Lifestyle intervention in obese pregnant women
– Effects on maternal outcomes and body composition of the newborn offspring
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- Effects on maternal outcomes and body composition of the newborn offspring

Author: Kristina Martha Renault

Affiliations:
Department of Obstetrics and Gynecology
Copenhagen University Hospital, Hvidovre
Denmark

Correspondence:
Kristina Martha Renault
Fodbygårdsvej 4
4700 Næstved
Denmark
Phone: +45 20 25 06 77
E-mail: Krenault@dadlnet.dk
Preface:

The present thesis is based on studies carried out from 2008 to 2012 at the Department of Obstetrics and Gynecology, Copenhagen University Hospital, Hvidovre.

Obesity is a global challenge. The prevalence of obesity in pregnancy has increased dramatically worldwide during the last 3 decades. Maternal obesity predicts short- and long-term adverse outcomes for the mother and the child. Furthermore, the risk of pregnancy complications is related to gestational weight gain (GWG). High GWG is associated with increased risk of long-term metabolic morbidity for the women and obesity in the offspring. Exploring causes behind the current intergenerational increasing incidence of obesity is therefore important.

My interest in obesity in pregnancy started during my employment as resident and trainee in Obstetrics and Gynecology. At that time, research in this field was limited and knowledge was sparse. In 2006 when I became a specialist in Obstetrics and Gynecology I was employed as an obstetrician at Copenhagen University Hospital, Hvidovre. Niels Jørgen Secher, who was Professor of Obstetrics at the department became my mentor, and a group of researchers with an interest in this field, representing the Department of Obstetrics and Gynecology, the Department of Endocrinology and the Department of Pediatrics was gathered.

We designed and performed a series of studies including the main study “the Treatment of Obese Pregnant Women (TOP) study”, a lifestyle intervention trial with randomization of 425 obese pregnant women. This thesis is based on these studies, and the focus was to evaluate the effects of the interventions on different maternal outcomes and on the body composition of the newborn offspring.

There is still ongoing research and data being collected in connection with the TOP study. Epigenetic analyses of cord blood from participants in the TOP study are being performed in collaboration with a study group from the Genetic and Molecular Epidemiology unit at Lund’s University Diabetes Centre in Sweden. Follow-up studies of the mothers and their offspring are performed in collaboration with Professor Kim Fleisher Michaelsen, Department of Nutrition, Exercise and Sports, University of Copenhagen and will provide knowledge on the long-term effect of lifestyle intervention during pregnancy.
Several people have contributed to the studies included in this thesis. First and foremost, I would like to express my deepest gratitude to my mentor Niels Jørgen Secher for being inspiring, for many hours of discussion, for always being available with backup when needed and for sharing his enormous network with me. Unfortunately, he died from cancer in June 2017.

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I want to acknowledge all my co-authors, who helped me conduct the studies and contributed to the papers included in this thesis. I will especially thank my pediatric collaborators Ole Pryds and Dina Cortes for their expertise, and Ole especially for being accessible with advice regarding statistical analyses. I owe special thanks to my dear friend and colleague Emma Malchau Carlsen for her exceptional engagement in the clinical examinations and DXA scans of the offspring and for many scientific and personal talks. I am looking forward to continuing our collaboration in future studies. I would also like to thank Jens-Erik Beck Jensen, Lars Hyldestrup and the staff at the DXA scanner for being very flexible, making it possible to scan newborn babies on short notice, and for being patient when the babies did not cooperate. In close collaboration with Sjurdur Olsen and Thorhallur Halldorsson at Centre for fetal programming, Serum Institutet we planned and performed the studies including dietary data. I am very grateful to Thorhallur for sharing his enormous knowledge and for contributing with thorough dietary analyses. These studies could not have been performed without his expertise. I am also grateful to Joanna Gesche, who as a medical student participated in analyses, and authored the paper on representativeness of participants in a lifestyle intervention study in obese pregnant women. I also owe acknowledgement to my dedicated co-authors: Birgitte Baldur-Felskov, Sofie Hædersdal, Jesper-Eugen-Olsen, and especially Kirsten Riis Andreasen who played a significant role in the initial planning of the studies and in data collection. And I owe special thanks to the dieticians Jane Hjort and Stine Larsen and to secretary Mette Harms Krøll for their enormous engagement.
I owe great thanks to the mothers and their infants who participated in the studies and to all my obstetric colleagues and the staff at the labour ward for helping with collection of blood samples, and to the Department of Obstetrics and Gynecology, Hvidovre Hospital, for supporting this research.

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Finally, I would like to thank my family for support and most of all I wish to thank my dear husband Thomas and our sons Christoffer and August for their love and patience. I am also grateful to Thomas for sharing his creativity with me, and in tribute to him I have covered my thesis with one of his beautiful paintings.

Kristina Martha Renault
The present thesis is based on studies carried out during the period 2008-2012 at Department of Obstetrics and Gynecology, Copenhagen University Hospital, Hvidovre, Denmark.

The thesis is based on the following papers:


### Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>DNBH</td>
<td>Danish National Board of Health</td>
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<tr>
<td>DXA</td>
<td>Dual-energy X-ray absorptiometry</td>
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<td>FFQ</td>
<td>Food Frequency Questionnaire</td>
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<tr>
<td>GA</td>
<td>Gestational age</td>
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<td>GDM</td>
<td>Gestational diabetes mellitus</td>
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<td>GI</td>
<td>Glycemic Index</td>
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<tr>
<td>GL</td>
<td>Glycemic Load</td>
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<td>GWG</td>
<td>Gestational weight gain</td>
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<tr>
<td>HAPO</td>
<td>Hyperglycemia and Adverse Pregnancy Outcome</td>
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<tr>
<td>hsCRP</td>
<td>High sensitivity CRP</td>
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<tr>
<td>IADPSG</td>
<td>International Association of Diabetes and Pregnancy Study Groups</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>IPD</td>
<td>Individual patient data</td>
</tr>
<tr>
<td>i-WIP</td>
<td>International Weight Management in Pregnancy Collaborative Network</td>
</tr>
<tr>
<td>i-WIP-3</td>
<td>International Weight Management in Pregnancy Collaboration: 3-year follow-up</td>
</tr>
<tr>
<td>LGA</td>
<td>Large for gestational age</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SKOT</td>
<td>Småbørn Kost og Trivsel” Danish abbreviation of small children’s diet and well-being</td>
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<tr>
<td>suPAR</td>
<td>Soluble urokinase plasminogen activator receptor</td>
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<tr>
<td>TOP</td>
<td>Treatment of Obese Pregnant Women</td>
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<tr>
<td>WHO</td>
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1. Introduction
The prevalence of obesity in pregnancy has increased dramatically worldwide during the last 3 decades. Maternal obesity predicts short- and long-term adverse outcomes for the mother and the child (1-3). Furthermore, the risk of pregnancy complications is related to gestational weight gain (GWG) (4;5); excessive weight gain is associated with two- to threefold excess weight retention after birth (6), and a high GWG is a predictor of obesity in infancy and adulthood (7;8).

