

ISBN 978-82-326-2568-0 (printed ver.)  
ISBN 978-82-326-2569-7 (electronic ver.)  
ISSN 1503-8181



Doctoral theses at NTNU, 2017:248

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Trondheim, September 2017

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Printed by NTNU Grafisk senter

*It all begins and  
ends in your mind.  
What you give power to,  
has power over you.  
If you allow it.*

- Leon Brown



## **TRENING I SVANGERSKAPET FOR KVINNER MED OVERVEKT ELLER FEDME**

Rundt en tredjedel av kvinner i fertil alder er overvektig eller har fedme, og andelen stiger i takt med økende overvekt/fedme i befolkningen generelt. Overvekt eller fedme i svangerskapet er forbundet med risiko for en rekke uheldige helseutfall som svangerskapsdiabetes, forhøyet blodtrykk, svangerskapsforgiftning, høy fødselsvekt på barnet, fødselskomplikasjoner, keisersnitt og forlenget sykehusopphold. Både mor og barn har økt sannsynlighet for å utvikle fedme, diabetes og hjerte-karsykdommer senere i livet. Gravide med overvekt/fedme har en tendens til å overstige anbefalt vektøkning i svangerskapet, og har i tillegg vanskeligere for å gå ned i vekt etter fødsel. Dette bidrar til ytterligere forsterkning av risikofaktorene knyttet til overvekt/fedme i svangerskapet.

En rekke studier har sett på effekten av livsstilsendring på risiko knyttet til overvekt/fedme i svangerskapet, men funnene er uklare. De fleste av studiene tar i bruk ulike typer tiltak, som diett, fysisk aktivitet og veiledning, noe som gjør det vanskelig å finne ut hvilke type tiltak som har best effekt. Bortsett fra ved enkelte helsetilstander, er gravide som befolkningen ellers, anbefalt å være fysisk aktiv gjennom svangerskapet i minst 30 minutter de fleste dagene i uken. Få randomiserte kliniske studier har sett på effekten av trening alene på risikofaktorer knyttet til overvekt/fedme i svangerskapet.

I perioden 2010-2015 utførte vi studien «Exercise Training In Pregnancy» (ETIP), en randomisert kontrollert klinisk studie, ved NTNU og St. Olavs Hospital i Trondheim, Norge. Vi inkluderte 91 gravide kvinner med en kroppsmasseindeks  $\geq 28$ , som ble tilfeldig fordelt i ei treningsgruppe eller ei kontrollgruppe. Deltakerne i treningsgruppa fikk tilbud om veiledet standardisert trening tre ganger i uken gjennom hele svangerskapet, i tillegg til vanlig svangerskapsomsorg, mens kontrollgruppa kun mottok vanlig svangerskapsomsorg. Treningsøkten for kvinnene i treningsgruppa bestod av 35 minutter med moderat gange/løp på tredemølle og 25 min styrketrening. Deltakerne gjennomgikk omfattende testing ved inklusjon (svangerskapsuke 12-18), på slutten av svangerskapet (svangerskapsuke 34-37), ved fødsel og tre måneder etter fødsel.

Hovedmålet med studien var å se på om et tilbud om regelmessig trening i svangerskapet hos gravide med overvekt/fedme kunne forebygge høy vekttoppgang i svangerskapet. Andre viktige utfallsmål var om treningen påvirket fødselsvekt hos barnet, og mors vektnedgang tre måneder etter fødsel. I tillegg undersøkte vi effekt av trening på svangerskapsdiabetes, blodtrykk, fødselskomplikasjoner, metabolske markører for mor og

barn ved fødsel og tre måneder etter fødsel, og på fysisk aktivitet under og etter svangerskapet.

Studien var basert på «intensjon om behandling» der alle tilgjengelige data ble inkludert i analysene, uavhengig av hvor mye deltakerne i treningsgruppa trente. Vi gjorde også analyser der vi sammenlignet kun de som trente etter protokollen, med kontrollgruppa.

Vi fant ingen forskjell i vektøkning i svangerskapet mellom treningsgruppa og kontrollgruppa, men sent i svangerskapet hadde de som var med i treningsgruppa lavere blodtrykk og færre tilfeller av svangerskapsdiabetes. Treningen i svangerskapet hadde ingen effekt på fødselsvekt hos barnet eller risikofaktorer ved fødsel, men kvinnene i treningsgruppa hadde lavere nivå av insulin og mindre grad av insulinresistens (HOMA2-IR-score) tre måneder etter fødsel. Rundt halvparten av kvinnene i treningsgruppa trente etter protokollen.

Konklusjonen er at tilbud til gravide kvinner med overvekt eller fedme, om å delta i et standardisert treningsopplegg i svangerskapet, ikke påvirket vekt, men reduserte risikoen for svangerskapsdiabetes og forhøyet blodtrykk. Å delta i treningsgruppen forebygget redusert insulinsensitivitet, og kan dermed bidra til å redusere framtidig risiko for utvikling av diabetes type 2. Vi fant ikke at trening i svangerskapet medførte risiko for uheldige hendelser, og studien støtter gjeldende anbefaling om regelmessig fysisk aktivitet og trening i svangerskapet også for kvinner med overvekt/fedme.

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Finansiering: Samarbeidsorganet Helse Midt-Norge (RHF) og NTNU, Diabetesforbundet og Fond til etter- og videreutdanning av fysioterapeuter, Slutføringsmidler fra Fakultet for medisin og helsevitenskap, NTNU.

## SUMMARY

As the prevalence of obesity is on the rise worldwide, the prevalence of overweight and obese women in childbearing age also increases.<sup>1,2</sup> At present, about one third of all women in fertile age are overweight or obese.<sup>1,3</sup> This is a major health concern. Maternal overweight or obesity is a risk factor for adverse outcomes during pregnancy, at delivery, and in the postpartum period for both mother and child. The consequences may have a major effect of both short-term and long-term health, and effective preventing strategies are not established. The most frequent adverse maternal health outcomes are increased risk of gestational diabetes mellitus (GDM),<sup>4</sup> gestational hypertension, preeclampsia, need for cesarean delivery, and prolonged hospital stay.<sup>5-8</sup> Adverse neonatal outcomes are high birth weight,<sup>9</sup> birth trauma related to macrosomia, preterm birth, low APGAR-score, insulin resistance,<sup>10,11</sup> perinatal death, and transfer to neonatal intensive care unit (NICU).<sup>7,12</sup> In addition, pre-pregnancy overweight and obesity are associated with future development of obesity and cardiometabolic diseases for both mother and child.<sup>13-15</sup> Compared to normal weight women, overweight and obese women have increased risk of excessive gestational weight gain (GWG),<sup>16</sup> and for high postpartum weight retention (PPWR).<sup>17,18</sup> Both GWG and PPWR accumulates other already present risks related to pre-pregnancy overweight and obesity.<sup>19,20</sup>

Results of previous research on lifestyle interventions during pregnancy to prevent adverse outcomes in overweight and obese women diverge.<sup>21-26</sup> Several studies assess the combined effect of physical activity and dietary guidance. Healthy pregnant women are recommended to be physically active at least thirty minutes per day on most days of the week.<sup>27-29</sup> Physical activity does tend to decrease significantly during pregnancy, especially among women with high body mass index.<sup>30</sup> Few randomized controlled trials (RCTs) have investigated the isolated effects of exercise training in pregnancy on gestational weight gain and clinical outcomes in overweight and obese women.<sup>23,31,32</sup>

The “Exercise Training in Pregnancy for obese women” trial (ETIP) was conducted in the period 2010-2015 at NTNU and St. Olavs Hospital, Trondheim, Norway. The primary aim of the trial was to investigate whether supervised exercise training during pregnancy could reduce gestational weight gain.<sup>33</sup> The secondary aim was to assess neonatal birth weight and PPWR. We also examined the effect of regular exercise training during pregnancy on health outcomes as GDM, blood pressure, circulation metabolic markers, neonatal body composition, birth complications, hospital stay, risk of type 2 diabetes mellitus, and the level of physical activity.



We included 91 healthy pregnant women with a body mass index  $\geq 28$  kg/m<sup>2</sup>, and they were randomly allocated to an exercise group or a control group. Both groups received standard maternal care. In addition the women in the exercise group were offered supervised training sessions three times per week until delivery. Each exercise session consisted of 35 minutes of moderate walking/running on a treadmill and 25 minutes of strength exercises. All participants underwent assessments at inclusion (gestational week 12-18), late pregnancy (gestational week 34-37), at delivery, and three months postpartum.

The ETIP trial was based on “intention to treat” (ITT), where all available data from the participants was used at all times, independent of whether the participants adhered to the intervention or not. In addition we performed “per protocol analyses” where we compared women in the exercise group who exercised as prescribed, with the women in the control group.

The results of the ETIP trial showed no effect of offering overweight and obese pregnant women supervised exercise training during pregnancy on gestational weight gain,<sup>34</sup> neonatal birth weight or PPWR. Women in the exercise group had indeed lower incidence of GDM and lower resting blood pressure in late pregnancy, as well as lower circulating insulin levels postpartum. About 50% of the women in the exercise group adhered to the exercise protocol. We registered no adverse events due to exercise training in the trial.

Our overall conclusion is that providing a supervised exercise program to overweight and obese pregnant women did not limit gestational weight gain, but reduced the risk of cardiometabolic disorders during pregnancy and in the postpartum period. Based on our findings, we recommend that regular supervised exercise training should be offered as standard maternal care, to overweight and obese women during pregnancy.

## **AKNOWLEDGEMENTS**

The present thesis was carried out at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), between March 2013 and March 2017. The research was funded by the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU), and The Norwegian Fund for Post-graduate Training in Physiotherapy. The Department of Circulation and Medical Imaging and the Norwegian Diabetes Association provided me with financial support in the preliminary phase before the PhD period. This clinical trial has been performed in collaboration with the Department of Women's Health and the Children's Clinic, St. Olavs Hospital, Trondheim University Hospital. NeXt Move Core Facility, NTNU and the Clinical Research Facility, St. Olavs Hospital provided equipment and personnel for the trial assessments.

The last 13 years I have mainly worked in the field of sports medicine, thus entering a new area of knowledge and methods has been developing, exiting, challenging, fun, and sometimes frustrating. The ETIP trial recruited 91 pregnant women, and I want to thank them all for their contribution to important knowledge. The trial required a lot of practical work, logistics, and helpful and experienced colleagues, and I want to share my sincerest gratitude to all who contributed in the trial and to my thesis. First of all I want to express my gratitude to my main supervisor Trine Moholdt. She introduced me to this field, and has followed me in every step of this journey. With a mentality of: "nothing is really difficult, impossible or take a long time, it's just to work hard", you have motivated me, sometimes exhausted me, but made the ETIP-trial and my PhD possible. I also want to share my great gratitude to my co-supervisor Professor Siv Mørkved who was the initiator of the ETIP project. She provided the project and my thesis with knowledge and major experience in the field of research and women's health, and was very helpful in clearing things up "when the though was going". Thank you Trine and Siv, for sharing your knowledge and passion for research, and for making me keep up the good work when the ETIP trial was not "easy going". I have learned a lot from you. Øyvind Salvesen shared great work to the statistics of my articles; thank you so much for patience, time, teaching, and good discussions. Thank you to Inggard Lereim for being a "mentor" who convinced me and supported me into entering the field of research from the field of sports medicine.

A special thanks goes to "the angels" at the Clinical Research Facility; Nina Backlund, Gøril Bakken Rønning, Anne Risdal and Guro Almvik for your enormous help in assessments

of the participants, and for being the most smiley, nice and helpful colleagues I have ever worked with. I also want to express thankfulness towards my co-workers in the ETIP study: Siri Ann Nyrnes and Pepe Salvesen for valuable contributions, good discussions and collaboration with the mother-child article. Than you to Charlotte Björk Ingul, Olga Vea, Ingrid Volløyhaug, Siri Marte Hollekim-Strand, Arnt Erik Tjønnå and Ragnhild Røsbjørgen, who contributed to the assessments in the study. It has been a pleasure to work with Ida Almenning, Sofie Buurgaard Lionett, Line Evensen, Fredrik Hjulstad Bækkerud and Kari Lundgren, and being a part of the exclusive EXCAR-Research Group. And Kari, I really appreciate our friendship and your support.

The colleagues at ISB and CERG have provided me with a lot of laughs, hugs, good and funny conversations, social events, and buckets of coffee in our lunch room. Thank you, Trude Carlsen, Line Skarsem Reitlo, Anne Marie Ormbostad Berre, Karin Solvang-Garten, Ingeborg Megård Leinan, Ingunn Lie, Ekaterina Zotcheva, Henning Ofstad Ness and Fredrik Hjulstad Bækkerud. Inge Lise Aamot, Siri Marte Hollekim-Strand and Linda Erntsen; I really appreciated our pep-talks and good laughs.

Huge thanks to the nicest neighbors in the world. Thank you Harriet Hestad, for pushing me both physically and mentally, and making me set goals, and thank you Tone Kjelsberg, for your help with my thesis.

Finally, I want to express my gratitude to my entire family for all support. A special thanks to Mom and Dad for teaching me the benefits of hard work. High five to my favorite little brother Per Kristian and his amazing wife Kristina. They tried hard to improve my thesis, and they certainly succeeded. Mother in law Grete; thank you, for all the support at home, and for taking care of Zalto. Dear Eirik, thank you for being a friend, coach and psychologist, for making the everyday-spinning wheel go around, and for putting your work second the last months. Brage and Halvor, thank you for laughter and hugs, activity and engagement, impulsivity and craziness – you are the best!

Trondheim, May 2017

Kirsti Krohn Garnæs

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## **LIST OF PAPERS**

The papers presented in this thesis are based on the randomized controlled trial “Exercise Training in Pregnancy (the ETIP trial)”.

### **Paper I**

Kirsti Krohn Garnæs, Siv Mørkved, Øyvind Salvesen, Trine Moholdt:

Exercise Training and Weight Gain in Obese Pregnant Women: A Randomized Controlled Trial (ETIP Trial).

*PLoS Med.* 2016 Jul 26;13(7):e1002079.

### **Paper II**

Kirsti Krohn Garnæs, Siri Ann Nyrnes, Kjell Åsmund Salvesen, Øyvind Salvesen, Siv Mørkved, Trine Moholdt:

Effect of supervised exercise training during pregnancy on neonatal and maternal outcomes among overweight and obese women. Secondary analyses of the ETIP trial: A randomized controlled trial.

*PloS One.* 2017; 12(3): e0173937.

### **Paper III.**

Kirsti Krohn Garnæs, Siv Mørkved, Kjell Åsmund Salvesen, Øyvind Salvesen, Trine Moholdt:

Exercise training during pregnancy reduces circulating insulin levels in overweight/obese women postpartum. Secondary analysis of a randomized controlled trial (the ETIP trial).

*In review.*

## **ERRATA**

In Paper I, data on gestational age at birth and number of weeks from inclusion in the ETIP trial to delivery was based on the women's self-reported information on term for delivery (ultrasound scan), and final date of delivery. In Paper II, we took use of data from the hospital records to assess term of delivery and final date of delivery, and lead to some minor adjustments: Mean gestational age at delivery was in Paper I reported to 39.5 weeks (range 27-42) in the exercise group and 39.4 weeks (range 37-42) in the control group. After consulting hospital records this was adjusted to 39.1 weeks (range 29-42) in the exercise group, and 39.5 weeks (range 37-42) in the control group.

Number of weeks (mean) from inclusion in the trial to delivery was in Paper I reported as 23.3 weeks (range 10-28) in the exercise group, and 24.7 weeks (range 19-30) in the control group, in Paper II adjusted to 23.9 weeks (range 17-28) in the exercise group, and 24.6 weeks (range 18-33) in the control group.

Adjustments for gestational age (weeks) resulted in changes in the preterm categories: One neonate in the control group who were registered as preterm, gestational week 36 was adjusted to 37. Another neonate in the exercise group who were registered born in gestational week 37 was adjusted to preterm, gestational week 36. In Paper I we reported of two neonates who were preterm, one in each group, this was in Paper II adjusted to two neonates born preterm in the exercise group.

## **ABBREVIATIONS**

ACOG	American College of Obstetricians and Gynecologists
BSA	Body Surface Area
BMI	Body mass index
CI	Confidence interval
ETIP	Exercise Training In Pregnancy
GDM	Gestational diabetes mellitus
GWG	Gestational weight gain
HOMA-IR	Homeostasis model assessment-insulin resistance
IDAPSG	International association of Diabetes and Pregnancy Study Group
IOM	Institute of Medicine
ITT	Intention to treat
NICU	Neonatal intensive care unit
OGTT	Oral glucose tolerance test
OR	Odds ratio
P	P-value
PPWR	Postpartum weight retention
RCT	Randomized controlled trial
SD	Standard deviation
WHO	World Health Organization



## DEFINITIONS

**Body mass index (BMI):** Body weight (kg)/body height (m)<sup>2</sup>. Underweight < 18.5 kg/m<sup>2</sup>, normal weight 18.5 - 24.9 kg/m<sup>2</sup>, overweight 25.0 - 29.9 kg/m<sup>2</sup>, and obesity ≥ 30 kg/m<sup>2</sup>. Obesity is often sub-divided into class I obesity (BMI 30-34.9 kg/m<sup>2</sup>), class II obesity (BMI 35.0 – 39.9 kg/m<sup>2</sup>, and class III obesity (BMI ≥ 40 kg/m<sup>2</sup>).<sup>35</sup>

**Body surface area:**  $\sqrt{(body\ weight\ (kg) * body\ height\ (cm))/3600}$  As defined by the Mosteller Formula.<sup>36</sup>

**Exercise:** Regular physical activity performed to improve fitness or health.<sup>37</sup>

**Excessive gestational weight gain:** Gestational weight gain above the recommendations of Institute of Medicine (IOM).

**Gestational age:** The number of weeks and days between the first day of the mother's last menstrual period and the day of delivery.<sup>38</sup>

**Gestational diabetes mellitus (GDM):** Glucose intolerance of variable degree with onset or first recognition during pregnancy. The WHO's diagnostic criteria for GDM when the study was commenced was: A fasting plasma glucose level ≥ 7.0 mmol/l or/and a plasma glucose ≥ 7.8 mmol/l at 120 minutes after a intake of 75 g glucose dissolved in 2.5 dl of water.<sup>39</sup>

**Gestational weight gain (GWG):** Weight gain of the mother from the time of conception to the onset of labor (Institute of Medicine).<sup>40</sup> In the current study we defined GWG as the difference between body weight measured at the time of inclusion in the trial (gestational week 12-18) and body weight measured at delivery.

**Hypertension:** Resting systolic blood pressure ≥ 140, and/or resting diastolic blood pressure ≥ 90.<sup>41</sup>

**Large for gestational age:** Birth weight above the 10<sup>th</sup> percentile, in this trial above 4000 g is used.<sup>42</sup>

**Maternal hypertension (pregnancy introduced hypertension):** Development of new hypertension, after gestational week 20, in absence of accompanying proteinuria.<sup>43</sup> In this trial we have defined maternal hypertension as resting systolic blood pressure ≥ 140, and/or resting diastolic blood pressure ≥ 90, without controlling for proteinuria.

**Normal weight:** Body mass index (BMI) = 18.5-24.9 kg/m<sup>2</sup>.<sup>35</sup>

**Obesity:** BMI  $\geq$  30.0 kg/m<sup>2</sup>.<sup>35</sup>

**Overweight:** BMI  $\geq$  25.0-29.9 kg/m<sup>2</sup>.<sup>35</sup>

**Physical activity:** Any type of bodily movement produced by skeletal muscles, and requires energy expenditure.<sup>37</sup>

**Placental weight ratio:** Placental weight (g) divided by the birth weight (g).<sup>44</sup>

**Postpartum weight retention (PPWR):** Postpartum body weight (kg) minus pre-pregnancy weight (kg). In the current trial we defined PPWR as body weight (kg) measured three months postpartum minus body weight (kg) measured at inclusion (early pregnancy, gestational week 12-18). We did also report data on PPWR based on self-reported pre-pregnancy body weight.

**Preterm birth:** Delivery at gestational week  $<$  37.<sup>45</sup>

**Small for gestational age :** Birth weight below the 10<sup>th</sup> percentile, in this trial below 2500 g is used.<sup>42</sup>

**Type 2 diabetes mellitus:** A chronic disease where the body is unable “to respond properly to the action of insulin produced by the pancreas”, which results in increased concentrations of glucose in the blood”.<sup>46</sup> Diagnosed by a fasting plasma glucose level  $\geq$  7.0 mmol/l and/or a plasma glucose  $\geq$  11.1 mmol/l 120 minutes after intake of 75 g glucose dissolved in 2.5 dl of water.<sup>39</sup>



## **INTRODUCTION**

### **Overweight and obesity**

Overweight and obesity is rapidly increasing worldwide and has become one of the most important public health problems in the world, affecting all ages and social groups.<sup>35,47</sup> Obesity is defined as “abnormal or excessive fat accumulation that may impair health”.<sup>35</sup> The World Health Organization (WHO) classifies overweight as a body mass index (BMI) 25.0 – 29.9 kg/m<sup>2</sup>, and obesity as BMI  $\geq$  30.0 kg/m<sup>2</sup>.<sup>35</sup> The prevalence of obesity has doubled from 1980 to 2014, and about 52% of the world’s population are either overweight (39%) or obese (13%).<sup>35</sup> Obesity is one of the leading risk factors for several lifestyle related health problems, as cardiovascular and metabolic diseases.<sup>48</sup>

### **Overweight and obesity in pregnancy**

Today, about one third of all women in fertile age are obese.<sup>3,49-52</sup> According to the public birth register in Norway about 22% was overweight and 12% obese when they entered the pregnancy in 2014.<sup>53</sup> Pre-pregnancy overweight or obesity is associated with several adverse outcomes during and after pregnancy both for mother and child,<sup>54</sup> and the risk accumulates with increasing BMI.<sup>5</sup>

Women who are overweight or obese when they become pregnant have an increased tendency to gain excessive weight during pregnancy, compared to normal weight women. This tendency is adding to their already present risks.<sup>16</sup> Overweight and obese women often have increased levels of circulating insulin, regardless of any diabetes diagnosis. In addition, they are more frequently insulin resistant, compared to normal weight women.<sup>55</sup> As reduced insulin sensitivity is a normal physiological response in pregnancy, these women will have a further reduction in insulin sensitivity during pregnancy. Being pregnant challenges the metabolic system, and due to peripheral insulin resistance and insufficient beta-cell function, overweight and obese women are at increased risk of reduced glucose tolerance and of developing gestational diabetes mellitus (GDM).<sup>56</sup> GDM is most commonly defined as “glucose intolerance of variable degree with onset or first recognition during pregnancy”.<sup>57</sup> These metabolic mechanisms also increases the risk of hypertension.<sup>56</sup> In addition, disturbances in the lipid metabolism, which may lead to increased levels of circulation lipids and triglycerides, are more often seen among overweight and obese pregnant women, compared to their normal weight counterparts.<sup>56,58</sup> Studies have also found that obesity may lead to increased baseline pro-inflammatory mediators, which are associated with adverse

maternal outcomes as preeclampsia,<sup>59</sup> and adverse neonatal outcomes as macrosomia, insulin resistance, and future risk of obesity.<sup>60</sup> In summary, women with a high BMI have already a metabolic system under stress. Added with metabolic changes during pregnancy, further stress is induced.

### Gestational weight gain

Weight gain during pregnancy normally lies between 10-13 kg, and about 4-6 of these kilos are fat.<sup>61</sup> Excessive gestational weight gain (GWG) is as an independent factor associated with several adverse pregnancy outcomes, together with pre-pregnancy overweight or obesity.<sup>6,62,63</sup> Mothers with pre-pregnancy BMI > 30, or mothers who exceed GWG recommendations according to IOM guidelines, or both, are at increased risk of having a child pre-disposed for overweight and obesity later in life, compared to normal weight pregnancies.<sup>62,64</sup> The Institute of Medicine's (IOM) has provided guidelines on weight gain during pregnancy, which differs according to pre-pregnancy BMI (Table 1).<sup>65</sup> Women who are overweight or obese are recommend to gain less weight than normal weight women during pregnancy, as this has been found to reduce the risk of adverse pregnancy outcomes.<sup>2,16,19,66-68</sup> The guidelines are however, not stratified by grade of obesity.

