pregnancy, and prepregnant BMI (<25, ≥25) in 12 categories in one model, keeping women with stable weight and with BMI <25 as reference category.

Main exposure in *Paper III* was interpregnancy BMI change and outcome was recurrence of GDM in second pregnancy. We used the theoretical framework directed acyclic graps (DAG) with DAGitty version 2.3 (www.dagitty.net)[171] to visualize the pathways between interpregnancy BMI change and GDM recurrence in *Paper III*.

Based on the DAG, the following potential confounders were adjusted for in the multivariable analyses: maternal age at second delivery (<25 (reference), 25-29, ≥30), year of second birth (1992-2001 (reference), 2002-2006, 2007-2014), maternal education (<10 years, ≥10 years (reference)), interpregnancy interval (<24 months, ≥24 months (reference)), maternal country of birth (Nordic (reference), non-Nordic, missing) and maternal smoking at the start of second pregnancy (no (reference), yes, missing). We considered GWG as an intermediate variable on the path between interpregnancy BMI change and GDM recurrence. Even though we did not have data on GWG, the variable is drawn into the DAG. BMI ≥25 was associated with an increased recurrence risk of GDM, was used as threshold in the interaction analysis and in the stratified analyses.

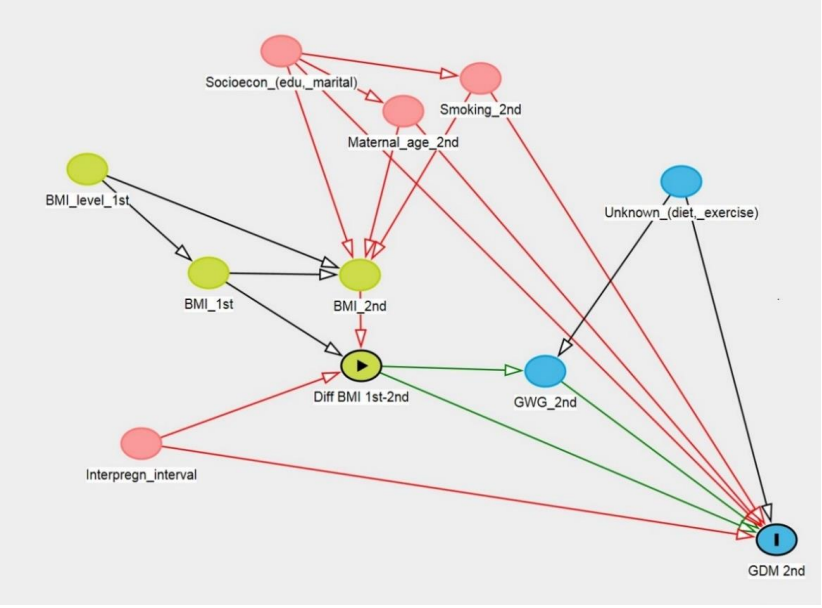

Figure 9. Proposed DAG for the pathways between interpregnancy BMI change (Difference (Diff) 1st-2nd) and recurrence of GDM in *Paper III*. (www.dagitty.net)[171]

3.5 Statistical analyses

Chi square tests

Chi-square test was used in all three papers to assess associations and linear trends between categorical variables.

Regression

In *Paper I* we used logistic regression to estimate the strength of the association between prepregnant BMI and perinatal mortality. Odds ratios (OR's) with 95% confidence intervals (CIs) were calculated for each BMI category. To evaluate whether recreational physical activity during pregnancy changed the association between BMI and perinatal mortality, we included (BMI (<30, ≥30 kg/m^2) x recreational physical activity (*active*, *non-active*)) as an interaction term in the multiplicative model (Wald test[150]). All analyses in *Paper I* were performed with SPSS version 20.

In *Paper II* and *Paper III* we estimated the strength of the association between interpregnancy weight change and the binary outcome GDM using general linear models with extension for the binary family in STATA IC statistical software version 14 and 15. Relative risks (RRs) with 95% CIs were calculated for each interpregnancy weight change category. To evaluate effect modification by BMI in first pregnancy, we included (BMI (<25, ≥25 kg/m^2) x interpregnancy weight change categories) as an interaction term in the multiplicative model, evaluated by likelihood ratio test. In *Paper II* we also evaluated a possible interaction between GWG in second pregnancy and interpregnancy weight change (see page 52) by adding the interaction term in the multiplicative model, evaluated by likelihood ratio test. Finally we compared the risk of GDM in women with BMI<25 and ≥25 in their first pregnancy by including interpregnancy BMI change as a continuous variable in the

interaction term, evaluated by likelihood ratio test, Poisson regression (*Paper II*). In this analysis, women with a weight loss of more than 1 BMI unit were excluded.

Missing information

In *Paper I*, 2,592 women (3.4%) had missing information on the covariates chronic hypertension (n=1,071) and smoking (n=1,790). In *Paper III* information on smoking and education were missing in 61 and 11 women, respectively. We handled missing information on covariates in *Paper I* and *III* by including simple imputation methods by assigning a separate value for the missing data in the logistic regression model. We also performed sensitivity analyses, assigning the missing category to both values, to see if the results from the logistic regression analyses changed (*Paper I*). We performed a sensitivity analysis on the 4,940 (6.4%) women who had been excluded due to missing information on recreational physical activity in *Paper I*, by assigning all women with missing information to the *active* group and then to the *non-active* group. Independent of the group to which they were assigned, adding the 4,940 women did not alter the association between prepregnant BMI and perinatal mortality.

In *Paper II*, 3,374 (13.9%) women had missing information on covariates. Missing values for smoking (n=2,592), maternal education (n=737), and maternal country of birth (n=155) were handled by missing imputation using chained equations (MICE) with logistic regression for smoking and maternal country of birth, and multinomal logistic regression for maternal education.[172] We compared our study populations with women who had missing information on BMI in first and/or second pregnancy in *Paper II* (Table S10) and *Paper III* (eTable1).

Table 7 presents a summary of methods used in this thesis.

Table 7. Overview of material and methods of this thesis.

	Paper I	*Paper II*	*Paper III*
Aims	To assess the risk of perinatal mortality by prepregnant BMI.	To assess the risk of GDM in 2nd pregnancy by interpregnancy weight change.	To assess recurrence risk of GDM by interpregnancy weight change.
Design	Nationwide, population-based historic cohort study from Norway. Prospectively collected Information.	Nationwide, population-based historic cohort study from Norway. Prospectively collected information.	Nationwide, population-based historic cohort study from Norway and Sweden. Prospectively collected information.
Data source	MoBa study MBRN	MBRN	MBRS MBRN
Population	Mother's first registered pregnancy. 1999-2008 N=77,246	Mothers with 1st and 2nd pregnancy. 2006-2014 N=24,198	Mothers with 1st and 2nd pregnancy (Sweden 1992-2010, Norway 2006-2014). N=2,736
Outcome	Perinatal mortality	GDM	GDM recurrence
Main exposure	Prepregnant BMI	Interpregnancy weight change	Interpregnancy weight change
Effect modification	Physical activity	Prepregnant BMI GWG	BMI in 1st pregnancy
Adjustments	Maternal age, parity, marital status, chronic hypertension, smoking.	Maternal age, year of delivery, education, interpregnancy interval, maternal country of birth, smoking	Maternal age, year of delivery, education, interpregnancy interval, maternal country of birth, smoking
Measure of association	OR 95% CI	RR 95% CI	RR 95% CI

3.6 Ethical considerations and methods

The papers included in this thesis comply with the guidelines of the Declaration of Helsinki,[173] and with the Vancouver Recommendations.[174] The study presented in *Paper I* was approved by the MoBa Steering Committee (PDB 591), and by the Western Regional Ethical Review Board (Project number 270.08, approval no: 2008/14908-CAG). The studies of *Paper II* and *Paper III* were approved by the Norwegian Regional Ethics Committee (REK VEST approval no: 2015/1728). The Study of *Paper III* was also approved in Sweden by the regional ethics committee at Karolinska Institutet, Stockholm (No.2012/1813-31/4).

Data were de-identified, and researchers did not have access to directly identifiable information. Our studies have only used data that already have been collected, which makes the possibility of physical harm to participants non-existent. Informed consent was obtained from all participants in the MoBa Study upon recruitment.[151] As researchers did not have any additional patient contact, informed consent was not required for the studies included in this thesis. We have been able to identify vulnerable groups within the population, and are aware of the possibility of causing harm on the group level if findings about specific groups are presented in an unthoughtful manner. Special care have been taken when publishing and distributing the research results, to avoid inadequate, unfortunate and stigmatizing conclusions that may cause harm to vulnerable groups within the society.

4. REVIEW OF PAPERS

4.1 Paper I

Prepregnant body mass index and recreational physical activity: effects on perinatal mortality in a prospective pregnancy cohort

Sorbye LM, Klungsoyr K, Samdal O, Owe KM, Morken NH. BJOG 2015; 122(10): 1322-30.

Objectives: We investigated the association between prepregnant BMI and perinatal mortality. Secondly, we evaluated if recreational physical activity modified the association.

Methods: We analysed 77,246 singleton pregnancies without congenital anomalies in data from the MoBa Study (1999–2008). Prepregnant BMI was classified as underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), obese (30–34.9) or morbidly obese (BMI ≥35). Perinatal mortality comprised stillbirth ≥22 weeks plus early neonatal death 0-7 days after birth. We obtained risk estimates by logistic regression and adjusted for maternal age, parity, marital status, chronic hypertension and smoking. Perinatal mortality was a rare outcome, and odds was used as an approximation for risk.

Results: An increased risk of perinatal death was seen in obese [OR 2.4, 95% CI 1.7–3.4] and morbidly obese women (OR 3.3, 95% CI 2.1–5.1) as compared to normal weight women. In the group participating in recreational physical activity during pregnancy, obese women had an OR of 3.2 (95% CI 2.2–4.7) for perinatal death relative to non-obese women. In the non-active group the corresponding OR was 1.8 (95% CI 1.1–2.8) for obese women compared with non-obese women. We found a difference in perinatal mortality risk related to obesity between the active and non-active groups (P-value for interaction = 0.046, multiplicative model).

Conclusions: Prepregnant obesity was associated with a two- to three-fold increase in risk of perinatal death when compared to normal weight women. Recreational physical activity during pregnancy modified the association: Among women with a

prepregnant BMI <30, the lowest risk of perinatal death was found among women performing recreational physical activity during pregnancy. For obese women, the lowest risk for perinatal mortality was found in women who did not participate in recreational physical activity during pregnancy.

4.2 Paper II

Gestational diabetes mellitus and interpregnancy weight change: A population-based cohort study

Sorbye LM, Skjaerven R, Klungsoyr K, Morken NH. PLoS Medicine. 2017; 14(8): e1002367.

Objectives: To assess the risk of GDM in second pregnancy by change in BMI from first to second pregnancy, and whether BMI and GWG modified the risk.
Methods: We utilized prospectively collected data from the population-based MBRN (2006-2014). Our study was based on 24,198 mothers and their two first pregnancies, where none of the mothers had GDM registered in their first pregnancy. Weight change, defined as prepregnant BMI in second pregnancy minus prepregnant BMI in first pregnancy, was divided into six categories by BMI units (kg/m^2). RR estimates were obtained by general linear models for the binary family and adjusted for potential confounders. Analyses were stratified by BMI in first pregnancy (<25, ≥25 kg/m^2) and GWG in second pregnancy (<14, ≥14 kg).
Results: The overall absolute risk of GDM in second pregnancy was 18.1 per 1,000 births (439 cases of 24,198). Compared to women with stable BMI (-1 to 1), women who gained weight between pregnancies had higher risk of GDM: Gaining 1 to 2 units: Adjusted RR 2.0 (95% CI 1.5-2.7); 2 to 4: RR 2.6 (2.0-3.5) and ≥4: RR 5.4 (4.0-7.4). Risk increased significantly both for women with prepregnant BMI below and above 25 at first pregnancy, although more strongly for the former group. Overweight/obese women with an interpregnancy weight loss >2 BMI units, had a 60% lower risk of GDM (adj RR 0.4, 95% CI 0.2-0.8). Interpregnancy weight change was stable in 47.6% of women (n=11,512), while 16.8% (n=4,076) of women had a

weight loss >1 BMI unit and 35.6% (n=8,610) of women gained weight ≥1 BMI unit. We could not find that the association between interpregnancy weight gain and GDM in second pregnancy differed between women who gained 0-13.9 kg, and those who gained ≥14 kg in second pregnancy.

Conclusions: The risk of GDM in second pregnancy increased by increasing weight gain from first to second pregnancy, and more strongly among women with BMI<25 in first pregnancy. Interpregnancy weight loss >2 BMI units was associated with a lower risk of GDM in women who were overweight/obese in their first pregnancy.

4.3 Paper III

Weight change between pregnancies and recurrence of gestational diabetes mellitus

Sorbye LM, Cnattingius S, Skjaerven R, Klungsoyr K, Wikström AK, Kvalvik LG, Morken NH. In Manuscript.

Objectives: The specific aim was to estimate the association between weight change from first to second pregnancy and recurrence risk for GDM.

Methods: We used prospectively collected population-based data on 614,432 mothers and their first two pregnancies, registered in the Swedish (1992-2010) and Norwegian (2006-2014) Medical Birth Registries. Weight change, defined as BMI in second pregnancy minus BMI in first pregnancy, was categorized in six groups by BMI units. RRs were obtained by general linear models for the binary family and adjusted for confounders. Analyses were stratified by BMI in first pregnancy (<25 and ≥25 kg/m^2).

Results: Overall recurrence rate for GDM in second pregnancy was 39% (1,078 of 2,763). Among overweight/obese women (BMI ≥25), recurrence risk of GDM decreased in those women who reduced their BMI by 1-2 units (adj RR 0.80, 95% CI 0.65-0.99) and >2 units (adj RR 0.72, 95%CI 0.59-0.89), and increased if their BMI increased by ≥4 units (adj RR 1.26, 95%CI 1.05-1.51), compared to those with stable

BMI (-1 to 1 units). Among normal weight women (BMI <25), the risk of GDM recurrence increased if their BMI increased by 2-4 units (adj RR 1.32, 95%CI 1.08-1.60) and ≥4 units (adj RR 1.61, 95%CI 1.28-2.02), compared to those with stable BMI between pregnancies. Of women with GDM in first pregnancy; 19.7% had a weight loss > 1 BMI unit, 39.8% were stable in weight and 40.5% increased their weight by ≥1 BMI unit. Among women with weight loss of >2 BMI units between first and second pregnancy, 85% were overweight/obese (BMI ≥25) and 15% were normal weight at the start of first pregnancy.

Conclusions: Weight loss from first to second pregnancy reduced the risk of GDM recurrence in overweight/obese women. Weight gain between pregnancies increased recurrence risk for GDM in both normal and overweight/obese women.

5. DISCUSSION

This chapter summarizes the methodolocical strengths and limitations of the papers included in this thesis, and dicusses to what extent limitations may have influenced our findings. Main results in the three papers are compared and discussed in relation to previous studies.

5.1 Methodological considerations

An overall goal in epidemiologic studies is to obtain valid and precise estimates ensuring accuracy in the epidemiologic estimates.[150] Obstacles to valid and precise estimates are classified as random and systematic errors.[150] Systematic errors are referred to as biases, and could be further separated into internal and external validity. Selection bias, information bias and confounding are important components of internal validity. Random errors is about precision, and together with validity define the accuracy of a study.[150] High validity and high precision are both necessary in order to make the estimates generalizable to the target population.

5.1.1 Study Design

Data sources used in this thesis are all defined as population-based registries, as the primary study aimed to include all individuals in the target population.[175] The main advantage in using population-based registries is that data already exists, which is practical. Such use is also ethical, and time/cost efficient.[176-178] The large number of participants with a long time follow-up is another advantage with population-based registries, and makes it possible to study rare outcomes like perinatal mortality and GDM. However, it is important to bear in mind that in very large datasets, even small associations will give statistically significant results. It is therefore essential in large population-based studies to also evaluate the clinical relevance of results rather than only looking at p-values.[178]

The disadvantage with this type of data is that collections are not under the control of the researcher. The reported variables may not cover all aspects of interest and confounder information may be lacking.[176-178] We were able to adjust for many possible confounders in the three papers, but certain dimensions could be missing as the reported number of variables were restricted. Exclusion of unmeasured confounding is therefore impossible. As for information bias, the prospective reporting of data makes misclassification of exposure and outcome non-differential.[176]

In *Paper I* the unit of analysis was the unique pregnancy. To deal with the challenge of dependency between pregnancies from the same mother, we only included the women's first registered pregnancy in MoBa. Pregnancies included in *Paper I* may therefore represent the mother's first, second, third or higher pregnancy. As the chances of a woman having a next pregnancy is contingent on the outcome of prior pregnancies, choosing only women's first births would introduce selection bias by selective ferility.[179] With our approach, we dispelled the challenge in choosing the women's first pregnancy as this group selects many women who stop reproducing after one pregnancy and in general have higher morbidity and mortality than women with two or more pregnancies.[180,181]

Pregnancies from the same woman are not independent events, and in *Paper II* and *Paper III* we utilised a longitudinal cohort design linking mothers to her first and second births. This family-design keeps the unique mother as the unit of analysis, and includes mothers with two or more births. We were able to predict risk of GDM in second pregnancy depending on information from first pregnancy. As data were not organised in sibship based on the woman's total reproduction (fixed sibship), we did not predict risk based on information from future pregnancies which would most likely introduce bias and is not considered an applicable method for predicting risk.[179,182,183]

With the family-design we were able to study heterogeneity in risk of GDM[184,185] In *Paper III,* women had GDM in first pregnancy, but glucose levels had normalized

after delivery, since they were not registered with pregestational diabetes in the second pregnancy. In the second pregnancy we were able to observe these women an additional time to estimate risk change of GDM when exposure changed (BMI). Recurrence risk persisting over time may be explained by genes (the persons genome is constant), but may also be attributed to shared environment (woman's dietary patterns, personal behavior, and environmental conditions).[179,184] The family-design has the potential to reveal information of the underlying mechanisms of GDM, by disentangling genetic and environmental factors.

5.1.2 Evaluation of Random Error

Random error is the variability in data that cannot be readily explained, and that remains after systematic error has been eliminated.[117] Random error reduces the precision of measurement, and affects all groups equally and are classified as non-differential errors.[116] Random errors decrease as study size increases, and the epidemiologic method for increasing precision is therefore to enlarge the sample size.[117,150]

Number of perinatal deaths and women with GDM were limited in the stratified analyses and in the adjusted multivariable model, despite large sample sizes. The small numbers in each strata increased the variability which decreased the precision, and was reflected in the wide CIs. Precautiousness in interpreting the strength of the associations is therefore warranted. Due to the population-based cohort design, it was not possible to increase study size or to keep the exposure groups similar in size, which could have reduced variability. Statistical efficiency and precision were improved by merging categorical variables, which may come with a cost of obscuring or hiding patterns.

In *Paper I* we used OR to express the strength of the association between prepregnant BMI and perinatal mortality. OR overestimates RR for frequent outcomes.[186] However, if the outcomes of interest are rare, the OR will be close to the RR.[186,187] According to Schmidt & Kohlmann, the OR may provide an acceptable

approximation of the RR if the incidence of interest is below 0.01 and the OR is below 3.0.[187] (see Figure 10). With an overall incidence of perinatal mortality of 0.0039 and with OR's ranging mainly below 3 in *Paper I*, OR is a valid measure of RR in *Paper I*.

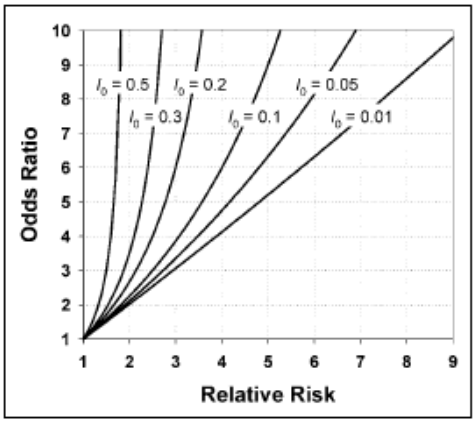

Figure 10. Relationship between odds ratio and relative risk for various incidence rates. (Schmidt & Kohlmann. *Int J Public Health.* 2008; 53(3):165-167. Reprinted with permission from Springer Nature).[187]

5.1.3 Evaluation of Systematic Error

Internal validity

Selection bias

Systematic errors that stem from the way study subjects are selected and from factors that influence study participation are defined as selection bias.[117] The large sample size which covers many geographic areas in Norway, together with the long

recruitment period are likely to increase variability and are major strengths of the MoBa Study.[151] Even though MoBa is a population-based cohort study, only 41% of invited women participated,[153] and selection bias due to self-selection is well known.[188] A validation study of the cohort found a socioeconomic gradient in the selection into the study, as women with lower socioeconomic status were underrepresented as well as a lack of diversity in ethnicity due to the selection criterias.[188] Selection bias is likely to influence incidence and prevalence estimates in *Paper I*. However, the association between prepregnant BMI and perinatal mortality is less prone to bias due to the prospective reporting of data.[188,189] When finding an increased risk of perinatal death in women with prepregnant obesity in this population, it is likely that associations are even stronger in a more heterogeneous population. Also, when investigating the association between prepregnant BMI and perinatal mortality it may be advantageous to study this in a homogenous population due to less variation in possible confounders.[150]

As *Paper II* and *Paper III* utilized data from nationwide population-based cohorts with compulsory notification of all births, selection bias are less likely. However, when selecting women with first and second pregnancy, we excluded women with only one lifetime pregnancy, and generally this population has higher morbidity and mortality than women with two or more pregnancies.[180,181] It was a perequisite for inclusion that women had their BMI reported in both pregnancies, which may have introduced selection bias due to high proportion of missing information on BMI. However, sensitivity analyses in women with missing information on BMI did not change associations. We also compared our study population with the population with missing information on BMI, and found the study population to be a representative sample. The reason for missingness was mainly that mother's height and weight was introduced in a late version of the electronic birth notification. Hospitals updated their software to this version at very different times, beginning very gradually in a few hospitals in 2006 and not being complete before 2014. Thus, missingness is linked to the delivery unit and not to the actual mother.