Good opportunities may exist to introduce lifestyle interventions aiming to reduce GWG during the antenatal period, and thereby to interrupt this intergenerational cycle of increasing obesity and the rising tide of non-communicable diseases due to obesity.

Based on observational studies (9), the Institute of Medicine (IOM) 2009 recommendations on GWG are 10–15 kg in normal weight women and a restriction to 5–9 kg in obese women (10). The criteria are frequently exceeded, and in a large American cohort, more than 50% of overweight and obese women exceeded IOM’s criteria (11).

In the present thesis, possible approaches for lifestyle interventions in pregnancy aiming to reduce GWG and other outcomes of such interventions are examined. The results of our main study, “the Treatment of Obese Pregnant Women (TOP) Study: A randomized controlled trial of the effect of intervention with diet and/or physical activity assessed by pedometer in obese pregnant women”, are analyzed and discussed.

2. Background

2.1 Prevalence and trends in obesity

Obesity and overweight are defined as abnormal or excessive fat accumulation that may impair health (12), and are generally classified according to the World Health Organization’s (WHO) definitions using Body mass index (BMI) as: overweight: BMI 25–29.9 kg/m² and obesity: BMI ≥ 30 kg/m².

The obesity epidemic is global, but the prevalence of obesity varies geographically and is affected by economic and racial differences. In the USA, representing a high-income country, 37% of women in the childbearing age were obese in 2013–14 (13). During the last decades, the risk of obesity has increased linearly in women, while the curve for both men and children seems to be leveling off (13;14).

In Europe, the prevalence of obesity among women during the childbearing age varies
between countries (12) and is highest in the UK (25.2%) and the lowest in Poland (7.1%). In England, 22% of women aged 25–34 years and 26% of women aged 35–44 years were obese in 2015 (15). In Denmark, maternal pre-pregnancy BMI has been registered in the Danish National Board of Health (DNBH) since 2004. There has been an increasing trend in the prevalence of maternal obesity, reaching 13.1% in 2011, but seems to have stabilized hereafter at 12.5% (16).

2.2 Obesity, obstetric and neonatal complications
The worldwide increase in the prevalence of obesity is reflected by a large number of publications, and there is now a great deal of high evidence showing that increasing BMI is associated with increasing risk of complications related to pregnancy and delivery for both the mother and the child (2;3;17;18). Obesity is a risk factor for miscarriage (17), and a high BMI is associated with increased risk of stillbirth and infant death (19). Obesity is also associated with increased risk of several malformations, particularly neural tube defects (20). Prenatal assessment of fetal size and detection of malformations during ultrasound can be difficult in obese women (21). Late pregnancy complications like gestational diabetes mellitus (GDM) (17), preeclampsia, and pregnancy-induced hypertension (22;23) are strongly associated with maternal obesity, and the risk of venous thromboembolism increases up to 4–5 times in pregnancy and in the post-partum period (24).

A very large American retrospective cohort study of more than 12,000 women without pre-gestational diabetes or other chronic diseases showed that maternal obesity was associated with several adverse neonatal outcomes including large for gestational age (LGA) and macrosomia (23;25). This may partly explain the increased risk of complications at birth, such as shoulder dystocia and post-partum hemorrhage, and instrumental delivery is more often required (26). Compared to normal-weight women, obese women more often deliver by cesarean section (27;28), and the risk of anesthetic as well as infectious complications to surgery is also associated with obesity (26;29).

3. Included studies
3.1 Aims
The purpose of our studies was to examine whether lifestyle intervention in obese pregnant women could restrict GWG and have an effect on maternal and neonatal outcomes. Further, we
aimed to examine which components of the intervention might account for any effects as a result of the intervention, and whether the diet of the pregnant women was associated with their offspring’s body composition.

Our main study, the TOP study was designed to measure

- The effect on maternal GWG of advice to increase physical activity intervention as assessed by pedometer, with or without dietary counseling, using comparison with a control group (Paper III).
- Secondarily, to assess whether incidences of pregnancy and delivery complications could be reduced by the interventions (Paper III).
- Improvements and relevance of different dietary factors targeted with respect to GWG (Paper V).
- The association between carbohydrate intake in obese pregnant women and their offspring’s body composition (Paper VI).
- The effect of lifestyle intervention on markers of maternal metabolism and inflammation (Paper VII).

Furthermore, to gain insight into selection and compliance, we examined the representativeness of participants attending a lifestyle intervention addressing obese pregnant women (Paper IV)

Initially, we performed two observational pilot studies to evaluate the use of a pedometer (Yamax Digiwalker SW-700/701) as an interventional tool in pregnancy. The aims were

- To compare physical activity in normal weight and obese women at different gestational ages (Paper I).
- To describe the level of physical activity and compliance to using the pedometer throughout pregnancy (Paper II)

3.2 Study design and choice of interventions
When we planned the TOP study, only a few randomized controlled studies on lifestyle intervention in obese women had been performed, but a small (n = 50) Danish study had shown that intensive dietary intervention in obese pregnant women could reduce GWG to around 6 kg (30).