**Table 1.** The Institute of Medicine's (IOM) recommendations for weight gain during pregnancy, according to body mass index (BMI) classification.

Pre-pregnancy BMI	Classification	Recommended weight gain
≤ 18.5	Underweight	12.5 - 18.0
18.5-24.9	Normal weight	11.5 - 16.0
25.0-29.9	Overweight	7.0 - 11.5
≥ 30	Obese	5.0 - 9.0

About 60% of overweight women gain more weight than recommended,<sup>1,2</sup> and pre-pregnancy overweight and obese women are about twice as likely to exceed the IOM recommendations as normal weight women.<sup>16,69</sup> Excessive GWG increases the risk of hypertension,<sup>70,71</sup> GDM, caesarean delivery,<sup>31,40</sup> having large babies,<sup>69</sup> preterm birth,<sup>40</sup> low five-minute Apgar score, PPWR, future risk of development of obesity, and high BMI in subsequent pregnancies.<sup>31,40</sup> A meta-analysis of seven observational studies, including women in all BMI categories, found a 21% risk of the neonate to develop childhood overweight if the mother exceeded the IOM recommendations for GWG.<sup>62</sup> Studies indicate that trimester-specific GWG are associated with different adverse outcomes.<sup>72</sup> Excessive GWG the first trimester is associated with

development of childhood obesity, and excessive GWG the second trimester associated with increased risk for giving birth to a neonate large for gestational age.<sup>72</sup> It has been suggested that women with class II obesity should gain less than 5 kg during pregnancy to reduce the risk related to maternal obesity. Women with class III obesity are recommended not to gain any weight during pregnancy.<sup>69</sup> Uncertainty remains whether lower weight gain will reduce adverse outcomes, and whether GWG below the guidelines is safe for mother and child.<sup>73-76</sup>

### **Adverse maternal outcomes**

The most common adverse maternal outcomes related to pre-pregnancy overweight or obesity are GDM, pre-eclampsia, hypertensive disorders, need for caesarean delivery, prolonged hospital stay, PPWR, and increased risk of future obesity, and cardiometabolic diseases.<sup>2,49,5,77,4,78</sup>

### **Gestational diabetes mellitus**

The international Diabetes Federation estimates that, according to the WHO definition of 1999, approximately 16% of pregnancies worldwide are complicated by GDM.<sup>79</sup> Normally, insulin resistance increases as the pregnancy advances, a result of physiological changes due to hormonal secretion from the placenta.<sup>80,81</sup> This increased insulin resistance compensates for the high demands of nutrition (glucose), to support fetal development and growth.<sup>81</sup> GDM develops if insulin secretion becomes inadequate for the degree of insulin resistance.<sup>80</sup> Unfortunately, no common agreement regarding screening GDM exists, therefore the diagnostic criteria may diverge between studies. Maternal obesity is probably the most important risk factor for developing GDM,<sup>78,4</sup> and both hyperglycemia and excessive GWG predispose for having a child with high birth weight (> 4000g) and high relative fat mass.<sup>82,83</sup> Women who develop GDM during pregnancy are at increased risk of developing type 2 diabetes mellitus later in life.<sup>81,84</sup>

### **Maternal blood pressure**

About 10% of all pregnant women have a form of maternal hypertension (blood pressure  $\geq$  140/90 mmHg), and maternal hypertension are together with pre-eclampsia, among the most common pregnancy disorders.<sup>85</sup> Obesity and excessive GWG in pregnancy are associated with higher blood pressure during pregnancy, and an increased risk of hypertension.<sup>86-88</sup> Maternal hypertension affects the risk of maternal, fetal and neonatal morbidity or in worst case mortality.<sup>89</sup> Maternal hypertension may affect blood flow to the uterus,<sup>90,91</sup> and is

strongly associated with higher neonatal blood pressure,<sup>92</sup> preterm birth, hemorrhage,<sup>93,94</sup> pre-eclampsia,<sup>95</sup> congenital heart defects in the fetus,<sup>96</sup> and both neonatal growth restriction and macrosomia.<sup>97</sup> Furthermore, research has shown that maternal hypertension may contribute to increased risk of obesity<sup>97</sup> and cardiovascular diseases later in life.<sup>98</sup>

### **Mode of delivery and birth complications**

The mode of delivery could impact health and well-being of both the mother and the newborn. Studies have found a significantly higher frequency of induced delivery, caesarean delivery and use of epidural, among obese women compared to normal weight women.<sup>99</sup> Both maternal obesity and excessive GWG increases the risk of caesarean delivery.<sup>8,100</sup> The rate of caesarean delivery is increasing and is now about 31% worldwide. Caesarean delivery is associated with complications for both mother and child during delivery and postpartum period,<sup>101,102</sup> and the increasing rate is a public health concern.<sup>103</sup> Possible complications are excessive blood loss, prolonged operative time, increased risk of wound infection, maternal and neonatal respiratory problems, anesthesia reactions, insufficient newborn sucking reflex, prolonged stay hospital stay and placental problems in future pregnancies.<sup>104,105</sup> Research has also found that caesarean delivery increases the risk of future obesity for the child, especially among pre-pregnancy obese women.<sup>106</sup> On the other hand, research suggests decreased risk of perineal tear among obese women compared to normal weight women.<sup>99</sup>

### **Postpartum weight retention**

Women who are overweight or obese when they enter pregnancy are at increased risk of high PPWR.<sup>17,18</sup> Excessive GWG increases this risk, as half of the short-term weight retention can be explained by GWG.<sup>107</sup> High PPWR may have important health consequences, and is associated with reduced insulin sensitivity, development of type 2 diabetes mellitus, hypertension, and cardiovascular disorders.<sup>108,109</sup> PPWR are a strong predictor for subsequent development of overweight and obesity.<sup>110</sup> Women are particularly prone to weight gain during their reproductive years, thus excess GWG and PPWR are important predictors for development of obesity and high pre-pregnancy BMI in future pregnancies.<sup>13,14</sup>

### **Adverse neonatal outcomes**

Maternal overweight and obesity increases the risk of high birth weight, low Apgar-score,<sup>111</sup> high placental weight ratio, preterm birth, insulin resistance,<sup>10,11</sup> and in addition, development of childhood obesity and metabolic diseases later in life.<sup>5</sup>

### **Birth weight and anthropometrics**

Babies born with high birth weight are at increased risk of birth complications, and for developing childhood and adult obesity, compared to babies born with “normal” weight (2500-4000g).<sup>112-114</sup> However, it is important to be aware that “normal” birth weight does not necessarily implicate the baby being metabolically “normal”. Women with maternal hyperglycemia may give birth to “normal” weight babies in a not optimal metabolic state, and with an increased risk of later obesity.<sup>113</sup> A study has also found that abdominal circumference of the newborn may be a stronger predictor of adverse metabolic outcomes later in life than birth weight alone.<sup>115</sup>

Maternal obesity are found to double the risk of childhood obesity.<sup>116</sup> As women with high pre-pregnancy BMI are at increased risk of GDM,<sup>4</sup> and both hyperglycemia and excessive GWG predispose for neonatal overgrowth, these women are at increased risk of having a child with high birth weight (> 4000 g), and high relative fat mass.<sup>9,82,83</sup> Blood glucose in the mother is transferred to the fetus through the placenta. Due to changes in the lipid metabolism of the mother, increased levels of triglycerides, lipids, and free fatty acids are being transferred to the fetus through the placenta. These factors contribute to increased risk of the fetus being born large for gestational age.<sup>55,117</sup> Brisbois and colleagues<sup>64</sup> searched among 135 studies for the most important predictors for development of obesity. They identified “maternal BMI” as one of the seven most pronounced “potential/possible” early markers associated with obesity. The neonatal birth weight may not be affected by the direct environment only, but also by epigenetic factors. The developmental origin of health and disease (DOHaD) hypothesis, suggests that prenatal and early postnatal environment could affect the epigenetic of the neonate, and thereby influence future health risks.<sup>118-120</sup> Research has found that prenatal physical activity is associated with birth weight, showing that babies born to mothers who were sedentary pre-pregnancy had a higher birth weight, compared to mothers who were active pre-pregnancy.<sup>121</sup> On the other hand, a large cohort study (HUNT) from Norway<sup>122</sup> investigated the association between pre-pregnancy physical exercise and neonatal birth weight among 2026 women, and found no association. They did, however,



reveal an association between pre-pregnancy BMI and both birth weight and macrosomia, however this was only present among the least active women.

### **Placental weight ratio**

Adequate placental function is of major importance for fetal growth and development. High levels of glucose may lead to placental dysfunction, reduced nutrient supply and growth restriction for the fetus.<sup>123</sup> Placental weight ratio is calculated by dividing the weight of the placenta by the weight of the baby, and reflects the efficiency of the placenta to adapt to the nutrition requirements of the fetus'.<sup>123</sup> Placental maladaptation may lead to both small for gestational age and large for gestational age newborn.<sup>124</sup> Maternal obesity, insulin sensitivity and GDM may all affect the function and the size of the placenta.<sup>125</sup> Maternal obesity is associated with increased placental weight, while GDM is associated with placental maladaptation.<sup>125</sup> Both low and high placental weight ratio can be signs of insufficient placental function, and increase the risk of adverse neonatal outcomes at delivery.<sup>44</sup> High placental weight ratio is associated with increased risk of obesity and cardiovascular disease later in life for the neonate.<sup>126-128</sup> High-glycemic carbohydrate intake and physical inactivity during the maternal period may increase the growth rate of the placenta.<sup>129</sup>

### **Preterm birth**

Studies indicate that overweight and in particular obese pregnant women are at increased risk of preterm delivery (< 37 weeks), compared to normal weight women.<sup>130,131</sup> Further, that morbid obese women (BMI  $\geq$  40) are at increased risk of extremely preterm delivery (< 28 weeks).<sup>8,131</sup> Obese pregnant women may be at increased risk of preterm delivery, due to infections and inflammations, premature rupture of membranes,<sup>131</sup> and medically indicated conditions such as preeclampsia.<sup>132</sup> Delivery before gestational week 37 are associated with adverse outcomes such as infant mortality, neonatal morbidity and long term disability.<sup>133</sup> Preterm delivery is also found to increase the baby's risk of obesity and cardiovascular risks later in life.<sup>134</sup> This risk of adverse outcomes increases with decreasing gestational age at delivery.<sup>135</sup>

### **Future risk of obesity cardio-vascular diseases**

Over the last few years there has been an increased awareness of how the fetus adapts to environmental conditions during the pregnancy, including how the intrauterine environment may "program" development of metabolic diseases and obesity later in life.<sup>15,136,137,138-140</sup>

High pre-pregnancy BMI is associated with lower insulin sensitivity and higher systolic blood pressure of the child.<sup>141</sup> “Maternal imprinting” is a term used to describe adaptive conditions in maternity that may permanently affect the risk of diseases for the neonate later in life.<sup>142,143</sup> “The Barker-hypothesis” explains these mechanisms as adaptations in fetal programming to maternal malnutrition, in which a high level of maternal glucose is transferred to the infant, leading to insulin resistance in the fetus and increased risk of obesity later in life.<sup>144</sup> Pre-pregnancy overweight and obesity, excessive GWG during pregnancy, and maternal hyperglycemia may affect epigenetic programming and imprint the fetus for increased risk of obesity and metabolic disorders in the future.<sup>145,146</sup> Some periods during the fetal development are more sensitive to influence adult body size, and the first trimester seems of special importance.<sup>146,147</sup> Studies indicate that GDM is highly correlated with fetal overgrowth, while research indicates that pre-pregnancy obesity has the highest correlation with childhood obesity.<sup>148</sup>

### **Exercise in pregnancy**

For many years, recommendations on physical activity and exercise training during pregnancy has been based mainly on social and cultural notions, rather than scientific evidence.<sup>149</sup> Historically, the pregnancy has been considered as a vulnerable period, in which physical activity and especially exercise training could put both the mother and the fetus at high risk.<sup>150</sup> Furthermore, women were advised to increase their calorie intake as the pregnancy proceeded.<sup>150</sup> More recent research has provided us with increased knowledge on the positive effects and safety of physical activity and exercise training during pregnancy. The first studies on the effect of physical activity on maternal health and birth outcomes were published in late 19<sup>th</sup> and in the beginning of the 20<sup>th</sup>.<sup>151</sup> Today, women are recommended to be physically active during pregnancy and the postpartum period to maintain a healthy weight, and to prevent negative health outcomes.<sup>29,35,152,153</sup> Exercise training during pregnancy is also found to lower the risk of developing type 2 diabetes among women with previous GDM.<sup>154</sup> Physical inactivity during pregnancy is as an independent factor, found to be associated with maternal obesity, GDM and pregnancy complications.<sup>155,156</sup> In the case of a normal, healthy pregnancy, research clearly shows positive effects of regular exercise during pregnancy.<sup>29,157</sup> Today, pregnancy is considered as an optimal time for initiating lifestyle changes.

In 1985, the American College of Obstetricians and Gynecologists (ACOG) published their first recommendations on physical activity and exercise training during pregnancy.<sup>153</sup> In

2002, the ACOG published reviewed guidelines, reinsured the safety of exercising during pregnancy, and recommended 30 minutes of moderate intensity of physical activity in most days of week.<sup>153</sup> The latest guidelines from ACOG (2015), recommends that all pregnant women without specific contraindications, to perform regular physical activity, and exercise at moderate intensity 20-30 minutes daily, on the most/all days of the week.<sup>29</sup> Physically active women are advised to remain active, whereas sedentary women and women with medical or obstetric complications are advised to be evaluated before entering an individualized planned exercise program during pregnancy.<sup>29,153</sup> Both groups are recommended to adjust their training over time. Recommendations from the Norwegian Directorate of Health are in line with the ACOG guidelines, recommending pregnant women to be physically active for at least 30 minutes, five days per week. This also includes women who have been previously sedentary.<sup>27</sup> Currently, no specific exercise guidelines for overweight or obese women aiming to reduce the risk of negative health outcomes exists.<sup>158</sup> However, these women are strongly encouraged to perform regular exercise during pregnancy.<sup>155</sup> Some previous studies have indicated higher risk of preterm delivery among women who exercise during pregnancy, compared to women who don't.<sup>159</sup> Later research has refuted this, finding no association between regular exercise training during pregnancy, and risk of preterm birth or reduction in birth weight.<sup>160,161</sup> Thangaratinam and colleagues,<sup>162</sup> searched in 26 studies, involving 468,858 women, for possible adverse effects of exercise during pregnancy, and found no adverse effects on either neonatal or maternal health.

Physical activity and exercise training during pregnancy can affect endurance capacity, improve muscle strength, joint mobility, reduce the risk of pelvic and lower back pain, and make daily activities easier.<sup>163,164</sup> In general, exercise contributes to reduce the amount of fat tissue by mobilizing fatty acids and improve the metabolic state.<sup>165,166</sup> Furthermore, exercise increases glucose uptake in skeletal muscles, and improve glucose tolerance.<sup>167</sup> Physical activity during pregnancy, may thereby contribute to reduced risk of GDM and maternal hypertension,<sup>25</sup> and to reduce negative effects of maternal obesity on the fetus' metabolic health status.<sup>168,169</sup> Moreover, physical activity and exercise training during pregnancy are shown to have a positive effect on psychologic well-being.<sup>170</sup>

Maternal exercise may increase the fetal heart rate by 10-30 beats per minute, which is considered as a small to moderate increase.<sup>171</sup> Exercise during pregnancy may cause an intermittent reduction in oxygen and substrate delivery to the fetus, however regular exercise may improve oxygen and substrate delivery to the fetus, at rest.<sup>129</sup> Exercise training and physical activity in first and second trimester stimulates placental growth, while it in the third

trimester mostly affects late fetal growth.<sup>129</sup> Research indicates that strenuous exercise is well tolerated by the fetus of both previously active and inactive women.<sup>171</sup> Vigorous exercise is not found to increase core body temperature of any concern,<sup>172</sup> but hard or prolonged exercise in very warm conditions is not recommended for pregnant women. Overheating may affect the fetus, in particularly the first trimester, and should be avoided by hydration and adjusting the environmental conditions.<sup>152,172</sup> A study among pregnant elite athletes has found that exercising at an intensity above 90% of maximum heart rate, can affect the wellbeing of the fetus by fetal bradycardia and decreased uterine volume blood flow.<sup>173</sup>

Going through a pregnancy implies anatomical, physiological, and biochemical changes to the body. Normal changes include weight gain, increased blood volume and heart rate, decreased blood pressure and vascular resistance.<sup>174,175</sup> Progressive lumbar lordosis, and increased joint- and ligament laxity, increase the risk of low back pain.<sup>176</sup> These changes, affect the work capacity during pregnancy, especially among obese women. Such risk should be handled by exercise programs planned by health care personnel. In pregnant women the parasympathetic neural system modulation seems to be lower at rest, and the sympathetic neural system blunted during exercise exceeding the aerobic threshold.<sup>174,177</sup> The cardiac autonomic neural activity is affected as gestational age progresses. A study by Nakagaki and co-workers,<sup>178</sup> observed a more rapid activation of the sympathetic neural system, and increased systolic blood pressure during exercise, with increasing gestational age. They compared mild to moderate exercise training in second trimester women, compared to third trimester women. They found that during exercise, blunting of the parasympathetic activity was more distinct in third trimester women compared to second trimester women. Their findings of significant more rapid sympathetic activity in the third trimester compared to the second trimester were only present when exercising, not at rest. These findings suggest that women in late pregnancy should exercise at a lower intensity than women in early pregnancy.

Physical activity and exercise training are found to be safe for both the mother and child,<sup>29,160,179</sup> even for women with risk factors as GDM, chronic hypertension, and overweight/obesity.<sup>180</sup> However, there are some contraindications for aerobic exercises during pregnancy.<sup>29</sup> Absolute contraindications include some heart and lung diseases, incompetent cervix, risk of premature labor, heavy bleedings, pre-eclampsia and severe anemia.<sup>29</sup> Other contraindications are more relative, such as anemia, poorly controlled type 1 diabetes mellitus, poorly controlled hypertension, extremely morbid obesity, and intrauterine growth restrictions.<sup>29</sup> Types of exercise that include high levels of body contact, risk of falling, or

other activities that puts the mother and the infant at high risk, should be avoided during pregnancy.<sup>27,29</sup>

Despite current exercise recommendations and the documented positive effects of regular exercise during pregnancy, women tend to decrease their physical activity significantly during pregnancy and in the postpartum period. Reduced activity level during pregnancy is especially pronounced among women with high BMI.<sup>30</sup> In a systematic review, Cambell and co-workers<sup>181</sup> investigated quantitative and qualitative data on weight management in pregnancy, and found that important factors contributing to a decline in physical activity and increased risk of excessive GWG during pregnancy were; “fear of harming themselves and the infant, general physical discomfort, discouragement to undertake physical tasks by the people around them, and positive view or encouragement toward over-eating”.<sup>181</sup> Factors that interfere with behavioral patterns during pregnancy may differ between countries, culture, and age-groups, and depend on social-economic status.

### **Effects of lifestyle interventions in pregnancy**

Research suggests that overweight and obese women may benefit from lifestyle interventions during pregnancy to prevent adverse maternal and neonatal health outcomes. Several types and combinations of interventions have been tested in RCTs. Despite this, the effects on maternal and neonatal health are still not clear. Most research has been conducted on the effect of the combination of diet and exercise, whereas few RCTs have aimed to investigate the effect of exercise training as the sole intervention, among overweight and obese pregnant women.<sup>182-184</sup> Former studies have used different types and combinations of intervention programs, varying from supervised and frequently monitored interventions to written and/or oral information regarding healthy diet and/or exercise training given at one visit early in pregnancy. Previous trials have often included pregnant women in all BMI categories, and some have provided sub-group analysis on overweight and obese women. As the number of participants in the different sub-groups has been low, there is a risk of type II error. Thus, comparisons between trials are complicated, and effects of the interventions are difficult to identify. Furthermore, both aerobic exercise alone, and combined aerobic exercise and resistance training, have been used in trials investigating the effect of exercise during pregnancy.

### **Diet and exercise intervention among women within all BMI categories**

Most studies on the effect of lifestyle interventions during pregnancy have included women within all BMI classifications, and more normal weight women than overweight and obese women have volunteered for participation. When looking at the effect of exercise- and diet interventions during pregnancy, independent of weight class, a meta-analysis by Thangaratinam and colleagues<sup>185</sup> found lower GWG in the intervention groups compared with the control groups. However, the largest effect was found in the groups receiving diet intervention only ( $p < 0.001$ ), which is in accordance to the findings of healthy diet during pregnancy being effective to reduce GWG.<sup>22,24,185,186</sup> Further, this meta-analysis found a reduction of pre-eclampsia ( $p = 0.006$ ), a tendency of lower risk of GDM, lower number of newborns large for gestational age, lower incidence of maternal hypertension, and lower rate of preterm delivery, in the intervention groups. No differences were found in gestational age at delivery, risk of caesarean delivery, or admission to neonatal intensive care. The meta-analysis of Thangaratinam and colleagues<sup>185</sup> found larger effects of dietary interventions on reduced risk of pre-eclampsia, GDM, and maternal hypertension, than of interventions combining diet and exercise, or exercise alone.

In a systematic review including 19 studies, Ruchat and Mottola<sup>187</sup> supported an effect of lower GWG in the intervention groups. Contrary to the study of Thangaratinam and colleagues, they observed a combination of diet and exercise to be most effective among women in all weight-classes. They observed less effect among women with high BMI, and therefore suggested that overweight and obese women probably need more guidance and support for lifestyle changes during pregnancy, compared to their normal weight counterparts. The reasons for equivocal results in the two reviews (published the same year), is probably different inclusion criteria and different search strategies. Thangaratinam and colleagues excluded women who were underweight, while Ruchat and Mottola excluded trials including women with GDM. Thangaratinam and colleagues searched for studies in many different databases, and thereby included a higher number of studies in their analysis, while Ruchat and Mottola only searched for studies in PubMed.

### **Combination of diet and exercise intervention among overweight and obese women**

When assessing both exercise and diet intervention programs including only overweight and obese pregnant women, a systematic review and meta-analysis of Oteng-Ntim and colleagues<sup>188</sup> (thirteen RCTs and six non-RCTs), found an effect on GWG, and a tendency of reduced risk of GDM. No significant findings were identified regarding birth weight or risk of

caesarean delivery. These findings were partly supported by a systematic review and meta-analysis of Choi and colleagues<sup>31</sup> seven studies, published the following year. The latter systematic review and meta-analysis investigated the effects of lifestyle interventions among overweight or obese women, including both physical activity and diet combined, and physical activity alone, on GWG. They found an overall effect on reduction of GWG in the groups who received physical activity intervention, alone or combined with diet ( $p = 0.035$ ). Supervised exercise interventions including three sessions per week showed the highest effect on limiting GWG.

### **Exercise intervention among women within all BMI categories**

When investigating studies that have used exercise training as the only lifestyle intervention among women within all BMI categories, a recent systematic review by Perales and co-workers<sup>189</sup> reported an effect of exercise training on cardiorespiratory fitness and urinary incontinence prevalence in late pregnancy. They found some trials reporting of lower GWG, and lower tendency of weight gain exceeding the IOM recommendations, in the exercise groups. The evidence was however weak and six high-quality trials did not find any significant effect of exercise training on GWG. Exercise training has been associated with reduced prevalence of excessive GWG, however few trials actually reports of significant effects, and this association is less pronounced with increasing pre-pregnancy BMI.<sup>23,24,31,32,189</sup> This was supported by a review from Wiebe and colleagues<sup>180</sup> who investigated the effect of supervised exercise during pregnancy on fetal growth. They found that exercise was associated with 31% less risk of having a newborn  $\geq 4000$  g, with lower GWG and with lower risk of GDM. However, when analyzing the subgroups according to BMI, no effect in any of these outcomes was seen among overweight and obese women.