Information bias

Information bias is systematic error that arise when information from study subjects is erroneous.[117] This is likely to misclassify subjects into the wrong category.

In all three papers self-reported height and weight may introduce misclassification bias due to overreporting of height and underreporting of weight.[190] However, in women of reproductive age self-reported height and weight only slightly differ from direct measures, and are regarded as valid estimates in research and clinical use.[191,192] Studying the impact of exposure misclassification on associations between pre-pregnancy BMI and adverse pregnancy outcomes, Bodnar et al. found the highest agreement between measured and self-reported BMI in severely obese women (≥35).[193] The consequences of errors in measuring BMI depend on wether the errors are differential or non-differential.[27] Differential misclassification is the most serious bias and happens when information is misclassified differentially for those with and without disease, or differently according to the persons exposure status.[117] As data on height and weight in all three papers was prospectively collected, misclassification of BMI or the outcome (perinatal mortality or GDM) is not dependent on the women's status for the other variable, and is likely to be non-differential (exposure therefore not likely to be related to the outcome).[27] As non-differential misclassification tends to bias the estimates towards the null effect, we may have underestimated associations.[117]

In *Paper III* BMI was reported both as prepregnant BMI and BMI in first trimester. As GWG is suggested to be 0.5-2.0 kg in first trimester of pregnancy,[39] classification of BMI may be obscured by GWG in first trimester. Misclassification may overestimate the level of BMI both in first and second pregnancy, however, it is not likely to misclassify interpregnancy BMI change.

We have used BMI as an indirect measure of body fat, as there is an association between body fat and BMI.[28] BMI does not take into account age, sex, bone structure, fat distribution or muscle mass,[27] and may overestimate body fat in muscular individuals, whereas it can underestimate body fat in persons who have lost muscle

mass. It is well known that overweight and obesity in the general adult population are associated with increased all-cause mortality.[3,4] Much of the controversy of using BMI as a measure of mortality risk has been due to confounding by smoking and from prediagnostic weight loss associated with severe disease in elderly people.[3,4] The relationship between BMI and mortality is found to be stronger in younger ages (20-49 years), than in older (>70 years), due to mentioned loss of lean mass associated with illness in elderly people.[3] However, although BMI represents a source of bias when predicting body fat at the individual level, it is considered a valid marker for body fat at the population level.[28] BMI is likely to be a valid measure of body fat in our studies as we have included healthy women of reproductive age.

Physical activity (*Paper I*) was indirectly assessed by self-administered questionnaires, which introduces the possibility of over-reporting of physical activity.[194,195] As data were prospectively collected, over-reporting of physical activity is most likely to be non-differential underestimating the true effect of physical activity.[150] As there is no accepted gold standard for measure of physical activity, self-reported assessment continues to be the most common method used in epidemiological studies of pregnant women.[196] We did not not have information on duration and intensity of the different recreational physical activities, which is a limitation. The Compendium of Physical Activities developed by Ainsworth and co-workers, has quantified energy cost of different physical activities by rate of energy expenditure expressed as metabolic equivalents.[168,169] We chose to include activities of moderate intensity defined as intensity metabolic equivalent levels of 3.0-6.0.[167,168] As these are standardized values for an average adult person, it may underestimate the energy expenditure performed by pregnant women. The validity of the MoBa questionnaire on recreational physical in week 17-20 has been validated in a sub sample of pregnant women in MoBa, where they found a positive association between self-reported recreational physical activity and objectively measured activity, supporting the validity of the questions used to quantify level of physical activity in pregnant women.[197]

The Medical Birth Regitries undergo regular evaluation of quality by comparing data in the registry with data from medical records.[155,157,158] Missing data is likely to affect all prevalence estimates, but will usually have little effect on risk estimates if lack of information is random.[157] Missing data tend to bias associations toward the null effect rather than to cause spurious associations, and holds as long as missing data occurs in equal proportions in the groups being compared.[150] As the MBRN is of high quality, a validation study comparing data in the MBRN with hospital medical records gave a positive predictive value for GDM of 89.4% (86.4-92.3%).[198] Women with GDM in first pregnancy were defined as a risk group for GDM in next pregnancy both in Sweden and Norway.[90,104,106] As they are routinely screened for GDM with an OGTT in their second pregnancy it is likely that we have an almost 100% registration of GDM in second pregnancy.

Stillbirths and early neonatal deaths may have different etiologic determinants and in the denoting gestational age-specific risk.[53] Due to limited cases in each strata in *Paper I*, we were not able to analyse stillbirths and early neonatal deaths separately. We excluded serious anomalies which represents an important etiologic difference in stillbirth and early neonatal death, and have not analyzed for age-specific or birthweight specific risk in perinatal mortality. It may therefore be reasonable to use perinatal mortality, combining stillbirths and early neonatal deaths, as the outcome.[53]

Confounding

Confounding is the confusion of effect, where the effect of the exposure is mixed with the effect of another variable.[117] A confounding variable must be associated with both the outcome and the exposure under study, but is not an effect of the exposure or an intermediate step in the causal pathway from exposure to disease.[117] The three studies included in this thesis are observational studies and non-experimental by nature, which make them vulnerable to bias by confounding.[150] Identification of confounding variables in our models was not based on statistical tests which are usually too insensitive to detect all important confounders.[150]

In *Paper I* we were not able to explore GWG as an intermediate variable as weight gain at the end of pregnancy was to be filled out in a questionnaire 6 months after birth and women who had experienced stillbirth or early neonatal death did not receive this questionnaire for ethical reasons. In *Paper II* we stratified the analyses by GWG. Having a GDM diagnose during pregnancy may change women's behavior due to advice on physical activity, nutrition and GWG which is likely to introduce reverse causation. As GWG correlates with gestational age, it may introduce bias in studies where the outcome also correlates with gestational age.[199]

The mechanisms behind perinatal death and development of GDM are not fully understood, and are likely to be a complex interplay between genetic, biological, social and environmental determinants. As our study is an observational study, we are not able to control for all potential confounding factors, and we can therefore not exclude the possibility of residual confounding by unmeasured or imperfectly measured risk factors.

High recurrence rates for perinatal outcomes like GDM, suggest genetic causes but may also reflect the precence of persistent environmental and social factors.[184] We have studied patterns of GDM recurrence by comparing recurrence in women who changed their weight from first to second pregnancy, keeping the genome stable. Recurrence risk may be distorted if GDM in first pregnancy changes other exposures to causal factors,[184] for example if women with GDM in first pregnancy change their smoking habits. We have therefore adjusted for other time-dependent variables like interpregnancy interval and year of delivery. Some other studies have controlled for recurrence risk by adjusting for previous GDM which may introduce bias.[200,201] GDM in first pregnancy may be a marker for a woman's elevated risk of GDM in second pregnancy. This elevated risk, may be due in part to effects of the same exposure in first pregnancy.[200]

External validity

External validity refers to how well our results and conclusions are generalizable to other populations. Internal validity is considered a perequisite for external validity.[150]

A representative population is important in describing prevalence and incidence of exposure and outcomes.[150] As women in the MoBa cohort differ from the general population of pregnant women,[188] generalizability of prevalence and incidence of exposure and outcomes in *Paper I* must be interpreted with caution. However, the association between prepregnant BMI and perinatal mortality is likely to be generalizable to other populations.[188,189]

Prevalence estimates of GDM and GDM recurrence in *Paper II* and *Paper III* are directly generalizable to the population of women who have two or more pregnancies, and most likely to the target population of pregnant women in Scandinavia. Due to the long follow-up time, it is likely that the populations studied are representative for the target population of pregnant women as about 95% of Norwegian women with two or more births have their second birth within 7 years following the first birth[181] and as 84% of women in Norway seems to have two or more pregnancies during their lifetime.[181]

In *Paper II* and *Paper III* the aim was to study the association between BMI change from first to second pregnancy and the risk of GDM/GDM recurrence in second pregnancy, and further to generate hypotheses of a causal relationship. For this sake, a probability sample from the target population with great variation and representativeness may defeat the goal of validity when it comes to identifying causal relations.[150] This comes from the fact that it is more difficult to control for confounding when factors vary within the population, more difficult to have informly accurate measurement and therefore harder to make valid inferences.[150] It was favourable in the two studies to have a selected cohort being more homogenous with respect to important confounders and for reporting more accurate information, rather than having a representative population of exposure and confounders.[150] This is well demonstrated in the famous study by Doll et al. where they investigated long-time

mortality in relation to smoking in a cohort of British male doctors in the UK born in 1900-1930.[202]

It is important to bear in mind that the epidemiological conclusions are directly applicable to the groups studied, but only indirectly to the individuals, and only to those individuals who are reasonably typical of the population we have studied (page 22).[116] However, we can express prognosis as a probability derived from population studies, and then on the basis of what happens on average.[116]

5.2 Discussion of results in Paper I-III

5.2.1 Paper I

Prepregnant body mass index and perinatal mortality

Increased risk of perinatal mortality in obese women when compared to normalweight women, is consistent with other epidemiologic studies.[11,79,80,82] Some studies have, however, revealed an increased risk of early neonatal death and stillbirth in both overweight and obese women, and large sample size characterises these studies.[7,8,63,64,72,83] The heterogeneity across studies regarding the threshold defining BMI categories, reference category, and outcome, makes it challenging to compare risk estimates between studies (see Table 4). A cohort study utilizing data from the Danish Medical Birth Registry revealed an increased risk of stillbirth both in overweight (OR 1.39, 95% CI 1.18-1.65), obese (1.60, 95% CI 1.27-2.01) and morbidly obese women (OR 1.86, 95% CI 1.39-2.47), when compared to normal weight.[7] This study is comparable to our as BMI represents prepregnant BMI, the similar categorising of BMI, distribution of BMI within groups and prevalence of stillbirths are similar to our population. Another Danish study also comparable to our, found an increased risk of stillbirth in overweight (adj OR 2.0, 95% CI 1.4-2.9) and obese women (adj OR 3.2, 95% CI 2.0-4.9).[63] A Swedish population-based cohort

study investigated the association between BMI and neonatal mortality (within 28 days) in term infants, and found an adj OR of 1.27 (95% CI 1.11-1.47), 1.71 (95% CI 1.39-2.10), and 2.40 (95% CI 1.82-3.17) for overweight, obese and morbidly obese women, respectively.[64] (see Table 4)

In direct contrast to our study, is a population-based cohort study from the North Western Perinatal survey in the UK.[81] The authors were not able to find an increased risk of stillbirth (>24w) or neonatal mortality (before 28 days) in overweight or obese women.[81] They even reported a lower risk (adj RR 0.57, 95% CI 0.39-0.82) of neonatal mortality in overweight, compared to normal weight women. BMI in their study population was reported around week 16 (which may have underestimated and misclassified BMI), 46.4% of women had BMI ≥25, 37% had missing information on BMI, and they were not able to adjust for smoking.[81]

Even though we were not able to falsify the null hypothesis that there is no difference in perinatal mortality between the overweight and the normal weight group, this is not considered evidence of no association. Several studies that have analysed stillbirths in strata of gestational age, have found the strongest association between BMI and stillbirth among term stillbirths.[63,72] We have included stillbirths from week 22, which may have weaken and obscured a potential association between overweight and stillbirths in term pregnancies. Though we analysed 299 perinatal deaths, we may have lacked power when categorizing variables and stratifying the analyses. The nature of the relationship between BMI and perinatal mortality may be obscured when categorizing the continuous BMI variable. In a cohort study from the UK that did not find an increased risk of fetal and infant death in the overweight group, found that the odds of both fetal and infant death consistently increased by 6-7% for each additional unit above 23 kg/m^2 acting throughout the overweight and obese range, when examining BMI as a continuous variable.[82]

The dose-response relation between increasing maternal BMI and risk of perinatal death in our study suggests that underlying biological mechanisms may explain the association. However, results from a large Swedish cohort study found that women

gaining 2 to < 4 BMI units from first to second pregnancy increased the risk of both stillbirth (within 28 days) and neonatal death, compared to women who were stable in weight.[17] For neonatal death this was evident only for women with BMI<25 in first pregnancy.[17] If temporal changes in BMI change the risk of stillbirth and early neonatal death, this may lend support to a causal relation between being overweight or obese and perinatal mortality. We were, however, not able to investigate the association between change in BMI and perinatal mortality due to our design.

Pathophysiological mechanisms for stillbirths and early neonatal mortality

Mechanisms behind the excess risk of perinatal death in obese women remain unknown though several explanations have been proposed.[77] Pregnancy complications such as gestational hypertension, GDM, preeclampsia and preterm delivery are more common among obese women,[7,78,203] suggesting that the association between BMI and perinatal mortality is mediated through these conditions. However, when we excluded women with gestational hypertension, GDM, preeclampsia and preterm birth (which is an important risk factor for early neonatal death[61]) in a sensitivity analysis, the association between BMI and perinatal mortality remained unchanged. This suggests that maternal comorbidity cannot account for the association between BMI and perinatal mortality.[63,64,79] Several studies have found the strongest association between BMI and stillbirth or neonatal death among term deliveries.[63,64,72]

Obese women may present with metabolic abnormalties like hyperinsulinemia (in advance of glucose dysregulation), without having the clinical diagnosis,[110] suggesting that the increased risk of stillbirth in obese women may be related to undiagnosed diabetes mellitus or glucose intolerance.[58,204] The endogenous hyperinsulinemia present in obese women, may induce rapid fetal growth in the fetus.[78] Together with the functional limitations of the placenta in transferring sufficient oxygen to meet the fetus' requirements, this may cause hypoxia and stillbirth.[78] However, birthweights of unexplained stillbirths among obese women are

found to be lower than the birthweight of all live births even after controlling for gestational age.[63,79] This suggests that intrauterine growth restrictions due to endothelial dysfunction and impaired early placental function, rather than excess fetal growth, causes stillbirth in obese women.[63] As the fetus' weight and length are estimated at the time of delivery and not at the time of death, gestational age and birthweight are likely to be biased; gestational age may be overestimated, and the fetus may have lost weight after death which underestimates weight.[56]

Obese women seem to be more prone to experience unexplained stillbirths and fetoplacental dysfunction, compared to normalweight women.[63,79] A Danish study found that overweight and obese women had a crude OR 1.9 (95% CI 1.0-3.7) and 3.6 (95% CI 1.8-7.6) respectively, for unexplained stillbirth compared to normal weight women with a stillbirth.[63] Stillbirths in overweight and obese women were associated with a 110% (crude OR 2.1, 95% CI 1.0-4.4) and 420% (crude OR 5.2, 95% CI: 2.5-10.9) increased risk of placental dysfunction.[63] The altered metabolic milieu and fetoplacental dysfunction in obese pregnancies, may increase delivery complications and reduce the fetus' ability to adapt to extra-uterine life, contributing to increased risk of early neonatal deaths.[63,205]

Effect modification by recreational physical activity during pregnancy

Regular physical activity in early pregnancy may stimulate placental growth, and be an important mechanism for enhancing functional capacity of the placenta.[132,206] This may explain the lower absolute risk of perinatal mortality in women with a prepregnant BMI <30 who performed recreational physical activity at least once a week during pregnancy (*Paper I*). However, in obese pregnant women physical activity during pregnancy was no longer protective of perinatal mortality, and the lowest risk of perinatal mortality in obese women was found in the *non-active* group. Even though the CIs were wide and overlapping, this unexpected finding in obese women raises the question if there is a heterogeneity in the effect of physical activity in pregnancy across maternal BMI categories. Could it be that physical activity does

not counteract the metabolic alterations present in obese pregnant women, which make them more vulnerable and less resistent to the higher stress associated with physical activity?

A prospective longitudinal cohort study of non-pregnant women investigating the joint effects of physical activity and BMI on coronary heart disease,[207] found that both BMI and level of physical activity were important and independent predictors of women`s mortality. The lowest mortality was found in women with BMI<25 who were physically active.[207] Higher level of physical activity was beneficial at all levels of adiposity, but did not eliminate the higher risk of mortality associated with obesity.[207] In contrast, results from a large observational study carried out in a non-pregnant European population, found that small increases in physical activity in inactive men and women were associated with reductions in all-cause mortality across all levels of BMI.[208] However, pregnant women differ in many ways and these results may not be valid in a pregnant population.

Few other studies have evaluated the association between physical activity and perinatal mortality. A Norwegian prospective cohort study found a lower risk of stillbirth in women who performed regular light physical activity (i.e ≥3 times per week) the last year prior to pregnancy, compared to women reporting light physical activity (i.e <1 per week).[129] Vigorous physical activity ≥3 times per week was associated with an increased risk of stillbirth compared to vigorous physical activity < 1 time per week (adj incidence rate ratio 2.46, 95% CI 1.23-4.90), also in normal weight women.[129]

Several cohort studies evaluating the association between physical activity and risk of GDM or preeclampsia, have confirmed a lower risk only in women with BMI <25,[125,127] while others have concluded that physical activity before and during pregnancy reduced the risk of GDM independent of maternal BMI.[126,209] A large cohort study from Denmark found an increased risk of preeclampsia in women who performed leisure-time physical activity exceeding 271 minutes per week during the first trimester (compared to non-exercisers), also for women with BMI <25.[210] Recent

RCT studies in overweight and obese women evaluating the effect of physical activity upon perinatal outcomes, have not been able to find an effect of physical activity on perinatal outcomes (only on maternal GWG).[211-213] Lack of robustness to inform evidence-based life-style interventions for obese pregnant women has made it both comprehensive and challenging to study the modifying role of physical activity upon perinatal outcomes. Cochrane reviews, and meta-analyses are not able to refine high quality of evidence due to heterogeneity and low compliance in the included studies.[213-215]

In our study we were not able to decide if the reported physical activity was undertaken during conception and throughout pregnancy. We did neither have information on whether women received clinical advise to stop being physically active or not. Prepregnancy physical activity levels strongly correlate with physical activity levels during pregnancy,[216,217] but we know from previous studies that only a small proportion of women meet the recommended levels of physical activities throughout pregnancy.[216,218] According to Mottola and Cambell, maternal BMI ≥25 is associated with quitting regular exercise by the third trimesteser of pregnancy.[219]

5.2.2 Paper II

BMI in first pregnancy, interpregnancy weight change and GDM

Though women did not have GDM in their first pregnancy, gaining ≥ 1 BMI unit increased suspectability to develop GDM in the subsequent pregnancy. We found an overall dose-response gradient between interpregnancy weight gain and risk of GDM in second pregnancy, which has been confirmed in other studies.[16,29,42] In a Swedish population-based cohort study, the overall OR's for GDM in the second pregnancy were 1.32 (95% CI: 1.08-1.62), 1.67 (95% CI 1.32-2.11), and 2.09 (95% CI 1.68-2.61) for women gaining 1 to <2, 2 to <3, and ≥3, respectively.[16] Reference category was women with stable weight (-1 to <1). This study also confirmed our association between interpregnancy weight gain and GDM in women who had a BMI ≥25 in both

pregnancies.[16] In contrast to our, this study found that for overweight/obese women, only those with an interpregnancy weight gain ≥3 BMI units, had an increased risk of GDM.[16] Even though the increased risk of GDM associated with interpregnancy weight gain applied to both women with prepregnant BMI <25 and ≥25 in our study, we found the strongest association in women with prepregnant BMI <25 in first pregnancy, similar to an American cohort study.[42] In contrast to our study, a Belgian population-based cohort study did not find an increased risk of GDM associated with interpregnancy weight gain in women who had prepregnant BMI ≥25 in first pregnancy, however, this study only included 7,897 women.[29] Even though we found the highest risk of GDM associated with interpregnancy weight gain in women who had prepregnant BMI <25, having prepregnant BMI≥25 in first pregnancy was associated with a higher baseline GDM risk across all interpregnancy weight change categories (see Fig 4 in *Paper II*).