Lifestyle intervention can include dietary counseling and physical activity instructions. Physical activity in pregnancy is reported to reduce the risk of GDM (31) and of macrosomia (32). The general recommendation is that pregnant women should be encouraged to be physical active at least 30 minutes per day
to reduce risk of complications in pregnancy (33). This recommendation seems particularly important for obese women but is difficult to achieve (34). Physical activity interventions often include attendance to classes (35;36) and can be time consuming and difficult to implement into daily life. In the National Institute for Health and Care Excellence (NICE) clinical guidelines on obesity, it is recommended that physical activity interventions for management of weight loss should include activities that can be incorporated into daily life (37).

A pedometer may be an effective tool for promoting lifestyle changes that include daily physical activity (38), and it is inexpensive and easy to implement. In non-pregnant women, pedometer readings correlate significantly with questionnaire-based estimates of physical activity (39), so the pedometer can also be an objective tool for monitoring all daily physical activity at work and during leisure time. Step counts are easy to quantify, and the method can be used to graduate participants according to the level of physical activity in daily life. The pedometer (Yamax Digiwalker SW-700/701) we used has been validated and is a very reliable tool for assessing steps (40). One limitation of the pedometer is that it cannot register movements in water, and swimming is a preferred physical activity among pregnant women. Women who cycle might also have an underestimated level of physical activity measured by pedometer. In comparison, an accelerometer might be more accurate because it can measure movements in all directions. But the pedometer is less expensive and is simple and easy for the participants to use.

In a randomized trial addressing obese non-pregnant diabetic subjects, a Mediterranean-style diet compared with a low-carbohydrate or low-fat diet caused weight loss and reduced insulin resistance and fasting glucose levels (41). A Norwegian randomized controlled trial showed that Mediterranean diet reduced the risk of preterm delivery (42). Our choice of diet was inspired by these trials, and we chose a calorie-restricted Mediterranean type of diet for our intervention.

We performed a randomized controlled trial (RCT) and used a study design with randomization into three groups (1:1:1): physical activity intervention assessed by pedometer + dietary intervention (PA+D), physical activity intervention assessed by pedometer alone (PA), and a control group receiving the usual hospital standard regimen for obese pregnant women (C). This design
allowed us to estimate the independent role of a physical activity intervention using a pedometer and the effect of supplementary dietary intervention. As step counts and dietary changes during pregnancy were registered, we could examine which components of the intervention might account for any effects as a result of the intervention.

The initially performed observational pilot studies evaluating the use of a pedometer were designed as a cross-sectional study (Paper I (43)) and a prospective longitudinal study (Paper II (44)).

3.3 Subjects and methods
The cross-sectional pilot study (43) comprised 338 pregnant women. Physical activity was assessed by pedometer for 7 consecutive days in six different groups, normal weight or obese, at gestational ages (GA) 11–13, 18–22, and 36–38. Our second pilot study, was a prospective longitudinal study of 70 normal weight and 70 obese women (44). Step counts were measured for 7 consecutive days every 4 weeks throughout pregnancy. Results of the pilot studies were used when designing the TOP study.

The power calculation for the TOP study relied on a mean GWG of 9.1 ± 8.5 kg found in 70 obese pregnant women (44). In order to detect a difference of GWG of 3 kg, 112 participants should be included in each group. Expecting up to 20% dropouts, we decided to include 140 pregnant women in each of the three groups (n = 420)

The TOP study was conducted from April 2009 to March 2012 and included 425 pregnant women with BMI ≥ 30 kg/m² and singleton pregnancies as described in paper III (45). As a part of the standard procedure in the department, all candidates were offered one consultation with a dietician in gestational weeks 11–14. Immediately after the dietary advice, eligible women were asked to participate in the study. Participants were randomized 1:1:1 into the three groups. They were all encouraged to aim for a GWG less than 5 kg.

The physical activity intervention consisted of encouragement to increase physical activity to 11,000 steps/day, corresponding to 150% of the average step count measured in the pilot study. If this was not obtainable, the participants were asked to set their own target. The advice was given individually, with a focus on increasing physical activity during leisure time. Activity was monitored by a pedometer (Yamax Digiwalker CW-700/750), and step
counts were registered on a chart, 7 consecutive
days every 4 weeks, and returned by mail.
When each period started, the participants
received a reminding text message.

The dietary intervention was administered by
trained dieticians with follow-up consultations
every 2 weeks alternating between telephone
and face-to-face contact. The participants were
recommended a hypocaloric diet (5000–7000
kJ) low in saturated fat corresponding to a
Mediterranean-style diet, which covers
preferential use of polyunsaturated fat by intake
of fish and oils. This diet is in line with Danish
national recommendations for a healthy diet
(46). Follow-up also included measurement of
weight, encouragement, and correcting advice
on the diet, especially if the weight gain
exceeded the recommended level or the
participant reported that they did not adhere to
the recommended diet.

Diet was registered by the participants at
baseline (GA 11–14) and at GA 36–37 using a
validated 360-item Food Frequency
Questionnaire (FFQ) (47;48) covering intakes
during the previous 4 weeks. The questionnaire
has been validated for pregnant women using a
7-day weighted food record (49) and
biomarkers of the intakes of protein, n-3 fatty
acids, retinol, and folic acid (47). Quantification
of nutrient intake was done by means of a
national food composition database
(http://www.foodcomp.dk) using standard
recipes and portion sizes. Glycemic index (GI)
and glycemic load (GL), which reflected the
quality and amount of carbohydrates were also
estimated.

GWG was calculated as the difference between
the measured weight and self-reported pre-
pregnancy weight and weight measured in GA
36–37.

At delivery, 389 of the 425 (91.5%) participants
were still included in the study, and 376 had
available blood samples. At GA 18–20 and 28–
30, a 2-hour oral glucose tolerance test (OGTT)
was performed and serum was analyzed for
insulin, c-peptide, lipid profile, leptin, high
sensitivity CRP (hsCRP), and soluble urokinase
plasminogen activator receptor (suPAR).