In a review of Perales and colleagues,<sup>189</sup> four trials found an effect of exercise on GDM, while 11 trials did not find any effects. In total they found a tendency of reduced risk of caesarean delivery among the women who were offered exercise training during pregnancy. Only one out of 12 trials included in this review, found an effect of exercise training on risk of maternal hypertension. The majority of trials did not find any significant effect of exercise training on birth weight or macrosomia. These were characterized by using supervised sessions, frequent training sessions over  $\geq 20$  weeks, and being of high methodological quality. Further, a systematic review and meta-analysis by Elliot-Sale and co-workers<sup>190</sup> investigated the effect of exercise during pregnancy among women in all weight

classes and found significant effect on GWG ( $p < 0.001$ ). This analysis did not include any restrictions regarding type of exercise program, duration or intensity.

### **Exercise intervention among overweight and obese women**

If we narrow down to the effect of exercise intervention during pregnancy among overweight and obese women only (see Table 2.), a systematic review of Sui and colleagues<sup>191</sup> found evidence for positive effect on GWG, but found no evidence of effect on other maternal and neonatal outcomes such as level of insulin, birth weight, Apgar score, or gestational age. A later systematic review and meta-analysis of exercise during pregnancy among overweight and obese women by Magro-Malosso and co-workers,<sup>184</sup> found no effect on gestational age, risk of caesarean delivery, neonatal birth weight, or still-birth, however they found a significant lower risk of preterm birth and for developing GDM. An overview of RCTs, comparable to the ETIP trial, assessing the effect of exercise training as the sole intervention among overweight and obese women, is presented in Table 2.

Research shows that lifestyle programs that aim to reduce GWG among overweight and obese women are most effective when comprising supervised exercise sessions and frequent counselling on diet and recommended weight gain, throughout the pregnancy.<sup>22,192,193</sup> Lifestyle programs based on written and oral communication and less frequent consultations are less effective in preventing excessive GWG.<sup>194,195</sup> Many trials on lifestyle changes in pregnancy among overweight and obese women, do not achieve desired outcomes. Research have proposed that interventions initiated in pregnancy for particularly obese women, may have limited effect due to already present high amount of fat tissue, insufficient metabolic condition, and decreased insulin resistance.<sup>196</sup> This, in combination with pregnancy related metabolic alternations and physiological adaptations, makes it less likely to achieve significant effect of lifestyle interventions.<sup>196</sup>

Intervention programs that aim for behavioral changes during pregnancy are limited in numbers, and the findings diverge. The level of physical activity tends to decrease during pregnancy, for most women. A systematic review by Currie and co-workers<sup>197</sup> investigated the effects of behavior change techniques during pregnancy to reduce the decline in physical activity during pregnancy among 14 studies, and found positive effects. They concluded that regular face-to-face consultations, including goal settings, planning, information and comparison of outcomes during pregnancy, had positive effect on maintaining the level of physical activity. Cambell and colleagues<sup>181</sup> assessed the effect of behavioral interventions during pregnancy on weight management in a systematic review. They provided subgroup



analyses according to BMI and found no effect of behavioral intervention on GWG among normal weight, overweight or obese women, despite often intense and tailored interventions.

**Table 2.** Randomized controlled trials assessing the isolated effects of exercise training in pregnancy among overweight and obese women. The results are presented as exercise group versus (vs) control group.

Author (year)	Study population and number of participants (N)	Design and intervention	Outcomes	Results	Loss to follow-up, adherence and comments
Wang et al. (2016) <sup>188</sup>	N = 300	Two-arm RCT	Primary outcome: GDM	GDM: 22.0% vs 40.6% ( $p < 0.001$ ).	Adherence: -
Wang et al. (2017) <sup>182</sup>	Age $\geq 18$ Pre-pregnancy BMI $\geq 24 \text{ kg/m}^2$ Gestational week $< 12.6$ (mean)	Exercise group: Frequency: 3x/week Duration each session: From 30 min, progressively to 45-60 min. Exercise mode: Stationary cycling, bouts of 30 sec. Intensity: Warm-up/cool down, 55%-65% (9-11 RPE), 30 sec bouts, 75%-85% (RPE15-16) of age-predicted heart rate. Supervision: Yes. Duration of intervention: Until gestational week 36-37. Control group: Standard maternal care	Secondary outcome: GWG (kg), insulin resistance (HOMA-IR), maternal hypertension, caesarean delivery, gestational age (weeks), preterm birth, macrosomia, birth weight (g), Apgar score.	GWG (kg): 8.4 kg vs 10.5 kg ( $p < 0.001$ ) HOMA-IR: 3.56 vs 4.07 ( $p = 0.1$ ) Maternal hypertension: 9.8% vs 13.2% ( $p = 0.4$ ) Birth weight: 3345.3 vs 3457.5 ( $p = 0.049$ ) Caesarean delivery: 29.5% vs 32.5% ( $p = 0.6$ ). Gestational age: 39.0 vs 38.9 ( $p = 0.5$ ). Preterm birth: 2.7% vs 4.4% ( $p = 0.5$ ) Apgar 1 min: 9.95 vs 9.80 ( $p = 0.1$ ) Apgar 5 min: 10.0 vs 9.9 ( $p = 0.1$ ) Macrosomia ( $> 4000 \text{ g}$ ): 6.3% vs 9.6% ( $p = 0.3$ )	Loss to follow-up: 24.7% Defined overweight as BMI between 24 and 28, obese as BMI $\geq 28$ . No postpartum data
Seneviratne et al. (2016) <sup>32</sup>	N = 75	Two-arm RCT	Primary outcome: Birth weight (g).	Birth weight: 3578 vs 3594 ( $p = 0.35$ )	Adherence: 33%

	<p>Age <math>\geq</math> 18</p> <p>Pre-pregnancy BMI <math>\geq</math> 25 kg/m<sup>2</sup></p> <p>Gestational week &lt; 20</p>	<p>Exercise group:</p> <p>Frequency: 3-5x/week</p> <p>Duration each session: 25-40 min</p> <p>Exercise mode: Home-based program, stationary cycling</p> <p>Intensity: 2x5 min warm-up/cool down, 40-59%, 15-30 min 60-70% of VO<sub>2</sub> reserve.</p> <p>Supervision: None</p> <p>Duration of intervention: Until gestational week 35</p> <p>Written program prescribing frequency and duration</p> <p>Exercise registered by heart rate monitor</p> <p>Control group:</p> <p>Standard maternal care</p>	<p>Secondary outcome:</p> <p>Pre-specified maternal and perinatal parameters.</p> <p>Postnatal weight loss 2 weeks after delivery</p>	<p>Apgar 1 min: 8.3 vs 8.0 (<math>p = 0.47</math>)</p> <p>Apgar 5 min: 9.2 vs 9.1 (<math>p = 0.87</math>)</p> <p>Length hospital stay (hours): 61 vs 80 (<math>p = 0.33</math>)</p> <p>NICU: 8% vs 8% (<math>p = 0.9</math>)</p> <p>Birth weight &gt; 4000 g: 26% vs 19% (<math>p = 0.43</math>)</p> <p>Gestational age (days): 274 vs 274 (<math>p = 0.20</math>)</p> <p>GWG (kg): 12.0 vs 13.2 (<math>p = 0.40</math>)</p> <p>GDM: 11% vs 5% (<math>p = 0.43</math>)</p> <p>Maternal hypertension: 3% vs 0%</p> <p>Preterm birth: 5% vs 3% (<math>p = 0.51</math>)</p> <p>Caesarean delivery: 47% vs 35% (<math>p = 0.29</math>)</p> <p>Systolic BP: 113.2 vs 118.5 (<math>p = 0.25</math>)</p> <p>Diastolic BP: 67.8 vs 70.0 (<math>p = 0.68</math>)</p> <p>Weight loss two weeks postpartum: 8.1 kg vs 7.5 kg (<math>p = 0.23</math>)</p>	<p>Loss to follow-up: 1.3%</p>
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Ong et al. (2009) <sup>23</sup>	<p>N = 12</p> <p>Age ≥ 18</p> <p>Pre-pregnancy BMI ≥ 30 kg/m<sup>2</sup></p> <p>Gestational week 18</p>	<p>Two-arm RCT</p> <p>Exercise group: Frequency: 3x/week Duration each session: 35-65 min. 10 min warm-up/cool-down, 15-45 min moderate as the weeks proceeded Exercise mode: Home-based exercise, stationary cycling. Intensity: 50-60% to 60-70% Supervision: Yes Duration of intervention: 10 weeks intervention period</p> <p>Control group: Standard maternal care</p>	<p>Primary outcome: OGTT and aerobic fitness</p> <p>Secondary outcome: GWG (kg).</p>	<p>OGTT, change in two hours test from pre to post: <math>p = 0.48</math> vs <math>p = 0.07</math></p> <p>Increase in aerobic fitness during pregnancy: <math>p = 0.064</math> vs <math>p = 0.699</math></p> <p>GWG: 3.7 vs 5.2 (<math>p = 0.155</math>)</p>	<p>Adherence: 94%</p> <p>Loss to follow-up: 0</p> <p>Detailed data not provided.</p> <p>No postpartum data</p>
Callaway et al. (2010) <sup>189</sup>	<p>N = 50</p> <p>Age ≥ 18</p> <p>Pre-pregnancy BMI ≥ 30 kg/m<sup>2</sup></p> <p>Gestational week 12</p>	<p>Two-arm RCT</p> <p>Exercise group: Individualized exercise program with an energy expenditure goal of 900 kcal per week Supervision: None Duration of intervention: Until gestational week 36</p> <p>Control group: Standard maternal care</p>	<p>Primary outcome: GDM, OGTT</p> <p>Secondary outcome: HOMA-IR and fasting insulin.</p>	<p>GDM: 23% vs 16% (<math>p = 0.57</math>)</p> <p>HOMA-IR: 3.04 vs 3.82 (<math>p = 0.18</math>)</p> <p>Fasting insulin: 14.59 vs 20.28 (<math>p = 0.05</math>)</p>	<p>Adherence: 73%</p> <p>Loss to follow-up: 30%</p> <p>GDM measured at gestational week 28</p> <p>No postpartum data</p>

Ruiz et al. (2013) <sup>200</sup>	<p>N = 275</p> <p>Age ≥ 18</p> <p>Pre-pregnancy BMI ≥ 25 kg/m<sup>2</sup></p> <p>Gestational week 9</p>	<p>Two-arm RCT</p> <p>Exercise group: Frequency: 3x/week Duration each session: 2x10 min warm-up/cool-down + 50-55 min.</p> <p>Exercise mode: Aerobic dance bouts of 3-4 min, 1 min break, once a week, resistance training twice a week, flexibility exercises</p> <p>Intensity: 60% of age-predicted maximum heart rate (10-12 RPE)</p> <p>Supervision: Yes</p> <p>Duration of intervention: Until gestational week 39.</p> <p>Control group: Standard maternal care</p>	<p>Primary outcome: GWG (kg)</p> <p>Secondary outcome: Birth weight (g), gestational age (weeks), mode of delivery, Apgar score, GDM, maternal hypertension, macrosomia.</p>	<p>GWG (kg): 11.1 vs 11.6 (p = 0.51)</p> <p>Exceeded IOM guidelines: 49.3% vs 58.9% (p = 0.14)</p> <p>Birth weight: 3269 vs 3305 (p = 0.45)</p> <p>Gestational age: 39.6 vs 39.6 (p = 0.92)</p> <p>Caesarean delivery: 25.9% vs 22.1% (p = 0.37)</p> <p>Apgar 1 min: 8.8 vs 8.7 (p = 0.80)</p> <p>Apgar 5 min: 9.8 vs 9.8 (p = 0.61)</p> <p>GDM: 6.2% vs 9.3% (p = 0.52)</p> <p>Maternal hypertension: 5.5% vs 7.8% (p = 0.13)</p> <p>Macrosomia: 1.4% vs 9.3% (p = 0.08)</p> <p>Preterm delivery: 2.7% vs 1.5% (p = 0.48)</p>	<p>Adherence: 97% (for the total group of women, all BMI categories)</p> <p>Loss to follow-up: 0</p> <p>Included also normal weight women, but provided detailed sub-group analysis in all variables.</p> <p>Preterm delivery was defined as delivery &lt; gestational week 36</p> <p>No postpartum data</p>
Santos et al. (2005) <sup>201</sup>	<p>N = 92 (72 analyzed)</p> <p>Age ≥ 20</p> <p>Pre-pregnancy BMI 26-31 kg/m<sup>2</sup></p> <p>Gestational week ≤ 20</p>	<p>Two-arm RCT</p> <p>Exercise group: Frequency: 3x/week Duration each session: 60 min, 5-10 min warm-up, 30 min of aerob intensity, 10 min cool-down.</p> <p>Exercise mode: Aerobic training for upper and lower</p>	<p>Primary outcome: Submaximal oxygen uptake (mL·min<sup>-1</sup>·kg<sup>-1</sup>).</p> <p>Secondary outcome: Respiratory exchange ratio, carbon dioxide output, heart rate at the anaerobic threshold, GWG (kg), birth weight</p>	<p>Submaximal oxygen uptake: 18.1 vs 15.8 (p &lt; 0.002)</p> <p>Respiratory exchange ratio: 0.86 vs 0.87 (p = 0.14)</p> <p>Carbon dioxide output: 15.5 vs 13.7 (p &lt; 0.008)</p> <p>Heart rate at the anaerobic threshold: 150 vs 143.7 (p = 0.16)</p>	<p>Loss to follow-up: 21.7%</p> <p>Adherence: 40%</p> <p>No postpartum data</p>

<p>Nascimento et al. (2011)<sup>183</sup></p>	<p>N = 82 Age ≥ 18 Pre-pregnancy BMI ≥ 26 kg/m<sup>2</sup> Gestational week 14-24</p>	<p>limbs, stretching, relaxation Intensity: 50-60% of age-predicted maximum heart rate (max 140 bpm) Supervision: Yes Duration of intervention: Until delivery  Control group: Standard maternal care and weekly relaxation and focus group discussions.</p> <p>Two-arm RCT  Exercise group : Frequency: 5x/week Duration each session: 40 min Exercise mode: Stretching, strength, relaxation, walking. Group or individual 1x/week. Home-based, 4x/week. Intensity: ≤ 140 beats per minute. Supervision: 1x/week Duration of intervention: Until delivery.  Control group: Standard maternal care.</p>	<p>(g), preterm birth, Apgar score.</p> <p>Primary outcome: GWG (kg)  Secondary outcome: Increased arterial BP, caesarean delivery, birth weight (g), LGA, gestational age (weeks), Apgar score.</p>	<p>GWG: 5.7 vs 6.3 (<math>p = 0.62</math>) Preterm birth: 4.9% vs 2.4% (<math>p = 0.62</math>) Apgar 1 min: 9 vs 9 (<math>p = 0.88</math>) Apgar 5 min: 10 vs 9 (<math>p = 0.15</math>)</p>	<p>Adherence: 62.5% Loss to follow-up: 2.4% No postpartum data</p>
		<p>Exceeding IOM guidelines: 47.5% vs 57.2% (<math>p = 0.43</math>)  Increased arterial BP: No difference between groups. Caesarean delivery: 65.8% vs 72.5% (<math>p = 0.52</math>) Birth weight (g): 3267.4 vs 3228.4 (<math>p = 0.79</math>) LGA: 24.2% vs 24.2% (<math>p = 1.00</math>) Gestational age:</p>	<p>Total GWG (kg) (ITT): 10.3 vs 11.5 (<math>p = 0.65</math>) Obese: 10.4 vs 10.9 (<math>p = 0.76</math>) Overweight: 10.0 vs 16.4 (<math>p = 0.001</math>)  Total GWG ("per protocol"): 5.9, vs 11.9 (<math>p = 0.021</math>).  Exceeding IOM guidelines: 47.5% vs 57.2% (<math>p = 0.43</math>)  Increased arterial BP: No difference between groups. Caesarean delivery: 65.8% vs 72.5% (<math>p = 0.52</math>) Birth weight (g): 3267.4 vs 3228.4 (<math>p = 0.79</math>) LGA: 24.2% vs 24.2% (<math>p = 1.00</math>) Gestational age:</p>		

Barakat et al. (2016) <sup>202</sup>	N = 222 Age ≥ 18 Pre-pregnancy BMI ≥ 25 kg/m <sup>2</sup> Gestational week 9-11	Two-arm RCT Exercise group: Frequency: 3x/week Duration each session: 50-55 min. 2x 10-12 min warm-up/cool-down Exercise mode: Aerobic exercise, aerobic dance, muscular strength, flexibility Intensity: Heart rate max 70% of age predicted maximum, 12-14 RPE. Supervision: Yes Duration of intervention: Until gestational week 38-39 Control group: Standard maternal care	Primary outcome: Diastolic and systolic arterial blood pressure. Secondary outcome: GWG (kg), birth weight (g), maternal hypertension, and other maternal and fetal outcomes.	38.5 vs 38.5 (p = 0.49) Apgar 1 min: < 7: 6 vs 4, > 7: 30 vs 33 (p = 0.52) Apgar 5 min: < 7: 1 vs 0, > 7: 35 vs 37 (p = 0.49)	Loss to follow-up: No data specified in overweight Adherence: No data specified No postpartum data This trial included all BMI categories, and provided specific data among overweight/obese women in some of their outcomes. P-value of comparison between overweight/obese and normal weight was not provided.
Abbreviations: GWG: Gestational weight gain. OGTT: Oral glucose tolerance test. BP: Blood pressure. ITT: Intention to treat. PP: Per protocol. LGA: Large for gestational age. NICU: Neonatal Intensive Care Unit. GDM: Gestational diabetes mellitus. RCT: Randomized controlled trial. BMI: Body mass index (kg/m <sup>2</sup> ). IOM: The Institute of Medicine. BPE: Beats per minute. RPE: Rate of perceived exertion.					

## **AIMS OF THE THESIS**

The primary aim of the ETIP trial was to investigate the effect of regular supervised exercise training offered during pregnancy compared to standard maternal care only, on GWG among women with pre-pregnancy BMI  $\geq 28$  kg/m<sup>2</sup>. Additional aims were to study effects on neonatal birth weight and PPWR, supplemented by several other clinically important maternal and neonatal outcomes. We assessed outcomes in early pregnancy, late pregnancy, at delivery, and three months postpartum.

The aims of the three papers were:

**Paper I.** To assess whether regular supervised exercise training offered during pregnancy could reduce GWG in women with pre-pregnancy BMI  $\geq 28$ , compared to standard maternity care. Secondary aims were to investigate the effects of exercise on clinically important outcomes as GDM, blood pressure, various blood measurements, body composition and level of physical activity.

**Paper II.** To investigate if regular supervised exercise training provided during pregnancy to women with pre-pregnancy BMI  $\geq 28$  could affect neonatal birth weight. We also examined possible effects of exercise training on neonatal outcomes as body composition, Apgar score, placental weight ratio, and admission to neonatal intensive care unit (NICU), and maternal outcomes as mode of delivery, perineal tears and length of hospital stay.

**Paper III.** To examine if regular supervised exercise training offered during pregnancy to women with pre-pregnancy BMI  $\geq 28$ , could reduce PPWR three months after delivery. We also analyzed body composition, blood pressure, various circulating markers of cardiometabolic health, and level of physical activity.





## **MATERIALS AND METHODOLOGICAL CONSIDERATIONS**

### **Study design**

The Exercise Training In Pregnancy (ETIP) trial was a single-center, two-armed RCT seeking to investigate the effects of supervised regularly exercise training during pregnancy compared to standard maternity care. Assessments were performed in early pregnancy (gestational week 12-18), late pregnancy (gestational week 34-37), at delivery and three months postpartum.

The participants were randomly allocated 1:1 to the intervention or the control group. The procedures followed in the ETIP trial were in accordance with ethical standards of research and the Helsinki Declaration. The Regional Committee for Medical and Health Research Ethics (REK Midt 2010/1522) approved the trial, and we registered the trial protocol in ClinicalTrials.gov (NCT01243554). The current trial was based on voluntary participation. All participants signed an informed written consent on behalf of themselves and their fetus before inclusion in the trial.

An RCT is considered to be the gold standard design to assess cause-effect relation and outcomes of a treatment. An RCT provides a clinical relevant evidence on the efficacy of an intervention.<sup>203</sup> The ETIP trial based on the principle “intention to treat”, which means that the analyses of the effect of the intervention included all women who were randomized to the trial. This maintains the balance in subjects characteristics provided by the randomization procedure, and prevents prognostic differences between the groups.<sup>204</sup> ITT-analyses reflect actual clinical practice compared to “per protocol” analyses, and prevents over estimation of the efficacy of the intervention (type 1 error).<sup>205</sup> We however, performed “per protocol” analyses to assess the isolated effects of actually following the intervention program.

Most neonatal and maternal outcomes in the trial were identified and described a priori, and stated in our published study protocol.<sup>33</sup> The outcomes were selected on the basis of frequently observed adverse outcomes in the literature, and most importantly; based on the clinical importance for the current and future health of both mother and child. The outcomes placenta weight, placenta weight ratio, and body surface area (BSA) were added to our protocol subsequently, but did not imply additionally assessments.

### **Study population**

Most of the participants were recruited through an enclosed invitation (Appendix 1) sent out along with the invitation for routine ultrasound scan (in gestational week 18) at St. Olavs

Hospital (communicated about gestational week 13-16). We also put out advertisements on Google and we distributed information sheets at St. Olavs Hospital, medical offices and health care stations. Information regarding the ETIP trial was sent to all general practitioners in Trondheim.

Our inclusion criteria were: Pregnant women aged  $\geq 18$  y, gestational week  $< 18$ , carrying one singleton live fetus at 11–14 week ultrasound scan, and with self-reported pre-pregnancy BMI  $\geq 28$  kg/m<sup>2</sup>. The participants had to be able to visit St. Olavs Hospital, Trondheim, for assessments and for most of the exercise sessions. Our exclusion criteria were: Diseases that could interfere with participation, high risk of preterm labor, and habitual exercise training (twice or more weekly) in the period before pregnancy. Our exclusion criteria were based on the ACOG (2003) absolute contraindications for aerobic exercise during pregnancy.<sup>206</sup>

Recruitment proved slower than expected in our trial. Certain changes to the study protocol after trial commencement were made to handle the situation. The time limit for completed testing at early pregnancy and inclusion in the trial was changed from gestational week 16 to gestational week 18 on 15<sup>th</sup> November 2012. On 22<sup>th</sup> March 2013 we changed the inclusion criteria BMI  $\geq 30$  to BMI  $\geq 28$  kg/m<sup>2</sup>. As a way to improve assessments of body composition by skinfold thickness measurement, additionally started to measure body composition by air displacement plethysmography, from 28<sup>th</sup> of June 2011. All changes were reported to and approved by the Regional Committee for Medical and Health Research Ethics. We were made aware that some eligible pregnant women felt uncomfortable by being characterized as overweight or obese, and therefore not willing to participate. As a consequence we revised the information sheet, replacing “overweight” and “obese” with BMI  $\geq 28$  kg/m<sup>2</sup>. The change did however not lead to any increased rate of enrollment.

Information on pre-pregnancy weight and height was self-reported, which adds some uncertainty to the main criteria for participation, BMI  $\geq 28$  kg/m<sup>2</sup>. However, this information was controlled for at baseline assessments, where weight and height were measured by standardized methods and by study personnel.