Overweight/obese women who reduced their BMI by ≥2 units between their first and second pregnancy, had a 60% lower risk of GDM compared to women with stable weight in our study. Previous studies have found a lower GDM risk associated with weight loss,[42,220,221] however not all.[16,29] Authors using similar design as used by us, have typically included women with GDM in first pregnancy and adjusted for previous GDM in the analyses.[29,42,220] Women with GDM in first pregnancy may have changed their behavior as a consequence of the GDM diagnosis, causing a dependency between exposure (BMI change) and past GDM. Adjusting for GDM in first pregnancy may be inadequate with the possibility of introducing bias in the estimates.[201]

Pathophysiological mechanisms behind GDM

The association between interpregnancy weight change and GDM was consistent across populations, as the association remained in strata of prepregnant BMI in first pregnancy, maternal age, maternal country of birth, and interpregnancy interval. Our results suggest weight change as a metabolic mechanism behind the increased risk of

GDM. Maternal overweight and obesity at the start of pregnancy represent well known risk factors for glucose intolerance during pregnancy,[12,87,114] and are likely to explain the higher baseline GDM risk in women with BMI ≥25 at the start of first pregnancy (see Fig 4 in *Paper II*). A normal pregnancy is characterized by a 50-60% physiological decrease in insulin sensitivity,[87,88] and the pancreatic β cells compensate for this by increasing insulin secretion.[84] Interpregnancy weight gain between first and second pregnancy, during a relatively short time frame (more than 60% of women in our study had an interpregnancy interval <24 months), may stress the glucose metabolism and cause a subclinically decreased insulin sensitivity both among normal weight and overweight women. This may explain the dose-response association between weight gain and GDM risk. This is consistent with the linear association between increase in inflammatory markers and increase in BMI found in non-pregnant adults.[222,223] As normal weight women tend to have a higher insulin sensitivity than overweight and obese women,[114] we suggest that an additive decrease in insulin sensitivity during second pregnancy, may overload the capacity and increase the suspectibility to develop GDM, especially in normal weight woman who are used to higher insulin sensitivity. This may explain the stronger association between interpregnancy weight gain and GDM in women with BMI <25 in first pregnancy. An interpregnancy weight loss >2 BMI units in overweight/obese women may improve the metabolic mechanisms, resulting in a lower risk of GDM. In overweight and obese non-pregnant individuals, weight loss has been found to improve the adiposity induced systemic inflammation, by decreasing the inflammatory markers and increasing the anti-inflammatory marker.[224]

Gestational weight gain

The association between interpregnancy weight change and GDM showed the same trend in strata of GWG (0-13.9 kg, ≥14 kg). Evaluating GWG as an effect modifier in the association between interpregnancy weight change and GDM, was comprehensive and challenging. As women's weight gain in second pregnancy is measured at the end

of pregnancy (and not at the time of the GDM diagnosis), only women's total weight gain was available. This may have introduced reverse causation as women diagnosed with GDM is closely monitored on weight restriction and prescription on nutrition and physical activity,[104] which are likely to influence GWG. When stratifying on GWG, we stratified on a possible intermediate variable on the causal pathway from interpregnancy weight change and GDM, which may have biased estimates.[225]

We found the highest risk of GDM in women with the lowest GWG, which is consistent with other studies.[14,29] A study from the Danish National Birth Cohort found an OR 2.3 (95% CI 1.9- 2.8) for GDM in women with GWG < 10 kg, compared to women with GWG of 10-15 kg.[14] In a population-based study from Belgium, the risk rate of GDM in second pregnancy by inadequate, adequate and excessive GWG (Defined according to IOM guidelines for recommended weight gain which are relative prepregnant BMI category[39]) in second pregnancy was 3.3%, 1.9% and 1.7%, respectively.[29] However, they found that overweight and obese women with excessive GWG during their first pregnancy, had an adjusted OR of 2.84 (95% CI 1.52-5.33) for GDM in their second pregnancy, compared with women with adequate weight gain.[29] This brings in the importance of the combination of prepregnancy BMI category and GWG. GWG depends on the woman's prepregnant BMI, and GWG seems to increase as prepregnant BMI decreases.[14,226] In the study from the Danish National Birth Cohort, authors found a mean GWG of 15.3 kg in underweight, 15.8 kg in normal weight, 14.7 kg in overweight, and 10.5 kg in obese women.[14] Above 40% of obese women gained less than 10 kg during pregnancy.[14] As we did not relate GWG to prepregnant BMI, this may also explain the inverse association between GWG and GDM.

We do not know whether interpregnancy weight change is a result of the woman's GWG during first pregnancy, or if it is due to weight change in the interpregnancy interval. Excessive GWG is associated with post partum weight retention,[40,143] and the risk for post partum weight retention seems to increase with increasing GWG irrespective of prepregnant BMI.[24] This is likely to move women into a higher BMI category at the start of her next pregnancy.

5.2.3 Paper III

Interpregnancy weight change and recurrence of GDM

We found that overweight/obese women (BMI≥25) with a weight loss of 1-2 BMI units or >2 BMI units, reduced their risk of GDM recurrence by 20% (adj RR 0.80; 95% CI 0.65-0-99) and 28% (adj RR 0.72, 95% CI 0.59-0.89), respectively in *Paper III*. This means, that even though overweight/obese women had GDM in their first pregnancy, they were not determined to have recurrent GDM in their second pregnancy. In women who gained weight from first to second pregnancy, we found an increased risk of GDM recurrence, both in women with BMI <25 and ≥25 in first pregnancy. GDM is not likely to be explained solely by genetic factors, if risk of GDM recurrence is changed by change in BMI.[179,184] This underlines the importance of behavioral and environmental factors in GDM recurrence, and that GDM recurrence is amenable to intervention.

Several studies have investigated the association between interpregnancy weight change and GDM in second pregnancy. These studies have either included women with and without GDM in first pregnancy,[42,220] excluded women with GDM in first pregnancy,[16,227] or used cross-sectional design.[228] The different design and methodology make interpretation of these results difficult and not comparable to our study. We have not found any previous studies investigating interpregnancy weight change and GDM recurrence in a high risk population of women with GDM in their first pregnancy. However, an American population-based cohort study investigated recurrence of preeclampsia in women with their first and second singleton pregnancies during 1989-2005.[229] Compared to women who were stable in weight (-2 to 2), women with a weight loss >2 BMI units had a 30% reduced recurrence risk of preeclampsia (adj RR 0.70, 95% CI 0.60-0.81), and women who gained >2 BMI units had a 29% increased recurrence risk (adj RR 1.29, 95% CI 1.20-1.38).[229] As with GDM, maternal BMI is positively associated with risk of preeclampsia,[230,231] and

preeclampsia seems to share the metabolic dysregulation characterized by insulin resistance, systemic inflammation and endothelial dysfunction.[114,205]

The change in GDM recurrence risk by weight change may be explained by a change in the systemic inflammation, which has been well demonstrated in non-pregnant individuals.[222-224] Weight loss in overweight and obese individuals has been found to improve the adiposity induced systemic inflammation, by decreasing the inflammatory markers and increasing the anti-inflammatory marker.[224] On the other hand, weight gain in non-pregnant individuals has been associated with increased inflammation.[222] If weight loss from first to second pregnancy decreases inflammation in overweight and obese women, this may further improve insulin sensitivity and β-cell function, resulting in a better ability to cope with the physiological demands of the subsequent pregnancy.

Prevalence of GDM recurrence

The overall GDM recurrence rate in our study was 39%, with a heterogeneity by BMI in first pregnancy with 33.6% and 43.6% in women with BMI <25 and ≥25, respectively. As GDM is strongly associated with prepregnant BMI,[12] GDM recurrence is likely to be dependent on maternal baseline BMI. GDM recurrence in our study is comparable to American studies with similar design, revealing an overall GDM recurrence rate of 38.2% (95% CI, 35.0-41.4) (age adjusted),[42] and 41.3% in second pregnancy.[232] Another American population-based study found a GDM recurrence rate in second pregnancy of 47.7%. BMI was not reported in this study and may be higher than the 28% overweight and 26% obese in our GDM population, which is likely to explain the higher GDM recurrence rate.

Recurrence rate of GDM is inconsistent across studies and, strongly influenced by maternal ethnicity and parity.[92,233] In a review of 13 studies recurrence rate varied between 30-84%,[92] and a meta-analysis of 18 studies found a pooled recurrence rate of 48% (95% CI 41-54%).[233] The difference in prevalence across studies may be

explained by difference in design (such as use of cross-sectional data), and different populations studied. Estimates of GDM recurrence has been found to be fairly consistent, regardless of different categorisation approaches,[234] and different screening strategies contributing to variation in recurrence rate seem relatively small.[92]

Primiparous women have lower recurrence of GDM compared to multiparous women,[228,233] and an American cohort study analysing GDM recurrence in first, second and third pregnancy, found that the magnitude of risk increased with the number of prior pregnancies with GDM.[232] As our population consists solely of women with their first and second pregnancy, this may explain lower recurrence rate in our study.

Maternal BMI in first pregnancy and maternal age at the start of second pregnancy were positively associated with GDM recurrence. The literature evaluating risk factors for GDM recurrence is however inconsistent,[92,228,235] and an explanation could be the use of cross-sectional studies when evaluating risk factors.[228,235] Standard cross-sectional design pools births to mothers with unequal sibship sizes and unequal history of GDM, and does not take into account the dependency between GDM risk and women's reproductive history.

6. CONCLUSIONS

6.1 Paper I

Prepregnant obesity was associated with a two- to three-fold increased risk of perinatal death when compared to normal weight women. Recreational physical activity during pregnancy modified the association: Women with prepregnant BMI < 30 had the lowest risk of perinatal mortality among women who performed recreational physical activity during pregnancy. However, for obese women, the lowest risk for perinatal mortality was found among women who were non-active during pregnancy.

6.2 Paper II

Women who increased their weight by ≥ 1 BMI unit from first to second pregnancy had increased risk of GDM in their second pregnancy, compared to women who were stable in weight (-1 to < 1 BMI unit change). Risk of GDM increased with increasing weight gain between pregnancies, both in women with prepregnant BMI <25 and for those with a BMI ≥25 in first pregnancy. Though the highest risk of GDM was found in women who were overweight or obese in first pregnancy, the strongest risk associated with interpregnancy weight gain was found in women with BMI <25 in first pregnancy. Overweight/obese women with a weight loss >2 BMI units from first to second pregnancy had a lower risk of GDM. Weight gain during second pregnancy did not seem to change our results.

6.3 Paper III

Overweight/obese women (BMI ≥25) with a weight loss above 1 BMI unit from first to second pregnancy had a 20-28% lower risk of GDM recurrence, compared to overweight/obese women with stable weight. Gaining weight between pregnancies was associated with increased risk of recurrence of GDM both in women who had

BMI < 25 and ≥ 25 in first pregnancy. GDM recurrence rate was 33.6% and 43.6% for women with BMI <25 and ≥ 25 in first pregnancy, respectively.

7. FUTURE IMPLICATIONS

Higher risk of perinatal mortality in offspring of obese women supports a high risk approach where obese women and their offspring should be monitored closely during pregnancy, delivery and in the early neonatal period. However, our results underline the importance of promoting healthy weight in the reproductive population prior to conception which should to be a public health priority.[5] This necessitates a population strategy approach, to change the obsogenic environment, and to shift the BMI distribution and lower the risk for all women at reproductive age.[236]

Current international and national guidelines on physical activity during pregnancy do not differentiate between women of different BMI categories, only between women who have been physically active prior to pregnancy and those who have not.[135,136,237] Future studies in obese pregnant women of their respons to physical activity, especially the sirculation in the feto-maternal unit, is needed. A major limitation in previous RCT studies is the low compliance in the obese groups, which make interpretation difficult.[211,212] Given the many comorbidities in obese women, physical ativity may need to be customised for obese women. The American College of Sports Medicine suggests that obese women previously sedentary, should begin with lower physical activity intensity than the level recommended for normal weight women.[137] To study rare outcomes like perinatal mortality, we need well-designed, large-scale prospective trials, suitably powered, with harmonised definitions and categorisations of physical activity, and that combine self-reported and objectively measured physical activity.

Maternal BMI at the start of pregnancy and weight change from first to second pregnacy were both associated with risk of GDM in second pregnancy in our study. Norwegian antenatal guidelines advice women with a prepregnant BMI above 25 to be screened for GDM by offering an oral glucose tolerance test in week 24-28,[105] however no attention has been given to maternal weight change between pregnancies. Antenatal care should give special attention to glucose tolerance in women who have increased their BMI ≥1 unit from first to second pregnancy, independent of their

prepregnant BMI. Maternal weight at the time of the GDM diagnosis should be registered in the medical birth registries in addition to weight at the time of delivery. This would enable us to study whether GWG plays a role in development of GDM. We should work from the perspectives that the reproductive cycle begins before conception and throughout the first year post-partum, and that maternal weight status throughout the entire cycle affects both the mother and her child.[39] Efforts should be made to promote healthy weight from preconception throughout reproduction. Today less than 10% of countries address healthy maternal weight across the entire spectrum of childbearing in their national policies.[238]

Despite a well-known high risk of GDM recurrence, care for women in the inter-conception period is lacking.[239] We lack knowledge of the possible benefits of inter-conception interventions for women with a history of GDM.[239,240] Women diagnosed with GDM in their first pregnancy, should be routinely followed up with a focus on diet and exercise in order to reach a healthy weight by the start of their second pregnancy.[240] In countries like Sweden and Norway, where almost every woman attends a post partum check-up and are followed up during the child's first year, may represent an ideal time to systematically focus on promoting healthy weight in the interconception window for women who were diagnosed with GDM in their first pregnancy or who were overweight/obese in their first pregnancy. We need well-designed large intervention studies to evaluate the effect of physical activity/nutrition on the risk of GDM in different populations of women (categories of weight change, BMI, GDM/no GDM in first pregnancy). Research on pathophysiological mechanisms behind GDM needs to be a part of this.

New Guidelines for GDM screening have received much attention both internationally and nationally,[241,242] claiming that the new criteria may triple the GDM prevalence without having an effect on outcome.[241] Arguments such as "too much medicine" and complicating otherwise normal pregnancies have been posed. Health workers have a responsibility to be cautious and not to cause pregnant women undue anxiety.[241] Rather than ignoring guidelines,[243] an international agreement on screening and diagnostic standards for GDM may increase adherence, consistency in

detection and treatment,[91] and strengthening of evidence-based research. There is a need for well-designed research that can evaluate the new Guidelines on GDM. A wide focus on GDM and effects on woman's long term health is needed, rather than the current narrow discussion concerning GDM and effects on birthweight.

8. SOURCE OF DATA

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9. PAPER I-III

I

DOI: 10.1111/1471-0528.13290
www.bjog.org

Pre-pregnant body mass index and recreational physical activity: effects on perinatal mortality in a prospective pregnancy cohort

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Accepted 7 December 2014. Published Online 3 February 2015.

Objective To examine the effect of maternal pre-pregnant body mass index (BMI) and recreational physical activity on perinatal mortality.

Design A prospective cohort study.

Setting The Norwegian Mother and Child Cohort (MoBa), 1999–2008.

Population Singleton pregnancies without congenital anomalies (n = 77 246).

Methods Pre-pregnant BMI was classified as underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), obese (30–34.9) or morbidly obese (BMI ≥35). Risk estimates were obtained by logistic regression and adjusted for confounders.

Main outcome measures Perinatal death (stillbirth ≥22 weeks plus early neonatal death 0–7 days after birth).

Results An increased risk of perinatal death was seen in obese [odds ratio (OR) 2.4, 95% CI (confidence interval) 1.7–3.4] and morbidly obese women (OR 3.3, 95% CI 2.1–5.1) as compared with normal weight women. In the group participating in recreational physical activity during pregnancy, obese women had an OR of 3.2 (95% CI 2.2–4.7) for perinatal death relative to non-obese women. In the non-active group the corresponding OR was 1.8 (95% CI 1.1–2.8) for obese women compared with non-obese women. The difference in perinatal mortality risk related to obesity between the active and non-active groups was statistically significant (P-value for interaction = 0.046, multiplicative model).

Conclusions Maternal obesity was associated with a two- to three-fold increased risk of perinatal death when compared with normal weight. For women with a BMI <30 the lowest perinatal mortality was seen in those performing recreational physical activity at least once a week.

Keywords Body mass index, Norwegian Mother and Child Cohort Study (MoBa), obesity, overweight, perinatal death, recreational physical activity.

Please cite this paper as: Sorbye LM, Klungsoyr K, Samdal O, Owe KM, Morken N-H. Pre-pregnant body mass index and recreational physical activity: effects on perinatal mortality in a prospective pregnancy cohort. BJOG 2015;122:1322–1330.

Introduction

The prevalence of excess weight and obesity is increasing at an alarming rate worldwide. On average, 15% of the adult population in Europe is obese.[1] There is growing evidence that pre-pregnant overweight and obesity represent significant risk factors for maternal and fetal complications during pregnancy, delivery and in the neonatal period.[2–4] A feared complication is the occurrence of perinatal death comprising stillbirth (fetal death ≥22 gestational weeks) and early neonatal death (death of a liveborn within the first 7 days after birth).[5] Perinatal death has short- and long-term consequences for the health and well-being of the mother and her family, and it represents a loss of social and economic development.[6,7]

Previous studies have reported an increased risk of stillbirth and early neonatal death among obese women.[8–10] A similar association has been found between overweight and

stillbirth.[11,12] Several mechanisms have been proposed for the increased risk of stillbirth in these women; however, no biological pathway has been established.[13,14]

The importance of physical activity in promoting health and well-being in the general population has been identified as vital for public health[15] and may also have an important role in the prevention of perinatal mortality. As there is no uniform categorisation of physical activity, previous studies vary according to the definitions used to classify intensity, amount and type of physical activity.[16,17] Studies have shown that moderate physical activity early in pregnancy may improve placental growth and function and hence have beneficial effects on pregnancy outcomes.[18,19] Physical activity before and during pregnancy may also modify the risk of gestational diabetes mellitus (GDM) and pre-eclampsia.[15,16,20] Only one study has found that women doing physical activities during pregnancy are less likely to have a stillbirth[21] but no previous study has assessed the direct modifying effect of recreational physical activity on the relationship between overweight and perinatal mortality. The objective of our study was to examine the effect of maternal pre-pregnant body mass index (BMI) and recreational physical activity on perinatal mortality.

Methods

Data sources

We used data from the Norwegian Mother and Child Cohort Study (MoBa),[22] with linked data from the Medical Birth Registry of Norway (MBRN),[23] using the unique personal identification number given to all Norwegian citizens at birth. The MBRN was established in 1967 and is based on compulsory notification of all live- and stillbirths from 16 weeks of gestation (12 weeks from 2001). Midwives and doctors attending the birth complete a standardised notification form with data on demographics, maternal health before and during pregnancy, previous reproductive history, complications during pregnancy and delivery and pregnancy outcomes.[24] MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[25] All pregnant women giving birth in Norway were invited to participate early in pregnancy through a postal invitation after signing up for the routine ultrasound examination (performed at 17–20 weeks of pregnancy). The ultrasound screening is provided free of charge and more than 95% of all pregnant women in Norway attend.[23] Participants were recruited during 1999–2008 from all Norwegian hospitals and maternity units with more than 100 annual deliveries. The proportion of women consenting to participate was 40.6%.[22] The MoBa study has collected data from numerous questionnaires during pregnancy and after delivery.

Inclusion and definitions

Singleton pregnancies without major congenital anomalies at gestational age ≥22 weeks were included. Congenital anomalies notified to the MBRN are diagnosed at birth or during the following stay at the delivery unit, or at the neonatal intensive care units for infants transferred to such units after birth. Diagnoses are notified as codes based on the International Classification of Diseases (ICD) version 10,[26] or as free text, coded at the MBRN according to the ICD10. Pregnancies resulting in offspring with major congenital anomalies (according to European Surveillance of Congenital Anomalies)[27] were excluded from the present study. Participants in MoBa were included if complete data on pre-pregnant weight and height were available. Women with pre-pregnant BMI below 15, above 60 and with maternal height below 1.40 m were excluded, as the recorded data were considered biologically implausible. Women contributed with their first registered pregnancy in the MoBa cohort.

The main outcome variable was perinatal death, obtained from the MBRN, and comprised stillbirth ≥ 22 weeks' gestation and early neonatal death (liveborn dying 0–7 days after birth).[23] The main exposure was pre-pregnant BMI calculated as weight in kilograms divided by pre-pregnant height in meters squared, and was obtained from the first MoBa questionnaire (Q1), completed in weeks 13–17 of pregnancy. BMI was categorised as underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), obese (30–34.9) and morbidly obese (≥35).[28] Normal weight women were the reference group. In the analyses including recreational physical activity, BMI was categorised as ≥30 representing obesity and <30 representing the reference group. We defined physical activity as participating in any combination of recreational physical activities. Information on recreational physical activity was retrieved from Q1 in which participants were asked how often they engaged in 14 different recreational activities during the last 3 months before pregnancy and until 13–17 weeks in pregnancy. Only women who had answered both the question on recreational physical activity in the last 3 months before pregnancy and until week 17 in the actual pregnancy were included. The questions were identical for the two periods and the level of each activity was defined as never, one to three times per month, once a week, twice a week, or at least three times per week. The following activities were included in a total score representing recreational physical activity 3 months before pregnancy and during the first 3 months of pregnancy: brisk walking, running/jogging/orienteering, bicycling, fitness training/resistance training, aerobics for pregnant women, low impact aerobics, high impact aerobics, dancing, skiing, ball games, swimming, horseback riding, strolling and other. 'Strolling' and 'other' were included in the analyses, but were coded as 0 score.

Women were categorised into two categories: *physically active* (performing recreational physical activity at least once a week) and *non-active* (performing recreational physical activity less than once a week).

Data on maternal smoking at the beginning of pregnancy (none, sometimes, daily) was retrieved from the MBRN. In cases with missing information, information in MoBa Q1 was used. Maternal age (from the MBRN) represented years at the time of delivery (<20, 20–35, >35 years), and parity (from the MBRN) represented the number of previous births (nulliparous or multiparous). Marital status (married/cohabitant or other) was retrieved from the MBRN. Education level was retrieved from MoBa Q1 and represented maternal fulfilled education at the start of pregnancy (9–12, 13–16, ≥17 years). The MBRN was notified of maternal medical conditions before and during pregnancy by means of check boxes or free text on the notification form, and free text was coded at the MBRN according to the ICD-10.