The level of hsCRP is increased during
pregnancy, and in a study with longitudinal
assessment of nine differential markers of
inflammation and endothelial function during
pregnancy (50), only plasma CRP levels were
higher in obese than in lean women throughout
pregnancy. In some studies, a relation between
hsCRP and development of GDM has been
observed (50;51). suPAR is a novel
inflammatory marker that has also been associated with lifestyle and risk of developing a range of lifestyle-related diseases in the general population (52). suPAR and hsCRP reflect different aspects of inflammation, with hsCRP linked to metabolic inflammation and BMI, while suPAR seems to be a marker of cellular inflammation and largely independent of BMI (53). As both markers reflect lifestyle, low-grade inflammation, and prognosis in the general population, we decided to measure both in our study.

At delivery, neonatal outcomes including birth weight and length were recorded for all offspring. Body composition of the newborn was assessed within 48 hours after delivery by dual-energy X-ray absorptiometry (DXA) in 231 of the newborn infants delivered at term (≥GA 37+0). A detailed description of this subpopulation is described in paper VI. DXA has been validated as method for determining newborn body composition and is reliable for estimating total fat mass and total fat-free mass (54). In other studies, newborn body composition has been measured with air plethysmography (55), skinfold thickness measurements, body circumferences, and bioimpedance (56;57). But DXA has the highest validity (55), and it is an advantage that regional body composition can be assessed, which is interesting because abdominal fat deposition is suspected to be related to long-term implications for the offspring.

4. Evaluation of the interventions

4.1 Evaluation of physical activity intervention as accessed by pedometer

In the pilot study, we showed that the median number of steps/day at mid-gestation at GA 20 was 8000–9000, indicating a relative high level of physical activity in our population. The activity level was somewhat lower early in pregnancy and was lowest late in pregnancy. Throughout pregnancy, the step counts were lower in obese than in normal weight participants. The willingness to use the pedometer was high in both pilot studies, but in the prospective longitudinal study, we found that compliance declined gradually with increasing gestation, particularly in the obese group. In general, the level of physical activity was higher during the week than at the weekends, with the lowest step count on Sundays. This might indicate that a physical activity intervention should focus on activity during leisure time. The participants evaluated their pre-pregnancy level of physical activity in a simple questionnaire, and a low level before
pregnancy was a strong indicator for low level of physical activity during pregnancy. This knowledge obtained in the pilot studies was used when designing the intervention study. Our results are challenged by a low compliance. In the pilot study in obese women, only 22/70 (31%) returned all the recordings until gestational week 33. Baseline characteristics were not significantly different when comparing compliant and non-compliant participants. A higher compliance was found in the TOP study, where 53% of the participants allocated to the physical activity intervention alone and 56% of those allocated to the combination of physical activity intervention and dietary intervention were still compliant at GA 33, indicating that the use of an intervention could be a motivational factor. In accordance with our results, low compliance has been described in other lifestyle intervention studies in obese pregnant women (58;59) and was also found in a study using accelerometers during pregnancy (60). Electronic registration of step counts and the possibility of interactive contact with the participant could have increased the compliance, but these were not available when the study was planned. But even if more advanced technologies had been developed and were available, the pedometer is still a valuable interventional tool.

4.2 Evaluation of the dietary intervention
The participants in the TOP study allocated to the two intervention groups did not have a reduced energy intake, as assessed by the FFQ, compared to the controls (Paper V (61)). But participants allocated to dietary intervention had a modest but significant increase in intakes of protein and polyunsaturated fatty acids and decreased intakes of added sugars and saturated fat compared to controls. There were some indications that those who were relatively physically active, as assessed by the pedometer output in week 17, in the group having physical activity intervention alone changed their diet in a similar direction as did the women allocated to physical activity and dietary intervention.

As recently demonstrated in a systematic review of studies on lifestyle intervention in obese and overweight women (62), there is a considerable variation in the methodological design of the interventions. Some have used a “low GI diet” (32;63-65), Mediterranean diet (42;45), or simple dietary counseling on a healthy diet (66–68). Compared to other studies the dietary intervention in the TOP study was quite intensive, with personal contact to a trained dietician, every 2 weeks. In most of the
studies, the dietary intervention is provided by face-to-face contact with a health trainer or a dietician (45;64;66), but in one study the counseling was provided through a brochure (67).

In the few studies evaluating the effect of intervention on specific dietary changes, the interventions resulted in a significant but modest decrease in saturated fat (64;66;67), increase in protein intake (67), reduction in glycemic load (64), decrease in sugar consumption, and increase in fiber consumption (66), thus indicating a more healthy dietary behavior.

5. Effects of lifestyle intervention in pregnancy on maternal outcomes

5.1 Effect on GWG and secondary clinical outcomes

The TOP study resulted in a reduction in GWG of 2.3 kg in the group allocated to both physical activity and dietary intervention and of 1.5 kg in the group allocated to physical activity intervention alone compared to the control group (Paper III (45)). GWG was analyzed across the study groups, and incorporating potential predictors of low GWG into a multiple regression analysis showed that the intervention with pedometer resulted in a GWG that was 1.4 kg lower than in women not assigned to the pedometer. There was no significant difference between the groups in birthweight or any other obstetric or neonatal outcomes, except for a lower rate of emergency cesarean section in the group allocated to dietary and physical activity intervention.

In a non-randomized setting, we examined the predictive value for GWG of individual factors changed by dietary intervention (Paper V (61)). We showed that foods with a high content of added sugars, particularly intake of sweets more than twice daily, relatively strongly predicted GWG, while the changes in protein or saturated fat appeared to be of little importance. This indicates that for obese pregnant women emphasis on reducing intakes of sweets, snacks, and soft drinks may be more important than encouraging strict compliance to specific types of diets. The main results of the TOP study will be discussed in relation to the current literature below (section 7).

5.2 Effect on metabolic markers

In the TOP study, the counseling regarding a hypo-caloric Mediterranean-style diet had no significant effect on any maternal metabolic parameters or the risk of GDM or preeclampsia (Paper VII (69)).
Pregnancy-related alterations in glucose and lipid metabolism seem to be related to adverse outcomes for the mother as well as for the offspring (70). Obese mothers have increased risk of insulin resistance leading to GDM and neonatal macrosomia (71). In pregnancy, plasma lipid concentrations increase as gestation advances (70). High levels of total cholesterol and plasma triglycerides are associated with obesity (51), and dyslipidemia in early pregnancy is associated with later development of preeclampsia (42;72).