The lost to follow-up rate in the ETIP trial at late pregnancy/delivery was 17.4% (n = 8) in the exercise group and 20.0% (n = 9) in the control group, with an additional lost to follow-up of 5.3% (n = 2) in the exercise group and 5.6% (n = 2) in the control group at the postpartum visit. The lost to follow-up rate in other RCTs including lifestyle interventions in overweight and obese women varies from 1.3% up to 30%.<sup>107,182,183,199,202,207-209</sup> Compared to previous trials, the number of lost to follow-up in our trial was rather high from early

pregnancy to late pregnancy/delivery, but low between delivery and the postpartum visit. When comparing age, BMI, parity, education and employment status we found no significant difference between the participants who completed the ETIP trial and the participants who dropped out (Table 3).

**Table 3.** Comparison of demographic data at baseline between the women who completed the trial, and the women who were lost to follow-up.

Baseline characteristics	Participants who completed the trial (N = 70)	Participants lost to follow-up (N = 21)	P-value
Age (years), mean $\pm$ SD	31.5 $\pm$ 4.1	30.1 $\pm$ 4.8	0.45
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	34.6 $\pm$ 4.2	34.3 $\pm$ 4.5	0.83
Parity			0.35
0	33 (47.1)	38.1 (8)	
1	29 (41.4)	42.9 (9)	
2	7 (10.0)	9.5 (2)	
> 3	1 (1.4)	9.5 (2)	
Education			0.34
Primary/secondary school	3 (4.3)	1 (5.6)	
High school	20 (29.0)	7 (38.9)	
University $\leq$ 4 years	18 (26.1)	7 (38.9)	
University $\geq$ 4 years	28 (40.6)	3 (16.7)	
Currently employed	58 (82.9)	15 (75.0)	0.68
Abbreviations: SD: Standard deviation. BMI: Body mass index (kg/m <sup>2</sup> ) Statistics: P-value for continuous variables was analyzed by Independent Samples T-test. P-value for categorical variables was analyzed by Pearson Chi-Square and Fisher's Exact Test.			

Few exclusion criteria were used in the trial, which support the intention of including a representative population of overweight/obese pregnant women. However, the participants had to be able to visit NTNU/St. Olavs Hospital for assessments at daytime, and for most of their training sessions. These criteria excluded women who were not able to take time off from work, or for other reasons were not flexible at daytime. However, the assessments were not very time-consuming, using two hours one day, and three hours the second day, both at the early- and late pregnancy assessments. The participants were offered exercise sessions both at daytime and afternoon to accommodate individual needs. Exercise sessions could also be performed at home or at a physiotherapy clinic. The generalizability of the trial is further discussed in the chapter of “Discussion”, under “Generalizability”.

## **Intervention**

The women in the intervention group were offered supervised exercise training starting immediately after randomization in gestational week 12-18, until assessments in gestational week 34-37. They were encouraged to continue until delivery, if they were able to. The exercise sessions were in accordance to the recommendations from the ACOG,<sup>28,29</sup> and the recommendations for physical activity during pregnancy from The Norwegian Directorate of Health.<sup>27</sup>

Our aim was that the women should perform three weekly sessions of 35 minutes moderate walking (including 10 minutes warm-up) or running on a treadmill, followed by 25 minutes of weight bearing strength training, and exercises for the pelvic floor muscles (Appendix 2). The participants were also encouraged to perform a home exercise program at least once weekly (Appendix 3). The intervention program in the ETIP trial included no dietary advice. No intervention was offered after delivery. The exercise sessions were supervised by a physical therapist. We offered the women exercise sessions both day-time and afternoon, preferable in groups, but also on individual basis.

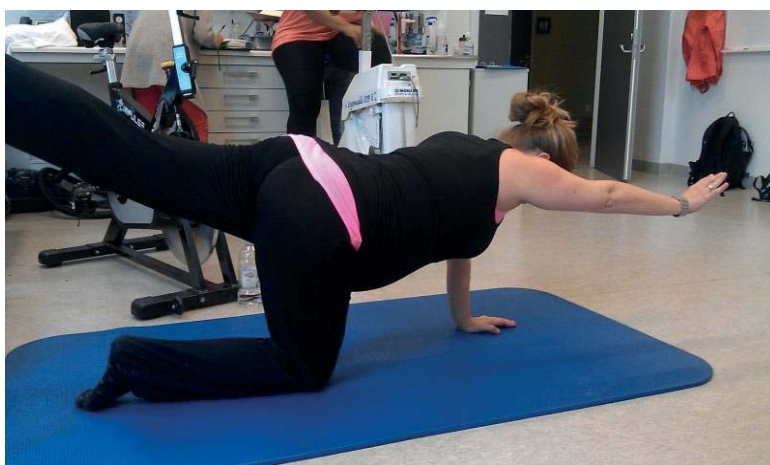
Intensity of the endurance training was set to ~80% of maximal capacity, corresponding to Borg scale 12–15.<sup>174</sup> The strength training was performed with three sets of ten repetitions with one minute rest between sets. The strength training program consisted of squats, push-ups, four foot standing diagonal lift, and oblique abdominal crunches. In addition, they performed three sets of 30 seconds of “plank exercise”, and for the pelvic floor muscles; three sets of ten repetitions of pulling up and holding the pelvic floor for 6-8 seconds was performed, supplemented with some rapid contractions in the end of each set. The exercise program was individually adjusted when needed, taking into account the level of strength, pregnancy related difficulties, and health problems. The women were told to avoid prolonged supine positions due to risk of obstruction of vena cava.

After each exercise session, the women registered duration, intensity (pulse and Borg scale), speed and incline of the treadmill, and comments on performance in a training diary kept at the hospital (Appendix 4). The home-based exercise program consisted of 35 minutes of moderate endurance training (Borg scale 12-15), and of 15 minutes strength training, based on the exercise program provided at the hospital. General physical activity and home-based exercises were registered daily by the women in a separate training diary (Appendix 5). The participants received a weight gain curve (Figure 3.) showing the IOM’s recommendations for weight gain during pregnancy.<sup>65</sup> The women regularly measured their body weight

(standardized hospital scale), registered their weight in this curve, and were encouraged to follow the recommendation for GWG. The women in the exercise group were offered a 30 minutes motivational interview during the intervention period to enhance adherence to the exercise protocol.



**Figure 1.** The endurance training was mainly performed by treadmill walking.

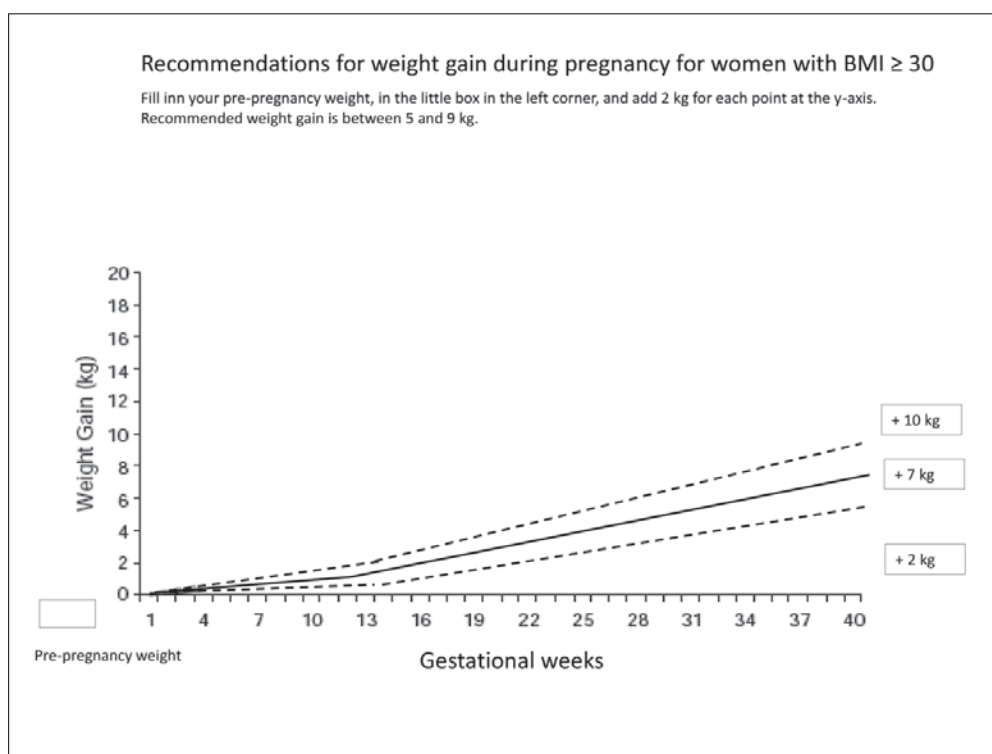


**Figure 2.** The strength training program comprised weight bearing exercises.

The control group received only standard maternal care. They were asked to continue their normal daily activities and were not discouraged from exercising on their own.

The exercise group and the control group both received standard maternal care during the pregnancy. At the time the study was conducted, The Norwegian National Directions for Standard Maternity Care for healthy pregnant women, included (free of charge); an ultrasound examination in gestational week 18, eight routine prenatal visits to a midwife, general

practitioner or an obstetrician, and information about healthy eating and healthy lifestyle provided in a brochure. The prenatal visits are usually undertaken in gestational week 8-12, 24, 28, 32, 36, 38, 40 and 41.<sup>210</sup> All participants, regardless of group allocation, received routine postpartum care (free of charge), including a home visit from a health care nurse within one week after delivery, and an appointment with a general practitioner 6-8 weeks postpartum.<sup>210</sup>



**Figure 3.** Curve of recommended weight gain during pregnancy, as distributed to the women in the exercise group.

Women participating in the control group with no intervention underwent the same health assessments at the hospital, during pregnancy, at delivery and three months postpartum as the women in the exercise group. This supplemented the standard maternity care, and may have had the effect of a “small intervention” for the control group, included increased motivation for lifestyle changes during pregnancy. This may have reduced the change of finding possible effect of the intervention, increased the risk of type II error, and lead to rejection of our primary hypothesis. The number of adverse pregnancy outcomes found in our trial was relatively low. This indicates a very healthy population included in the trial, and suggests that

several women in the control group also had a healthy lifestyle during pregnancy. An exact estimate of the effect of the intervention would ideally have required an intervention group who did exactly what we told them to, and a control group who reduced their physical activity and exercise during pregnancy, which the tendency often is.

We have not reported diet or dietary changes in our trial, and are aware of this being a limitation to our results. Diet and a possible change in diet may especially affect body weight and body composition, and blood parameters. We asked the participants to continue their habitual diet throughout the study period, however it is possible that some of the women were inspired to introduce a healthier diet during the pregnancy as a result of being a part of a trial focusing on maternal and neonatal health. On the other hand, studies have also found that increased level of exercise and thereby increased energy expenditure, could be compensated by eating more.<sup>211</sup> Not adjusting for diet in our analyses may have added a confounding factor to our data. However, as this is an RCT, the impact of diet should be evenly distributed between groups, and therefore would not be a major limitation in finding effects of exercise.

The type and execution of exercise training vary a lot between RCTs on lifestyle interventions during pregnancy. Few studies report the use of strict individually guided training programs.<sup>23</sup> Some studies are based on group exercise programs,<sup>183,212</sup> others on home-based exercise programs.<sup>213</sup> Finally, many studies are based on advice, guidance and information about healthy lifestyle.<sup>194,195</sup> Most exercise programs in well-conducted RCTs are based on the recommendations of physical activity during pregnancy from ACOG.<sup>28</sup> Several RCTs on exercise training in pregnancy combine endurance training at light to moderate intensity with strength training, with duration of 45-60 minutes per session, two to three times per week from about gestational week 14 until gestational week 36-38.<sup>164,200,208,214</sup> The amount, intensity and duration of the exercise sessions in our ETIP trial are similar to several other well designed RCTs on exercise in pregnancy. Cut-off point for inclusion (gestational week) differs between trials, from gestational week 6<sup>212</sup> to 24,<sup>214</sup> which is of major importance when measuring the effect of exercise. In the ETIP trial, women were in average included in gestational week 16.4. Starting the exercise interventions earlier in pregnancy may have influenced neonatal and maternal outcomes. For many women however, the first trimester of the pregnancy is characterized by discomfort and a high risk of abortion, and the risk of bias related to recruitment and adverse events is present. In our trial we offered the women in the intervention group to participate in exercise training after the assessments provided in late pregnancy (gestational week 34-37), and therefore included number of weeks until delivery when analyzing weeks eligible for exercise training during the intervention



period. The number of women exercising at preferred frequency and intensity decreased after late pregnancy visit, mostly due to pregnancy related difficulties.

Our intervention protocol consisted of a supervised exercise program. Among different exercise program used in trials, supervised exercise sessions are shown to affect maternal and neonatal outcomes the most, compared to programs performed at home or at training center, based on information or limited consultations during pregnancy.<sup>31</sup> When we registered adherence to the exercise protocol, exercise sessions at the hospital and at home were registered as follows: One hospital session was registered when attending to an organized exercise session at the hospital. An exercise session at home was registered when lasting for 50 minutes or more, containing endurance- or resistance training. The home exercise program was based on the same exercises as used in the exercise sessions at the hospital. The cut-off values for adherence was based on estimation of what we regarded as the least required amount of exercise to expect effect on the outcomes in the trial. Our cut-off values were defined as: (1) attending  $\geq 42$  organized exercise sessions, (2) attending  $\geq 28$  exercise sessions + performing  $\geq 28$  home exercise sessions, or (3) performing  $\geq 60$  home exercise sessions. To count as a home session, the exercise training had to amount to  $\geq 50$  minutes of either aerobic and/or strength training. The participants could perform these sessions at any point in time during their pregnancy. However, when and how often these exercise sessions were performed could have differed between participants and could have impacted outcomes in the trial.

The exercise program provided in the ETIP study did not require equipment, and where therefore easy to perform at home, if the women were not able to come to the hospital for exercise session. Due to the characteristics of the exercise program, it could be performed by the women them self in the postpartum period. The endurance part of the exercise session, walking or running at a treadmill, could be performed outside. Walking/running was replaced with stationary cycling if individually adjustments were needed due to pain or difficulties. Walking/running is a weight bearing exercise, and might be seen as more challenging to perform than cycling. However, it is easier to reach steady state heart rate at  $\sim 80\%$  of maximal capacity by weight bearing exercise, and we experienced few difficulties in performing walking among the participants. The participants were free to individually adjust treadmill speed and incline for optimal performance. To monitor exercise intensity, we used the 6-20 Borg scale of perceived exertion. The women also wore a heart rate monitor during exercise, but due to a tendency of blunted heart rate response to exercise during pregnancy, the Borg scale is a more reliable measurement of intensity during pregnancy.<sup>174</sup>

The cut-off lower limit for inclusion in the ETIP trial was gestational week 12. We experienced however, that many women contacted us close gestational week 18, and several women contacted us for participation after they had exceeded gestational week 18. We therefore added Google advertisement for recruitment, attempting to include the women in an earlier gestational stage, to prolong the intervention period. Very few participants were recruited by general practitioners in Trondheim city, despite them all being informed about the current trial.

## **Assessments**

All women underwent the same test protocol at early pregnancy (gestational week 12–18), at late pregnancy (gestational week 34–37), at delivery, and three months postpartum. Assessments of the neonate were performed at the St. Olavs Hospital at delivery, and within three days after delivery. The neonatal and maternal outcomes at delivery were identified a priori, and were stated in the ETIP trial published study protocol.<sup>33</sup> Selection of outcomes was based on most frequently observed clinical important risk factors related to pre-pregnancy overweight and obesity.

### **Anthropometric measurements of the mother**

**Body weight** was measured at early pregnancy, late pregnancy, delivery and three months postpartum, by a calibrated electronic scale (Seca 770, Medema, Norway) to the nearest 0.1 kg. Pre-pregnancy body weight was based on self-report. Body weight at delivery was measured by midwife/hospital personnel, in accordance to the hospital routines at reception for delivery.

GWG was the primary outcome of the ETIP trial and was calculated as the difference between early pregnancy weight at the baseline visit, and weight at delivery (Paper I). PPWR, which was the main outcome in Paper III, was defined as the difference between postpartum weight and weight at the baseline visit in early pregnancy. The PPWR measurements were supplemented with a PPWR estimate based on the women's self-reported pre-pregnancy weight data. The principal investigators KKG and TM performed the weight measurements at early pregnancy and late pregnancy. If measurement of body weight could not be completed at delivery, we used the women's self-reported weight ( $n = 7$ ).

Pre-pregnancy weight and height was self-reported, and are less reliable than the measurement provided by the study personnel or hospital personnel. In our primary analyzes

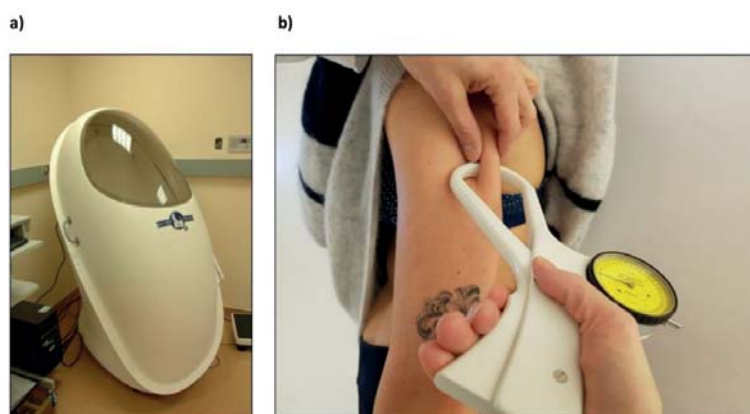
of GWG and PPWR we therefore chose to use weight measured at the first visit in early pregnancy, to ensure higher accuracy. Using standardized equipment and protocol for weight measurements at all time points strengthen the validity of our primary outcome data.<sup>215</sup> However, adding the PPWR analysis with self-reported data of pre-pregnancy weight, was important to complement the information on the total weight gain during pregnancy.

**Body height** was measured at early pregnancy by a wall-mounted stadiometer (Seca 222, Medema, Norway).

**BMI** was at all time points calculated as weight in kilograms divided by the square of height in meters. BMI does not provide detailed information on body composition and fat storage. We therefore measured body composition by Bod Pod and skinfold thickness. The body composition measures are outlined below.

**Waist circumference** was measured using a measuring tape at the level of the umbilicus, after expiration. This method implies limitations, such as difficulties in placing the tape at the exact same position on every participant, individually differences in body posture, and the gastrointestinal content may vary from day to day and affect the waist circumference. We did not measure the waist circumference in fasting state, which could have affected the results.<sup>216</sup> This waist circumference was clearly affected by varied abdominal sizes due to the participants being pregnant, and was mainly for comparing of between-group differences at the postpartum visit.

**Body composition** was assessed by both Bod Pod (air displacement plethysmography) measurement (BOD POD, COSMED, The Metabolic Company, Italy), and skinfold thickness measurement (Harpenden Skinfold Caliper Holtain Ltd, UK) (Figure 4.).



**Figure 4.** a) The Bod Pod was used for measurement of body composition. b) The Harpenden Caliper was used for measurement of skinfold thickness.

The participant entered the BOD POD fasting, with empty bladder, wearing only underwear and a swim cap. Bod Pod is safe for the women and the fetus, and is considered the gold standard for body composition measurements.<sup>217</sup> Bod Pod is found to be valid for overweight and obese women,<sup>218</sup> however, studies indicate overestimation of fat mass in adults classified with extreme obesity according to BMI.<sup>219</sup> The Bod Pod protocol took use of predicted thoracic gas volume, however a study by Henriksson and colleagues<sup>220</sup> found that predicted thoracic gas volume tends to be overestimated in pregnant women compared to non-pregnant women, and therefore should be individually estimated.

Measurement of skinfold thickness is a valid estimation of maternal body composition, especially in late gestation.<sup>221</sup> Skinfold thickness measurement was performed at the right side of the body, at commonly used sites; subscapular, biceps, and triceps, in accordance to the standardized measurement protocol of Holtain Ltd.<sup>221,222</sup> We used an average of three measurements at each site in our analyses. The accuracy of the measurement is highly dependent on the investigators performance when reproducing repeated measurements. The internal reliability in skinfold measurement is found to be good in trained investigators, but the accuracy of the measurement decreases between investigators.<sup>223</sup> Only two investigators (TM and KKG) performed the measurements in the ETIP trial, with one investigator (KKG) most frequent. We did not assess the reliability of our skinfold measurement.

All anthropometric measurements in the ETIP trial were performed by study-personnel non-blinded for group allocation, and may have introduced bias to the data. The waist circumference and skinfold thickness measurements, in particular, are sensitive for internal validity, and subjective accuracy.

### **Maternal blood pressure**

Resting systolic and diastolic blood pressure was measured in a fasting state, on the right arm, in a seated position, after 15 min of supine resting, using a CASMED 740 MAXNIBP (CAS Medical Systems, USA). Three blood pressure measurements were recorded with two minutes interval in-between, and a mean of the three measurements were used in the analysis. If the device failed in recording, another blood pressure measurement was recorded. Resting blood pressure  $\geq 140/90$  mm/Hg after gestational week 20, was defined as maternal hypertension.<sup>43</sup> We used different sizes of cuffs (single hose 27.5-36.5 cm and single hose 22-47 cm), appropriate for the women's upper arm circumference.

Measured blood pressure can vary due to factors such as; accuracy of the equipment, measurement technique, individually variations during the day, the participant's state of

stress, use of drugs, and anxiety.<sup>224</sup> The variability in blood pressure seems to increase with increasing blood pressure.<sup>224</sup>

### **Maternal blood measurements**

Venous blood was sampled after an overnight  $\geq 10$  hours fast. Blood sampling was undertaken at the Clinical Research Facility, NTNU/St. Olavs Hospital, by laboratory personnel.

Assessment of GDM was an important outcome (Paper I). Different procedures for glucose measurement and classification exist. We measured glucose by a standardized oral glucose tolerance test (OGTT) (75 g of glucose dissolved in 2.5 dl of water) and diagnosed GDM according to the 2009 WHO definition: Fasting plasma glucose  $\geq 7.0$  mmol/l and/or 120-min plasma glucose  $\geq 7.8$  mmol/l.<sup>39</sup> However, in 2013, after commencement of the ETIP trial, WHO in collaboration with the International Association of Diabetes and Pregnancy Study Groups (IADPSG), adjusted the diagnostic criteria to fasting plasma glucose  $\geq 5.1$  mmol/l and/or 120-min plasma glucose  $\geq 8.5$  mmol/l.<sup>57,225</sup> We therefore decided to report GDM by both classifications in Paper I. Incidence of type 2 diabetes mellitus were measured at the postpartum visit, defined as fasting plasma glucose  $\geq 7.0$  mmol/l, and/or 2 hour concentration  $\geq 11.1$  mmol/l.<sup>39</sup> Medical disagreements exist whether women with increased glucose in early postpartum can be diagnosed with type 2 diabetes mellitus.<sup>39</sup> Type 2 diabetes mellitus is therefore reported as “fulfilling the diagnose criteria” in Paper III.

To specific investigate the effect of exercise on the women’s glycemic control, we measured insulin sensitivity. Insulin sensitivity was calculated by homeostatic assessment of insulin resistance, HOMA2-IR, which was calculated by  $((\text{glucose mmol/l} \times \text{insulin pmol/l})/22.5)$ .<sup>226</sup>

All blood measurements were assessed by Roche Modular P, except from insulin assessed by ELISA (IBL International) using a DS2 ELISA processing system (Dynex Technologies). The ELISA - system is, compared to radioimmunoassay, found to be a very precise, accurate, sensitive and specific measurement of insulin, and is often used in human clinical studies.

All blood samples were taken and assessed by the same personnel at the Clinical Research Facility. An exact protocol for sampling, analyzing and storage of the material was followed.<sup>33</sup> Eventual deviations from procedures were consecutively registered. Three women (one in the exercise group and two in the control group) performed their glucose tolerance test at their general practitioner. Their procedures for blood sampling and analyses were not

controlled. A copy of the results of blood measurements was sent to each woman's general practitioner.