Statistical analyses

Univariate logistic regression was used to estimate the association between pre-pregnant BMI and perinatal death. Odds ratios (OR) with 95% confidence interval (CI) were calculated for each BMI group with normal weight as the reference group. Multivariate logistic regression models were used to adjust for maternal age at delivery, parity, marital status, smoking and chronic hypertension. All potential confounders were modelled as categorical factors, as shown in the footnotes to Table 2. To estimate the role of recreational physical activity as a moderator in the relationship between BMI and perinatal death, we studied whether there was a significant interaction between BMI and physical activity in a multiplicative model, using logistic regression analysis. Associations were considered statistically significant at the 5% level. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, version 20, www.spss.com).

Results

The MoBa cohort included 95 200 mothers and 108 843 pregnancies were available when analysing MoBa Q1. In the primary analyses, 77 246 pregnancies were included. As shown in Figure 1, women with pregestational diabetes, multiple pregnancies or offspring with major congenital anomalies were excluded, as these are independent factors predisposing for perinatal death.[29–31] In the logistic regression analyses, women with missing data on smoking or chronic hypertension (2592 mothers, 3.4%) were included by simple imputation methods by assigning a separate value for the missing data. Women who had answered the questionnaire on recreational physical activity from the first version of Q1 were excluded as the questions differed from those in the latter version. In the analyses assessing recreational physical activity, information on this variable was missing for 4940 mothers (6.4%), giving 72 306 pregnancies for the secondary analyses.

Among the included women, 65.6% were classified as normal weight, 3.1% as underweight, 21.7% as overweight, 7.0% as obese and 2.6% as morbidly obese according to their pre-pregnant BMI (Table 1). The overall perinatal mortality was 3.9 per 1000 births ($n = 299$). Generally, there was a significant trend towards increasing perinatal mortality with increasing BMI (Table 2).

In the univariate analyses, obese mothers had a more than doubled risk of a perinatal loss compared with normal weight mothers, and morbidly obese mothers had a three-fold increased risk of perinatal death (Table 2). Maternal age, parity, education, marital status, smoking and chronic hypertension were evaluated as potential confounders for the relationship between BMI and perinatal death. However, education was not significantly related to perinatal mortality and was not included in the final model. The final logistic regression model only slightly changed the crude estimates (Table 2).

The levels of recreational physical activity before and during pregnancy according to maternal BMI are illustrated in Figure 2. For women with a BMI at and above 18.5, the proportion participating in recreational physical activity decreased linearly with increasing level of BMI (Figure 2). The level of physical activity decreased in pregnancy across all BMI groups.

Overall, performing physical activity at least once a week was associated with a non-significant decrease in perinatal mortality relative to not participating in physical activity, with crude OR at 0.8 (0.6–1.1) for physical activity before pregnancy and OR 0.8 (0.7–1.1) for physical activity during pregnancy. For *physically active* women in pregnancy the absolute risks of perinatal mortality (per 1000) in underweight, normal weight, overweight and obese women were 3.53, 2.91, 3.58 and 9.85. The corresponding absolute risks for the *non-active* women were 4.76, 3.84, 3.85 and 6.78. Due to limited numbers of deaths in each group, all confidence intervals were wide and overlapping. Hence, in women with a BMI below 30, the lowest absolute perinatal mortality was found in women performing recreational physical activity at least once a week during pregnancy. However, in obese women (BMI ≥30) the lowest absolute perinatal mortality was in the *non-active* group. The same trend was found for women engaging in physical activity prior to pregnancy.

Being obese (BMI ≥30) was associated with a 150% excess risk of a perinatal loss compared with women with BMI <30 (crude OR 2.5, 95% CI 1.9–3.4). When testing the interaction between BMI and recreational physical

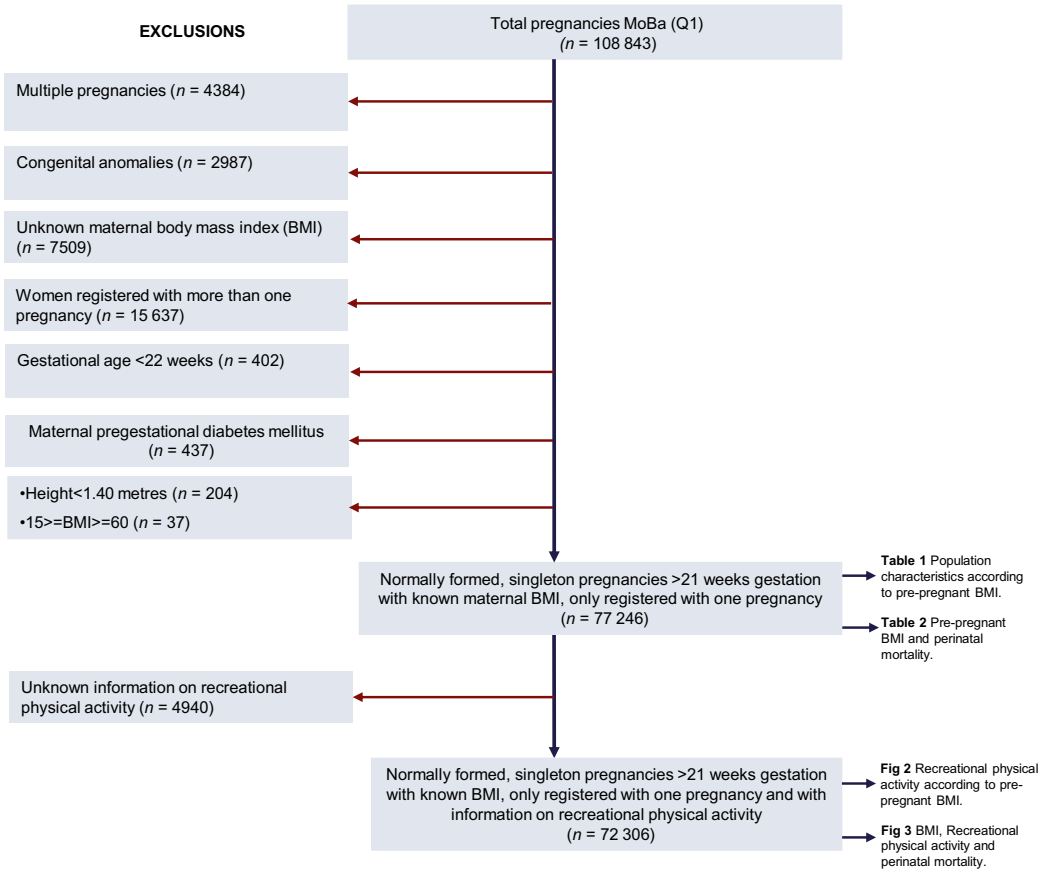

Figure 1. Flowchart showing inclusion of mothers in the study, The Mother and Child Cohort Study 1999–2008.

activity (≥once a week) during pregnancy in a logistic regression model, the interaction term was statistically significant (*P*-value for interaction = 0.046, multiplicative model). Obese women in the *non-active* group (n = 25 432) had an 80% excess risk of a perinatal loss (crude OR 1.8, 95% CI 1.1–2.8) compared with women with BMI <30, and the corresponding excess risk for obese women performing physical activity at least once a week during pregnancy (n = 46 874) was 220% (crude OR 3.2, 95% CI 2.2–4.7). Adjusting for confounders only marginally changed the estimates (ORs 1.7 (95% CI 1.1–2.8) and 3.1 (95% CI 2.1–4.5), respectively.

In a sensitivity analysis, we assigned all the 4940 women with missing information on recreational physical activity to the active group and then to the non-active group. Independent of the group to which they were assigned, adding the 4940 women with missing information on recreational physical activity did not alter our results or conclusions.

Testing the interaction between BMI and recreational physical activity before pregnancy, the interaction term was not statistically significant (*P*-value for interaction = 0.172, multiplicative model). Including recreational physical activity as a potential confounder in the logistic regression model in addition to the previously described confounders, the adjusted OR of a perinatal loss for women with BMI ≥30 relative to BMI <30 was 2.4 (95% CI 1.8–3.3) when adjusting for physical activity before pregnancy and 2.4 (95% CI 1.8–3.2) when adjusting for physical activity during pregnancy.

Figure 3 shows the relationship between BMI and perinatal mortality when using four BMI categories stratified on recreational physical activity during pregnancy (at least

Table 1. Population characteristics according to pre-pregnant body mass index (n = 77 246), The Norwegian Mother and Child Cohort Study 1999–2008

Body mass index	<18.5 (%)	18.5–24.9 (%)	25–29.9 (%)	30–34.9 (%)	≥35 (%)	Total (%)
Total	2423 (3.1)	50 676 (65.6)	16 791 (21.7)	5376 (7.0)	1980 (2.6)	77 246 (100)
Maternal age						
<20 years	99 (4.1)	497 (1.0)	115 (0.7)	47 (0.9)	17 (0.9)	775 (1.0)
20–35 years	2049 (84.6)	41 750 (82.4)	13 578 (80.9)	4373 (81.3)	1594 (80.5)	63 344 (82.0)
>35 years	275 (11.3)	8429 (16.6)	3098 (18.5)	956 (17.8)	369 (18.6)	13 127 (17.0)
Parity						
Nulliparous	1239 (51.1)	23 410 (46.2)	6809 (40.6)	2161 (40.2)	769 (38.8)	34 388 (44.5)
Multiparous	1184 (48.9)	27 266 (53.8)	9982 (59.4)	3215 (59.8)	1211 (61.2)	42 858 (55.5)
Education						
9–12 years	1000 (41.3)	15 377 (30.3)	6627 (39.5)	2610 (48.5)	1085 (54.8)	26 699 (34.6)
13–16 years	755 (31.2)	20 209 (39.9)	6547 (39.0)	1846 (34.3)	635 (32.1)	29 992 (38.8)
≥17 years	492 (20.3)	12 438 (24.6)	2832 (16.9)	661 (12.3)	181 (9.1)	16 604 (21.5)
Missing	176 (7.3)	2652 (5.2)	785 (4.7)	259 (4.8)	79 (4.0)	3951 (5.1)
Married/cohabitant						
Yes	2228 (92.0)	48 754 (96.2)	16 203 (96.5)	5135 (95.5)	1869 (94.4)	74 189 (96.0)
No	195 (8.0)	1922 (3.8)	588 (3.5)	241 (4.5)	111 (5.6)	3057 (4.0)
Maternal smoking						
None	2056 (84.9)	44 345 (87.5)	14 644 (87.2)	4713 (87.7)	1747 (88.2)	67 505 (87.4)
Sometimes	72 (3.0)	1527 (3.0)	525 (3.1)	162 (3.0)	53 (2.7)	2339 (3.0)
Daily	227 (9.4)	3573 (7.1)	1277 (7.6)	400 (7.4)	135 (6.8)	5612 (7.3)
Missing	68 (2.8)	1231 (2.4)	345 (2.1)	101 (1.9)	45 (2.3)	1790 (2.3)
Chronic hypertension*						
No	2375 (98.0)	49 760 (98.2)	16 499 (98.3)	5243 (97.5)	1913 (96.6)	75 790 (98.1)
Yes	3 (0.1)	174 (0.3)	98 (0.6)	68 (1.3)	42 (2.1)	385 (0.5)
Missing	45 (1.9)	742 (1.5)	194 (1.2)	65 (1.2)	25 (1.3)	1071 (1.4)
Gestational diabetes mellitus						
No	2420 (99.9)	50 428 (99.5)	16 600 (98.9)	5256 (97.8)	1876 (94.7)	76 580 (99.1)
Yes	3 (0.1)	248 (0.5)	191 (1.1)	120 (2.2)	104 (5.3)	666 (0.9)
Gestational hypertensive disorders**						
No	2301 (95.0)	47 946 (94.6)	15 400 (91.7)	4679 (87.0)	1651 (83.4)	71 977 (93.2)
Yes	77 (3.2)	1988 (3.9)	1197 (7.1)	632 (11.8)	304 (15.4)	4198 (5.4)
Missing	45 (1.9)	742 (1.5)	194 (1.2)	65 (1.2)	25 (1.3)	1071 (1.4)

*Blood pressure ≥140/90 mm Hg prior to pregnancy or before week 20.
**Includes both pre-eclampsia/eclampsia (blood pressure ≥140/90 mm Hg in at least two readings ≥6 hours apart accompanied by proteinuria (two urinary dipstick readings of ≥1) and gestational hypertension (blood pressure ≥140/90 mm HG only during pregnancy).

Table 2. Perinatal death (PDOD) in relation to pre-pregnant body mass index (BMI) (n = 77 246), The Norwegian Mother and Child Cohort Study 1999–2008

Maternal BMI	Total no.					
	Births	PDOD (per 1000)	Crude OR*	95% CI	Adjusted OR**	95% CI
<18.5	2423	9 (3.7)	1.1	0.6–2.2	1.1	0.6–2.2
18.5–24.9	50 676	166 (3.3)	1.0	Reference	1.0	Reference
25.0–29.9	16 791	61 (3.6)	1.1	0.8–1.5	1.1	0.8–1.5
30–34.9	5376	42 (7.8)	2.4	1.7–3.4	2.4	1.7–3.3
≥35	1980	21 (10.6)	3.3	2.1–5.1	3.1	1.9–4.9

*P-value for trend = 0.001.
**Odds ratio adjusted for maternal age [<20, 20–35(reference), >35 years], parity [nulliparous/multiparous (reference)], marital status [married/cohabitant yes (reference)/no], chronic hypertension [yes/no (reference)] and smoking [none (reference), sometimes, daily].

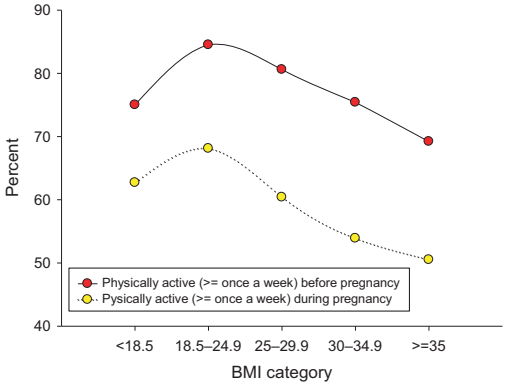

Figure 2. Recreational physical activity during last 3 months before pregnancy and in the first 3 months of pregnancy, according to body mass index (BMI) category (n = 72 306). The Mother and Child Cohort Study 1999–2008.

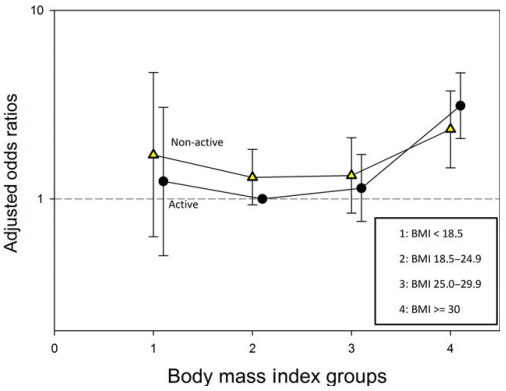

Figure 3. Pre-pregnant body mass index (BMI), recreational physical activity in pregnancy and the risk of perinatal mortality. Logistic regression analysis adjusted for maternal age, parity, marital status, chronic hypertension and smoking (n = 72 306). The Norwegian Mother and Child Cohort Study, 1999–2008.

once a week, yes/no). Normal weight women performing physical activity at least once a week were chosen as the common reference group due to the lowest absolute risk of perinatal death in this group. For all BMI groups except the highest, the OR point estimates of a perinatal loss were higher among the non-active than the active women, although confidence intervals overlapped. In the highest BMI group (≥30), however, this relation was reversed. Among the obese women, the non-active women had a lower OR point estimate of a perinatal loss than the active women, but again, confidence intervals overlapped (Figure 3).

We compared obese women in the physically *active group* (n = 3656) with the *non-active* group (n = 3244) with regard to maternal age, parity, marital status, education, smoking and maternal comorbidity. Obese women in the *active* group had a higher proportion of nulliparous women ($P < 0.001$, Chi-squared test), lower proportions of women with the lowest education, and higher proportions of women with the highest education ($P < 0.001$). Chronic hypertension ($P = 0.029$) and GDM ($P = 0.003$) were less common in the *active* group. There were no statistical differences with regards to smoking ($P = 0.836$), marital status ($P = 0.247$), maternal age ($P = 0.559$) or pre-eclampsia ($P = 0.460$) between the *active* and *non-active* groups of obese women.

We looked closer at obese women with a perinatal loss (n = 58) and obese women with no loss (n = 6842) with regard to the pattern of recreational physical activity before and during pregnancy. Among the obese women with a perinatal loss, 60% were *physically active* both before and during pregnancy, 17% were *physically active* before pregnancy and *non-active* during pregnancy, 21% were *non-active* both before and during pregnancy, and only one woman was *non-active* before pregnancy and *physically active* during pregnancy. The corresponding figures for obese women with no loss were 50%, 24%, 23% and 3%. The differences were, however, not statistically significant ($P = 0.402$, Chi-squared test).

Discussion

Main findings

Obese mothers had a two- to three-fold increased risk of a perinatal loss compared with normal weight women, and recreational physical activity during pregnancy played a role in this relationship. Unexpectedly, the OR of a perinatal loss associated with BMI ≥30 was higher among women performing recreational physical activity at least once a week during pregnancy than among non-active women, when compared with corresponding women with BMI <30. When using four BMI categories, women in all categories except the highest (≥30) had lower OR point estimates of perinatal loss when they were active than non-active during pregnancy, although the differences were not statistically significant.

Previous studies demonstrate that maternal pre-pregnancy obesity is associated with an increased risk of perinatal loss when compared with normal pre-pregnancy weight[4,9,10,13] but conflicting findings exist.[3] We found a non-significant increase in the risk of a perinatal loss among overweight women (BMI 25–29.9), similar to other studies.[9,10] However, there are large population-based studies and meta-analyses that have concluded that overweight women have an increased risk of stillbirth[4,12,13] and

perinatal mortality,[13] illustrating the importance of large sample sizes when studying rare outcomes.

Recreational physical activity may prevent gestational diabetes and pre-eclampsia.[15,16,20] Unexpectedly, we found a stronger association between obesity (BMI ≥30) and perinatal mortality among women participating in recreational physical activity during pregnancy than among women who did not. For physical activity during pregnancy, the associations between obesity (BMI ≥30 versus <30) and perinatal mortality differed significantly between the active and non-active groups. Another study from the MoBa cohort, assessing the effect of physical activity on pre-eclampsia, concluded that the protective effect was strongest for women with a BMI <25 and absent in women with a BMI >30.[32] To our knowledge, only one previous study exists[21] that has reported an association between physical activity during pregnancy and a reduced prevalence of stillbirth. That study did not, however, take BMI into consideration and the generalisability of the study was limited.[21] A prospective study from the Danish National Birth Cohort that treated physical activity during pregnancy as a confounder, did not find that physical activity significantly influenced the association between obesity and stillbirth.[33]

Strengths and limitations

The use of data from this large prospective population-based cohort together with a long recruitment period contribute to variability and strengthen our study.[25] The MoBa study has been validated and represents a valid source for exposure–outcome association studies.[34] Record linkage with the MBRN with compulsory notification of perinatal deaths ensured ascertainment of the outcome variable. Possible misclassification in exposure is non-differential and unrelated to the outcome due to the prospective design.

There are, however, some limitations to our study. The MoBa cohort is not quite representative of the Norwegian population, as women with lower socioeconomic status are underrepresented.[34] Although this selection bias has implications for generalising prevalence estimates, it does not seem to have implications for exposure–outcome associations.[34] Lack of diversity in ethnicity limits the generalisability to more inhomogeneous populations.[25] We relied on self-reported data on weight, height and recreational physical activity. Due to social desirability, self-reported weight is likely to be underreported and height overreported,[35] causing a possible misclassification of the exposure variable. This is likely to result in an underestimation of the true BMI and the risk associated with overweight and obesity.

The MoBa questionnaires on recreational physical activity in weeks 15–17 have been validated in a subsample of pregnant women and a significant association between self-reported and objectively measured recreational physical activity was found.[36] However, there is evidence that physical activity is generally overreported, making underestimation of the true effect of physical activity likely.[37] An overreporting of activity with the following underestimation of true effect would be independent of pregnancy outcome, and non-differential. We lacked information on the intensity and duration of recreational physical activity and, according to Bouchard et al.,[38] it is important take these factors into account when assessing the nature of recreational physical activity. Other domains of physical activity may interfere with the relationship between pre-pregnant BMI and perinatal death. This was beyond the scope of our study, but should be included in future studies.

Despite a large sample size, the number of perinatal deaths was limited, and the numbers were too few to analyse the potentially modifying effect of physical activity when using more than two categories of BMI.

Interpretation

The biologic underpinnings of the excess risk of perinatal death in obese women remain unknown, although several mechanisms have been proposed.[12] The presence of endothelial dysfunction in obese women may be associated with impaired early placental function causing stillbirth.[9,33] According to Kristensen et al.[9] a similar trend for causes of neonatal death (0–28 days) was not found. Obesity has been associated with a five-fold increase in risk of stillbirth due to placental dysfunction.[33] In an intervention study using an animal model, a high fat diet early in life led to increases in body fat, serum leptin and triglycerides prior to pregnancy and a three-fold increase in fetal death and decreased neonatal survival.[39] The outcome was associated with a poor development of the placental vasculature with reduced blood flow to the placenta and reduced oxygenation of fetal tissues. This may contribute to hypoxia, poor fetal growth and fetal and neonatal mortality, and underlines the importance of future studies focusing on the placental effect.