It could be due to lack of power that we did not find an effect of the interventions. But consistent with our finding, most other studies evaluating the effect of lifestyle interventions in pregnancy found no effect on any metabolic parameters (64;66;73). However, some studies have found a modest effect on serum insulin (30;74). Another Danish RCT, the LiP study performed by Vinter and colleagues, addressed a population of 360 obese women with BMI ≥ 30 kg/m² with a mixed intervention with focus on physical activity (36). In accordance with our study, there was a modest reduction in GWG but no significant effect on other secondary outcomes. The intervention resulted in lower insulin resistance in the intervention group than in the control group. But these effects might be too modest and appear too late in pregnancy to have any impact on the development of clinical adverse outcomes.

5.3 Effect on inflammation

In paper VII, we also explored the impact of lifestyle intervention on hsCRP at GA 28–30, and we found lower levels in both intervention groups compared to the control group (64). The differences were relatively large, as hsCRP was 28% lower in the group receiving combined intervention and 23% lower in the group receiving only physical activity intervention. Participants demonstrating a high level of physical activity by obtaining the 11,000 steps per day aimed for had a lower hsCRP compared to non-compliant women. Women reporting high carbohydrate intake in late gestation had higher hsCRP concentrations in late gestation than women reporting the lowest intake. So, we assume that the effect may partly be mediated by more physical activity and partly by changes in the intake of carbohydrates and the GL. We did not find any effect on the level of suPAR of lifestyle interventions in obese pregnant women (69).

Inflammatory mediators have been linked to the pathogenesis of obesity-related morbidity (51;75), indicating that a reduction of the level of low-grade inflammation in obese pregnant
women may be beneficial for the women and their offspring. There are conflicting data regarding suPAR as a marker of complications during pregnancy. Toldi and colleagues found that suPAR was elevated in preeclampsia and suggested that measurement of suPAR levels is a suitable tool for the detection of systemic inflammation in pregnancy (76). But in a study by Haedersdal and colleagues, suPAR measured in the second trimester could not predict later complications (77). However, in our study, suPAR was not affected by lifestyle interventions.

Previous studies have suggested that a high intake of carbohydrates of low quality is associated with higher levels of inflammation in obese subjects (78;79). And a systematic review by Buiken and colleagues from 2014 exploring the association between carbohydrate quality and inflammatory markers concluded that evidence for anti-inflammatory benefits was more consistent for low GI/GL diets than for high-fiber or whole-grain diets (80). This supports our results.

To our knowledge, no other lifestyle intervention studies in obese pregnant women have detected an interventional effect on hsCRP. In a Norwegian study by Khoury and colleagues, pregnant women with BMI 19–32 kg/m² were randomized to a control or to an “anti-inflammatory” diet corresponding to a Mediterranean-style diet (42). No effect on hsCRP was found. HsCRP is an unspecific measure of inflammation, so further studies are needed to distinguish the source of inflammation. And long-term follow-up on the offspring is needed to evaluate any benefits for them.

6. Effects of lifestyle intervention in pregnancy on the offspring

6.1 Effect of lifestyle intervention on the newborn offspring body composition

The interventions in the TOP study did not influence birthweight (45) or newborn body composition (81). In a secondary analysis of 222 obese women participating in the TOP study described in paper VI, we observed that maternal intake of digestible carbohydrates and the quality of carbohydrates in terms of GI and GL in late pregnancy were positively associated with the offspring’s total fat and abdominal fat mass assessed by DXA within 48 hours after birth (82). The association was modified by the maternal 2-h OGTT values measured during or near gestational week 29. In women who had 2-h glucose values between 6.7 and 7.7 mmol/l, a significant association was found, and the magnitude of association was further
strengthened in women who had 2-h glucose values ≥ 7.8 mmol/l.

As hypothesized by Pedersen in 1952 (83) and later confirmed in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study (71), intrauterine growth and neonatal fat mass are closely related to maternal plasma glucose levels. During pregnancy, hyperglycemia can be modified by pharmacotherapy and dietary counseling, which reduce the risk of pregnancy complications, including excessive birth weight (84). A reduction in carbohydrate intake or an improvement in carbohydrate quality in terms of glycemic response may reduce the risk of fetal overgrowth among women with decreased glucose tolerance. But the results of studies on dietary intervention aiming to reduce carbohydrate intake and improve carbohydrate quality have differed (32;63;65;85).

In a study from Cleveland, Ohio, USA, of 76 neonates of overweight/obese women and 144 neonates of normal weight women, it was concluded that not only GWG but also the result of the glucose tolerance screening, even if it was below the abnormal threshold, influenced the fat mass of the newborns of the obese women (57). Analyses of the data from the HAPO study confirmed this, and it was even concluded that the combination of the perinatal risk factors such as obesity and GDM had a greater impact than either one alone (86). Neither study, however, explicitly examined the association between diet and the offspring body composition.

In our cohort of newborn offspring of obese pregnant women, the mean fat percent was 11.2 ± 4.3%. The observed difference in relative fat mass comparing mothers in the lowest and the highest quartile of daily carbohydrate intake, adjusted for co-variates, was 2%. In a previous study, we found that determinants of fat mass with comparable importance were GWG and pre-gestational BMI (81). These factors can be difficult to modify. As improving the quality and/or reducing the amount of carbohydrate intake may be easier to achieve, our results indicate that diet quality should perhaps be given more attention in the clinical setting, and this should not just be confined to women who pass the threshold for the diagnosis of gestational diabetes.