### **Maternal physical activity**

We collected data on the women's level of physical activity before pregnancy, during pregnancy and in the postpartum period. This was done by self-reported questionnaires in early pregnancy (Appendix 6), at late pregnancy (Appendix 7), and three months postpartum (Appendix 8). The women were asked if they adhered to the recommendations of moderate physical activity at least for 150 minutes per week, and of frequency, duration, and intensity of their physical activity. Our questions differed between "physical activity" and "exercise training". "Physical activity" was defined as: Any bodily movement produced by skeletal muscles that requires energy expenditure, and "exercise training" was defined as: Physical activity performed regularly to improve fitness or health.<sup>37</sup>

In the ETIP trial information sheet, we informed the participants of possible benefits of physical activity and exercise during pregnancy. We experience a high focus in the society on the health benefits of being physical active. Self-reported data implies a risk of bias, by the participants being tempted to report a level of physical activity and/or exercise training which they think is expected or preferred by the study personnel. There is possibility that the exercise group reported of more frequent physical activity and/or exercise training than they actually performed, and that the control group reported of less physical activity and/or exercise training than they actually performed, to accommodate expectations of the trial.

### **Maternal outcomes at delivery**

We collected maternal birth data from St. Olavs Hospital records and "Natus birth journal," a standard electronic journal system for maternity, delivery and postpartum hospital stay at St. Olavs Hospital.

*Mode of delivery* was registered as 'normal', 'operative', or 'caesarean section'. 'Operative' was divided in 'vacuum-assisted delivery' and 'forceps-assisted delivery'. In 'caesarean section' we included both 'acute caesarean section' and 'elective caesarean section'.

*Perineal tears* was graded from 1-4 where 1 is less severe and 4 most severe. In our trial we reports of only perineal tears grade 3 and 4.

*Maternal hospital stay* represents the duration of the mother's stay at the hospital. The stay was in the journal registered in hours, which we transformed into days.

The St. Olavs Hospital records and the “Natus birth journal,” are considered as a valid and reliable source of information, and the data was assessed by personnel blinded for group allocation.

### **Breastfeeding**

We collected data on breastfeeding from self-reported questionnaire provided at the postpartum visit three months after delivery (Appendix 9). We asked the women if they were exclusively breastfeeding or not when leaving the hospital, and at three months postpartum. A small risk of recall bias should be present three months after delivery. Health benefits of breastfeeding are well communicated in Norway, therefore some women may have registered a higher prevalence of breastfeeding than what was actually the case.

### **Demographic data**

The participants received standardized questionnaires at early pregnancy where they reported parity, smoking, education, and current employment.

The assessments in the ETIP trial were undertaken by principal investigators (KKG and TM), trained nurses and laboratory personnel. The limited number of personnel collecting data and performing the assessments have reduced the risk of low inter-reliability and strengthened our results. Blinding is important to ensure high internal validity in an RCT. In the ETIP trial, weight measurement at delivery and blood analyses were the only assessments done by personnel blinded for group allocation. The statistician conducting the statistical analyses was also blinded for group allocation. Because of the nature of the study, all other assessments and intervention administration were done non-blinded. Blinding of the study personnel would have been optimal, but was not possible due to the limited resources available in the ETIP trial. Non-blinded assessors may have increased the risk of unconsciously lead the test results in favor of one group. Since most of the questions asked were related to recent experiences, recall bias was most likely not a problem in the ETIP trial. However, self-reported data can be affected by the participant’s eagerness to please the investigators when answering the questions.

### **Neonatal anthropometric measurements**

*Weight, length, head circumference and placenta weight* was measured at delivery by birth attendants, in accordance to hospital routines, and registered in the St. Olavs Hospital medical

journal and the “Natus birth journal”. Placenta weight ratio (PWR) was calculated by placenta weight divided on birth weight, and is an often used indication of the function of placenta and fetus nutrition during pregnancy.<sup>125</sup>

*Abdominal and right upper arm circumferences* were measured with use of measuring tape. Abdominal circumference was measured at the level of the umbilicus at normal expiration, upper arm circumference was measured at the middle between olecranon and humeral head. An average of two or three (if available) measurements was used in the analyses.

*Skinfold thickness measurement* was performed by a Harpenden Skinfold Caliper, (Holtain Ltd, UK) at the right side of the body, at the two sites: subscapularis; bottom of the angelus inferior scapula, and triceps; in the middle between the olecranon and the humeral head. An average of two or three measurements was used in the analyses.

*BMI* was calculated as weight in kilograms divided by the square of height in meters. *Body Surface Area (BSA) (m<sup>2</sup>)* was calculated by the Mosteller Formula<sup>36</sup> as  $\sqrt{(body\ weight\ (kg) * body\ height\ (cm))/3600}$ . All these data are seen as reliable data due to following the Hospital journal procedures.

#### **Other neonatal measurements**

*Preterm birth* was defined as delivery before gestational week 37.

*Apgar score* was in the journal registered for one, five, and 10 minutes. We have reported data on Apgar score at one and five minute, as Apgar score at one and five minutes are stronger associated with severe outcomes than Apgar score at 10 minutes. These data was assessed in accordance to the procedures of St. Olavs Hospital, by birth attendants blinded for group allocation. We therefore consider these data to be reliable.

Assessments of the children were undertaken at the St. Olavs Hospital, by birth attendants at delivery, and by investigator KKG at a visit within three days after delivery. Information on date of birth, gestational age, Apgar score, and transfer to NICU was recorded in ‘Natus birth journal’.

The measurements of abdominal and upper arm circumference and skinfold thickness were very sensitive for movements, required a calm infant, and were challenging to perform. Ideally, the caliper should be hold in position from 15 seconds up to 60 seconds, but 60 seconds measurement was difficult to perform due to movements of the child, and sometimes also uncomfortable parents. Therefore, only 15 seconds hold measurements are reported in the trial. In accordance to our test protocol, a mean of three measurements of skinfold thickness



and abdominal and upper arm circumference, was used in the analysis. However, due to a challenging test protocol, sometimes two, or rarely one measurement was provided, and used in our final analyses. The examination of the neonate was performed on a table in warm conditions, with one or both parents present. If the examination was experienced as stressful for the infant or the parents, it was stopped. Using measuring tape and skinfold caliper in infants may have challenged the accuracy of repeated measurements, and the internal validity affected by sometimes limited ability to repeat the measurements three times as described in the protocol. Anthropometric measurements were assessed  $2.6 \pm 1.2$  (mean) days after delivery in both groups.

## **Ethics**

The trial was approved by the Regional Committee for Medical and Health Research Ethics (REK midt 2010/1522), and registered in ClinicalTrials.gov (NCT01243554). The procedures followed in the ETIP trial were in accordance with ethical standards of research and the Helsinki Declaration. The participants gave their informed written consent to participate. Participation in the trial was voluntary and the women were informed that they could withdraw from the trial at any time, without any consequences related to access to health services for themselves or their fetus.

The measurements methods used in the trial did not imply any known risks to the mother or the fetus/neonate. Assessments were discontinued if the women felt any discomfort. The intervention program in the ETIP trial, was based on international<sup>28</sup> and national<sup>27</sup> recommendations on physical activity and exercise during pregnancy. We did not provide any limitation for maximum heart rate during the women's endurance training. The Borg-scale (corresponding to Borg scale 12–15)<sup>174</sup> was used to monitor intensity during the exercise sessions, supplemented by “talk test” to adjust the women's range of exhaustion. The strength training program was specially designed for pregnancy, with focus on safety and prevention of pregnancy related disorders. Both the endurance- and the strength training session was supervised and monitored by a physical therapist, and individually adjusted if needed.

The exercise training was stopped if the women felt uncomfortable, reported pain, or experienced three or more contractions with duration of  $\geq 45$  seconds within 30 minutes. If vaginal bleedings or other pregnancy related complications occurred during exercise or assessments, a physician/gynecologist or a midwife at St. Olavs Hospital was contacted, and the women's general practitioner informed. We experienced only two women who needed

adjustments in their exercise program due to frequent contractions, however, these occurred in late pregnancy. No women had to stop exercising due to prolonged contractions  $\geq 45$  seconds. Health care personnel at St. Olavs Hospital were consulted once during the trial period, because of a suddenly event related to exercise. This was due to unexpected drop in blood pressure during exercise.

The women in the control group were asked to continue their normal daily activities and were not discouraged from exercising on their own. All participants were through the information paper initially informed about possible positive health consequences of being physical active during pregnancy. All women who completed testing at the postpartum visit received infant food worth US\$65. All participants have been informed about the main outcomes in the trial after publication.

No adverse events related to the trial intervention occurred.

### **Randomization procedure**

The participants were allocated 1:1 to the intervention group or the control group after early pregnancy (baseline) assessments. Allocation to the trial was performed by a computer random number generator, administrated by a computer technician at the Unit for Applied Clinical Research, NTNU. The randomization had varying block sizes, defined by a computer technician at the Unit for Applied Clinical Research.

The investigators who enrolled women for participation did not have excess to the randomization generator or the full randomization list, and got the group allocation after registration of each participant. The randomization system used in the current trial reduced the risk of selection bias, balances known and unknown factors between the groups, and thereby support the assumption of no systematic differences between groups at baseline.

### **Blinding**

Maternal weight at delivery, neonatal birth weight, blood sampling and analyses, and maternal and neonatal birth data were assessed by personnel blinded for group allocation. Other measurements and intervention administration were unmasked. Detailed description of consideration related to blinding is found in the chapter "Assessments".

Blinding of all study personnel and personnel processing the data would have been the most optimal solution to ensure high internal validity, and to minimize risk of bias. However, conducting a clinical trial with comprehensive assessments at four time-points, and a

supervised exercise program performed over several years, is very resource demanding. In this case, the personnel who planned the trial also performed the exercise sessions and many of the assessments. Blinding the main investigators would have been too resource demanding, and was not feasible in our trial. By knowing the group allocation, there was a risk of the investigators to be biased, particularly when assessing skinfold thickness and waist- and arm circumference. This must be care taken when concluding the findings of these outcomes.

### **Power calculation and sample size**

The sample size in the ETIP-trial was calculated based on prior studies,<sup>227,228</sup> and a 6-kg difference in mean weight gain from baseline to delivery between the exercise and the control group was seen as clinically relevant. According to this, a two-sided independent sample *t*-test with a 5% level of significance, a standard deviation (SD) of 10, and a power of 0.90 gave a study population of 59 in each group. Dropout was estimated to 15%, and we aimed to include 150 women.

Due to the low speed of inclusion and a prolonged inclusion period, we had to stop the inclusion before we reached the planned number of participants in the trial. Thus, our trial ended up with a sample size of  $N = 91$ , lower than expected. The chance of type II error must be taken into account when discussing the results. On request from reviewers (in Paper II), we performed a post-hoc sample size calculation based on the primary outcome of that paper; neonatal birth weight. Based on previous trials,<sup>229,230</sup> we considered 250 g difference between groups in mean birth weight with a SD of 430 g, to be clinically relevant. With an alpha 0.05 and beta 0.2, we would have needed 94 participants in the trial to demonstrate a significant difference in birth weight between groups. An underpowered trial may cause type II error, and risk of not finding a present effect. However, our trial may be used in estimation of needed sample size in future randomized clinical studies.

### **Statistical analyses**

The principal analyses in the trial were based on “intention to treat (ITT)”, where all outcome measures (primary and secondary) were analyzed according to which treatment arm the women were randomized to, and regardless of adherence to the exercise protocol. All available data were used at all time points. Due to randomization, we assumed no systematic differences between groups at baseline. All baseline data were however, analyzed for

difference between groups by an independent sample t-test. Continuous variables were tested for normality. The exercise group was considered as the reference group in all analyses.

In Paper I, the effect of treatment on outcomes at late pregnancy was assessed by mixed linear models for continuous outcomes, and mixed logistic models for dichotomous outcomes. When analyzing the primary outcome GWG, the effect of time and treatment was taken as a fixed effect using the levels; 'baseline', 'training late pregnancy', 'control late pregnancy', 'training delivery' and 'control delivery'. When analyzing the secondary outcomes, the effect of time and treatment was taken as a fixed effect using the levels; 'baseline', 'training late pregnancy', and 'control late pregnancy'. The participant ID was included as a random effect, to account for repeated measurements.

In Paper II the effects of the exercise intervention were assessed by independent sample t-test. Dichotomous data were analyzed by Fisher's Exact test or Pearson Chi Square Test.

In Paper III, the effect of the intervention on outcomes at three months postpartum was for continuous variables, assessed by mixed linear models. The effect of the intervention and time was specified as a fixed effect with the levels 'baseline', 'training late pregnancy', 'control late pregnancy', 'training postpartum' and 'control postpartum'. The participant ID was included as a random effect, to account for repeated measurements. We observed variance in heterogeneity across time, so we specified the covariance structure for the error term as diagonal. The effect of the intervention on dichotomous outcomes postpartum was assessed by exact logistic regression, were we adjusted for baseline (early pregnancy) outcome if available.

We performed "per protocol" analyses in all three papers, including only the women in the exercise group who adhered to the exercise protocol, as described in the original protocol. Per protocol analyses were performed on both primary and secondary outcomes. Adherence to the exercise protocol was defined as (1) attending  $\geq 42$  organized exercise sessions, (2) attending  $\geq 28$  exercise sessions + performing  $\geq 28$  home exercise sessions, or (3) performing  $\geq 60$  home exercise sessions. The exercise had to be  $\geq 50$  min of either aerobic and/or strength training to count as a home session.

Supplementary analyses were done in all three papers. In Paper I, we did supplementary analyses of GWG were we adjusted for gestational age at delivery. In Paper II we performed analyses of all outcomes adjusted for parity and gestational age at delivery. In addition we investigated the association between early pregnancy BMI and the variables birth weight and risk of caesarean delivery. In Paper III we did supplementary mixed model

analyses of PPWR, where we adjusted for lactation, postpartum physical activity and number of days since delivery. In addition, we examined possible association between PPWR and the variables lactation, postpartum physical activity and GWG.

Baseline data and testing for normality were analyzed by IBM SPSS Statistics 22. In Paper I and III continuous outcomes were analyzed by Stata version 13.1, dichotomous outcomes by R version 2.13.1. In Paper II the analyses were performed by using IBM SPSS Statistics 22R version 2.13.1, adjustments and association by Stata version 13.1. All results are given as mean values with 95 % confidence intervals, and *p*-values less than 0.05 were considered significant.

The statistical methods used in the ETIP trial, was considered to be the most appropriate method to investigate the effect of the intervention in the study group. The methods chosen used all available data at all time points, which increased the number of data points that contributed to the total data set, and reduced the bias related to adherence to the trial. The models used in Paper I and Paper II made use of the baseline data, not only by adjusting for, but also by estimating the variability. Taking into consideration the baseline values when estimating the effect of time, adds more accuracy to the data. In the estimation model in Paper I and Paper II, the baseline data was taken as a mean of both groups in accordance to the randomization principle of no systematic differences between groups at baseline assumed. When assessing the effect of the exercise intervention on outcomes postpartum in Paper III, we found different variances between the groups at the time-points ‘late pregnancy’, ‘delivery’ and ‘three months postpartum’. To take this into account, we used exact logistic regression to analyze the continuous postpartum variables. The difference in variance at ‘late pregnancy’ was not adjusted for in Paper I and may have affected the comparisons between groups somewhat.

Several factors may potentially affect the outcomes in the trial. In Paper I, we performed supplementary analyses where we adjusted for gestational age at delivery, in Paper II, we adjusted for parity and gestational age at delivery, and in Paper III, we adjusted for number of days since delivery, lactation and physical activity. In addition, we performed supplementary analyses in all three papers excluding the two participants in the trial (in the exercise group) who had pre-term birth. These adjustments resulted in non-significant changes in the outcome variables, and minimal differences between groups at baseline. The variables gestational age at delivery, lactation, and physical activity postpartum may be affected by the intervention in the current trial. Adjusting for these variables could mask effects of the intervention, and were therefore not included in our analyses. To carefully

decide models of analyzing differences between groups, we investigated the association between baseline BMI and the variables birth weight and, in Paper I, the association between baseline BMI and gestational age, and risk of caesarean delivery, in Paper II, and the association between PPWR and the variables GWG, lactation and physical activity, in Paper III. No significant associations were found. These findings contributed to not include any adjustments in our model-based analyses.



## SUMMARY OF RESULTS

### Group characteristics

We included 91 pregnant women in the ETIP trial (Figure 5). Recruitment started on 20<sup>th</sup> September 2010 and continued until 1<sup>th</sup> March 2015, the final date for collection of the primary outcome measure was 20<sup>th</sup> June 2015. We aimed to include 150 pregnant women in the ETIP trial, but experienced fewer eligible participants than expected, and had to stop the enrollment in March 2015.

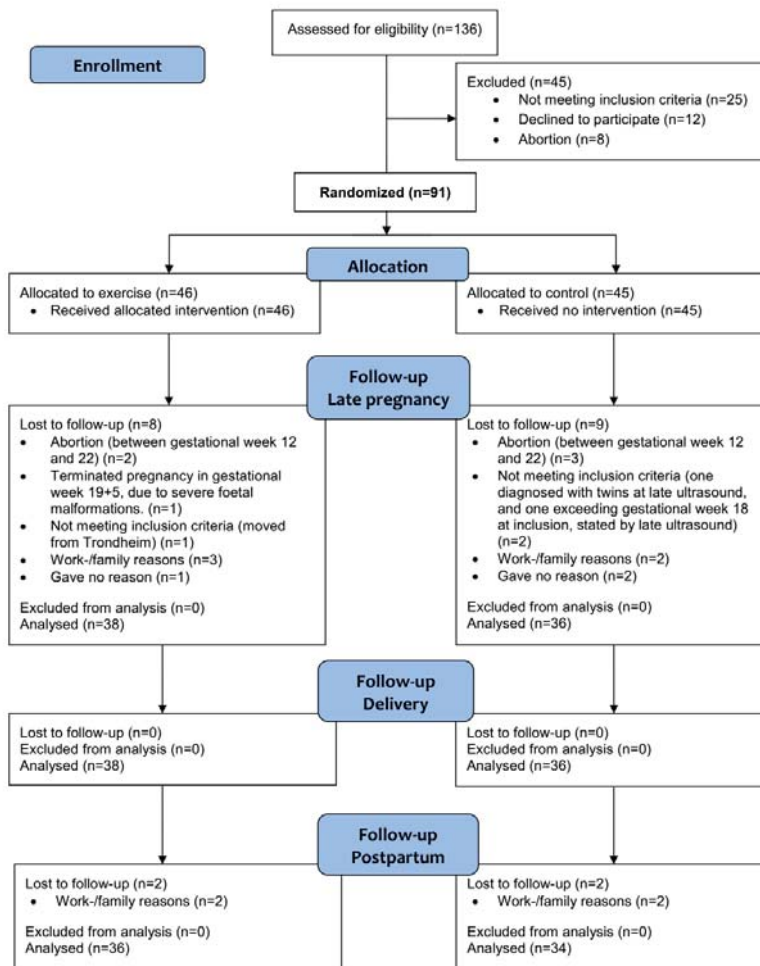


Figure 5. Flow chart of the ETIP trial (Consort 2010 Flow Diagram).



There were no significant differences in baseline characteristics (early pregnancy, gestational week 12-18) between the exercise group and the control group, except from mean fasting glucose (exercise group 4.6 mmol/l vs control group 5.0 mmol/l,  $p = 0.02$ ) (Paper I). At inclusion (early pregnancy) the mean BMI for the exercise group was 33.9 kg/m<sup>2</sup>, for the control group 35.1 kg/m<sup>2</sup>. Eight of the included women (three in the exercise group and five in the control group) had an early pregnancy BMI between 28.0 and 29.9 kg/m<sup>2</sup> and were classified as overweight, the rest of the participants had a BMI  $\geq 30.0$  kg/m<sup>2</sup> and classified as obese. At baseline, mean age was 31.1 years in the exercise group, and 31.4 years in the control group. Gestational week at inclusion was  $16.5 \pm 2.0$  in the total group of women (exercise  $16.8 \pm 1.8$ , control  $16.3 \pm 2.1$ ). No differences between groups were found in self-reported pre-pregnancy physical activity habits (frequency, duration and intensity). Seventy-nine percent ( $n = 34$ ) of the women in the exercise group, and seventy-four percent ( $n = 32$ ) in the control group reported of walking as physical activity one to three times per week ( $p = 0.74$ ). Fifty-five percent in the exercise group and fifty-three percent in the control group reported of fulfilling the recommendations of 30 minutes of physical activity per day, in the period before pregnancy ( $p = 0.84$ ).

Two women in the control group were excluded from the trial after randomization. One woman because she was carrying twins, discovered at late ultrasound, after inclusion. One woman were excluded due to higher gestational age at inclusion than she was aware of (exceeding gestational week 18), discovered at late ultrasound. One woman in the exercise group was excluded from the trial after randomization because she moved from the Trondheim area.

The exercise group had two cases of preterm birth (pregnancy weeks 29 and 34). Because of severe fetal malformations found at the routine second trimester ultrasound scan, one woman in the exercise group terminated the pregnancy at week 19+5. Three babies in each group needed admission to the NICU immediately after birth. Two women delivered their babies at other hospitals than St. Olavs Hospital (one in each group), and their specific birth data are missing.

The total lost to follow-up rate in the ETIP trial was 21.7% ( $n = 10$ ) in the exercise group and 24.4% ( $n = 11$ ) in the control group.

## **Main results**

The aim of the ETIP trial was to investigate effects of regular supervised exercise training offered during pregnancy, compared to standard antenatal care, in women with pre-pregnancy BMI  $\geq 28$  kg /m<sup>2</sup>. We assessed outcomes early in pregnancy, late in pregnancy, at delivery and three months postpartum. The number of weeks (mean) from inclusion in the trial to delivery was  $23.9 \pm 3.1$  weeks in the exercise group, and  $24.6 \pm 3.5$  weeks in the control group. Gestational age (mean) at delivery was  $39.1 \pm 2.3$  weeks in the exercise group, and  $39.5 \pm 1.3$  weeks in the control group.

The results from the trial are described in details in the three papers included in my thesis. A summary of the main results will be presented here.

### **Adherence to the exercise protocol and to the recommendations for physical activity**

Nineteen (50%) women in the intervention group adhered to the exercise protocol. The number of exercise sessions (mean  $\pm$  SD) during pregnancy among all women in the intervention group was  $31.7 \pm 15.3$  (Range 0-53) supervised sessions at the hospital, and  $19.2 \pm 16.5$  (Range 0-72) exercise sessions at home. This gave a weekly average of  $1.30 \pm 0.8$  supervised sessions, and  $0.8 \pm 0.7$  home-based sessions.

During pregnancy, 61-66% reported of fulfilling the recommendations of minimum 150 minutes of physical activity per week, however the number of women who performed regular exercise training was significantly higher in the exercise group (77%) compared to the control group (23%) ( $p < 0.01$ ). Three months postpartum, about 70% in both groups reported of fulfilling the recommendations of a minimum of 150 minutes of physical activity per week, with a tendency of more women in the exercise group (46.4%) reporting regular exercise training, compared to in the control group (25.0%) ( $p = 0.16$ ).

### **Paper I: Gestational weight gain and outcomes in late pregnancy**

We found no difference between the exercise group and the control group in GWG. The exercise group gained 10.5 kg, and the control group 9.2 kg (95% CI -1.58, 4.05,  $p = 0.35$ ). Approximately half of the women in both groups exceeded the IOM guidelines for recommended GWG during pregnancy.

Among secondary outcome measurements, we found significantly lower incidence of GDM, as according to the WHO 2009 definition,<sup>39</sup> among the women in the exercise group ( $n = 2$ ), compared to the control group ( $n = 9$ ) ( $p = 0.04$ ). We also found significantly lower

resting systolic blood pressure among the exercising women (120.4 mmHg), compared to the women in the control group (128.1 mmHg) ( $p = 0.006$ ), in late pregnancy. No differences between groups at late pregnancy were found in BMI, body composition, or other blood measurements.

GWG among the women who exercised per protocol (9.9 kg) was not significant different from the control group ( $p = 0.73$ ). However, per protocol analyses showed significant lower systolic and diastolic blood pressure among the women who exercised as intended (115.7 mmHg/75.1 mmHg), compared to the women control group (128.1 mmHg/80.2 mmHg) ( $p < 0.01/p = 0.02$ ).