Regular physical activity during pregnancy may stimulate placental growth and be an important mechanism for improving placental functional capacity.[18,40] A physiologic explanation could be the link with the intermittent reductions in uterine blood flow that occurs during sustained weight-bearing exercise and the expanded blood volume observed in pregnant exercisers.[18] However, our study suggests the possibility that the effect of physical activity on perinatal mortality is dependent on maternal BMI. It is a possibility that metabolic alterations in obese women make them more vulnerable and less adaptive to stress during physical activity in pregnancy. Our results were unexpected and need to be tested in other studies. If replicated, investigations on the underlying mechanisms explaining the inter-

action between categories of BMI and physical activity on risk of perinatal loss are needed.

Our study underlines the importance of preventing obesity in women before conception in order to reduce perinatal mortality in their offspring. As a predictor, obese women do seem to have increased risk of perinatal losses and should be monitored closely during pregnancy. Current guidelines on physical activity in pregnancy do not differentiate between pre-pregnant BMI categories, only between those who have been physically active before pregnancy and those who have not.[41] Given the many comorbidities associated with obesity, guidelines on physical activity may need to be customised for obese women.

Conclusions

Pre-pregnant obesity was associated with a two- to three-fold risk increase of perinatal death when compared with normal weight. For women with a BMI <30, the lowest risk of perinatal death was found among women performing recreational physical activity. For obese women, the risk associated with overweight was highest in those participating in recreational physical activity during pregnancy. Our results were unexpected and need to be replicated. The use of self-reported data may represent a bias in our study; however, misclassifications are likely to be non-differential. Future studies should endeavour to use objective measures of physical activity in addition to self-reported data.

Disclosure of interests

There are no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject of this manuscript.

Contribution to authorship

LMS takes the responsibility for the integrity of the data and the accuracy of the data analysis. LMS designed the study, performed the analyses of data and was responsible for the interpretation of data analysis and the completion of the manuscript. KK contributed to interpretation of data analysis and the completion of the manuscript. OS contributed to designing the study and completion of the manuscript. KMO gave supportive help in making the syntax for the variable on recreational physical activity and contributed to the completion of the manuscript. NHM designed the study and contributed to interpretation of data analysis and completion of the manuscript.

Details of ethics approval

Informed consent was obtained from all participants in MoBa upon recruitment.[24] The current study has been approved by the MoBa steering committee, and was received ethical approval from the Western Regional Ethical Review Board (project number 270.08, approval no: 2008/14908-CAG) on 8 January 2009. Data contained no personal identifiable information, ensuring that the data were anonymous.

Funding

The Schering Plough Research Foundation through the Norwegian Gynaecological Society has contributed with a research grant and is acknowledged. Haukeland University Hospital, Department of Research and Development, has granted financial support through a 6-month scholarship.

Acknowledgements

MoBa is supported by the Norwegian Ministry of Health, and the Ministry of Education and Research, NIH/NIEHS (contract no. N01-ES-75558), NIH/NINDS (grant no. 1 UOI NS 047537-01 and grant no. 2 UOI NS 047537-06A1). We are grateful to all the families in Norway who took part in this ongoing cohort study. ■

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II

PLOS | MEDICINE

RESEARCH ARTICLE

Gestational diabetes mellitus and interpregnancy weight change: A population-based cohort study

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Citation: Sorbye LM, Skjaerven R, Klungsoyr K, Morken NH (2017) Gestational diabetes mellitus and interpregnancy weight change: A population-based cohort study. PLoS Med 14(8): e1002367. https://doi.org/10.1371/journal.pmed.1002367

Academic Editor: Ronald C. W. Ma, Chinese University of Hong Kong, CHINA

Received: February 17, 2017

Accepted: June 26, 2017

Published: August 1, 2017

Data Availability Statement: Data belongs to the Norwegian Institute of Public Health and are only available to researchers who have applied for the data at the Medical Birth Registry of Norway and have the necessary approval from a Regional Ethical Committee in Norway. For contact with the Medical Birth Registry of Norway, see: Folkehelseinstituttet@fhi.no, contact person: Marta Ebbing

Funding: This study was funded by a 3-year scholarship from The Norwegian National Advisory Unit on Women's Health at Oslo University

Abstract

Background

Being overweight is an important risk factor for Gestational Diabetes Mellitus (GDM), but the underlying mechanisms are not understood. Weight change between pregnancies has been suggested to be an independent mechanism behind GDM. We assessed the risk for GDM in second pregnancy by change in Body Mass Index (BMI) from first to second pregnancy and whether BMI and gestational weight gain modified the risk.

Methods and findings

In this observational cohort, we included 24,198 mothers and their 2 first pregnancies in data from the Medical Birth Registry of Norway (2006–2014). Weight change, defined as prepregnant BMI in second pregnancy minus prepregnant BMI in first pregnancy, was divided into 6 categories by units BMI (kilo/square meter). Relative risk (RR) estimates were obtained by general linear models for the binary family and adjusted for maternal age at second delivery, country of birth, education, smoking in pregnancy, interpregnancy interval, and year of second birth. Analyses were stratified by BMI (first pregnancy) and gestational weight gain (second pregnancy). Compared to women with stable BMI (−1 to 1), women who gained weight between pregnancies had higher risk of GDM—gaining 1 to 2 units: adjusted RR 2.0 (95% CI 1.5 to 2.7), 2 to 4 units: RR 2.6 (2.0 to 3.5), and $\geq$4 units: RR 5.4 (4.0 to 7.4). Risk increased significantly both for women with BMI below and above 25 at first pregnancy, although it increased more for the former group. A limitation in our study was the limited data on BMI in 2 pregnancies.

Conclusions

The risk of GDM increased with increasing weight gain from first to second pregnancy, and more strongly among women with BMI < 25 in first pregnancy. Our results suggest weight change as a metabolic mechanism behind the increased risk of GDM, thus weight change should be acknowledged as an independent factor for screening GDM in clinical guidelines.

Hospital, Rikshospitalet, Norway. The research fellow in this scholarship is the corresponding author LMS. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors of this manuscript declare no competing interests.

Abbreviations: a, adjusted; BMI, Body Mass Index; GDM, Gestational Diabetes Mellitus; MBRN, Medical Birth Registry of Norway; RR, relative risk; HELLP, Hemolysis Elevated Liver enzymes and Low Platelet count.

Promoting healthy weight from preconception through the postpartum period should be a target.

Author summary

Why was this study done?

- Being overweight during pregnancy is an important risk factor for Gestational Diabetes Mellitus (GDM); however, the underlying mechanisms are not clear.
- Recent evidence has found that women who increase their weight from first to second pregnancy increase the risk of GDM, suggesting weight as a causal mechanism behind GDM.
- Research is not consistent on whether the association is dependent on the woman's weight status when she enters her first pregnancy.

What did the researchers do and find?

- In this observational cohort study, we used data from the population-based Medical Birth Registry of Norway and included 24,198 mothers with their first and second pregnancy during 2006–2014.
- We investigated if a change in Body Mass Index (BMI) between first and second pregnancy affected the risk of GDM in the second pregnancy and if the association was dependent on the woman's prepregnant BMI in first pregnancy
- The risk of GDM in second pregnancy increased with increasing weight gain between pregnancies, and more strongly among women who had a BMI below 25 (kilo/meters squared) in first pregnancy.
- Decreasing BMI by >2 units from first to second pregnancy had a preventive effect on GDM in overweight and obese women.

What do these findings mean?

- Weight gain between pregnancies should be evaluated as an independent risk factor for screening GDM in clinical antenatal guidelines.
- Our results need to be replicated in other populations, and they underline the importance of future research on pathophysiologic mechanisms behind the development of GDM.
- Efforts to promote healthy weight in the reproductive population need to expand their focus to include healthy maternal weight from preconception throughout reproduction.

Introduction

Worldwide, overweight has reached epidemic proportions [1, 2], with serious consequences for reproductive health. Being overweight during pregnancy increases the risk of complications in pregnancy, in childbirth, and for the newborn child [3–7] and is an important risk factor for Gestational Diabetes Mellitus (GDM) [8–11]. GDM is defined as glucose intolerance of various degrees that is first detected during pregnancy [12], and the prevalence of GDM has increased, with variation by countries [11, 13–15]. GDM increases the risk of immediate adverse pregnancy and infant outcomes [16] and, in the long term, the risk of metabolic syndrome and Type 2 Diabetes Mellitus in the mothers [17–19]. Children born to GDM mothers have an increased risk of high birthweight and being overweight in adolescence [20].

The underlying genetic, physiological, and environmental factors behind the development of GDM are not fully understood [12, 21]. Both prepregnant Body Mass Index (BMI) and gestational weight gain are risk factors for GDM, but evidence of an independent or joint effect is inconsistent [22–24]. Most observational studies have not been able to evaluate shared genetic and early environmental risk factors within families. Recent studies have suggested interpregnancy weight change as part of the causal mechanism behind the risk of GDM and other adverse pregnancy outcomes in the second pregnancy; however, knowledge of this is scarce [25–27]. It has also been suggested that the effect of interpregnancy weight change may depend on the woman's prepregnant BMI during her first pregnancy [25–27]. One study found that women gaining weight between their first and second pregnancy increased their risk for GDM in their second pregnancy, even though they were normal weight during both pregnancies [25]. Previous studies have not been able to study the importance of gestational weight gain upon this association. We estimated the association between prepregnancy BMI changes from the first to the second pregnancy and GDM in the second pregnancy for women giving birth in Norway. Secondly, we explored the roles of prepregnant BMI in first pregnancy and gestational weight gain in second pregnancy as effect modifiers.

Methods

Data sources

This observational cohort study complies with the guidelines of the Declaration of Helsinki. The project was approved by the Regional Ethics Committee, REK VEST (2015/1728). Informed consent was not required as data were de-identified, and the researchers did not have any additional patient contact. We used prospectively collected data from the population-based Medical Birth Registry of Norway (MBRN) [28]. Using the unique national identification number, each child born was linked to his/her mother, so that each record consisted of the mother and her successive 2 first births (2006–2014). The MBRN was established in 1967 and is based on compulsory notification of all live- and stillbirths from 16 weeks of gestation (12 weeks from 2002). Midwives and doctors attending the birth complete a standardized notification form on demographics, maternal health before and during pregnancy, previous reproductive history, complications during pregnancy and delivery, and pregnancy outcomes [29]. Data on maternal height and weight prior to conception are self-reported. Weight at the end of pregnancy is defined as maternal weight measured at last antenatal visit or when arriving at the delivery ward. The collection of maternal height and weight information in MBRN began in 2006 when Norway adopted a revised electronic birth notification system, but the implementation of the system by all delivery units was not complete until 2014. The proportion of

registered maternal height and weight in MBRN steadily increased from 0.1% in 2006 to 71.6% of births in 2014 [S1 Fig]. Complete data on prepregnancy height and weight is available for 24% of the women having their first 2 deliveries during 2006–2014. During this period, the distribution of women across the different BMI categories has been stable over time, suggesting that even in years with low reporting, the data are likely representative for the population [30]. Data on country of birth (Nordic defined as Norway, Sweden, Denmark, Finland, and Iceland) was obtained from The National Population Registry, Statistics Norway. Maternal education, defined as the highest achieved years of education classified according to The Norwegian Standard Classification of Education, was obtained from the National Education Database, Statistics Norway.

Inclusions and definitions

Fig 1 shows a flow chart of the included and excluded women in the study.

Prepregnant BMI was calculated from weight in kilograms (kg) divided by height in meters squared (m^2). Our main exposure was interpregnancy weight change defined as prepregnant BMI in second pregnancy minus prepregnant BMI in first pregnancy. Gestational weight gain in second pregnancy was calculated as weight (kg) at the end of pregnancy minus prepregnant weight. A total of 105,429 women delivered their first 2 births during 2006–2014. To be included, women had to have prepregnancy height and weight reported for both pregnancies (n = 24,677).

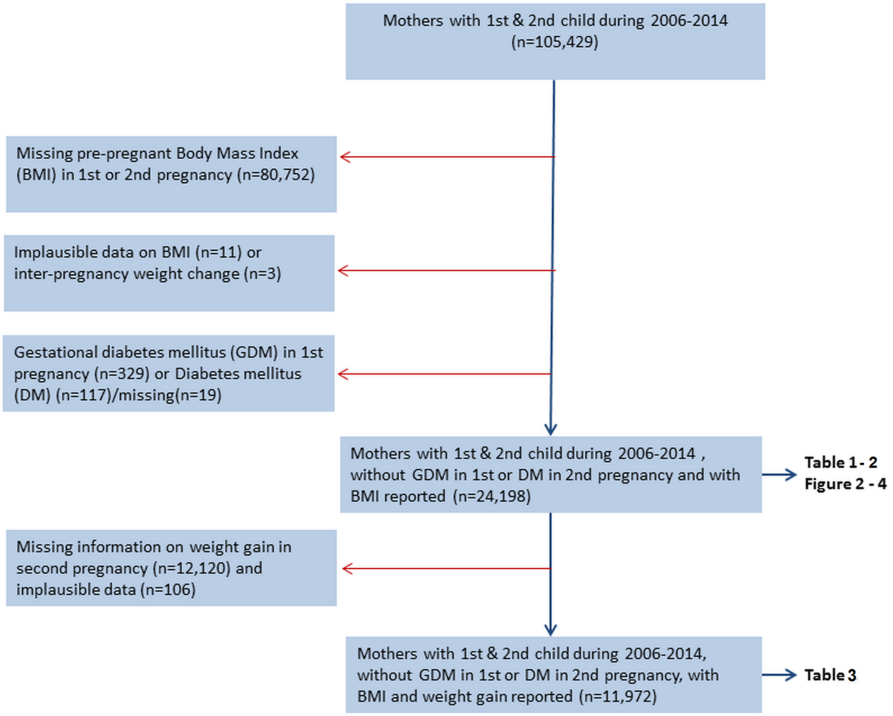

Fig 1. Flow chart showing inclusion and exclusions, The Medical Birth Registry of Norway, 2006–2014.

https://doi.org/10.1371/journal.pmed.1002367.g001

We excluded women with prepregnant BMI below 15 ($n = 11$) and interpregnancy weight change above +30 and below −30 BMI units (kg/m^2) ($n = 3$), as they were considered implausible. To evaluate first-time occurrence of GDM in the second pregnancy, women diagnosed with GDM in their first pregnancy were excluded ($n = 329$). In the analyses exploring the potential effect modifying role of gestational weight gain in second pregnancy, only women who had their weight registered both before and at the end of their second pregnancy were included in the analysis ($n = 11{,}972$). A weight gain above 70 kg during second pregnancy was considered implausible ($n = 6$)

We categorized prepregnancy BMI into underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (≥30) [31]. Prepregnant BMI in first pregnancy was further dichotomized into <25 kg/m^2 versus ≥25 kg/m^2 for stratified analyses. We categorized interpregnancy weight change into 6 groups: <−2, −2 to <−1, −1 to <1 (reference), 1 to <2, 2 to <4, and ≥4 kg/m^2[26, 27]. Gestational weight gain was grouped into the following: weight loss, 0–7.9 kg, 8–15.9 kg, and ≥16 kg [32]. In stratified analyses, women with a weight loss were excluded, and gestational weight gain was dichotomized by the median value: 0–13.9 kg and ≥14 kg. The main outcome was GDM (yes/no), notified by a check box on the birth notification form or as free text coded at the MBRN according to the International Classification of Diseases (ICD) version 10. The diagnostic criteria and screening strategy for GDM are given in the national guidelines for antenatal care and obstetrics made by the Norwegian Society of Gynecology and Obstetrics (in 1998, 2008, and 2014) [33]. GDM is diagnosed when fasting plasma glucose levels are <7.0 millimole (mmol)/liter (l) and serum blood glucose following an oral glucose tolerance test (OGTT) (2 hours after intake of 75 grams oral glucose) is ≥7.8 mmol/l but <11.1 mmol/l. Women follow a standardized antenatal program with regular visits, which include urine stix testing for glucose at each visit. Independent of gestational week, an OGTT is recommended when the stix is positive (≥+++). Women with risk factors (age > 38 years, close relatives with Gestational Diabetes type 1/2, immigrants from the Indian Subcontinent or North Africa, prepregnant BMI > 27 kg/m^2, or prior GDM) will be offered an OGTT as early as possible in pregnancy, and if negative, it will be repeated in week 28–30 [33].

Maternal smoking habits were reported at the end of pregnancy, and women could answer "no," "occasionally," "daily," or they could decline to answer ($n = 2{,}592$). Daily and occasional smokers ($n = 110$) were considered smokers. Interpregnancy interval was calculated as the date of the second birth minus the date of first birth minus the pregnancy length of the second pregnancy, and it was categorized into <12, 12 to <24 (reference), 24 to <36, and ≥36 months. In stratified analyses, the interpregnancy interval was dichotomized: <24 and ≥24 months. The gestational age of the second pregnancy was based on second trimester ultrasound estimations or, if missing, on the mother's last menstrual period.

Statistics

Chi-square tests were used to investigate associations and linear trends between variables. General linear models with extension for the binary family were used to estimate the association between interpregnancy weight change from the first to second pregnancy and the risk of GDM in the second pregnancy. Relative risks (RRs) with 95% CI were calculated for interpregnancy weight-change categories. Maternal age at second delivery (<25, 25–29, 30–34, ≥35 years), country of birth (Nordic/non-Nordic), highest achieved years of education (<11, 11–14, ≥14 years), smoking during pregnancy (yes/no), interpregnancy interval (<12, 12 to <24, 24 to <36, ≥36 months), and year of the second birth (continuous variable) were considered as possible confounders [34] and were adjusted for in the multivariable binary regression

model. The presented adjusted models (n = 20,824) had missing information on covariates in 3,374 (13.9%) women. Missing values for smoking, maternal education, and maternal country of birth were therefore handled by missing imputation using chained equations (MICE) with logistic regression for smoking and maternal country of birth and multinomial logistic regression for maternal education [35] [S1 Table]. When evaluating a potential effect modification by prepregnant BMI in the first pregnancy (BMI $<$ 25 and BMI $\geq$ 25), and gestational weight gain ($<$14 and $\geq$14) in the second pregnancy, we included an interaction term in the multiplicative model evaluated by Likelihood ratio test. To compare the risk of GDM in women with BMI $\geq$ 25 and BMI $<$ 25 in the first pregnancy, we included interpregnancy BMI change as a continuous variable in the interaction term (Likelihood ratio test, Poisson regression). Associations were considered statistically significant at the 5% level. All statistical analyses were performed using STATA IC Statistical software version 14 and Statistical Package for the Social Sciences, version 23 (www.spss.com).

Results

A total of 24,198 mothers were included in the main analysis. Of these, 12,078 (50%) women had information on gestational weight gain (GWG) in their second pregnancy and were included in the analysis evaluating effect modification by GWG. Population characteristics by GDM in second pregnancy are shown in Table 1.

The overall absolute risk of GDM in second pregnancy was 18.1 per 1,000 pregnancies (439/24,198), and the prevalence of GDM increased with increasing level of prepregnant BMI in second pregnancy (p for trend $<$0.001). Interpregnancy weight change from the first to second pregnancy was relatively stable (−1 to $<$1 BMI units) in 47.6% of women (n = 11,512), while 16.8% (n = 4,076) of women had a weight loss of $>$1 BMI unit and 35.6% (n = 8,610) of women gained weight $\geq$1 BMI unit. To evaluate the representativeness of our study population, we compared the study population with the general population in MBRN during 2006–2014 [S10 Table].

During the second pregnancy, 0.8% (100/12,078) of women lost weight ($<$0 kg), 10.5% had a GWG of 0 kg to 7.9 kg, 53.7% had a GWG of 8 kg to 15.9 kg, and 34.9% had a GWG of $\geq$16 kg. Overall, we found a negative correlation between interpregnancy weight change (kg/m^2) and gestational weight gain (kg) in second pregnancy (r −0.20, $p < 0.001$, n = 12,078). For each BMI unit increase from the first to second pregnancy, gestational weight gain in the second pregnancy decreased by 0.53 kg (β: −0.53, 95% CI: −0.58 to −0.49).

Interpregnancy weight change and GDM in second pregnancy

Overall, the risk of GDM in the second pregnancy increased with increasing interpregnancy weight gain between the first and second pregnancy [Fig 2] [Table 2].

Women who gained between 1 and 2 BMI units (kg/m^2) had a doubled risk (adjusted [a] RR 2.0, 95% CI: 1.5–2.7), women gaining between 2 and 4 units had a 2.6x risk (a RR 2.6, 95% CI: 2.0–3.5), and women gaining $\geq$4 BMI units had a 5-fold risk of GDM in second pregnancy (a RR 5.4, 95% CI: 4.0–7.4) compared to women with stable interpregnancy weight (−1 to $<$1). The adjusted model with and without missing imputation can be seen in [S1 Table].