Based on the results of the HAPO study (71), revised criteria for the diagnosis of GDM were proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010 (87). According to these criteria, the diagnosis of GDM is made when any single threshold value on a 75-g 2-hour
OGTT is met or exceeded (fasting glucose value, 5.1 mmol/l, 1-h glucose value 10.0 mmol/l, 2-h value 8.5 mmol/l). These criteria were adapted by WHO in 2013 (88) and have now been implemented in several countries. Because of considerations regarding the cost-benefit of increasing the frequency of diagnosing and treating GDM, implementation of these criteria is still being debated, and in Denmark, a 2-h value of 9.0 mmol/L as a single criterion is still used. Secondary analyses from the North American HAPO study centers provide evidence of adverse outcomes for women diagnosed GDM based on the IADPSG criteria but not on the less strict traditional Carpenter-Croustan criteria (89). In our cohort of Danish obese women with impaired glucose tolerance but not diagnosed GDM, we observed that maternal intake of digestible carbohydrates and the quality of carbohydrates in terms of GI and GL in late pregnancy was positively associated with the offspring’s fat mass at birth (82). Our results underscore the rationale that lowering the criteria for diagnosing GDM and for proposing dietary treatment would be beneficial for the offspring.

6.2 Follow-up of the offspring

There are only a few studies of follow-up of the offspring after intervention studies in pregnancy. At 2.8 years’ follow-up of 157 offspring of participants in the LiP study (90), lifestyle intervention had no effect on body size, body composition measured by DXA, or metabolic risk factors (91;92). No data on maternal diet were provided.

A follow-up study was performed at 6 months postpartum in 698 participants and offspring from the UPBEAT study, a large RCT from the UK with mixed lifestyle intervention and recommendation of a diet designed to reduce glycemic load (64). Significant lower subscapular skinfold thickness was found in the offspring of mothers in the intervention group compared to the controls (93). This might be mediated by maternal diet, as participants in the intervention group increased healthy dietary behavior and reduced modestly GWG antenatally. Maternal dietary GL and saturated fat intake were still reduced 6 months postpartum. In two RCTs on treatment of GDM with lifestyle intervention during pregnancy (84;94), follow-up of 199 offspring at age 4–5 years (95) and 500 offspring (96) at age 5–10 years found no significant difference in BMI or metabolic measures between offspring in the control group and the intervention group.
It can be difficult to achieve a high participation rate in follow-up studies, and these studies are therefore often underpowered.

7. Main results of the TOP study in relation to the current literature

When we planned our study, knowledge in this field was sparse. Because of the dramatic increase in the prevalence of obesity, there has been emphasis on prevention strategies. In parallel with our study, several large RCTs on lifestyle intervention in pregnancy have been conducted (36;64;65;97–101), and a number of meta-analyses and reviews (59;102-104) have been published. Most of the studies have targeted reduction of GWG, with GWG as primary outcome, but in some studies the primary outcome was birthweight or development of GDM.

The LiP study performed by Vinter and colleagues addressed a population of 360 obese women with a mixed intervention with focus on physical activity (36). In accordance with our study, there was a reduction in GWG of 1.6 kg and no significant effect on other secondary outcomes. The DALI study (101), a recently published large European multi-center RCT randomizing 436 pregnant women with BMI ≥ 29 kg/m² from nine different countries to physical activity and/or healthy eating intervention, aimed to prevent GDM. Consistently GWG was reduced with 2.2 kg in the combined intervention group compared to controls, but no effect on GDM risk or other maternal or neonatal outcomes was reported.

The two largest RCTs so far, UPBEAT from the UK, with randomization of 1555 obese women (64), and LIMIT from Australia, with randomization of 2212 overweight or obese pregnant women (66), were carefully designed and powered to evaluate the effect of lifestyle interventions on maternal and neonatal outcomes. In the UPBEAT study, participants in the intervention group were recommended a diet designed to reduce glycemic load. They did alter their dietary composition, but there was no difference between the groups in the incidence of GDM or LGA. A modest reduction of GWG of 0.6 kg was reported. In the LIMIT study, although behavioral changes corresponding to those found in other studies were reported, no difference in GWG was found, but women in the intervention group were less likely to give birth to an infant with birthweight > 4000 g.

Two Cochrane reviews from 2015 have assessed the effect of diet or exercise or both in pregnancy. One review by Muktabhant and colleagues (103) found high-quality evidence
indicating that lifestyle intervention can reduce the risk of excessive GWG. There was no clear difference in any other outcomes. Exercise appeared to be an important part of controlling weight gain in pregnancy. The other review by Bain and colleagues (102) assessed the effect on GDM and found no clear effect. A large systematic review of lifestyle interventions in pregnancy by Thangaratinam and colleagues (59) included 44 relevant RCTs. Overall there was a 1.42 kg reduction in GWG (95%CI 0.95 to 1.89 kg) with any intervention compared to control. It was concluded that lifestyle interventions in pregnancy can reduce maternal GWG and improve outcomes for both mother and baby. Interventions based on diet were most effective, but only interventions based on physical activity alone were associated with reduced birth weight.

Knowledge about the isolated effect on physical activity intervention for obese pregnant women is sparse. Two systematic reviews (58;105) have concluded that exercise intervention could reduce GWG (58), and that women in the intervention groups had lower risk of preterm birth and of developing GDM (105). But there was no significant effect on birth weight. The interventions used in the studies in these reviews were very diverse. In contrast, a meta-analysis of studies on physical exercise programs during pregnancy in all BMI groups showed that physical activity could reduce birthweight and was safe for the child (106). A RCT by Clapp (32) showed that moderate intensity exercise during pregnancy was associated with reduction of fat mass at birth and in childhood, but there was no information on overweight or obese participants.

In conclusion, the primary results of the TOP study are in accordance with the literature published during the study period. The International Weight Management in Pregnancy Collaborative Network (i-WIP) is coordinating an Individual Patient Data (IPD) meta-analysis to assess whether various dietary or physical activity interventions have differential effects based on parity, BMI, and preexisting medical conditions (107). The TOP study is among the 36 studies participating with data in these analyses. The first results are expected to be published shortly.

Most of the performed lifestyle intervention studies are in Caucasian women, and the interventions start during the second trimester. A recently published Chinese RCT including women with BMI $\geq 24 \text{ kg/m}^2$ (108) showed that cycling exercise initiated in GA 10 and performed for at least 30 minutes three times
per week significantly reduced the risk of developing GDM and GWG (2.1 kg) and reduced the birthweight of offspring. This might indicate that studies in non-Caucasian populations result in more significant clinical effects than studies in Caucasian populations. Maybe high compliance is easier achieved in a Chinese population. In most populations, it seems to be a challenge to achieve inclusion in early pregnancy.