### **Paper II: Neonatal and maternal outcomes at delivery**

We found no differences in birth weight between the groups. Neonatal birth weight (mean) in exercise group was 3719 g, compared to 3912 g in the control group (95% CI -460.96, 74.89,  $p = 0.16$ ). Mean difference in birth weight was 193 g.

No differences between groups at delivery were found in secondary neonatal outcomes as gestational age, BSA, body composition, Apgar score, placental weight ratio, preterm birth, and admission to NICU, or in maternal secondary outcomes as length of hospital stay, mode of delivery and perineal tears.

In the exercise group 35% of the neonates had birth weight exceeding 4000 g, versus 52% in the control group ( $p = 0.16$ ). Mean Apgar score at 1 minute was 8.4, and at 5 minutes 8.5, in both groups. Three neonates in each group were transferred to NICU. Two neonates in the exercise group were born preterm, one in gestational week 27 and one in 34. About 60% of the women in both groups had a normal vaginal delivery, and the length of the hospital stay was in average 4.6 days, for both groups. No women in the exercise group had pre-eclampsia compared to two women in the control group ( $p = 0.24$ ).

Neonatal birthweight in children of women exercising per protocol was 3742 g, with no difference compared to the control group ( $p = 0.24$ ). Per protocol analyses showed no differences between groups.

### **Paper III: Postpartum weight retention and other outcomes 3 months after delivery**

We found no differences in PPWR between groups three months after delivery. The exercise group retained -0.8 kg, and the control group -1.6 kg (95% CI -1.83, 3.84,  $p = 0.54$ ).

Among secondary outcomes at the postpartum visit, we found a significantly lower level of insulin in the exercise group (106.3 pmol/l,) compared to the control group (141.4 pmol/l) (95% CI -62.78, -7.15,  $p = 0.01$ ). HOMA2-IR was higher in the control group (5.0) compared to the exercise group (3.5) (95% CI -2.89, 0.01,  $p = 0.05$ ).

No differences between groups were found in other secondary outcomes as BMI, waist circumference, body composition, resting blood pressure, blood measurements. No women in the exercise group fulfilled diagnostic criteria for type 2 diabetes, compared to three women in the control group ( $p = 0.19$ ). About 75% of the women in both groups were fully breastfeeding or breastfeeding 3-4 meals per day three months postpartum.

Per protocol analyses showed no difference in PPWR between the women who exercised per protocol (-0.1 kg) compared to the control group (-1.6 kg) (95% CI -1.82, 5.11,  $p = 0.35$ ). However, per protocol analyses showed significant lower resting systolic and diastolic blood pressure among the women who had exercised as intended during pregnancy. Systolic blood pressure was 117.0 mmHg in the exercise group, compared to 124.2 mmHg in the control group (95% CI -12.39, -1.56,  $p = 0.01$ ), whereas diastolic blood pressure was 73.1 mmHg in the exercise group, compared to 78.4 mmHg in the control group (95% CI -9.29, -1.44,  $p < 0.01$ ).



## **DISCUSSION**

Our primary aim was to examine the effect of providing regular supervised exercise training during pregnancy on GWG among women with pre-pregnancy BMI  $\geq 28$  kg/m<sup>2</sup>. Additional aims were to measure effects on neonatal birth weight and PPWR, supplemented by several other clinically important maternal and neonatal outcomes. We assessed outcomes in early pregnancy, late pregnancy, at delivery, and three months postpartum.

We found no effect of exercise training on GWG, neonatal birth weight or PPWR. However, the women in the exercise group had significantly lower prevalence of GDM and lower systolic blood pressure in late pregnancy than the women in the control group.

### **Changes in body weight and body composition during pregnancy and postpartum**

We did not find any effect of offering regular exercise training during pregnancy on our primary outcome, GWG. Furthermore, no difference was found between the exercise and the control group on our secondary outcomes; neonatal birth weight, and PPWR three months after delivery.

Analysis of adherence to the intervention program showed that only half of the women in the exercise group followed the exercise program as intended. This may have influenced the efficacy of the intervention program in the exercise group, and may also have reduced potential difference between the groups. However, no effect of the exercise program on GWG was found when we compared the women who exercised “per protocol,” with the control group. The women who did not exercise “per protocol” may differ from the women who did, on factors that may interfere with trial outcomes, such as having higher BMI, being less fit, or having more pregnancy related health problems. However, these sub-analyses were hampered by low sample size and low statistical power. Most of the women in the ETIP trial had a pre-pregnancy BMI of 30 or more. Studies have found that GWG decreases as the BMI increases.<sup>99</sup> In the ETIP trial the number of women with baseline BMI  $\geq 35$  was higher in the control group than the exercise group. This may have reduced possible difference in GWG between our two study groups. No effect of exercise training on GWG was supported by our measurements of body composition and skinfold thickness, which showed no difference between the groups in amount of fat mass or muscle mass, at late pregnancy. Our findings strongly indicate limited effect on GWG of providing supervised regular exercise during pregnancy. The frequency, duration, load and intensity of the exercise program provided,

correspond to an estimated energy expenditure of one session of about 400 kcal. This may not have been sufficient to support reduced weight gain, change in body composition, or increased muscle mass. As the pregnancy proceeded, several women in the exercise group had to lower the intensity of the endurance training, causing decreased energy expenditure throughout the pregnancy.

Few RCTs comparable to ours,<sup>23,32,183,200,231</sup> have found a significant effect on GWG of exercise training as sole intervention, among overweight and obese women (see Table 2). Nascimento and colleagues<sup>183</sup> found significantly lower GWG among overweight women (10.0 vs 16.4 kg,  $p = 0.001$ ), but not among obese women, or in the group as a total. It is important to notice that participants, who abandoned the study over time, were excluded in this trial. Furthermore they found significantly lower GWG among the women who exercised “per protocol” compared to the women in the control group (5.9 vs 11.9 kg,  $p = 0.021$ ), including the total group of women. In this study, the adherence to the exercise protocol was higher (62%), and drop out lower (2%) compared to the ETIP trial. Two of these comparable RCTs have found a significant effect on GWG: Santos and co-workers<sup>201</sup> (5.7 kg vs 6.3 kg,  $p = 0.62$ ) and Wang and colleagues<sup>182</sup> (8.4 kg vs 10.5 kg,  $p < 0.001$ ). The trial intervention of Santos and co-workers<sup>201</sup> is very comparable to the ETIP trial in intensity and duration, and in number of weeks from pre to post assessments. However, their results must be handled with care due to very low adherence to the exercise protocol (40%). The trial of Wang and colleagues<sup>182</sup> had a higher sample size ( $n = 245$ ) than the other comparable trials, and found a higher difference in GWG than Santos and colleagues. They found significant differences in weight gain within week 25 ( $p < 0.001$ ), but no difference between week 25 and 36 ( $p = 0.9$ ). Compared to the ETIP trial, the women in the exercise group in the trial of Wang and co-workers were included earlier, within the first trimester, and attended a higher number of exercise sessions during the intervention period ( $73 \pm 10$ ), than the women in the ETIP trial ( $32 \pm 15$  supervised sessions at the hospital, plus  $19 \pm 17$  home-based exercise sessions). The trial of Wang and colleagues diverged from the other trials, in including high intensity interval training in their intervention program. The trial included interval training (stationary cycling) with 30 seconds bouts of high intensity, 75%-85% (RPE15-16) of age-predicted heart rate. Few exercise trials among pregnant women, and especially among overweight and obese pregnant women, have provided high intensity intervals in their training protocol. High intensity interval training may be challenging to perform among previously sedentary overweight and obese women as the pregnancy proceeds. Interval training may however be easier to perform in stationary cycling in up straight position, compared to in weight bearing

exercises, such as walking/running. Compared to the most other comparable trials, they started the intervention program earlier in pregnancy (gestational week 12.6), and thereby implemented a longer intervention period. It is however important to be aware of that Wang and co-workers defined overweight as  $BMI \geq 24 \text{ kg/m}^2$ , and that the mean BMI of the participants was significant lower compared to the ETIP trial. In our trial, most of the women were obese when entering the pregnancy. Previous trials on lifestyle changes in pregnancy have found more effect on overweight women than obese women,<sup>184</sup> and a wider range of GWG among obese women compared to overweight and normal weight women.<sup>183,185,231</sup>

We found no significant effect of the intervention program on neonatal birth weight. This is in line with several other RCTs, except from the before mentioned trial of Wang and co-workers.<sup>182</sup> Wang and co-workers<sup>182</sup> found a significant effect on lower birth weight among the exercising women, compared to the control group (3345.3 vs 3457.5,  $p = 0.049$ ). The observed difference in birth weight was however rather small, and may not be considered as clinically significant. Previous trials,<sup>229,230</sup> have considered 250 g difference between groups in mean birth weight, with a SD of 430 g, as clinically relevant. A recently published meta-analysis by Margo-Malosso and co-workers,<sup>184</sup> including women in all BMI categories, found no effect of exercise training on neonatal birth weight. Furthermore, no difference was found between groups in other neonatal anthropometric measurements at delivery. Studies have found that the first trimester seems to be of special importance in fetal development, being more sensitive to influence birth weight and adult body size.<sup>146,147</sup> Our trial did not include participants until the second trimester, which may have limited the effect of the intervention on neonatal birth weight.

We found a tendency of lower birth weight and a lower number of neonates exceeding  $\geq 4000 \text{ g}$  in the exercise group. These differences were however not significant. These tendencies in the ETIP trial are in line with a study by Barakat and colleagues<sup>202</sup> who investigated the effect of exercise among women in all BMI categories, and found that women who did not exercise during pregnancy were more likely to give birth to neonates  $> 4000 \text{ g}$  OR, 2.53,  $p = 0.04$ ). Barakat and colleagues included a high number of women in their trial ( $n = 840$ ), and started their intervention very early in pregnancy, in gestational week 9-11. This may be important factors in revealing effect of the intervention. We found a relatively high proportion of neonates with birth weight exceeding 4000 g in the total group of participants (35% vs 52%,  $p = 0.16$ ). This is consistent with studies demonstrating that maternal obesity is a risk factor for giving birth to neonates large for gestational age, even in the absence of GDM.<sup>148</sup> Taking into consideration the limited number of trials finding



significant effect of lifestyle intervention on birth weight, and the lack of difference between groups in the ETIP trial in weight gain and body composition, little effect of the intervention on neonatal birth weight could be expected.

No difference in PPWR was observed between the groups three months after delivery. Both groups had however returned back to their early pregnancy weight at the postpartum visit. Taken into account the increased risk of high PPWR among women with pre-pregnancy overweight and obesity,<sup>17,18</sup> it is rather surprising that the women retained early pregnancy weight only a few months postpartum. These results are clinically very important for the women's future health and obesity risk. A possible explanation of no weight retained and no difference between groups, is lifestyle changes during pregnancy in both groups. The control group may have become motivated for changes in lifestyle by participation in the ETIP trial and by eagerness to "perform well" in the health assessments during the intervention period. At the three months postpartum visit, the majority of the participants in both groups reported of regular breastfeeding. Breastfeeding is found to be negatively associated with PPWR, and may have contributed to rapid postpartum weight reduction in both groups.<sup>232</sup>

Few trials that have assessed the effect of exercise among overweight and obese pregnant women, have reported of PPWR or other health outcomes postpartum. Studies among women of all BMI categories have shown divergent results regarding PPWR. Price and co-workers<sup>164</sup> investigated the effect of moderate aerobic exercise four days a week from gestational week 12-14 through gestational week 36, and found no difference in weight retention six weeks postpartum, (2.5 vs. 0.7 kg), despite of good compliance in the intervention group (77%). Choi and colleagues<sup>31</sup> provided a systematic review and meta-analysis on the effect of diet, supervised physical activity, and a combination of the two, among overweight and obese women. They found that a combination of exercise and diet was most effective in reducing PPWR, regardless of BMI. In contrast to this, Ronnberg and co-workers<sup>107</sup> (n = 267) compared, the effect of weight monitoring, information on recommended weight gain and exercise prescription by the midwife, with standard maternal care, on PPWR 16 weeks postpartum. They found significant less weight retention four months postpartum among the women in the intervention group. Furthermore, Ronnberg and colleagues found that maternal non-compliance with IOM guidelines increased the risk of higher weight retention postpartum. In addition, they also found a strong positive correlation between GWG and PPWR. This study included pregnant women in all weight classes, although the majority (70%) had normal BMI. The statistically significant difference between

the intervention group and the control group was not present one year postpartum. Sagedal and co-workers<sup>233</sup> examined the effect of exercise training during pregnancy, twelve weeks postpartum, among women in all weight classes. They found no effect on PPWR in the ITT-analysis, but identified significant less weight retained among participants who adhered to the intervention protocol ( $p = 0.039$ ). Supplementary analyses in some studies have also suggested positive effects of exercise on PPWR among women adhering to the intervention protocol.<sup>164,233-235</sup>

Due to large variation in intervention programs, method of calculating PPWR, and point of time to measure PPWR, it is difficult to compare trials. Studies reporting a positive effect of lifestyle intervention on PPWR are characterized by including both dietary and physical activity components, weight monitoring, and frequent contact between participants and health- or study personnel. Pre-pregnancy BMI has been found to be a strong predictor of PPWR, where the association increases with increasing BMI.<sup>234</sup> Explicitly reporting on PPWR for overweight and obese women should be encouraged. On the other hand, trials that have found an effect of lifestyle intervention on GWG,<sup>236,237</sup> have not identified significant effect on PPWR. Some RCTs have suggested a positive effect of exercise training on PPWR only among women adhering to the intervention protocol,<sup>164,233-235</sup> however, we did not observe such effects in the present study when analyzing per protocol.

### **Glycemic control**

We found lower incidence of GDM among the women in the exercise group compared to the women in the control group. Similar findings are not frequently reported in previous trials.<sup>83</sup> A recently published meta-analysis by Margo-Malosso and colleagues<sup>184</sup> showed significantly lower incidence of GDM among overweight and women who exercised during pregnancy (RR = 0.61), compared to sedentary pregnant women. However, six of the trials included in this meta-analysis also provided dietary advises. A Cochrane review<sup>25</sup> of the effect of exercise on prevention of GDM among women in all weight classes, found no effect of exercise on GDM incidence. Only two<sup>23,199</sup> of the included trials investigated the effect of exercise in overweight and obese women. Trials that find an effect of exercise on GDM are often characterised by including individually adjusted supervised exercise sessions, and by the exercising women achieving a heart rate of approximately 70-80% of predicted maximal heart rate in their aerobic sessions. In the ETIP trial the exercise sessions were supervised,

and the women were motivated to walk on a intensity of ~80% of maximal capacity during the treadmill walking.

Exercise training as an intervention during pregnancy may reduce the risk of developing GDM by improving the glucose tolerance and insulin sensitivity.<sup>238,239</sup> Studies that include a combination of exercise and diet interventions have found better effect on incidence of GDM than trials including exercise only.<sup>23,25,199,240</sup> The RADIEL study<sup>241</sup> included both exercise and diet in their intervention program, and found a 39% reduced incidence of GDM among women at high risk of GDM. Both exercise and diet interventions are known to affect the risk of developing type 2 diabetes mellitus in the general population. The American Diabetes Association (ADA) recommends non-pregnant obese women at risk of developing type 2 diabetes, to lose seven percent of their body weight, and to follow the recommendations of 150 minutes of physical activity per week.<sup>242</sup> Further do the ADA suggest a calorie intake restriction of 30% (a minimum of 1800 kcal per day) for obese women with GDM. Research has found that exercise, and high intensity exercise in particular, improves glycemic control among non-pregnant subjects, even with no change in BMI.<sup>243</sup> It is likely to assume these mechanisms to be valid for pregnant women too. The preferred intensity of the endurance training in ETIP trial was about 80% of maximal heart rate, corresponding to Borg scale 12-15. This intensity is somewhat harder compared to some other comparable trials,<sup>183,200,202</sup> and may have lowered the risk of GDM in the exercise group. It is not known whether the participants in the exercise group changed their diet during pregnancy, however significant changes may have also affected the incidence of GDM.

At the three months postpartum visit, women in the exercise group had significantly lower levels of insulin. None of the women in the exercise group fulfilled the diagnostic criteria for type 2 diabetes three months after delivery, whereas three women in the control group fulfilled this diagnostic criterion. The difference was not significant. These are clinically important findings, assuming that exercise during pregnancy, may prevent development of metabolic disorders in risk groups as sedentary overweight and obese women. Twice as many women in the exercise group reported of performing regular exercise three months after delivery, compared to in the control group. This may explain the difference between the groups in levels of insulin postpartum. Regular exercise postpartum was defined in our trial as performing  $\geq 90$  minutes of moderate exercise and/or performing  $\geq 45$  minutes of high intensity exercise weekly. Few trials investigating effects of exercise during pregnancy among overweight and obese women have assessed outcomes in the postpartum

period. The ETIP trial highlights the importance of interventions during pregnancy on the future health of the women.

## **Blood pressure**

Regular physical activity is demonstrated to reduce the risk of developing high blood pressure and hypertension for the general population.<sup>244</sup> We found a significant lower systolic blood pressure in late pregnancy among women in the exercise group. This finding was supported by differences in both the systolic and the diastolic blood pressure being significant in the per-protocol analyses. This is an important clinical finding assuming that exercise during pregnancy may reduce the risk of metabolic disorders later in life. We are not aware of any trials investigating the effect of exercise during pregnancy on overweight and obese women that demonstrate an effect on blood pressure and maternal hypertension in late pregnancy and postpartum.

Our findings of lower systolic blood pressure among the exercising women are in line with comparable trials investigating women within all BMI categories.<sup>200,202</sup> Barakat and colleagues<sup>202</sup> in contrast, found reduced incidence of maternal hypertension among normal weight women who performed regular exercise three times per week during pregnancy ( $p = 0.009$ ), but not among overweight and obese women. Wang and co-workers,<sup>182</sup> who investigated the effect of high intensity interval training among overweight and obese women, found no effect on maternal hypertension. A tendency of lower blood pressure in the exercise group compared to the control group three months after delivery, may be a result of more women reporting of regular exercise training postpartum in the exercise group.

## **Neonatal and maternal outcomes at delivery**

We found no effect of the exercise intervention on any of our neonatal or maternal outcomes at delivery. Our findings are supported by several other RCTs providing supervised exercise training during pregnancy for overweight and obese women.<sup>183,32,103,182,184,236</sup>

Maternal obesity and excessive weight gain during pregnancy are both associated with increased risk of childhood obesity and development of metabolic diseases, which indicates that the intrauterine metabolic environment may affect the fetus' future health risks.<sup>15,64</sup> Some studies have found that high pre-pregnancy BMI is a stronger predictor of high neonatal birth weight and future risk of obesity and metabolic disorders, than maternal glucose status and excessive GWG.<sup>245-248</sup> Excessive GWG during pregnancy and maternal hyperglycemia are

likely to imprint the fetus for childhood and adult obesity.<sup>145</sup> Babies with high birth weight ( $\geq 4000$  g) are at increased risk of both childhood obesity and adult obesity compared to babies born at 2500-4000 g.<sup>112</sup> A relatively high proportion of neonates in our study had a birth weight exceeding 4000 g. This is consistent with another study demonstrating that maternal obesity is a risk factor for getting larger newborns, even in the absence of GDM.<sup>148</sup> The factors mentioned above strongly indicate that the mother's state of health during the perinatal period can affect the child's risk of obesity later in life. The pregnancy may be a critical window for preventing childhood obesity by reducing GWG and improving maternal glucose.

### **Physical activity and exercise adherence**

About 55% of women in both groups reported compliance with the recommendations of at least 150 minutes of physical activity during the week, before entering the pregnancy. Previous research has shown a tendency of reduced amount of physical activity during the pregnancy. In the ETIP trial however, the number of women who reported of compliance with the recommendations of physical activity, increased during pregnancy in both groups (61-66%). As expected due to the intervention program, significantly more women in the exercise group were exercising regularly during the pregnancy, compared to women in the control group. At the three months postpartum visit, even a higher amount of the women in both groups reported of adherence to the recommendations of weekly physical activity (75%). There was a tendency however, of more women in the exercise group performing regular exercise training, compared to the control group, indicating lifestyle changes in the exercise group. Considering that self-reported data on physical activity tends to be overestimated, the findings of the ETIP trial demonstrate an increased level of physical activity from pre-pregnancy to three months after delivery, in both groups. The increased level of physical activity in the control group, both during pregnancy and postpartum, may have contributed to reduced differences between the groups in the trial outcomes. This may indicate that not only the exercise group, but also the control group was affected by attending the trial; becoming more aware of and motivated for healthy living. This effect is likely of clinical importance for prevention of adverse outcomes caused by overweight or obesity.

Collecting data on daily physical activity among the participants may be very important when assessing outcomes related to energy expenditure. Unfortunately, few trials on exercise intervention report such data. Improving the women's physical activity habits

would provide major clinical importance for preventing adverse long term health complications for both mother and child.

The recommendations by ACOG on exercise and physical activity during pregnancy are perhaps too little known, and therefore not fully utilized by health care personnel in motivating risk groups in particular for physical activity during pregnancy. The amount and intensity of the physical activity required to ensure an effect on adverse outcomes is still unclear. The pregnancy is perceived as an ideal period for lifestyle changes to support the well-being of the mother and the fetus. Yet the pregnancy can also be a time of emotional changes that may impair the motivation for lifestyle changes.<sup>249</sup> Previous experience with physical activity and exercise may affect the results, however the general observation is that the level of physical activity and exercise reduces during pregnancy among all pregnant women. Challenges related to low adherence to the exercise protocol among pregnant women is often reported. The exercise program in the ETIP trial was *offered* to the intervention group, and all women in the exercise group were included in the analyses independent of adherence to the exercise sessions. Therefore, the results of the trial do not fully reflect nor the effect or the efficacy of the intervention program.

## **Strengths**

Diet and exercise are important contributors to maternal and fetal health. Previous research has experienced difficulties in separating the preventive mechanisms, and concludes which of these factors that affect maternal and neonatal health outcomes the most. Therefore, the aim of our trial was to investigate the effect of exercise as the sole intervention, to better assess isolated effects of exercise training during pregnancy. We provided supervised exercise sessions in our intervention program that are found to improve the effect of an exercise intervention during pregnancy.<sup>31</sup> The exercise sessions were supervised by a physical therapist, which adjusted the exercises individually if needed, monitored intensity, duration and exercise performance, and motivated the women to follow the intervention program.

Our exercise program did not require any equipment. Although women in our trial walked/ran on a treadmill, the endurance component of the training could have been undertaken as outside walking/running. The strength exercises were performed using women's own body weight. Our program could therefore easily be performed at home when the women were not able to come to the hospital. The participants in the exercise group registered daily physical activity and exercise training (including their home-based exercise

program) in a training diary during the pregnancy, were informed about individually recommended weight gain, and registered their weight weekly. Information to pregnant women regarding individually recommended GWG, and system for regular registration of weight during pregnancy, are shown to moderate the GWG.<sup>250</sup>

We assessed all participants' level of physical activity and exercise training, the period before pregnancy, during pregnancy, and within three months after delivery through questionnaires. These data gave important information regarding the subjects' characteristics before entering the pregnancy, and possible changes in lifestyle during pregnancy. Our primary outcome in the trial, GWG, was calculated on basis of objectively measured body weight by study personnel at early pregnancy, and at delivery by hospital personnel blinded for group allocation. This makes our data more reliable compared to several trials using self-reported weight, especially at baseline, in their outcome data. We also consider it a strength that we supplemented our weight data with data on body composition, which reduced potential bias related to change in body composition. The importance of body weight is *per se* uncertain, and fat percentage has been found to be more associated with adverse outcomes during pregnancy than body weight.<sup>246</sup>

We consider our study population quite homogenous, compared to several other trials. We included only overweight and obese women, with eight women not classified as obese (with a BMI of 28.3-29.9). They were all previously sedentary, which reduced the risk of selection bias in the trial. The lost to follow-up rate in the ETIP trial, 23.1% (seventeen at late pregnancy, and another four at postpartum), is comparable to other RCTs providing exercise as intervention.