Prepregnant BMI in first pregnancy, interpregnancy weight change, and GDM

In stratified analyses by prepregnant BMI in the first pregnancy, the risk estimates for GDM increased with increasing weight gain between pregnancies and were stronger in women with BMI $<$ 25 in the first pregnancy [Fig 3] [S2 Table]. Women who were overweight (BMI $\geq$ 25)

Table 1. Population characteristics according to GDM in second pregnancy. A population-based cohort study ($n = 24,198$), The Medical Birth Registry of Norway, 2006–2014.

	GDM in Second Pregnancy			
	Yes	**%**	**Total**	***p*-value***
BMI in first pregnancy (kg/m^2)				
<18.5	13	1.2	1,065	<0.001
18.5–24.9	169	1.1	16,052	
25–29.9	142	3.0	4,812	
≥30.0	115	5.1	2,269	
BMI in second pregnancy (kg/m^2)				<0.001
<18.5	5	0.6	897	
18.5–24.9	120	0.8	14,812	
25–29.9	137	2.5	5,534	
≥30.0	177	6.0	2,955	
Gestational weight gain in second pregnancy (kg)				<0.001
<−0.1	4	4.0	100	
0–7.9	57	4.5	1,274	
8–15.9	104	1.6	6,489	
≥16.0	50	1.2	4,215	
Missing	224	1.8	12,120	
Maternal age (years)				<0.001
<25	32	1.1	3,014	
25–29	142	1.7	8,476	
30–34	151	1.7	8,987	
≥35	114	3.1	3,721	
Maternal country of birth				<0.001**
Nordic	315	1.6	19,828	
Non-Nordic	121	2.9	4,215	
Missing	3	1.9	155	
Maternal education (years)				0.034
<11	73	2.1	3,460	
11–13	124	2.0	6,323	
≥14	225	1.6	13,678	
Missing	17	2.3	737	
Smoking				0.516**
No	370	1.8	20,616	
Yes	15	1.5	990	
Missing	54	2.1	2,592	
Interpregnancy interval (months)				<0.001
<12	70	1.5	4,806	
12 to <24	151	1.5	10,342	
24 to <36	114	2.0	5,811	
≥36	104	3.2	3,210	
Missing	0	0.0	29	

*Chi-square test for linear trend.

**Pearson Chi square.

BMI, Body Mass Index; GDM, Gestational Diabetes Mellitus

https://doi.org/10.1371/journal.pmed.1002367.t001

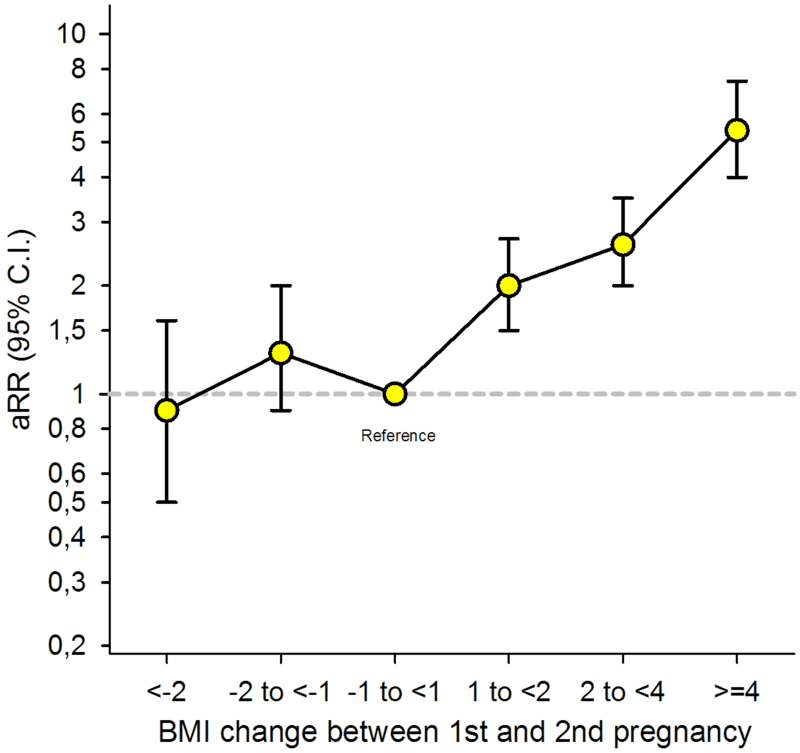

Fig 2. Overall adjusted (a) relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by change in Body Mass Index (BMI) between the first and second pregnancy (n = 24,198), The Medical Birth Registry of Norway 2006–2014. Analysis adjusted for maternal age during the second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking during pregnancy (no [reference],/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

https://doi.org/10.1371/journal.pmed.1002367.g002

in their first pregnancy and who reduced their BMI by ≥2 units prior to their second pregnancy, had a 60% lower risk of GDM in the second pregnancy [a RR 0.4, 95% CI: 0.2–0.8].

Results from the different adjusted models with and without missing imputation are seen in [S3 Table]. When excluding second pregnancies with gestational age below 37 weeks, multiple pregnancies and hypertensive disorders (hypertension during pregnancy, preeclampsia, eclampsia, and Hemolysis Elevated Liver enzymes and Low Platelet counts [HELLP]) (n = 1,755), results remained unchanged [S4 Table]. The prevalence of GDM in second pregnancy was significantly higher in non-Nordic compared to Nordic women (2.9% versus 1.6%, $p < 0.001$) [Table 1]. When we stratified the analysis by the mother's country of birth [S5 Table] and maternal age [S6 Table], the association between interpregnancy weight change and GDM in the second pregnancy remained unchanged. Stratifying the analyses by interpregnancy interval (<24 and ≥24 months) revealed a stronger association between interpregnancy weight gain and GDM in women with an interval below 24 months [S7 Table] (p = 0.001 for interaction, Likelihood-ratio test, n = 20,824).

Table 2. Overall risk for GDM in second pregnancy by interpregnancy change in BMI (n = 24,198), The Medical Birth Registry of Norway 2006–2014.

Interpregnancy BMI Change (kg/m^2)			RR for GDM in Second Pregnancy			
	Total	GDM /1000	Crude RR	95% CI	aRR*	95% CI
<−2	15/1,692	8.9	0.8	0.5–1.4	0.9	0.5–1.6
−2 til <−1	34/2,384	14.3	1.3	0.9–1.9	1.3	0.9–2.0
−1 til <1	126/11,512	10.9	1.0	Reference	1.0	Reference
1 til <2	79/3,814	20.7	1.9	1.4–2.5	2.0	1.5–2.7
2 til <4	97/3,279	29.6	2.7	2.1–3.5	2.6	2.0–3.5
≥4	88/1,517	58.0	5.3	4.1–6.9	5.4	4.0–7.4
Total	439/24,198	18.1	24,198		20,824	

a, adjusted; BMI, Body Mass Index; GDM, Gestational Diabetes Mellitus; RR, relative risk.

*Analysis adjusted for maternal age during the second pregnancy (<25 (reference), 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no[reference],/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of the second birth (continuous).

https://doi.org/10.1371/journal.pmed.1002367.t002

There was a significant interaction between prepregnant BMI (<25 and ≥25) in the first pregnancy and interpregnancy weight change (p = 0.009, Likelihood-ratio test). To test if the association between interpregnancy weight gain and GDM was stronger in women with BMI < 25 in their first pregnancy, we excluded women with interpregnancy weight change <−1 unit (n = 4,076) and added interpregnancy weight change as a continuous variable in the interaction term. Likelihood-ratio test confirmed the heterogeneity in risk (p < 0.001, Poisson regression analysis). To compare the risk of GDM in the second pregnancy in women with

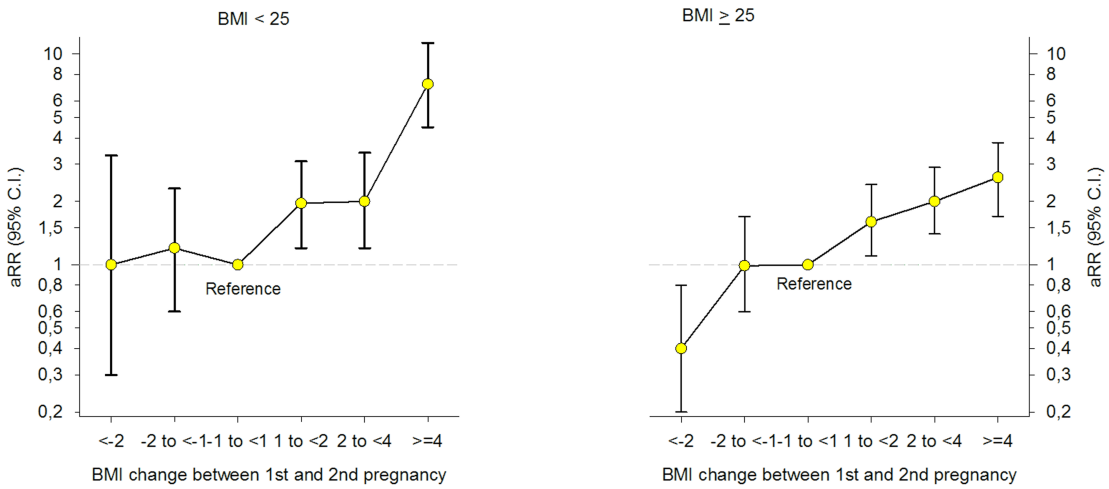

Fig 3. Adjusted (a) relative risk (RR) for Gestational Diabetes Mellitus (GDM) by change in Body Mass Index (BMI) between first and second pregnancy, stratified by BMI < 25 and BMI ≥ 25 in first pregnancy (n = 24,198), The Medical Birth Registry of Norway 2006–2014. Analyses adjusted for maternal age in the second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking during pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of the second birth (continuous).

https://doi.org/10.1371/journal.pmed.1002367.g003

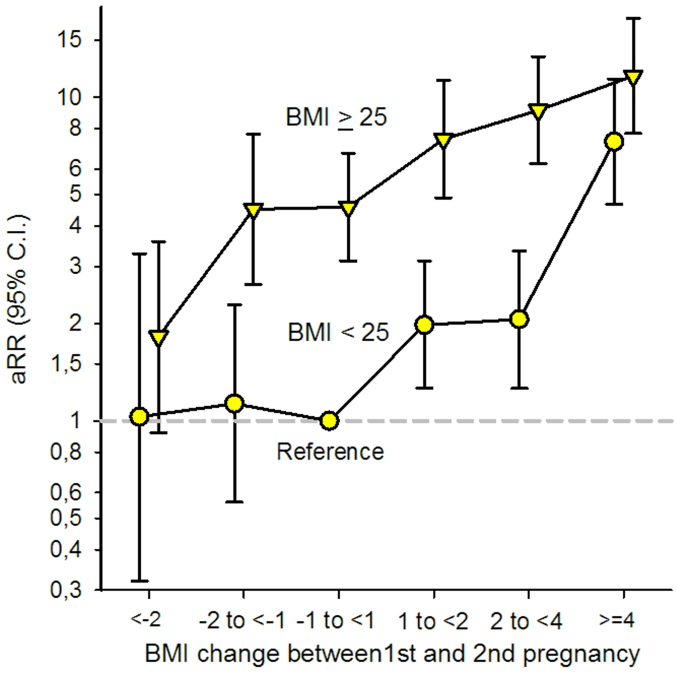

Fig 4. Adjusted (a) relative risk (RR) for Gestational Diabetes Mellitus (GDM) by change in Body Mass Index (BMI) between first and second pregnancy and BMI < 25 and BMI ≥ 25 in first pregnancy (*n* = 24,198), The Medical Birth Registry of Norway 2006–2014. Analysis adjusted for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking during pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

https://doi.org/10.1371/journal.pmed.1002367.g004

prepregnant BMI in their first pregnancy below or above 25 in 1 model, we included both groups in the same model using women with stable BMI (−1 to <1 BMI unit) and a prepregnant BMI < 25 in their first pregnancy as the common reference category. Having BMI ≥ 25 in the first pregnancy was associated with a higher risk of GDM across all interpregnancy weight change categories when compared to women in the reference group [Fig 4].

The role of prepregnant BMI in second pregnancy

We defined prepregnant BMI in the second pregnancy as part of the exposure and the effect that we wished to study; therefore, we did not adjust for BMI in the second pregnancy. In order to find out if the association between interpregnancy weight change and GDM was independent of BMI in second pregnancy, we analyzed women who had prepregnant BMI below 25 both in their first and second pregnancy (n = 14,857) and found the same trend [S8 Table]. In this population, 0.8% (n = 118) developed GDM during the second pregnancy. When stratifying the analyses according to BMI in second pregnancy (n = 24,198), the association between interpregnancy weight gain and GDM remained [S9 Table].

Gestational weight gain in second pregnancy, interpregnancy weight change, and GDM

Overall, we found an inverse linear association between gestational weight gain and GDM in second pregnancy (p for trend <0.001). After excluding women with negative gestational weight gain, the crude RR of GDM in the second pregnancy of women with gestational weight gain 0–13.9 kg was 2.0 (95% CI: 1.5–2.7), compared to women with ≥14 kg (n = 11,972). When we adjusted for prepregnant BMI in second pregnancy and confounders in our model, the RR of GDM in women with gestational weight gain 0–13.9 kg compared to women with ≥14 kg, was 1.9 (95% CI: 1.4–2.5). Testing for an interaction between gestational weight gain (0–13.9 and ≥14 kg) in the second pregnancy and interpregnancy weight change in a binary regression model gave a nonsignificant interaction term (p = 0.822, Likelihood-ratio test, n = 9,978). When we assessed the risk of GDM by interpregnancy weight change in strata of gestational weight gain in second pregnancy, we confirmed the positive association in both groups. The strongest association was found in women gaining ≥14 kg in their second pregnancy, although estimates were not significantly different [Table 3].

Discussion

Principal findings

We found a higher risk of GDM in women who increased their weight by ≥1 BMI unit from their first to second pregnancy compared to women with stable weight (−1 to <1 unit change). The risk estimates for GDM increased with increasing weight gain and applied to both normal-weight (prepregnant BMI < 25) and overweight (prepregnant BMI ≥ 25) women in their first pregnancy. Women with a BMI < 25 in their first pregnancy had the strongest association between interpregnancy weight gain and GDM. A preventive effect on GDM was seen in overweight women (first pregnancy) who reduced their weight by ≥2 BMI units until the second pregnancy.

Interpregnancy weight change, BMI in first pregnancy, and the risk of GDM

Previous studies on interpregnancy weight change and risk of GDM are generally consistent with our findings with some exceptions [25, 36–39]. A Swedish population-based study found

Table 3. RR for GDM in second pregnancy by interpregnancy change in BMI, stratified by GWG in second pregnancy (n = 11,972), The Medical Birth Registry of Norway 2006–2014.

BMI Change Units kg/m2	GWG in second pregnancy 0–13.9 kg						GWG in second pregnancy ≥14.0 kg					
	N	GDM /1000	CrudeRR	95% CI	a RR*	95% CI	N	GDM /1000	Crude RR	95% CI	a RR*	95% CI
<−2	3/281	10.7	0.7	0.2–2.2	0.6	0.1–2.4	3/504	6.0	0.8	0.2–2.8	0.6	0.2–2.8
−2 to <−1	7/494	14.2	0.9	0.4–2.0	0.8	0.3–1.9	6/679	8.8	1.2	0.5–3.0	0.9	0.3–2.8
−1 to <1	40/2,561	15.6	1.0	Reference	1.0	Reference	22/3,059	7.2	1.0	Reference	1.0	Reference
1 to <2	18/994	18.1	1.2	0.7–2.0	1.1	0.6–1.9	15/981	15.3	2.1	1.1–4.1	2.1	1.0–4.2
2 to <4	38/967	39.3	2.5	1.6–3.9	2.2	1.4–3.6	15/695	21.6	3.0	1.6–5.8	2.8	1.4–5.8
≥4	32/508	63.0	4.0	2.6–6.4	4.2	2.5–6.9	11/249	44.2	6.1	3.0–12.5	4.4	1.8–10.4
Total	138/5,805	23.8			4,808		72/6,167	11.7			5,170	

*Adjusted for maternal age in second pregnancy (<25 (reference), 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/Non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking during pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

a, adjusted; BMI, Body Mass Index; GDM, Gestational Diabetes Mellitus; GWG, gestational weight gain

https://doi.org/10.1371/journal.pmed.1002367.t003

that the risk for GDM in the second pregnancy increased linearly with interpregnancy weight gain and was also present in women whose BMI was <25 in both pregnancies [25], consistent with our results. However, for overweight and obese women (BMI > 25 in first pregnancy), they found that only those with a large interpregnancy weight gain of ≥3 BMI units had an increased risk of GDM [25]. A regional cohort study from Belgium found an increased risk of GDM in women who had an interpregnancy weight gain of ≥1 BMI unit but only among women with BMI < 25 in their first pregnancy[37]. An American study also found, as we did, that the risk of GDM associated with interpregnancy weight gain applied both to women with BMI below and above 25 in first pregnancy. The risk estimates were also higher in women who had BMI < 25 in their first pregnancy, similar to our results [36].

We found a preventive effect of losing weight ≥2 BMI units from first to second pregnancy in women who had BMI ≥ 25 in first pregnancy, when compared to women with stable BMI in this group. Some studies have confirmed this [36, 38, 39], while others have not found any preventive effect of reducing weight on the risk of GDM [25, 37].

Gestational weight gain and GDM

Obese women tend to gain less weight during pregnancy and also have the highest baseline risk of GDM; therefore, it is important to take BMI into consideration when examining gestational weight gain and GDM. We found the highest risk of GDM in women who had the lowest gestational weight gain, which has been confirmed in other studies [22, 37]. Reverse causation is a possible explanation, as women with GDM are closely monitored and receive advice on nutrition and physical activity, which may lead to lower gestational weight gain during the second pregnancy. Few studies have included gestational weight gain during second pregnancy when exploring the association between interpregnancy weight change and GDM. A study from Belgium found that inadequate gestational weight gain in second pregnancy was associated with GDM both in women who were normal weight or overweight in their first pregnancy [37].

Pathophysiological mechanisms behind GDM

GDM is characterized by a decreased insulin sensitivity together with an inadequate insulin response [12]. Obesity is an important risk factor for glucose intolerance during pregnancy [12, 40], explaining the increased risk of GDM in women with a prepregnant BMI ≥ 25 in their first pregnancy when compared to women with BMI < 25 [Fig 4]. A normal pregnancy is characterized by a 50%–60% physiological decrease in insulin sensitivity (before conception until late pregnancy) [21, 40], and the pancreatic β cells compensate for this by increasing their insulin secretion [12]. Results from our study suggest that increasing weight between first and second pregnancy, during a relatively short time (more than 60% of the women in our study had an interpregnancy interval of <24 months; Table 1), may stress the glucose metabolism and cause a subclinical decreased insulin sensitivity among normal-weight women as well as overweight women. Normal-weight women generally have a higher insulin sensitivity than overweight and obese women [40]. We suggest that an additive effect of the physiological decrease in insulin sensitivity during pregnancy may overload the capacity and increase the susceptibility to develop GDM, especially in normal-weight women who are used to higher insulin sensitivity.

Strength and limitations

We used data from a large population-based register with compulsory notification and negligible selection bias. Data were family-based, collected prospectively with a longitudinal design

and included several confounding factors that made it possible to evaluate weight change as a causal mechanism behind GDM. BMI represents prepregnant BMI and is not obscured by an effect of gestational weight gain upon the risk of GDM, in contrast to most studies reporting BMI before week 15 of pregnancy [25, 38, 39] or week 16–17 [36]. A limitation in our study was the limited proportion of information on BMI available in both first and second pregnancy during the study period. However, comparing the study population with the population with missing information on BMI [S10 Table], our study population is likely to be representative. Maternal weight gain during pregnancy depends on prepregnant weight [22]. When evaluating effect modification by gestational weight gain, we stratified on a possible intermediate variable on the causal path from prepregnant BMI in second pregnancy (part of our exposure) and GDM, which may have introduced bias in our estimates [41]. We cannot exclude unmeasured confounding, as we were not able to take into account other time-varying variables associated with GDM, such as family history of GDM, mothers weight gain in childhood/early adulthood, prepregnant diet, and vigorous exercise [34]. Data on height and weight are self-reported, and as height tends to be overreported whereas weight is under-reported, this might cause bias due to misclassification [42]. However, several studies have found self-reported height and weight in women of reproductive age and in pregnant women to be valid [43, 44]. As data are collected prospectively, misclassification of BMI is independent of a later GDM diagnosis and therefore likely to be nondifferential, which would tend to bias risk estimates toward the null and underestimate the risk of GDM. We did not include gestational weight gain during first pregnancy in our model and were therefore not able to make a distinction between gestational weight gain in first pregnancy and interpregnancy weight change. According to observational studies, gestational weight gain is strongly associated with short- and long-term postpartum weight retention [22, 45].

Health implications

Pregnant women who increase their weight by ≥1 BMI unit from their first to second pregnancy should be closely monitored during their second pregnancy to reveal development of GDM, irrespective of prepregnant BMI. Antenatal guidelines for monitoring GDM in pregnancy should add interpregnancy weight change as an independent risk factor for GDM with a routine stress-test of glucose tolerance during pregnancy in women with weight gain more than 1 BMI unit. A possible preventive effect on GDM of losing weight between pregnancies in overweight women needs to be replicated in other studies. Efforts that are targeting women who are overweight in pregnancy and childbirth should expand in focus to promote healthy weight from preconception throughout reproduction. Today, less than 10% of countries' national policies address healthy maternal weight across the entire spectrum of childbearing [46].