8. Limitations of lifestyle intervention studies in pregnancy

One limitation of most interventional studies is the external validity, which rarely is investigated. We found (Paper IV) that non-participating women had a higher parity and were younger, and they were more often single, smokers, and unable to communicate in Danish. They also had a lower compliance to measurements of OGTT during pregnancy (109). All these factors indicate that women who might benefit the most from lifestyle intervention are not represented in the study. For ethical reasons, eligible women declining to participate were not included in this study of representativeness, but it must be emphasized that women accepting participation may represent the women most motivated for lifestyle changes. Women enrolled in a control group might change their lifestyle due to the awareness of participating in a study. This demonstrates that, in general, a possible considerable selection bias may exist in the performed lifestyle intervention studies. Moreover, most of the trials have been performed in high-income populations and have included a high proportion of Caucasian women. Selection bias and lack of compliance with the study protocols recommending lifestyle changes might reflect the failure to achieve sufficient contrast between intervention groups. Other explanation of the modest clinical effect could simply be that the length of pregnancy is too limited a period to achieve sufficient lifestyle changes, or that the ability to increase the level of physical activity is reduced in advanced pregnancy.

Many of the lifestyle intervention studies seem to be underpowered. In an RCT, the size of the randomization groups is based on a power calculation relying on measurements of the primary outcome. We had expected a higher effect of our intervention than we found and aimed to detect a minimal difference of 3 kg in GWG. Further, the power was too low to detect an effect on the secondary outcomes. But this
issue is being met by the performance of an IPD meta-analysis including 36 RCTs coordinated in the i-WIP collaboration.

9. Perspectives
Obesity is a global challenge and exploring how the intergenerational cycle of increasing obesity and rising tide of non-communicable diseases can be interrupted is important. As a part of this, the focus of this thesis is to evaluate effects of lifestyle intervention in obese pregnant women on maternal outcomes and on the body composition of the newborn offspring.

During the last decade, a large number of randomized lifestyle intervention studies have been performed, as elaborated above. Some interventions have increased healthy dietary behavior and modestly reduced GWG but were inadequate for improving clinical outcomes. Based on the results from all these studies, we speculate that compliance to the diet allocated seems more important than the type of assigned diet. And motivating women to shift their diet and comply with Mediterranean, low GI, or other types of healthy diet is difficult to achieve in practice. Changing dietary habits is a complex task, and not only the composition of macronutrients, but also the food structure and processing should be taken into account in the evaluation of a diet (110). Understanding how such factors affect energy balance and pathways involved in hunger, satiety, absorption, and metabolism is currently not well understood (110).

For limiting GWG, our results indicate that for obese pregnant women emphasis on reducing intakes of sweets, snacks, and soft drinks may be relatively more important than encouraging strict compliance to specific types of diets. The underlying craving for sweets in study participants may be difficult to modify but should be considered in future investigations.

The timing of the interventions might be important. In a meta-analysis, Song and colleagues (111) included 29 RCTs with more than 11,000 pregnant women, addressing the effect of lifestyle interventions on the risk of GDM. A subgroup analysis showed that interventions starting before GA 15 achieved 22% reduction in risk of GDM, while no significant effect was found in the subgroup of interventions starting later than GA 15. These results indicate that interventions should be started in the first trimester if an effect on maternal metabolism is to be achieved. This might reflect that obese women have increased lipogenesis and an increased level of low-grade
inflammation along with altered maternal and placental function starting in the first trimester (112;113). It is even speculated that weight loss should be achieved before pregnancy. Therefore, interpregnancy and pre-pregnancy studies for short- and long-term benefits for the mother and offspring should be the focus of future studies (112).

Evaluation of cost-effectiveness is mandatory when evaluating and implementing interventions. In our study design, we were aware of the need to limit the costs of the intervention, and especially the pedometer intervention can be considered as a “low-cost physical activity intervention”. But evaluation of benefits will always be largely theoretical, and long-term follow-up of the participants of the intervention-studies and their offspring is needed.

Follow-up studies are often underpowered, and building on the existing i-WIP project (107), the International Weight Management in Pregnancy Collaboration Network is launching a 3-year follow-up study (i-WIP-3) (114) to determine the effects of antenatal dietary and lifestyle interventions in pregnancy for overweight and obese women on longer-term health outcomes in the women and their children at 3–5 years after birth. Seven studies with available data, including the TOP study, are included in the protocol for this study.

The offspring of participants in the TOP study are followed as a cohort “SKOT II” (“Småbørn Kost og trivsel”, the Danish abbreviation for small children’s diet and well-being) (115), in a detailed protocol with collection of data at 9, 18, and 36 months. The SKOT II cohort is compared with the SKOT I cohort consisting of children of healthy primarily normal-weight mothers. The data collected will be available for the “i-WIP-3” collaboration. Furthermore, we are planning a 10–11 year follow-up of the mothers and the offspring in a more thorough study protocol.

Maternal lifestyle and exposure to environmental factors may by epigenetic mechanisms such as alteration of DNA methylation and modulation of gene expression during gestation possibly alter the offspring’s physiological and behavioral outcomes. Our knowledge and understanding of the complexity of fetal metabolic programming and responsiveness to epigenetic modulation is limited, and there is considerable ongoing research in this field. In collaboration with a study group from the Genetic and Molecular Epidemiology unit at Lund’s University Diabetes Centre in Sweden, epigenetic analyses
of cord blood from participants in the TOP study are being performed.

10. Summary

Obesity is a global challenge. To interrupt the intergenerational cycle of increasing obesity and rising tide of non-communicable diseases, it has been suggested that there are good opportunities to introduce lifestyle interventions during the antenatal period. We designed and performed “the Treatment of Obese Pregnant Women (TOP) study”, a lifestyle intervention trial with randomization of 425 obese pregnant women. Initially, we performed two observational pilot studies evaluating the use of a pedometer as an interventional tool in pregnancy, and this thesis is based on these studies.