## **Limitations**

The main limitation of the ETIP trial is a lower sample size than planned. Initially we estimated to include 150 participants, but only 91 participants were randomized into the trial. Including fewer participants than required by the power calculation will implied a risk for not showing an effect even if it was present (type 2 error). However, our data on the trial's primary outcome, GWG, did not reveal any tendencies in difference in weight gain during pregnancy, either not if analyzing per protocol. We would likely not have found any difference in GWG with a higher sample size. Low adherence to the exercise protocol in the intervention group is another limitation of the trial. The ETIP trial was based on the "intention to treat" (ITT) principle, and was by this highly dependent on adherence to the exercise

protocol to reveal an effect of the intervention. To investigate the effect of following the exercise protocol, we supplemented our analyses with “per protocol” analyses. These were however, hampered by a low sample size in the exercise group. Compliance with the exercise protocol may have been associated with health status and prognostic factors of the participants.<sup>251</sup>

The dose of exercise training in our study might have been too low to impact body weight and body composition, despite of providing an exercise protocol with use of higher intensity than several other comparable trials.

To accommodate slow recruitment in the trial we lowered the BMI inclusion criteria from 30 to 28. As a result, eight women classified as overweight, were included in the trial. This change reduced the homogeneity of the study group slightly, however we do not consider the outcomes of the trial were significantly affected, or the internal validity reduced.

Mean gestational week for inclusion was 16 for the total group of women, consequently most women were in second trimester when entering the trial. Ideally we would have reached eligible women at an earlier state in the pregnancy, thereby enabling a longer intervention period. The risk of miscarriage is relatively high before pregnancy week 12, and inclusion into the trial during the first trimester would introduce high risk of drop-outs. Also, it could be difficult to determine if early miscarriage was related to the exercise training or not.

At baseline the control group had significantly higher fasting glucose, and more women had a BMI  $\geq 35$ , compared to the exercise group. Because of this, more women in the control group compared to the exercise group could have been provided with extended counseling on weight, diet and exercise from health care personnel during pregnancy, in accordance to the guidelines for maternal care. This would potentially have reduced the difference between groups and affected the outcomes of the trial. Unfortunately, we have not recorded the amount of such extra follow-up in our trial.

The ETIP trial focused on exercise as intervention, and in the current thesis, no information regarding the participants’ dietary habits during pregnancy was included or adjusted for. Both exercise and diet are important contributors to healthy lifestyle during pregnancy, and change in diet could affect some of the outcomes in our trial, especially weight and body composition. Our intention was that all participants included in the trial continued their habitual eating during pregnancy. It is possible that some of the women were inspired to eat healthier during the pregnancy as a consequence of participating in the trial, and/or participating in the exercise group. We assume however, that these mechanisms would



be equally distributed between groups. In fact, some studies have shown that increased physical activity among previous sedentary may lead to compensated increased dietary intake.<sup>211</sup>

Some of the study assessments were performed non-blinded for group allocation. Interpretation of the trial results must be done with this in mind. Having all study personnel in the ETIP trial blinded for group allocation was unfortunately not possible due to limited resources.

Volunteering for an exercise trial may reflect an awareness and motivation for healthy lifestyle changes during pregnancy. Furthermore, both groups attended comprehensive health assessments during and after the pregnancy, which may have increased their awareness of healthy living during the pregnancy. One may argue that the control group received more than standard maternal care only, by participating in health assessments four times during their participation in the trial. This may potentially have contributed to motivation for behavioral changes in the control group, and thereby reduced differences between groups.

## **Generalizability**

We had few exclusion criteria in our trial, and offered training sessions at different times of the day and week, which should support that a non-selected sample of participants was eligible. The ETIP trial included approximately 10% of all eligible pregnant women with pre-pregnancy BMI  $\geq 28$ , in the area of St. Olavs Hospital. If we compare our data with data from the Norwegian Medical Birth Registry,<sup>53</sup> of age, parity and distribution within BMI obese grades I, II, III, our population was representative of the general Norwegian population of women with BMI  $\geq 28$  who gave birth in 2014. Comparing the ETIP trial with the Norwegian Medical Birth Register shows these results: Mean age; 31.4 vs 29.4 years, primiparous; 45% vs 44%, smoking; 7% vs 3%, currently employed; 78% vs 75%. The Norwegian Medical Birth Registry does not provide detailed information on educational status, however we know from previous research that people who volunteer for participation often have higher education than those not willing to participate. We mainly recruited women from the area of Trondheim city, which may represent a higher level of education compared to women living in more rural communities. We did not find large cohort studies providing detailed demographic data on pregnant women with BMI  $\geq 28$ , to compare with our data. Whether the ETIP population is representative for the general comparable population, in education, physical activity habits and general health status is therefore uncertain.

It is possible that women who volunteered to participate in an exercise trial are healthier, more familiar with exercise training, extra aware of the possible benefits of lifestyle changes during pregnancy, and thereby more motivated for physical activity and exercise training in pregnancy, than women who did not volunteer for the trial. On the other hand, we only included previously sedentary women, which may have increased the risk of low adherence to the exercise protocol, compared to obese women who exercise regularly. We recruited women at an early stage in pregnancy, where many women experience nausea, fatigue and sleepiness. Thereby the risk of recruiting women with less pregnancy complications was present. If we compare the results in the ETIP trial with data from large cohort studies on the same population,<sup>20,182,252,253</sup> we see that the number of adverse outcomes in our trial together was low. This can indicate a quite healthy population in our trial. In summary, we regard the study participants in the ETIP trial to be fairly representative for Scandinavian pregnant women with pre-pregnancy BMI of 28 or more.

### **Implications for clinical practice and future research**

More and more women enter pregnancy as overweight or obese, and strategies to prevent associated risks are highly needed. We aimed to increase knowledge about exercise as a strategy to reduce risks related to high pre-pregnancy BMI and excessive GWG. The trial intervention program was based on today's recommendations for exercise during pregnancy, and designed for easy implementation into clinical practice.

The importance of GWG as an independent risk factor for adverse outcomes during pregnancy may be questioned as several trials finding an effect of exercise training on GWG, do not find any effect on other maternal and neonatal outcomes.<sup>22,182,183</sup> We found an effect of exercise training during pregnancy on GDM, maternal blood pressure in late pregnancy, and level of circulating insulin postpartum. These findings are of major clinical importance for both present and future health for the mother and the child. Health care professionals need evidence-based guidelines for exercise in pregnancy, targeting overweight and obese women. These should be implemented in standard maternal care. Health care professionals, especially general practitioners and midwives who consult pregnant women, are in a unique position to inform, help and guide overweight and obese women through the pregnancy. However, several studies that have found an effect of a lifestyle intervention among normal weight women, have not identified the same effect among overweight, and especially not, obese women. This indicates that different strategies are needed aiming at different risk groups. Our

trial could contribute to improved preventive strategies and routines for maternal care for obese women at high risk for adverse pregnancy outcomes.

The exercise program and intensity monitoring used in the ETIP trial can be implemented in clinical practice. Supervised exercise sessions require qualified personnel and imply financial costs, which may be a limitation for some centers or communities providing maternal care. However, we argue that supervised exercise sessions, or at least individual programs with frequent follow-ups, should be a part of standard maternity care for obese pregnant women to ensure adherence to exercise training throughout pregnancy.

We did not experience any adverse events related to the intervention in our trial, indicating that moderate intensity exercise is safe also for previously sedentary obese pregnant women.

Pregnancy can be a golden moment for lifestyle changes. Pregnant women are frequently in contact with health care personnel during pregnancy. The pregnancy is thereby an ideal time to motivate women to be physically active and eat healthy. Women can also be more adaptable for changes when they know that their lifestyle not only affects their own health, but also the health of their unborn child. However, we experienced that it was difficult to motivate the women to adhere to the exercise program.

Studies have found effects of behavior change techniques to reduce the decline in physical activity during pregnancy.<sup>197</sup> Successful interventions were regular face to face consultations, including goals, planning, information, and comparison of outcomes during pregnancy. However, a systematic review<sup>181</sup> of the effect of behavioral interventions during pregnancy on weight management, found no effect of behavioral intervention on GWG among normal weight, overweight or obese women, despite often intense and tailored interventions.

Our findings support today's recommendations of exercise training and physical activity during pregnancy. More studies are warranted on how to implement exercise training as a preventive and therapeutic tool in maternal care, and on how to increase exercise adherence in pregnancy.

Based on present knowledge and the findings of the ETIP trial, there is a need for further studies on prevention of adverse outcomes related to pre-pregnancy overweight and obesity. We should explore the specific preventive effect of exercise training at different levels of doses and intensity. There is still a lack of knowledge on the effect of exercise training in pregnancy to reduce maternal blood pressure and the risk of pre-eclampsia among

women with high BMI. Preventing these conditions are of major importance for the present and future health for both the mother and the child.

Several well-conducted trials on lifestyle changes during pregnancy in overweight and obese women are inconclusive due to low numbers. Multi-center trials should be emphasized to ensure a higher sample size. Studies of motivational strategies for behavioral changes during pregnancy are necessary, and may be of major importance to increase the adherence to the intervention programs. Finally, we should develop strategies to implement preconception counselling and supervised exercise programs for obese women in the health care system.



## **CONCLUSIONS**

Providing regular supervised exercise training during pregnancy for overweight and obese women did not affect GWG, compared to standard maternal care. However, we found lower systolic blood pressure and lower incidence of GDM in late pregnancy in the exercise group, compared to in the control group. The exercise intervention did not affect birth weight or other neonatal and maternal outcomes at delivery. Three months postpartum we found no difference between groups in PPWR, and at this point in time both groups had returned to their pre-pregnancy weight. We found lower levels of circulating insulin and higher insulin sensitivity in the exercise group compared to the control group three months after delivery, indicating a positive effect of exercise training during pregnancy on future risk for metabolic diseases. Though our trial was limited by low sample size and low adherence to the exercise protocol, our findings show that exercise training and physical activity during pregnancy is important to prevent adverse pregnancy outcomes among overweight and obese women.

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# Paper I



RESEARCH ARTICLE

# Exercise Training and Weight Gain in Obese Pregnant Women: A Randomized Controlled Trial (ETIP Trial)

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## Abstract

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**Citation:** Garnæs KK, Mørkved S, Salvesen Ø, Moholdt T (2016) Exercise Training and Weight Gain in Obese Pregnant Women: A Randomized Controlled Trial (ETIP Trial). *PLoS Med* 13(7): e1002079. doi:10.1371/journal.pmed.1002079

**Academic Editor:** Nicholas J Wareham, University of Cambridge, UNITED KINGDOM

**Received:** March 4, 2016

**Accepted:** June 3, 2016

**Published:** July 26, 2016

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**Data Availability Statement:** All relevant data are within the paper and its supporting information files.

**Funding:** (1) The Norwegian Fund for Post-Graduate Training in Physiotherapy, supported the study with NOK 2 800 000 (7-370-00/08A), received by SM. URL: <http://fysiofondet.no/>. (2) The Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU), supported the study with NOK 2 856 000 (46056728) received by KKG. URL: <https://www.ntnu.no/dm/rad/samorg>. The funders had no role in study design, data collection

## Background

The effectiveness of exercise training for preventing excessive gestational weight gain (GWG) and gestational diabetes mellitus (GDM) is still uncertain. As maternal obesity is associated with both GWG and GDM, there is a special need to assess whether prenatal exercise training programs provided to obese women reduce the risk of adverse pregnancy outcomes. Our primary aim was to assess whether regular supervised exercise training in pregnancy could reduce GWG in women with prepregnancy overweight/obesity. Secondary aims were to examine the effects of exercise in pregnancy on 30 outcomes including GDM incidence, blood pressure, blood measurements, skinfold thickness, and body composition.

## Methods and Findings

This was a single-center study where we randomized (1:1) 91 pregnant women with a prepregnancy body mass index (BMI)  $\geq 28$  kg/m<sup>2</sup> to exercise training ( $n = 46$ ) or control (standard maternity care) ( $n = 45$ ). Assessments were done at baseline (pregnancy week 12–18) and in late pregnancy (week 34–37), as well as at delivery. The exercise group was offered thrice weekly supervised sessions of 35 min of moderate intensity endurance exercise and 25 min of strength training. Seventeen women were lost to follow-up (eight in the exercise group and nine in the control group). Our primary endpoint was GWG from baseline testing to delivery. The principal analyses were done as intention-to-treat analyses, with supplementary per protocol analyses where we assessed outcomes in the women who adhered to the exercise program ( $n = 19$ ) compared to the control group. Mean GWG from baseline to delivery was 10.5 kg in the exercise group and 9.2 kg in the control group, with a mean difference of 0.92 kg (95% CI  $-1.35, 3.18$ ;  $p = 0.43$ ). Among the 30 secondary outcomes in late pregnancy, an apparent reduction was recorded in the incidence of GDM (2009 WHO definition) in the exercise group (2 cases; 6.1%) compared to the control group (9 cases;



and analysis, decision to publish, or preparation of the manuscript.

**Competing Interests:** The authors have declared that no competing interests exist.

**Abbreviations:** BMI, body mass index; CRP, C-reactive protein; ETIP, Exercise Training in Pregnancy; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HDP, high-density lipoprotein; IADPSG, International Association of Diabetes and Pregnancy Study Groups; IOM, Institute of Medicine; LDL, low-density lipoprotein; NTNU, Norwegian University of Science and Technology; RCT, randomized controlled trials

27.3%), with an odds ratio of 0.1 (95% CI 0.02, 0.95;  $p = 0.04$ ). Systolic blood pressure was significantly lower in the exercise group (mean 120.4 mm Hg) compared to the control group (mean 128.1 mm Hg), with a mean difference of  $-7.73$  mm Hg (95% CI  $-13.23$ ,  $-2.22$ ;  $p = 0.006$ ). No significant between-group differences were seen in diastolic blood pressure, blood measurements, skinfold thickness, or body composition in late pregnancy. In per protocol analyses, late pregnancy systolic blood pressure was 115.7 (95% CI 110.0, 121.5) mm Hg in the exercise group (significant between-group difference,  $p = 0.001$ ), and diastolic blood pressure was 75.1 (95% CI 71.6, 78.7) mm Hg (significant between-group difference,  $p = 0.02$ ). We had planned to recruit 150 women into the trial; hence, under-recruitment represents a major limitation of our results. Another limitation to our study was the low adherence to the exercise program, with only 50% of the women included in the intention-to-treat analysis adhering as described in the study protocol.

## Conclusions

In this trial we did not observe a reduction in GWG among overweight/obese women who received a supervised exercise training program during their pregnancy. The incidence of GDM in late pregnancy seemed to be lower in the women randomized to exercise training than in the women receiving standard maternity care only. Systolic blood pressure in late pregnancy was also apparently lower in the exercise group than in the control group. These results indicate that supervised exercise training might be beneficial as a part of standard pregnancy care for overweight/obese women.

## Trial Registration

ClinicalTrials.gov [NCT01243554](https://clinicaltrials.gov/ct2/show/study/NCT01243554)

### Author Summary

#### Why Was This Study Done?

- Maternal obesity is associated with increased risk of several adverse pregnancy outcomes.
- The aim of our study was to investigate whether exercise training during pregnancy can reduce gestational weight gain and prevent negative health outcomes, such as gestational diabetes mellitus and high blood pressure, among overweight/obese pregnant women.

#### What Did the Researchers Do and Find?

- Ninety-one overweight/obese pregnant women were randomly allocated to an exercise group or a control group in early pregnancy (starting in pregnancy week 12–18).
- Women in the exercise group were asked to attend supervised sessions of combined endurance and resistance training three times weekly.

- Women in both groups gained on average about 10 kg. In late pregnancy, there seemed to be fewer women in the exercise group with gestational diabetes mellitus, and the exercising women had lower systolic blood pressure compared to those in the control group.

### What Do These Findings Mean?

- Providing an exercise program to overweight/obese pregnant women did not reduce gestational weight gain compared to standard pregnancy care.
- Exercise training might reduce the incidence of gestational diabetes mellitus and lower systolic blood pressure in late pregnancy in this population.

## Introduction

Maternal obesity is a risk factor for adverse pregnancy outcomes, such as gestational diabetes mellitus (GDM) [1], gestational hypertension, preeclampsia, need for cesarean delivery, and large for gestational age [2–4]. Because the prevalence of overweight and obesity among reproductive-age women is increasing, effective preventive strategies are urgently needed.

Excessive gestational weight gain (GWG) is also associated with negative obstetric outcomes [1,5,6]. The 2009 Institute of Medicine (IOM) guidelines on GWG suggest that underweight women (body mass index [BMI]  $\leq 18.5$  kg/m<sup>2</sup>) should gain 12.5–18.0 kg during pregnancy; normal weight women (BMI 18.5–24.9 kg/m<sup>2</sup>), 11.5–16.0 kg; overweight women (BMI 25.0–29.9 kg/m<sup>2</sup>), 7.0–11.5 kg; and obese women (BMI  $\geq 30.0$  kg/m<sup>2</sup>), 5.0–9.0 kg [7]. Overweight and obese women are about two times more likely than normal weight women to exceed these recommendations [8]; thus, there is a special need to find feasible and effective interventions to reduce GWG in women with a high BMI.

Previous research on clinical effects of lifestyle interventions during pregnancy in overweight/obese women has shown conflicting results [9–14]. Most studies have assessed the combined effect of physical activity and dietary guidance. To our knowledge, there are only three previous randomized controlled trials (RCTs) [14–16] assessing the isolated effects of exercise training in pregnancy on GWG and clinical outcomes in overweight and obese women. These studies found no significant difference in GWG between exercise and control groups. However, one study was limited by a small study sample ( $n = 12$ ) [14], and one study reported results from only a subgroup [15].

Few studies exist on GDM prevention via exercise training in obese women [17–19], and to our knowledge no previous RCT has shown that GDM can be prevented by exercise training as the sole intervention [14,18,20,21]. However, according to a recent meta-analysis [22], structured physical exercise programs during pregnancy decrease the risk of GDM. Hence, there is still a need to establish the potential effects of exercise training on GDM prevention, and especially so in overweight/obese women.

To address the shortcomings in the research on effective prevention of GWG and of GDM, our aim was to assess whether regular supervised exercise training could reduce GWG and improve clinical outcomes, compared to standard maternity care, in women with a prepregnancy BMI of 28 kg/m<sup>2</sup> or more.

## Methods

### Design and Participants

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK midt 2010/1522) and registered in ClinicalTrials.gov (NCT01243554). The Exercise Training in Pregnancy (ETIP) trial was a single-center, parallel-group RCT of regular exercise training during pregnancy compared to standard maternity care in women with prepregnancy BMI  $\geq 28$  kg/m<sup>2</sup>. The study protocol has been published previously [23]. The trial was performed at the Norwegian University of Science and Technology (NTNU) and St. Olavs Hospital, Trondheim University Hospital, in Trondheim, Norway.

We made the following changes to the protocol after trial commencement: body composition was measured using air displacement plethysmography starting 28 June 2011, to improve assessments of body composition. The time limit for completed baseline testing and inclusion into the study was changed from gestational week 16 to gestational week 18 on 15 November 2012, and we changed the inclusion criteria for BMI from  $\geq 30$  to  $\geq 28$  kg/m<sup>2</sup> on 22 March 2013. We changed the time limit for inclusion and the BMI criteria to increase recruitment into the trial. All changes were reported and approved by the Regional Committee for Medical and Health Research Ethics. The procedures followed in the ETIP study were in accordance with ethical standards of research and the Helsinki Declaration.

At recruitment, women received written information, and they signed informed consent on behalf of themselves and their offspring before participation and randomization. Inclusion criteria were prepregnancy BMI  $\geq 28$  kg/m<sup>2</sup>, age  $\geq 18$  y, gestational week  $< 18$ , and carrying one singleton live fetus at 11–14 wk ultrasound scan. The participants had to be able to come to St. Olavs Hospital for assessments and exercise classes. Exclusion criteria were high risk for preterm labor, diseases that could interfere with participation, and habitual exercise training (twice or more weekly) in the period before inclusion. Women were recruited through invitations sent along with notices for routine ultrasound scan at the hospital, and additionally through Google advertisements. The women received infant food worth US\$65. The participants in this study gave written informed consent to publication of their case details.

### Intervention and Outcomes

The exercise group was offered, in addition to standard maternity care, exercise sessions at the hospital three times weekly, from baseline (gestational week 12–18) until delivery. The exercise sessions were supervised by a physical therapist and were in accordance with the recommendations from the American College of Obstetricians and Gynecologists [24]. Each session lasted 60 min and consisted of treadmill walking/jogging for 35 min (endurance training) and resistance training for large muscle groups and the pelvic floor muscles for 25 min. The intensity of the endurance training was set to ~80% of maximal capacity (corresponding to Borg scale 12–15) [25]. The resistance training consisted of squats, push-ups, diagonal lifts on all fours, and oblique abdominal crunches, with three sets of ten repetitions of each exercise separated by a 1-min rest between sets. Participants also did three sets of the “plank exercise” for 30 s. We adjusted the program according to each woman’s strength level. The pelvic floor exercises consisted of three sets of ten repetitions of pulling the pelvic floor up and holding the contraction for 6–8 s.

In addition, the women were asked to follow a 50-min home exercise program at least once weekly (35 min of endurance training and 15 min of strength exercises) and to do daily pelvic floor muscle exercises. We registered adherence to the supervised exercise program, and the participants reported their home exercise in a training diary. The participants received a weight

gain curve showing recommended weight gain throughout pregnancy in accordance to 2009 IOM guidelines [7], and were encouraged to compare their own weight gain with this curve. The women were invited to attend one motivational interview session [23], either individually or in a group, during the intervention period.

The control group received ordinary maternity care by their midwife, general practitioner, and/or obstetrician. The Norwegian national directions for standard maternity care among healthy pregnant women at the time the study was conducted included offering of an ultrasound examination by gestational week 18 and providing information about healthy eating and healthy lifestyle [26]. The women in the control group were asked to continue their normal daily activities and were not discouraged from exercising on their own.

All participants underwent the same test protocol at baseline (gestational week 12–18) and at late pregnancy (gestational week 34–37). In addition, the hospital personnel measured the women's body weight immediately before delivery.

Our primary outcome measure was GWG calculated as the difference between weight at baseline and weight at delivery. Maternal body weight at baseline, in late pregnancy, and before delivery was measured with a calibrated electronic scale (Seca 770, Medema, Norway) to the nearest 0.1 kg, with the participant wearing indoor clothing, without shoes. If the hospital staff did not have time to measure the women's weight right before delivery, we used women's self-reported weight at the time of delivery to calculate the outcome measure.

Secondary outcome measures were BMI, body composition, physical activity level, skinfold thickness, blood pressure, various blood tests, incidence of GDM, and incidence of maternal hypertension in late pregnancy. Height was measured at baseline with a wall-mounted Seca 222 stadiometer. BMI was calculated as weight in kilograms divided by the square of height in meters. Systolic and diastolic blood pressure were measured on the right arm after 15 min of supine resting using a CASMED 740 MAXNIBP (CAS Medical Systems). We used the average of three measurements taken at 2-min intervals. Skinfold thickness was measured on the right side of the body at the sites subscapular, biceps, and triceps, using a Harpenden Skinfold Caliper (Holtain). We used the average of three measurements for each site. Body composition was measured using air displacement plethysmography (BOD POD, COSMED). The participant entered the BOD POD wearing only underwear and a swim cap. Physical activity level was measured by a questionnaire where the participants reported their frequency, duration, and intensity of weekly physical activity.