Conclusion

Women who increased their weight by ≥1 BMI unit from first to second pregnancy had increased risk of GDM in the second pregnancy compared to women with stable weight (−1 to <1 BMI unit change). This applied to women with prepregnant BMI below and above 25 in the first pregnancy; however, the strongest association was found in women with BMI < 25. We found a preventive effect on GDM in overweight women (first pregnancy) who reduced their weight by ≥2 BMI units until the second pregnancy. Our results support a metabolic mechanism behind the increased risk of GDM, represented by the weight change itself.

Supporting information

S1 STROBE statement.
(DOC)

S1 Analysis plan.
(DOCX)

S1 Fig. Statistics from the Medical Birth Registry of Norway showing percent (%) of women who have their Body Mass Index (BMI) reported (grey columns) and the proportions of women in the different BMI categories (colored lines) during 2006 to 2014.
(TIF)

S1 Table. Overall relative risk (RR) for Gestational Diabetes Mellitus (GDM) By interpregnancy change in Body Mass Index (BMI), with and without missing imputation in the adjusted analyses. *All variables from the analysis model, including the outcome variable GDM, were included as imputation variables. In addition, we included the following auxiliary variables in the imputation: prepregnant BMI in second pregnancy, father's education, mother's marital status, birthweight of the child in the second pregnancy, gestational age, preterm birth, preeclampsia or hypertension in pregnancy, and placenta abruptio. The number of imputations was set to 20. **All models are adjusted for maternal age during second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous) in addition to smoking during second pregnancy. a) Adjusted analysis without missing imputation. Include only cases with complete information on smoking, education, and maternal country of birth. b) Missing imputation on smoking and education. c) Missing imputation on smoking, education, and maternal country of birth. The imputation allows computed values to be used in the imputation of another variable.
(DOCX)

S2 Table. Risk for Gestational Diabetes Mellitus (GDM) by interpregnancy change in Body Mass Index (BMI), stratified by prepregnant BMI in first pregnancy (*n* = 24,198), the Medical Birth Registry of Norway 2006–2014. *Adjusted for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).
(DOCX)

S3 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) by interpregnancy change in Body Mass Index (BMI), stratified by prepregnant BMI in first pregnancy; adjusted analyses with and without missing imputation. *All variables from the analysis model, including the outcome variable GDM, were included as imputation variables. In addition, we included the following auxiliary variables in the imputation: prepregnant BMI in second pregnancy, father's education, mother's marital status, birthweight of the child in the second pregnancy, gestational age, preterm birth, preeclampsia or hypertension in pregnancy, and placenta abruptio. The number of imputations was set to 20. **All models are adjusted for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous) in addition to smoking in second pregnancy. a) Adjusted analysis

without missing imputation. Include only cases with complete information on smoking, education, and maternal country of birth. b) Missing imputation on smoking and education. c) Missing imputation on smoking, education and maternal country of birth. The imputation allows computed values to be used in the imputation of another variable.
(DOCX)

S4 Table. A. Overall relative risk (RR) for Gestational Diabetes Mellitus (GDM) by interpregnancy change in Body Mass Index (BMI) (n = 22,443). *When excluding second pregnancies with gestational age below 37 weeks, multiple pregnancies, and pregnancies with hypertensive disorders in second pregnancy (hypertension during pregnancy, preeclampsia, eclampsia, and HELLP). **Adjusted for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no[reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous). B. RR for GDM by interpregnancy change in BMI, stratified by prepregnant BMI in first pregnancy. *When excluding second pregnancies with gestational age below 37 weeks, multiple pregnancies and pregnancies with hypertensive disorders in second pregnancy (hypertension during pregnancy, preeclampsia, eclampsia, and HELLP). **Adjusted for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).
(DOCX)

S5 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), stratified by maternal country of birth (n = 24,043), the Medical Birth Registry of Norway. *Adjusted for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).
(DOCX)

S6 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), stratified by maternal age at second pregnancy (n = 24,198), the Medical Birth Registry of Norway. *Adjusted for maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no[reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).
(DOCX)

S7 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), stratified by interpregnancy interval (n = 24,169), the Medical Birth Registry of Norway. *Adjusted for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference]/yes), 24–35, ≥36 months), and year of second birth (continuous).
(DOCX)

S8 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), in women with BMI < 25 in both pregnancies (n = 14,857), the Medical Birth Registry of Norway. *Adjusted for maternal age

in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no[reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous). **Adjusted analyses with missing imputation on maternal smoking, education and country of birth.
(DOCX)

S9 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), stratified by prepregnant BMI in second pregnancy (*n* = 24,198), the Medical Birth Registry of Norway 2006–2014.
*Adjusted (a) for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference],/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).
(DOCX)

S10 Table. The study population (*n* = 24,198) compared to the population with missing information on prepregnant Body Mass Index (BMI) in first and second pregnancy (*n* = 79,284). *Mothers with first and second pregnancy between 2006–2014, without Gestational Diabetes Mellitus (GDM) in first pregnancy and without diabetes mellitus prior to first and second pregnancy.
(DOCX)

Acknowledgments

We would like to thank Jannicke Igland from the Core Facility in Biostatistics and Data Analysis at the University of Bergen for handling missing imputation in STATA. We are grateful to Lisa De Roo for proofreading and making improvements to the readability and grammar of the manuscript.

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S1 STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***
Corresponding Author: Linn Marie Sorbye

	Item No	Recommendation	Author's Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	See Title and "Methods and Findings" in the Abstract.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	See "Background" and "Methods and Findings" in the Abstract.
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	See Introduction, paragraph 2.
Objectives	3	State specific objectives, including any prespecified hypotheses	See Introduction, paragraph 2.
Methods			
Study design	4	Present key elements of study design early in the paper	See Title, "Methods and Findings" in the Abstract and "Data sources" in Methods, paragraph 1.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	See "Data sources" in Methods, paragraph 1.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	See "Inclusions and definitions" in Methods, paragraph 1 and Fig1.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	See "Inclusions and definitions", in Methods, paragraph 1 and 2. Diagnostic criteria see "Inclusions and definitions", paragraph 2.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	See "Data sources" and "Inclusions and definitions", paragraph 1 and 2.
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	See "Inclusions and definitions", paragraph 1 and Fig1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses.	See "Inclusions and definitions", paragraph 1 and 2. See Table1

		If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	See "Statistics". Missing imputation described in "Statistics". See stratified analyses S5Table, S6Table and S7Table.
		(*b*) Describe any methods used to examine subgroups and interactions	See "Pre-pregnant BMI in first Pregnancy, inter-pregnancy weight change and GDM" in Findings, paragraph 2.
		(*c*) Explain how missing data were addressed	See "Statistics"
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	See "Pre-pregnant BMI in first Pregnancy, inter-pregnancy weight change and GDM" in Findings, paragraph 2.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	See "Inclusions and definitions" in Methods, paragraph 1 and Fig1 shows the flow-chart.
		(b) Give reasons for non-participation at each stage	See "Inclusions and definitions" in Methods, paragraph 1.
		(c) Consider use of a flow diagram	See Fig1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See Table1.
		(b) Indicate number of participants with missing data for each variable of interest	See Table1.
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	See Table1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	See all Figures, Tables and Supplementary Tables
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	See additional information on absolute risk in Tables.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	See all Supplementary files

Discussion			
Key results	18	Summarise key results with reference to study objectives	See "Principal findings" and "Inter-pregnancy weight change, BMI in first pregnancy and the risk of GDM" in the Discussion.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	See "Strength and limitations" in the Discussion.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	See the six different paragraphs of the Discussion.
Generalisability	21	Discuss the generalisability (external validity) of the study results	See "Health Implications".
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See information in the "Financial Disclosure" field in the submission form.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

S1 Analysis plan

June 2016

Study title: Inter-pregnancy Weight Change, Gestational Weight Gain and Gestational Diabetes Mellitus

Investigators: Linn Marie Sørbye, Rolv Skjærven (Project leader), Kari Klungsøyr and Nils-Halvdan Morken (Main supervisor)

Research group: Reproductive Epidemiology with a Life-Course Perspective, Department of Global Public Health and Primary Care, University of Bergen, 5020 Bergen, Norway.

Ethics: The project is approved by the Regional Ethics Committee, Western region of Norway (REK VEST 2015/1728). Data are de-identified in accordance with the Medical Birth Registry of Norway (MBRN) Regulations and the Privacy Act. We aim to follow the guidelines of the Declaration of Helsinki.

Hypothesis:

There is an association between inter-pregnancy weight change from first to second pregnancy and the risk of Gestational Diabetes Mellitus in second pregnancy. The association depends on pre-pregnant Body Mass Index (BMI) in first pregnancy and gestational weight gain in second pregnancy.

Specific Aims:

1) Investigate the risk of Gestational Diabetes Mellitus in Second Pregnancy by inter-pregnancy weight change from first to second pregnancy
2) Investigate pre-pregnant BMI in first pregnancy and gestational weight gain in second pregnancy as effect modification variables

Study design: Observational Cohort Study using family-design.

Data Sources: Data from the population-based Norwegian Medical Birth Registry. Data are prospectively recorded. Each birth is linked to its mother by the unique identification number.

Study Population: Mothers with their first and second pregnancy during 2006-2014.

Varables:

Main exposure: Inter-pregnancy weight change from first to second pregnancy (BMI units)

Main outcome: Gestational Diabetes Mellitus in second pregnancy (yes/no)

Effect modifying variables: Pre-pregnant BMI in first pregnancy and gestational weight gain (weight loss, 0-7.9, 8-15.9 kilo and ≥16 kilo) in second pregnancy

Possible confounders: Maternal age in second pregnancy, maternal country of birth, maternal education, maternal smoking in second pregnancy, inter-pregnancy interval and year of second birth.

Statistics: Chi-square test will be used to investigate associations and linear trends between categorical variables. To estimate the association between categories of inter-pregnancy weight change and the risk for Gestational Diabetes Mellitus we will use general linear models with extension for the binary family in STATA. Relative risk with 95% confidence interval will be made for each of the inter-pregnancy weight change categories.
Statistical analyses will be performed using STATA IC Statistical software version 14 and Statistical Package for the Social Sciences version 23 (SPSS).

During the process

April 2017

The analysis plan was made prior to the analyses.

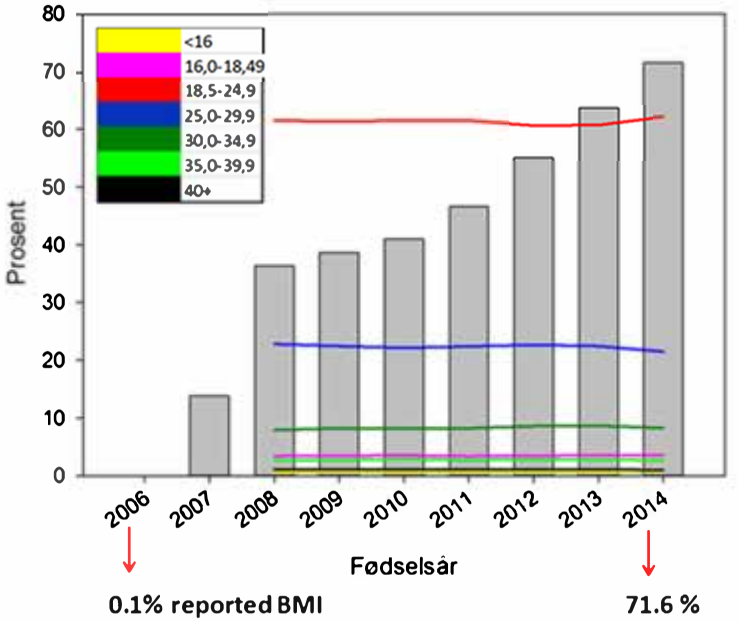
Stratified analyses: In addition to adjusting for confounders in the multiplicative model, we also stratified the analyses according to inter-pregnancy interval (<24 and ≥24 months), mothers country of birth (Nordic, non-Nordic women), smoking in second pregnancy (yes, no), education (<11, 11-13, ≥14 years), maternal age at the second pregnancy (<30, ≥30 years) and mothers height (<1.68, ≥1.68 cm); The association between inter-pregnancy weight change (<-2, -2 to <-1, -1 to <1 (reference), 1 to <2, 2 to <4 and ≥4 BMI units) and risk of Gestational Diabetes Mellitus revealed the same pattern in the stratified analyses as in the overall analysis.

Sensitivity analyses: We performed sensitivity analyses where we excluded pregnancies with gestational age below 28 or 36 weeks, multiple pregnancies or pregnancies with hypertensive disorders in second pregnancy (hypertension during pregnancy, preeclampsia, HELLP), and results remained unchanged.

Comparing populations: Due to missing cases of inter-pregnancy weight change, we compared the study population with the population that had missing data.

Interaction analyses: To evaluate effect modification by pre-pregnant BMI in first pregnancy (<25, ≥25) and gestational weight gain in second pregnancy (<14, ≥14 kg), we included the interaction term in the multiplicative model evaluated by Likelihood ratio test in STATA. Due to limited cases we were not able to look at gestational weight gain in more than 2 categories when evaluating the effect modifying role of gestational weight gain in second pregnancy. We decided to use the median value as threshold when categorising gestational weight gain (<14, ≥14 kg).

S1 Fig. Statistics from the Medical Birth Registry of Norway showing percent (%) of women who have their body mass index (BMI) reported (grey columns) and the proportions of women in the different BMI categories (coloured lines) during 2006 to 2014.



Modified from https://www.fhi.no/nyheter/2015/fodselsstatistikk-for-2014-publiser/

S1 Table. Overall relative risk (RR) for Gestational Diabetes Mellitus (GDM) By interpregnancy change in Body Mass Index (BMI), with and without missing imputation in the adjusted (a) analyses.

BMI Change Units (kg/m^2)	N	GDM/1000	Relative risk for GDM in second pregnancy			
			Crude RR	Model a) a RR**	Model b)* a RR**	Model c)* a RR**
< -2	15/1,692	8.9	0.81	0.89	0.86	0.85
-2 til < -1	34/2,384	14.3	1.30	1.31	1.32	1.35
-1 til < 1	126/11,512	10.9	1.00	1.00	1.00	1.00
1 til < 2	79/3,814	20.7	1.89	1.96	1.83	1.82
2 til < 4	97/3,279	29.6	2.70	2.64	2.54	2.55
≥ 4	88/1,517	58.0	5.30	5.44	5.06	5.05
Total	439/24,198	18.1	24,198	20,824	23,686	23,837

*All variables from the analysis model, including the outcome variable GDM, were included as imputation variables. In addition, we included the following auxiliary variables in the imputation: prepregnant BMI in second pregnancy, father's education, mother's marital status, birthweight of the child in the second pregnancy, gestational age, preterm birth, preeclampsia or hypertension in pregnancy, and placenta abruptio. The number of imputations was set to 20.

**All models are adjusted for maternal age during second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous) in addition to smoking during second pregnancy.

a) Adjusted analysis without missing imputation. Include only cases with complete information on smoking, education, and maternal country of birth.

b) Missing imputation on smoking and education.

c) Missing imputation on smoking, education, and maternal country of birth. The imputation allows computed values to be used in the imputation of another variable.

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S2 Table. Risk for Gestational Diabetes Mellitus (GDM) by interpregnancy change in Body Mass Index (BMI), stratified by prepregnant BMI in first pregnancy (*n* = 24,198), the Medical Birth Registry of Norway 2006–2014.

BMI Change Units kg/m2	Prepregnant BMI < 25 first pregnancy						Prepregnant BMI ≥ 25 in first pregnancy					
	N	GDM /1000	Crude RR	95% CI	a RR*	95% CI	N	GDM /1000	Crude RR	95% CI	a RR*	95% CI
< -2	4/600	6.7	1.1	0.4-2.9	1.0	0.3-3.3	11/1,092	10.1	0.3	0.2-0.7	0.4	0.2-0.8
-2 to <-1	13/1,611	8.1	1.3	0.7-2.4	1.1	0.6-2.3	21/773	27.2	0.9	0.6-1.5	0.9	0.6-1.7
-1 to < 1	57/9,156	6.2	1.0	Reference	1.0	Reference	69/2,356	29.3	1.0	Reference	1.0	Reference
1 to < 2	36/2,788	12.9	2.1	1.4-3.1	2.0	1.2-3.1	43/1,026	41.9	1.4	0.98-2.1	1.6	1.1-2.4
2 to < 4	33/2,143	15.4	2.5	1.6-3.8	2.1	1.3-3.4	64/1,136	56.3	1.9	1.4-2.7	2.0	1.4-2.9
≥4	39/819	47.6	7.7	5.1-11.4	7.2	4.5-11.3	49/698	70.2	2.4	1.7-3.4	2.6	1.7-3.8
Total	182/17,117	10.6			14,677		257/7,081	36.3			6,147	

*Adjusted (a) for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

S3 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) by interpregnancy change in Body Mass Index (BMI), stratified by prepregnant BMI in first pregnancy; adjusted (a) analyses with and without missing imputation.

BMI Change Units (kg/m^2)	BMI < 25 (kg/m^2) in first pregnancy				BMI ≥ 25 (kg/m^2) in first pregnancy			
		Model a)	Model b)*	Model c)*		Model a)	Model b)*	Model c)*
	Crude RR	a RR**	a RR**	a RR**	Crude RR	a RR**	a RR**	a RR**
< -2	1.07	1.03	0.99	1.20	0.34	0.40	0.39	0.35
-2 til < -1	1.30	1.14	1.12	1.34	0.93	0.99	0.96	0.94
-1 til < 1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1 til < 2	2.07	1.96	1.95	1.99	1.43	1.61	1.60	1.40
2 til < 4	2.47	2.04	2.03	2.31	1.92	2.01	1.94	1.81
≥ 4	7.65	7.18	7.20	7.29	2.40	2.58	2.57	2.23
Total	17,117	14,677	15,011	16,842	7,081	6,147	6,248	6,995

*All variables from the analysis model, including the outcome variable GDM, were included as imputation variables. In addition, we included the following auxiliary variables in the imputation: prepregnant BMI in second pregnancy, father's education, mother's marital status, birthweight of the child in the second pregnancy, gestational age, preterm birth, preeclampsia or hypertension in pregnancy, and placenta abruptio. The number of imputations was set to 20.

**All models are adjusted for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous) in addition to smoking in second pregnancy.

a) Adjusted analysis without missing imputation. Include only cases with complete information on smoking, education, and maternal country of birth.

b) Missing imputation on smoking and education.

c) Missing imputation on smoking, education and maternal country of birth. The imputation allows computed values to be used in the imputation of another variable.

S4 Table. A. Overall relative risk (RR) for Gestational Diabetes Mellitus (GDM) by interpregnancy change in Body Mass Index (BMI) (*n* = 22,443).

Interpregnancy BMI change	Risk for Gestational Diabetes Mellitus*					
	Cases GDM	Total	Crude RR	95% CI	a RR**	95% CI
<-2	14	1,575	0.87	0.50-1.51	0.96	0.53-1.75
-2 til < - 1	33	2,201	1.46	0.99-2.16	1.52	0.99-2.32
-1 til < 1	110	10,745	1.00	Reference	1.00	Reference
1 til <2	72	3,540	1.99	1.48-2.67	2.13	1.56-2.93
2 til <4	83	3,010	2.69	2.03-3.57	2.59	1.89-3.55
3.5≥4	81	1,372	5.77	4.35-7.64	5.87	4.27-8.06
Total	393	22,443	22,443		19,300	

*When excluding second pregnancies with gestational age below 37 weeks, multiple pregnancies, and pregnancies with hypertensive disorders in second pregnancy (hypertension during pregnancy, preeclampsia, eclampsia, and HELLP(Hemolysis Elevated Liver enzymes and Low Platelet count)).

**Adjusted (a) for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no[reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

S4 Table. B Relative risk (RR) for Gestational Diabetes Mellitus (GDM) by interpregnancy change in Body Mass Index (BMI) (*n* = 22,443), stratified by prepregnant BMI in first pregnancy.

BMI Change Units kg/m2	Pre-pregnant BMI <25 in first pregnancy*				Pre-pregnant BMI ≥25 in first pregnancy*			
	Crude RR	95% CI	a RR**	95% CI	Crude RR	95% CI	a RR**	95% CI
<-2	1.19	0.43-3.28	1.19	0.37-3.85	0.36	0.19-0.70	0.41	0.20-0.83
-2 to < - 1	1.47	0.80-2.69	1.33	0.65-2.72	1.03	0.63-1.70	1.13	0.66-1.92
-1 to < 1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
1 to <2	2.20	1.43-3.39	2.16	1.35-3.46	1.48	0.99-2.20	1.72	1.13-2.61
2 to <4	2.37	1.50-3.74	2.02	1.19-3.43	1.97	1.37-2.82	1.96	1.32-2.90
≥4	7.79	5.10-11.90	7.29	4.49-11.83	2.72	1.87-3.96	2.83	1.87-4.28
Total	16,022		13,723		6,421		5,577	

*When excluding second pregnancies with gestational age below 37 weeks, multiple pregnancies and pregnancies with hypertensive disorders in second pregnancy (hypertension during pregnancy, preeclampsia, eclampsia, and HELLP).

**Adjusted (a) for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

S5 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), stratified by maternal country of birth (*n* = 24,043), the Medical Birth Registry of Norway.