The purpose of our studies was to measure the effect of intervention with counseling on a hypocaloric Mediterranean-style diet and/or physical activity intervention assessed by pedometer on gestational weight gain (GWG), maternal and neonatal outcomes and on markers of maternal metabolism and inflammation. Further, we aimed to examine which components of the intervention might account for any effects. We examined improvements in the dietary composition and

the relevance of different dietary factors targeted with respect to GWG. We focused on carbohydrate intake, and in an observational setting, we examined the association with body composition of the offspring at birth assessed by Dual-energy X-ray absorptiometry (DXA).

We found that physical activity intervention as assessed by pedometer is useful in obese pregnant women. The pedometer is a valuable interventional tool, as it is inexpensive and simple and easy to implement in daily life.

Compared with a control group, GWG was reduced with 2.3 kg in the group receiving physical activity intervention and dietary intervention and with 1.5 kg in the group receiving physical activity intervention alone. There was no significant difference between the groups in birthweight or any other obstetric or neonatal outcomes, except for a lower rate in emergency cesarean section in the group allocated to both interventions. Participants allocated to dietary intervention had a modest but significant increase in intakes of protein and polyunsaturated fatty acids and decreased intakes of added sugars and saturated fat compared to controls, indicating a change of diet in a healthier direction. These modest effects are comparable with the results of other interventional studies.
We found no significant effect of the TOP study interventions on any metabolic parameters, but the intervention significantly reduced the level of hsCRP, representing a marker of inflammation during pregnancy. Secondary analyses indicate that the effect may partly be mediated by more physical activity, and partly by changes in the intake of carbohydrates and in Glycemic Load.

In our analyses, we observed that foods with a high content of added sugars, particularly intake of sweets more than twice daily, relatively strongly predicted GWG, while the changes in protein or saturated fat appeared to be of little importance. Our results indicate that for obese pregnant women emphasis on reducing intakes of sweets, snacks, and soft drinks may be relatively more important than encouraging strict compliance to specific types of diets.

In our cohort of obese women, we also observed that even those without GDM but with impaired glucose tolerance, intake of digestible carbohydrates and the quality of carbohydrates in terms of Glycemic Index and Glycemic Load in late pregnancy were positively associated with the offspring’s fat mass assessed by DXA at birth.

We examined the representativeness of participants attending a lifestyle intervention and found that non-participating women had a higher parity and were younger, and more often were single, smokers, and unable to communicate in Danish, indicating that women who might benefit the most from lifestyle intervention were not represented in the study.

In conclusion, we designed a randomized controlled trial on lifestyle intervention for obese women. In the randomized setting, GWG reduction was significant but modest. Our results indicate that dietary advice and glycemic control are important for restricting GWG and fat mass in the newborn offspring of obese women with glucose intolerance, even if the threshold for diagnosing GDM is not reached. Future follow-up studies of participants and their offspring and epigenetic studies can contribute to knowledge on the long-time effects of the interventions.

11. Summary in Danish
Fedme er en global udfordring. Fedme og overvægt medfører risiko for fedmerelaterede sygdomme og for at få børn der bliver overvægtige. Der kan derfor være gode muligheder for at indføre livsstilsinterventioner, som sigter mod at reducere vægtøgning i


Intervention med vejledning om øget fysisk aktivitet monitoreret med skridttæller er effektfuld til overvægtige gravide kvinder. Skridttælleren er et værdifuldt interventionsredskab, da den er billig og let kan implementeres i dagligdagen.

Sammenlignet med en kontrolgruppe blev den gestationelle vægtøgning reduceret med 2,3 kg i gruppen, der modtog rådgivning om øget fysisk aktivitet og lav-kalorisk middelhavs kost og med 1,5 kg i gruppen, der kun blev opfordret til fysisk aktivitet. Der var ingen signifikant forskel mellem grupperne i fødselsvægt eller andre kliniske udfald, bortset fra en lavere forekomst af akut kejsersnit i gruppen som fik begge interventioner. Deltagere som fik kostvejledning, havde en beskeden, men signifikant stigning i indtag af protein og flerumættede fedtsyrer og nedsat indtag af tilsat sukker og møttet fedt fedt sammenlignet med deltagere i kontrolgruppen, hvilket indikerer kostændring i en sundere retning. Disse beskedne virkninger er sammenlignelige med resultaterne fra andre livsstilsinterventionsstudier for gravide.

De metaboliske parametre blev ikke påvirkede af TOP-studieinterventionerne, mens hsCRP blev signifikant reduceret. Sekundære analyser tyder på, at effekten delvist kan være forårsaget
af øget fysisk aktivitetsniveau, dels ved ændringer i mængden og kvaliteten af kulhydrater.

Vi observerede at fødevarer med et højt indhold af tilsat sukker, især indtag af slik mere end to gange dagligt, stærkt prædikterede stor vægtøgning i graviditeten, mens ændringerne i protein eller mættet fedt syntes at have lille betydning. Vores resultater tyder på, at for overvægtige gravide kan betydningen af at reducere indtag af slik, snacks og sodavand være vigtigere end vejledning i nøje overholdelse af bestemte typer diæter.

Endvidere observerede vi, at hos kvinder som ikke udviklede graviditets diabetes, men blot havde nedsat glukosetolerance, var mængden og kvaliteten af kulhydratindtagelse sidst i graviditeten positivt associeret med børnenes fedtprocent, vurderet ved DXA efter fødslen.

I livsstilsinterventionsstudiet undersøgte vi repræsentativiteten af deltagerne, og fandt at ikke-deltagende kvinder havde en højere paritet, var yngre og oftere var single, rygere og ikke dansk talende end deltagende kvinder. Dette tyder på, at kvinder, der kunne have særlig stort udbytte af livsstilsintervention slet ikke var repræsenteret i undersøgelsen.

Fremtidige opfølgende undersøgelser af deltagere og deres afkom og epigenetiske undersøgelser kan bidrage til viden om interventionernes langtidseffekter.
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