BMI Change Units kg/m2	Nordic women				Non-Nordic women			
	Crude RR	95% CI	a RR*	95% CI	Crude RR	95% CI	a RR*	95% CI
<-2	0.82	0.45-1.50	0.79	0.41-1.52	0.80	0.25-2.63	1.36	0.40-4.60
-2 to < - 1	1.27	0.83-1.96	1.24	0.78-1.97	1.29	0.57-2.94	1.54	0.58-4.11
-1 to < 1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
1 to <2	1.99	1.45-2.73	1.97	1.41-2.75	1.55	0.85-2.82	1.94	0.95-3.96
2 to <4	2.55	1.86-3.48	2.46	1.76-3.45	2.66	1.61-4.41	3.30	1.78-6.11
≥4	4.74	3.41-6.58	4.61	3.22-6.60	5.55	3.40-9.06	7.74	4.27-14.02
Total	19,828		17,707		4,215		3,117	

*Adjusted (a) for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

S6 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), stratified by maternal age at second pregnancy (*n* = 24,198), the Medical Birth Registry of Norway.

BMI Change Units kg/m2	Maternal age <30 years				Maternal age ≥30 years			
	Crude RR	95% CI	a RR*	95% CI	Crude RR	95% CI	a RR*	95% CI
<-2	0.57	0.20-1.60	0.76	0.27-2.16	1.07	0.58-2.0	1.01	0.51-2.01
-2 to < - 1	1.36	0.71-2.61	1.36	0.64-2.87	1.34	0.85-2.13	1.30	0.78-2.15
-1 to < 1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
1 to <2	2.29	1.42-3.69	2.77	1.64-4.69	1.75	1.24-2.48	1.69	1.16-2.46
2 to <4	3.46	2.25-5.32	3.46	2.11-5.67	2.49	1.78-3.50	2.32	1.60-3.36
≥4	6.68	4.36-10.24	7.01	4.29-11.44	5.20	3.64-7.43	4.72	3.16-7.05
Total	11,490		9,812		12,708		11,012	

*Adjusted (a) for maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no[reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

S7 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), stratified by interpregnancy interval (*n* = 24,169), the Medical Birth Registry of Norway.

BMI Change Units kg/m2	Interpregnancy interval < 24 months				Interpregnancy interval ≥ 24 months			
	Crude RR	95% CI	a RR*	95% CI	Crude RR	95% CI	a RR*	95% CI
<-2	1.14	0.57-2.29	1.14	0.52-2.51	0.53	0.23-1.22	0.69	0.30-1.61
-2 to < - 1	1.21	0.69-2.13	1.13	0.59-2.17	1.43	0.86-2.36	1.51	0.87-2.61
-1 to < 1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
1 to <2	2.38	1.61-3.53	2.40	1.56-3.70	1.43	0.96-2.12	1.60	1.05-2.43
2 to <4	4.25	2.99-6.04	4.44	3.01-6.56	1.47	0.97-2.21	1.40	0.88-2.14
≥4	4.99	3.27-7.61	5.71	3.54-9.19	4.94	3.49-6.98	5.07	3.46-7.43
Total	15,148		12,979		9,021		7,845	

*Adjusted (a) for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference]/yes), 24–35, ≥36 months), and year of second birth (continuous).

S8 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), in women with BMI < 25 in both pregnancies (*n* = 14,857), the Medical Birth Registry of Norway.

Interpregnancy BMI change (kg/m^2)			RR for GDM in second pregnancy					
	Total	GDM /1000	Crude RR	95% CI	a RR*	95% CI	a RR**	95% CI
<-2	4/600	6.7	1.07	0.39-2.94	1.03	0.32-3.32	1.19	0.43-3.29
-2 til < - 1	13/1,611	8.1	1.30	0.71-2.36	1.13	0.55-2.29	1.32	0.71-2.46
-1 til < 1	56/8,990	6.2	1.00	Reference	1.00	Reference	1.00	Reference
1 til <2	26/2,290	11.4	1.82	1.15-2.90	1.87	1.14-3.08	1.78	1.12-2.85
2 til <4	15/1,216	12.3	1.98	1.12-3.49	1.79	0.94-3.41	1.83	1.02-3.27
≥4	4/150	26.7	4.28	1.57-11.65	5.95	2.12-16.65	4.27	1.53-11.94
Total	118/14,857	7.9			12,771		14,633	

*Adjusted (a) for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no[reference]/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

**Adjusted analyses with missing imputation on maternal smoking, education and country of birth.

S9 Table. Relative risk (RR) for Gestational Diabetes Mellitus (GDM) in second pregnancy by interpregnancy change in Body Mass Index (BMI), stratified by prepregnant BMI in second pregnancy (*n* = 24,198), the Medical Birth Registry of Norway 2006–2014.

BMI Change Units kg/m2	Pre-pregnant BMI <25 in second pregnancy						Pre-pregnant BMI ≥ 25 in second pregnancy					
	N	GDM /1000	Crude RR	95% CI	a RR*	95% CI	N	GDM /1000	Crude RR	95% CI	a RR*	95% CI
<-2	7/1,091	6.4	1.0	0.5-2.2	1.1	0.5-2.5	8/601	13.3	0.5	0.2-0.96	0.5	0.2-1.2
-2 to < - 1	16/1,848	8.7	1.4	0.8-2.4	1.3	0.7-2.4	18/536	33.6	1.2	0.7-1.9	1.2	0.7-2.1
-1 to < 1	57/9,114	6.3	1.0	Reference	1.0	Reference	69/2,398	28.8	1.0	Reference	1.0	Reference
1 to <2	26/2,290	11.4	1.8	1.1-2.9	1.8	1.1-3.0	53/1,524	34.8	1.2	0.9-1.7	1.3	0.9-1.9
2 to <4	15/1,216	12.3	2.0	1.1-3.5	1.8	0.9-3.4	82/2,063	39.7	1.4	1.0-1.9	1.4	0.98-2.0
≥4	4/150	26.7	4.3	1.6-11.6	6.0	2.1-16.6	84/1,367	61.4	2.1	1.6-2.9	2.1	1.5-3.0
Total	125/15,709	8.0	15,709		13,526		314/8,489	37.0	8,489		7,298	

*Adjusted (a) for maternal age in second pregnancy (<25 [reference], 25–29, 30–34, ≥35 years), maternal country of birth (Nordic [reference]/non-Nordic), maternal education (<11, 11–13, ≥14 [reference] years), smoking in pregnancy (no [reference],/yes), interpregnancy interval (<12, 12–23 [reference], 24–35, ≥36 months), and year of second birth (continuous).

S10 Table. The study population (*n* = 24,198) compared to the population with missing information on prepregnant Body Mass Index (BMI) in first and second pregnancy (*n* = 79,284).

	Study population*		Total population*	
	n	**%**	***n***	**%**
Gestational Diabetes Mellitus (GDM) in second pregnancy				
No	23,759	98.2	78,015	98.4
Yes	439	1.8	1,269	1.6
Maternal age (years)				
<25	3,014	12.5	9,265	11.7
25-29	8,476	35.0	25,538	32.2
30-34	8,987	37.1	30,481	38.4
≥35	3,722	15.4	14,000	17.7
Maternal country of birth				
Nordic	19,828	81.9	65,681	82.8
Non-Nordic	4,215	17.4	13,025	16.4
Missing	155	0.6	578	0.7
Maternal education				
<11 years	3,460	14.3	10,569	13.3
11-13 years	6,323	26.1	18,336	23.1
≥14 years	13,678	56.5	48,125	60.7
Missing	737	3.0	2,254	2.8
Smoking				
No	20,616	85.2	61,045	77.0
Yes	990	4.1	3,048	3.8
Missing	2,592	10.7	15,191	19.2
Inter-pregnancy interval (months)				
<12	4,806	19.9	13,814	17.5
12 to <24	10,342	42.7	31,874	40.4
24 to <36	5,811	24.0	19,714	25.0
≥36	3,210	13.3	13,498	17.1
Missing	29	0.1	384	0.5
Total	24,198	100	79,284	100

*Mothers with first and second pregnancy between 2006–2014, without GDM in first pregnancy and without diabetes mellitus prior to first and second pregnancy

10. APPENDIX

Appendix 1

Questionnaire 1, page 14. The Mother and Child Cohort Study.

Physical activity

123. How often do you exercise? (Fill in each line for both before and during this pregnancy.)

	Last 3 months before this pregnancy					During this pregnancy				
	Never	1-3 times a month	1 time a week	2 times a week	3 or more times a week	Never	1-3 times a month	1 time a week	2 times a week	3 or more times a week
1 Walking	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2 Brisk walking	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3 Running/jogging/orienteering	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4 Bicycling	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 Training studio/weight training	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6 Special gymnastics/aerobics for pregnant women	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7 Aerobics/gymnastics/dance without running and jumping	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8 Aerobics/gymnastics/dance with running and jumping	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9 Dancing (swing/rock/folk)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 Skiing	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11 Ball sports	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12 Swimming	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13 Riding	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
14 Other	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

124. How often do you do exercises for the following muscle groups? (Fill in each line for both before and during this pregnancy.)

	Last 3 months before pregnancy					During pregnancy				
	Never	1-3 times a month	1 time a week	2 times a week	3 or more times a week	Never	1-3 times a month	1 time a week	2 times a week	3 or more times a week
Abdominal muscles	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Back muscles	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pelvic floor muscles (muscles around the vagina, urethra, anus)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

125. How often are you so physically active in your leisure and/or at work that you get out of breath or sweat?

	Last 3 months before this pregnancy		During this pregnancy	
	Leisure	At work	Leisure	At work
Never	☐	☐	☐	☐
Less than once a week	☐	☐	☐	☐
Once a week	☐	☐	☐	☐
2 times a week	☐	☐	☐	☐
3-4 times a week	☐	☐	☐	☐
5 times a week or more	☐	☐	☐	☐

A little more about yourself and how you are keeping now

126. Do you agree or disagree with the following statements? (Fill in only one box in each line.)

	Disagree completely	Disagree	Disagree somewhat	Don't agree or disagree	Agree somewhat	Agree	Agree completely
My life is largely what I wanted it to be	☐	☐	☐	☐	☐	☐	☐
My life is very good	☐	☐	☐	☐	☐	☐	☐
I am satisfied with my life	☐	☐	☐	☐	☐	☐	☐
To date, I have achieved what is important for me in my life	☐	☐	☐	☐	☐	☐	☐
If I could start all over, there is very little I would do differently	☐	☐	☐	☐	☐	☐	☐

127. How do these statements describe your relationship? (Only answer if you have a partner.) (Fill in only one box in each line.)

	Agree Completely	Agree	Agree somewhat	Disagree somewhat	Disagree	Disagree completely
My husband/partner and I have a close relationship	☐	☐	☐	☐	☐	☐
My partner and I have problems in our relationship	☐	☐	☐	☐	☐	☐
I am very happy in my relationship	☐	☐	☐	☐	☐	☐
My partner is usually understanding	☐	☐	☐	☐	☐	☐
I often think about ending our relationship	☐	☐	☐	☐	☐	☐
I am satisfied with my relationship with my partner	☐	☐	☐	☐	☐	☐
We often disagree about important decisions	☐	☐	☐	☐	☐	☐
I have been lucky in my choice of a partner	☐	☐	☐	☐	☐	☐
We agree about how children should be raised	☐	☐	☐	☐	☐	☐
I think my partner is satisfied with our relationship	☐	☐	☐	☐	☐	☐

APPENDIX II Electronic birth notification, The Medical Birth Registry of Norway.

Meldingsinfo

Meldingstype: ○ Originalmelding ○ Endringsmelding
Meldingsreferanse
Meldingsreferanse til tidligere melding
MIG versjon
Avsenderprogram, type
Avsenderprogram, versjon

Protokollnr | Utskrivningsdato, mor | Utskrivningsdato, barn | Jordmor v/fødsel | Jordmor v/utskrivning | Lege | Lege barsel/barneavd. | Kvalitetssikret av

Sivile opplysninger

Foretaksnummer | Institusjonsnavn

Mors sivilstatus
○ Gift ○ Ugift/enslig ○ Separert ○ Registrert partner
○ Samboer ○ Skilt ○ Enke ○ Annen sivilstatus

Slektskap mellom barnets foreldre: ○ Ja ○ Nei
Hvis ja, hvorledes i slekt

Fars fødselsnr | Fars fulle navn

Mors fødselsnr
Annen id mor | Type annen id mor
Mors fornavn | Mors mellomnavn | Mors etternavn
Mors postnr | Mors poststed
Mor bosatt i Norge ○ Ja ○ Nei ○ Uvisst | Mors pikenavn
Mors bokommune, nr og navn

Svangerskapet

Siste menstr. 1. blødn.dag
Siste menstr. dato, sikker: ○ Sikker ○ Usikker ○ Uregelmessig ○ Ukjent

Tidligere svangerskap
Levendefødte | Dødfødte (f.o.m. 24. uke)
Sp.abort/Dødfødte (12.-23.uke) | Spontanaborter (under 12. uke)

Fødselstermin | Trimester ○ 1. ○ 2. ○ 3.
Terminmetode: ○ Ultr.-Terminhjulet ○ Ultr.-eSnurra ○ Ultr.- annet ○ Innset. befruktet egg ○ Naegels regel ○ Annet
Annen prenatal diagnostikk: ○ Ja ○ Nei
Type prenatal diagnostikk: ☐ Chorionbiopsi ☐ Amniocentese ☐ Tidlig ultralyd ☐ Utvidet ultralyd ☐ Annet, spesifiser
Patologiske funn ved prenatal diag.: ○ Ja ○ Nei
Hvis ja, spesifiser patologisk funn

Spesielle forhold før svangerskapet:
☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon
☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykdom
☐ ~~Epilepsi~~ ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Tidl. epilepsi
☐ Vedvar. epilepsi ☐ Annet, spesifiser

Regelmessig kosttilskudd: ☐ Nei
Før sv.sk: ☐ Multivit. ☐ Folat/folsyre ☐ Annet, spes.
I sv.sk: ☐ Multivit. ☐ Folat/folsyre ☐ Annet, spes.

Spes. forhold under sv.skapet:
☐ Intet spesielt ☐ Blødning < 13 uke ☐ Blødning 13-28 uke
☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes ☐ Hypertensjon alene
☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34.uke ☐ HELLP syndrom
☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh.
☐ Infeksjon,spes. ☐ Annet, spes.

Legemidler i svangerskapet: ○ Ja ○ Nei
Hvis ja, spesifiser

Røyking
☐ Skriftlig orient. gitt til mor ☐ Samt. ikke for røykeoppl.
Mors røykevaner
Før sv.sk. beg.: ○ Nei ○ Av og til ○ Daglig, antall
I 1. trimester: ○ Nei ○ Av og til ○ Daglig, antall
I 3. trimester: ○ Nei ○ Av og til ○ Daglig, antall

☐ Samt. ikke for yrkesoppl.
Mors yrke: ○ Ikke yrkesaktiv ○ Yrkesaktiv,heltid ○ Yrkesaktiv,deltid
Yrke
Bransje

Mors vekt før sv.sk
Mors vekt ved sv.sk slutt
Mors høyde

Fødselen

Fødsel utenfor institusjon
○ Hjemme, planlagt ○ Hjemme, ikke planl. ○ Under transport ○ Annet sted

Leie:
○ Normalt bakhode ○ Sete ○ Vanlig ○ Dobbel fot ○ Tverrleie
○ Avvik. hodefødsel ○ Occiput posterior ○ Ufullst. rotasj. ○ Ansiktsleie ○ Panneinnstilling
○ Annet, spesifiser

Fødselstart: ○ Spontan ○ Indusert ○ Sectio
Evt. induksjonsmet: ☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet spes.
Indikasjon for induksjon:
☐ Overtid ☐ Preekl./hypertensjon ☐ Diabetes/sv.diabetes ☐ Langvarig vannavg. ☐ Oliga-/polyhydramnion ☐ Flerlinger
☐ Mors helse-/allmenntidst. ☐ Psykisk ind./fødselsangst ☐ Stort barn ☐ Intraut. vekstretardasjon ☐ Annen fosterindikasjon ☐ Intraut. fosterdød ☐ Eget ønske
☐ Annet, spesifiser

Inngrep
☐ Ingen ☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Valuumekstraktor ☐ Episiotomi
☐ Sectio ☐ Framhjelp v/setefødsel ☐ Ekstern vending ☐ Annet, spesifiser
Framhjelp v/setefødsel: ☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode
Sectio, planlagt før fødsel: ○ Ja ○ Nei
Sectio utført som: ○ Elektiv ○ Akutt ○ Sectio øyeblikkelig ○ Sectio innen 20 min ○ Annen akutt-sectio
Indikasjon for inngrep:
☐ Sectio pga tidligere sectio ☐ Tidl. traumatisk fødsel ☐ Eget ønske u. annen indik. ☐ Mislykket induksjon ☐ Stort barn
☐ Truende asfyksi ☐ Navlesnorsfremfall ☐ Abruptio placentae ☐ Eklampsi ☐ Placenta previa ☐ Seteleie
☐ Tverrleie ☐ Protrahert forløp ☐ Misl. tang/vakuum ☐ Annet, spesifiser

Komplikasjoner
☐ Ingen ☐ Vannavg. 12-24 timer
☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforl.
☐ Placenta previa ☐ Abruptio placentae ☐ Perinatalruptur(gr. 1-2)
☐ Sphincterruptur(gr.3-4) ☐ ~~Blødn.> 1500 ml, transf.~~ ☐ Blødn. 500-1500 ml
☐ Eklampsi under fødsel ☐ Navlesnorfremfall ☐ Truende intraut. asfyksi
☐ Risvekk., med. simulert ☐ Langsom fremgang ☐ Uterus atoni
☐ Blødn. > 1500 ml. ☐ Blodtrans/erytrocytt trans. ☐ Annet, spes

Anestesi/analgesi
☐ Ingen ☐ Lystgass ☐ Petidin ☐ Epidural ☐ Spinal ☐ Pudendal ☐ Infiltrasjon ☐ Paracervical blokk ☐ Narkose ☐ Akupunktur ☐ Vannpapler ☐ Annet, spesifiser

Fosterovervåkning
☐ Trestetoscop ☐ Håndh. doppler ☐ CTG ☐ STAN ☐ Ultralyd-blodstr.måling
Enh ved blod-/erytrocytt-trans. ☐ Scalpmåling

Placenta
☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter ☐ Koagler
☐ Utskraping ☐ Manuell uthenting ☐ Annet, spesifiser
Placentavekt

Navlesnor
☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier ☐ Omslyng rundt hals
☐ Annet omslyng ☐ Ekte knute ☐ Annet, spesifiser
Navlesnor-lengde

Fostervann
☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion ☐ Misfarget ☐ Stinkende, infisert
☐ Blodtilblandet ☐ Annet, spesifiser

Komplikasjoner hos mor etter fødsel
☐ Intet spesielt ☐ Feber > 38,5° ☐ Trombose ☐ Eklampsi post partum ☐ Mor overflyttet
☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

Navlesnor ved fødsel: PH navlearterie | PH navlevene | PCO2 navlearterie | PCO2 navlevene

Barnet

Barnets fødselsnummer
Fødselsdato Klokken

Pluralitet For flerfødsel:
○ Enkeltfødsel ○ Flerfødsel
Nummer
Av totalt

Kjønn: ○ Gutt ○ Pike ○ Usikkert kjønn(for dødf.)
Annet kjønn

Barnets vekt ☐ Mangler oppl.
Hodeomkrets ☐ Mangler oppl.
Total lengde ☐ Mangler oppl.
Evt. sete-issemål

Apgar score
1 min ☐ Mangler oppl.
5 min ☐ Mangler oppl.
10 min

Barnet var: ○ Levendefødt ○ Dødfødt/sp.abort

For dødfødte: ○ Død før fødsel ○ Død under fødsel ○ Ukjent dødstidspkt
For dødfødt, død før innkomst: ○ Ja ○ Nei ○ Usikkert
Dødsårsak

Levendefødte, død innen 24 timer
Livet varte: Timer | Minutter
Levendefødte, død senere
Dato | Klokken

Overflyttet barneavd.: ○ Ja ○ Nei
Dato overflyttet
Overflyttet til
Indikasjon for overflytting:
☐ Respirasjonsproblemer ☐ Prematur
☐ Medfødte misdannelser ☐ Perinatale infeksjoner
☐ Annet, spesifiser

Neonatale diagnoser:
☐ Intet spesielt ☐ Hypoglyk (<2 mmol/l) ☐ Medf. anemi (Hb < 13,5 g/dl)
☐ Hofteleddsdyspl. beh. m/pute ☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom
☐ Intrakraniell blødning ☐ Cerebral irritasjon ☐ Celebral depresjon ☐ Abstinens
☐ Neonatale kramper ☐ Konjunktivitt beh. ☐ Navle./hudinf.beh. ☐ Perinat. inf. bakterielle
☐ Perinat. inf. andre ☐ Fract. claviculae ☐ Annen fractur ☐ Facialisparese
☐ Plexusskade ☐ Annet, spesifiser
Annen fractur

Behandlingskoder:
☐ Systemisk antibiotika ☐ Respiratorbehandling
☐ Lysbehandlet icterus ☐ Utskifting icterus ☐ Annet, spesifiser
Årsak til behandlet icterus:
☐ AB0 uforlik. ☐ RH immunisering
☐ Annen årsak, spesifiser

Tegn til medfødte misdannelser: ○ Ja ○ Nei
Hvis ja, spesifiser medf. misd.

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 978-82-308-3565-4