After a 10-h fast, we drew venous blood for fasting plasma glucose and other blood measurements. The participants then drank 75 g of glucose dissolved in 2.5 dl of water, and blood was drawn again after 2 h (120-min plasma glucose). According to the study protocol [23], GDM was to be diagnosed by the 2009 WHO definition: fasting plasma glucose  $\geq 7.0$  mmol/l and/or 120-min plasma glucose  $\geq 7.8$  mmol/l [27]. However, in 2013 WHO, in collaboration with the International Association of Diabetes and Pregnancy Study Groups (IADPSG), endorsed adjusted diagnostic criteria for classification of GDM: fasting plasma glucose  $\geq 5.1$  mmol/l and/or 120-min plasma glucose  $\geq 8.5$  mmol/l [28]. GDM is therefore reported here by both definitions. Plasma glucose, high-sensitivity C-reactive protein (CRP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, HbA1c, ferritin, and hemoglobin were measured using a Roche Modular P. We assessed insulin with ELISA (IBL International) using a DS2 ELISA processing system (Dynex Technologies). All assays were performed according to the manufacturer's instructions. The inter- and intra-assay coefficients of variation were 2.1% and 1.5% for glucose, 3.8% and <1% for high-sensitivity CRP, 2.5% and 0.9% for total cholesterol, 2.8% and 0.8% for HDL cholesterol, 2.4% and 0.8% for LDL cholesterol, 2.9% and 0.9% for triglycerides, and 5.3% and 9.5% for insulin.

Homeostatic assessment of insulin resistance (HOMA2-IR) was calculated as  $[\text{glucose} \times \text{insulin}] / 22.5$  [29].

## Statistical Methods

Sample size was calculated based on prior studies [30,31] using a 6-kg clinically relevant difference in mean weight gain between the exercise and the control group, from baseline to delivery. According to this, a two-sided independent sample *t*-test with a 5% level of significance, a standard deviation of 10, and a power of 0.90 gave a target study population of 59 in each group. Dropout was estimated at 15%; therefore, we aimed to include 150 women.

After baseline assessments, the participants were randomly allocated 1:1 to the intervention or the control group. Allocation was done using a computer random number generator developed and administrated at the Unit for Applied Clinical Research, NTNU. The randomization had varying block sizes, with the first, the smallest, and the largest block defined by the computer technician at the Unit for Applied Clinical Research. The investigators enrolling the patients (K. K. G. and T. M.) got the allocation results on screen and by e-mail after registration of each new participant into the study and did not have the full randomization list available.

Weight measurement at delivery and blood analyses were done by personnel blinded for group allocation. All other assessments and intervention administration were done non-blinded. The statistician conducting the statistical analyses was blinded for group allocation.

The trial and the principal analyses were based on intention to treat. All available data were used at all time points. We also performed, as described in the original protocol, per protocol analyses including only the women in the exercise group who adhered to the exercise protocol [23]. Baseline data were tested for normality and analyzed by an independent sample *t*-test and by Fisher's exact test.

The outcome measurements were analyzed in accordance to the treatment arm to which patients were randomized, regardless of nonadherence. The effect of treatment on the primary and secondary outcomes was assessed with mixed linear models for continuous outcomes and mixed logistic models for dichotomous outcomes. For the primary outcome, the effect of time and treatment was taken as a fixed effect having the levels baseline, training late pregnancy, control late pregnancy, training delivery, and control delivery. For the secondary outcomes, the effect of time and treatment was taken as a fixed effect having the levels baseline, training late pregnancy, and control late pregnancy. Due to randomization, no systematic differences between groups at baseline were assumed. To account for repeated measurements, participant ID was included as a random effect. The analyses were performed using R version 2.13.1, Stata version 13.1, and IBM SPSS Statistics 22. All results are given as mean values with 95% confidence intervals, and *p*-values less than 0.05 were considered significant. We did supplementary analyses of GWG where we adjusted for gestational age at delivery.

Per protocol analyses [23] including only the women in the exercise group who adhered to the exercise protocol were performed on both primary and secondary outcomes. Adherence to the exercise protocol was defined as (1) attending  $\geq 42$  organized exercise sessions, (2) attending  $\geq 28$  exercise sessions + performing  $\geq 28$  home exercise sessions, or (3) performing  $\geq 60$  home exercise sessions. The exercise had to be  $\geq 50$  min of either aerobic or strength training to count as a home session.

## Results

Fig 1 outlines the flow of participants during the trial.

CONSORT 2010 Flow Diagram

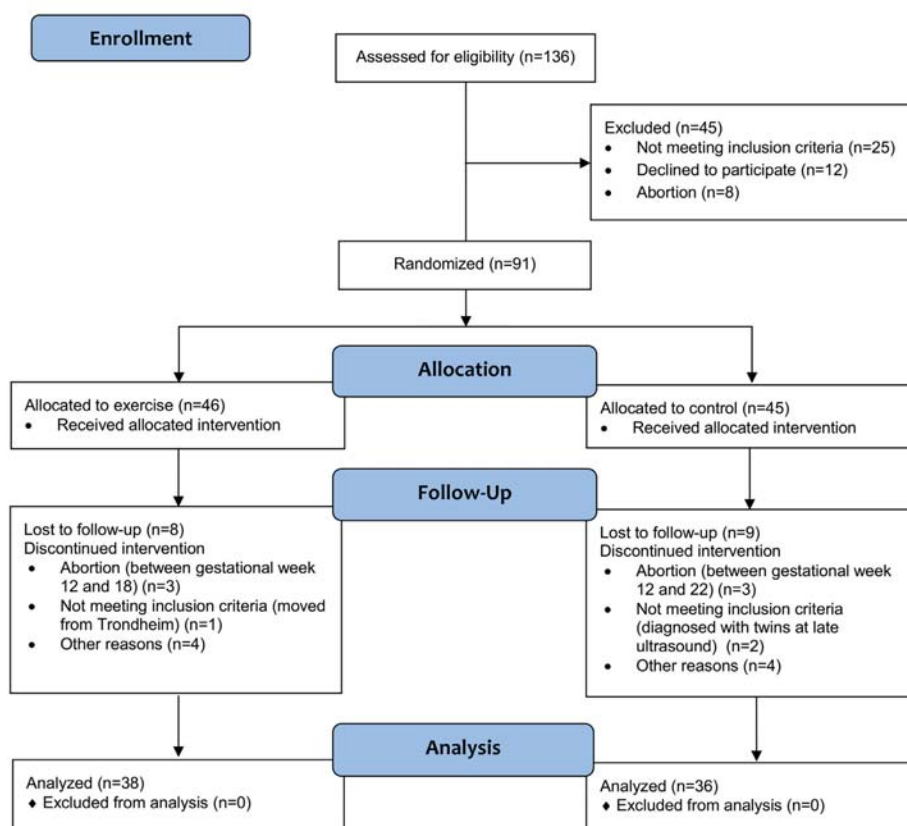


Fig 1. Flow chart of the ETIP study.

doi:10.1371/journal.pmed.1002079.g001

Recruitment started on 20 September 2010 and was continued until 1 March 2015. The final data collection date for the primary outcome measure was 20 June 2015. The aim of our study was to include 150 participants, but enrollment was stopped on 1 March 2015 at 91 randomized participants, due to the prolonged time for inclusion and fewer eligible participants than expected. Table 1 shows the baseline characteristics of the participants.

There were no significant differences between groups at baseline, except from mean fasting glucose (4.6 mmol/l in the exercise group, 5.0 mmol/l in the control group;  $p = 0.02$ ). Table 2 shows the model-based analyses for the continuous primary and secondary outcomes. The mean number of weeks from inclusion to delivery was 23.3 (range 10–28) in the exercise group and 24.7 (range 19–30) in the control group. Mean gestational age was 39.5 wk (range 27–42 wk) in the exercise group and 39.4 wk (range 37–42) in the control group.

**Table 1. Baseline characteristics of all women included in the ETIP study.**

Baseline Characteristic	Exercise Group (n = 46)	Control Group (n = 45)
<b>Age (years)</b>	31.3 ± 3.8	31.4 ± 4.7
<b>Weight (kg)</b>	95.3 ± 12.8	98.3 ± 14.2
<b>Height (cm)</b>	167.6 ± 5.9	167.1 ± 6.5
<b>BMI (kg/m<sup>2</sup>)</b>	33.9 ± 3.8	35.1 ± 4.6
<b>Weight classification</b>		
Overweight, BMI 28.0–29.9 kg/m <sup>2</sup>	3 (6.6%)	5 (11.1%)
Class 1 obesity, BMI 30.0–34.9 kg/m <sup>2</sup>	28 (62.2%)	19 (42.2%)
Class 2 obesity, BMI 35.0–39.9 kg/m <sup>2</sup>	11 (24.4%)	15 (33.3%)
Class 3 obesity, BMI ≥ 40.0 kg/m <sup>2</sup>	3 (6.6%)	6 (13.3%)
<b>Parity</b>		
0	22 (47.8%)	19 (42.2%)
1	19 (41.3%)	19 (42.2%)
2	5 (10.9%)	4 (8.9%)
≥3	0 (0.0%)	3 (6.7%)
<b>Current smoking</b>	2 (4.7%)	4 (8.9%)
<b>Education</b>		
Primary/secondary school	1 (2.3%)	3 (7.0%)
High school	15 (34.1%)	12 (27.9%)
University ≤4 y	14 (31.8%)	11 (25.6%)
University >4 y	14 (31.8%)	17 (39.5%)
<b>Currently employed</b>	38 (82.6%)	33 (73.3%)
<b>GDM</b>		
WHO 2009 definition*		
4 (8.7%)	4 (8.7%)	4 (8.9%)
WHO/IADPSG 2013 definition**		
8 (18.2%)	8 (18.2%)	13 (29.5%)
<b>Maternal hypertension</b>	3 (7.0%)	4 (9.5%)
<b>Body composition***</b>		
Fat mass (kg)	40.0 ± 7.7	44.1 ± 10.3
Fat mass (percent)	43.1 ± 3.8	44.8 ± 5.5
Fat-free mass (kg)	52.4 ± 5.6	53.3 ± 6.1
Fat-free mass (percent)	56.9 ± 3.8	55.2 ± 5.5
<b>Skinfold thickness</b>		
Biceps area (mm)	20.3 ± 8.9	22.3 ± 8.8
Triceps area (mm)	28.8 ± 7.0	31.2 ± 7.2
Subscapular area (mm)	30.5 ± 8.6	33.1 ± 7.9
<b>Blood pressure</b>		
Systolic blood pressure (mm Hg)	126.3 ± 20.9	127.9 ± 12.9
Diastolic blood pressure (mm Hg)	75.0 ± 10.0	78.0 ± 8.4
<b>Blood measurements</b>		
Fasting glucose (mmol/l)	4.6 ± 0.4	5.0 ± 0.8
120-min glucose (mmol/l)	6.2 ± 1.1	6.1 ± 1.6
Insulin (pmol/l)	158.3 ± 62.5	150.0 ± 70.8
HbA1c (percent)	5.2 ± 0.3	5.4 ± 0.4
Insulin C-peptide (nmol/l)	0.7 ± 0.7	0.7 ± 0.4
Triglycerides (mmol/l)	1.4 ± 0.4	1.5 ± 0.2
Ferritin (pmol/l)	147.4 ± 97.5	84.9 ± 49.4

(Continued)

Table 1. (Continued)

Baseline Characteristic	Exercise Group (n = 46)	Control Group (n = 45)
HDL cholesterol (mmol/l)	1.6 ± 0.3	1.8 ± 0.3
LDL cholesterol (mmol/l)	3.0 ± 0.9	3.0 ± 0.5
Total cholesterol (mmol/l)	5.0 ± 1.3	5.1 ± 1.2
Hemoglobin (g/l)	127.0 ± 100.0	126 ± 8.0
High-sensitivity CRP (mg/l)	8.4 ± 3.5	10.2 ± 5.0
HOMA2-IR	2.6 ± 1.2	2.5 ± 1.2

Observed data are presented as mean ± standard deviation or number of participants (percent). Missing: number of participants with missing data in each group is 0 to 3 for all variables except for body composition, where 14 are missing in the exercise group and 12 in the control group.

\*Fasting plasma glucose ≥ 7.0 mmol/l or 120-min plasma glucose ≥ 7.8 mmol/l.

\*\*Fasting plasma glucose ≥ 5.1 mmol/l or 120-min plasma glucose ≥ 8.5 mmol/l.

\*\*\*Body composition was measured by air displacement plethysmography (BOD POD).

doi:10.1371/journal.pmed.1002079.t001

### Gestational Weight Gain

We found no significant differences in GWG between the exercise group and the control group (Table 2). Body weight at delivery was self-reported by five women in the exercise group and four women in the control group. The proportion of women exceeding the IOM guidelines for recommended GWG was similar in the two groups (Table 3). Adjusting for gestational age in the analyses did not affect the GWG comparison between groups significantly (mean difference 0.56,  $p = 0.67$ ).

### Gestational Diabetes Mellitus

In late pregnancy, two women (6.1%) in the exercise group and nine women (27.3%) in the control group had developed GDM according to the WHO 2009 definition [27], with a statistical difference between groups ( $p = 0.04$ ; Table 3). According to the WHO/IADPSG 2013 definition of GDM [28], there was no significant difference between the groups (Table 3). There was no significant difference in fasting glucose, 120-min glucose, insulin, or HbA1c level between the groups (Table 2).

### Blood Pressure and Other Secondary Outcomes

In late pregnancy we found a significantly lower systolic blood pressure ( $p = 0.006$ ) in the exercise group compared to the control group (Table 2). There were no significant differences in other secondary outcome measures (Tables 2 and 3).

### Physical Activity

The proportion of women reporting to be physically active for at least 30 min each day in late pregnancy was equal in the two groups: 61% in the exercise group and 66% in the control group ( $p = 0.73$ ). The proportion of women reporting regular exercise training in late pregnancy was significantly higher in the exercise than in the control group: 77% and 23%, respectively ( $p < 0.01$ ).

### Per Protocol Analyses

In the exercise group, 50% of the women fulfilled the training intervention as described in the study protocol [23]. In the per protocol analyses, we found no significant difference in weight



**Table 2. Primary and secondary outcomes in late pregnancy and at delivery.**

Outcome at Late Pregnancy/Delivery	Baseline Mean	Exercise Group (n = 38)		Control Group (n = 36)		Between-Group Comparison		
		Final Mean	95% CI	Final Mean	95% CI	Mean Difference	95% CI	p-Value
<b>GWG (kg) (primary outcome)</b>		10.5	8.9, 12.0	9.2	6.8, 11.6	1.29	-1.58, 4.05	0.35
<b>Weight (kg)</b>	96.8	107.1	103.9, 110.3	106.1	102.9, 109.3	0.92	-1.35, 3.18	0.43
<b>BMI(kg/m<sup>2</sup>)</b>	34.5	37.4	36.4, 38.4	37.0	36.1, 38.0	0.35	-0.45, 1.15	0.85
<b>Body composition*</b>								
Fat mass (kg)	42.2	46.4	43.8, 49.0	45.0	42.4, 47.7	1.35	-0.98, 3.68	0.26
Fat mass (%)	44.0	43.7	42.5, 45.0	43.3	42.0, 44.6	0.43	-0.67, 1.52	0.45
Fat-free mass (kg)	53.0	57.7	56.0, 59.4	58.3	56.6, 60.0	-0.59	-2.28, 1.11	0.50
Fat-free mass (%)	55.8	56.5	55.2, 57.8	56.5	55.2, 57.8	-0.05	-1.17, 1.07	0.93
<b>Skinfold thickness</b>								
Biceps area (mm)	21.3	18.5	16.2, 20.8	18.3	15.9, 20.6	0.23	-2.42, 2.89	0.86
Triceps area (mm)	30.0	28.0	26.1, 29.8	29.8	28.0, 31.6	-1.82	-3.82, 0.17	0.07
Subscapular area (mm)	31.8	30.8	28.6, 33.0	31.0	28.8-33.2	-0.26	-2.63, 2.12	0.83
<b>Blood pressure</b>								
Systolic BP (mm Hg)	124.5	120.4	116.4, 124.3	128.1	124.0, 132.2	-7.73	-13.23, -2.22	0.006
Diastolic BP (mm Hg)	76.0	76.6	73.8, 79.3	80.2	77.3, 83.0	-3.61	-7.42, 0.20	0.06
<b>Blood measurements</b>								
Fasting glucose (mmol/l)	4.7	4.6	4.4, 4.8	4.5	4.3, 4.7	0.09	-0.20, 0.37	0.56
120-min glucose (mmol/l)	6.0	6.2	5.6, 6.7	5.8	5.3, 6.4	0.33	-0.44, 1.10	0.40
Insulin (pmol/l)	142.4	209.0	179.9, 238.2	208.4	177.1, 238.9	0.9	-39.4, 41.1	0.97
HbA1c (%)	5.2	5.4	5.3, 5.5	5.4	5.3, 5.5	-0.06	-0.20, 0.08	0.41
Insulin C-peptide (nmol/l)	0.6	0.7	0.6, 0.9	0.8	0.7, 1.0	-0.10	-0.31, 0.11	0.37
Triglycerides (mmol/l)	1.4	2.6	2.3, 2.9	2.4	2.0, 2.7	-0.25	-0.77, 0.13	0.24
Ferritin (pmol/l)	127.0	29.7	7.0, 52.4	37.7	14.8, 60.9	-8.20	-40.18, 23.64	0.62
HDL cholesterol (mmol/l)	1.7	1.6	1.5, 1.7	1.7	1.6, 1.8	-0.08	-0.22, 0.06	0.27
LDL cholesterol (mmol/l)	2.8	3.6	3.3, 3.8	3.6	3.4, 3.9	-0.06	-0.43, 0.30	0.73
Total cholesterol (mmol/l)	5.0	6.1	5.8, 6.5	6.4	6.0, 6.8	-0.28	-0.81, 0.25	0.30
Hemoglobin (g/l)	127.0	118.0	115.0, 120.0	117.0	114.0, 120.0	1.1	-2.9, 5.1	0.59
High-sensitivity CRP (mg/l)	10.7	6.6	4.4, 8.8	6.5	4.3, 8.7	0.09	-3.01, 3.18	0.96
HOMA2-IR	2.5	3.6	3.2, 4.1	3.7	3.2, 4.2	-0.04	-0.68, 0.59	0.90

Intention-to-treat model-based analyses with baseline mean (all participants), mean and 95% CI at late pregnancy/delivery for the exercise group and the control group, and comparison between groups presented as mean difference, 95% CI, and p-value. The mother's weight was measured and BMI calculated at delivery, the rest of the measurements were at gestational week 34–37. The number of participants with missing data in the exercise group varied between 0 and 5, in the control group between 0 and 3, for all variables except for body composition, where 12 participants in each group had missing data. The effect of treatment was assessed with linear mixed models. For the primary and secondary outcomes, the effect of time and treatment was taken as a fixed effect. Due to randomization, there were no systematic differences between groups at baseline. To account for repeated measurements, participant ID was included as a random effect.

\*Body composition was measured by air displacement plethysmography (BOD POD).

BP, blood pressure.

doi:10.1371/journal.pmed.1002079.t002

gain and mean weight at delivery between the per protocol exercise group and the control group (S1 Table). Resting systolic and diastolic blood pressure were significantly lower in the per protocol exercise group (115.7 mm Hg/75.1 mm Hg) compared to the control group (128.1 mm Hg/80.2 mm Hg), with  $p = 0.001$  and  $p = 0.02$ , respectively. A tendency toward lower incidence of GDM (5.9% in the per protocol exercise group, 27.3% in the control group,  $p = 0.11$ ) and maternal hypertension (11.1% in the per protocol exercise group, 21.2% in the control group,  $p = 0.14$ ) was seen in the per protocol exercise group (S2 Table).

**Table 3. Secondary outcomes in late pregnancy and at delivery.**

Outcome at Late Pregnancy/Delivery	Exercise Group (n = 38), n (Percent)	Control Group (n = 36), n (Percent)	Between-Group Comparison		
			Odds Ratio	95% CI	p-Value
<b>GDM</b>					
WHO 2009 definition*	2 (6.1)	9 (27.3)	0.1	0.016, 0.949	0.04
WHO/IADPSG 2013 definition**	5 (14.7)	8 (24.2)	0.5	0.126, 2.349	0.42
<b>Maternal hypertension</b>	3 (9.1)	7 (22.6)	0.2	0.019, 1.976	0.17
<b>GWG greater than IOM recommendations</b>	21 (58.3)	16 (44.4)	0.6	0.225, 1.453	0.35

Intention-to-treat analysis based on observed data for the exercise and the control group and comparison between groups are presented as number of participants (percentage), odds ratio, 95% CI, and p-value. The analyses of GDM and hypertension were done on the basis of blood tests and blood pressure measurements in late pregnancy. The analysis of GWG relative to IOM recommendations was done on the basis of weight measurements at delivery. The number of participants with missing data in the exercise group varied between 0 and 5, in the control group between 0 and 3. Data were analyzed by a mixed logistic regression model.

\*Fasting plasma glucose  $\geq$  7.0 mmol/l or 120-min plasma glucose  $\geq$  7.8 mmol/l.

\*\*Fasting plasma glucose  $\geq$  5.1 mmol/l or 120-min plasma glucose  $\geq$  8.5 mmol/l.

doi:10.1371/journal.pmed.1002079.t003

## Adverse Events

No adverse events were reported during the exercise training or study assessments (Table 4).

## Discussion

### Main Findings

We found no difference in GWG between women randomized to an exercise training program versus standard maternity care, but found an apparent reduction in the incidence of GDM and lower systolic blood pressure in late pregnancy among the women randomized to the exercise training program. In the per protocol analyses including only the women who had adhered to the exercise program (n = 19), exercise training also seemed to reduce diastolic blood pressure in late pregnancy.

### Gestational Weight Gain

Our findings of no difference in GWG and body composition between groups are in line with several other clinical trials on overweight or obese pregnant women [14–16,32–34]. However, a systematic review by Sui and Dodd [20] that included 216 participants (five randomized trials) found that supervised exercise interventions were associated with lower GWG among overweight or obese pregnant women. But the trials included in this systematic review differed with

**Table 4. Abortions, premature deliveries, and other adverse events occurring during follow-up.**

Adverse Event	Exercise Group (n = 46)	Control Group (n = 45)
Abortion before gestational week 22	3 (6.5%)	3 (6.7%)
Delivery before gestational week 37	1 (2.2%)	1 (2.2%)
Other adverse events	0	0

Data are presented as number (percent).

doi:10.1371/journal.pmed.1002079.t004

respect to the type and duration of exercise, and a clinically relevant difference in weight gain was not precalculated. Also Barakat et al. [35] and Haakstad and Bø [36] found significantly lower GWG among women who participated in supervised exercise during pregnancy. However, these two studies included women from all weight classes, and their findings might not translate specifically to overweight/obese women. We can only speculate about why there was no difference in GWG between the two groups in the ETIP study. The proportion of women whose self-reported activity level fulfilled the recommended 30 min of daily physical activity in late pregnancy was higher in the exercise group, but some of the women in the control group exercised on their own. Only 50% of the women in the exercise group adhered to the exercise protocol as prescribed a priori [23]. A possible effect of regular exercise during pregnancy may have been missed in our study due to the relatively low adherence to the training protocol. Protocol adherence is a challenge in all exercise studies. We tried to improve adherence by offering motivational talks throughout the intervention period, as well as adjusting the training times so that more women would be able to attend. The low adherence may have been due to pregnancy symptoms such as tiredness and nausea, limited previous experience with exercise training, or difficulties in prioritizing time for exercise. Furthermore, the intervention protocol might have been too comprehensive for these women. Further studies should carefully consider how exercise adherence can be obtained in this population.

Although the exercise training program in our study followed the current recommendations for exercise in pregnancy, it is possible that the exercise frequency and/or intensity of our program were not sufficient to affect the outcome measures related to weight gain. As our study population had a relatively low fitness level, the amount of energy spent during the exercise sessions was rather low (~400 kcal/session) and was probably not sufficient to affect the energy balance significantly. It is also possible that some of the women in the exercise group compensated for energy expenditure during the exercise sessions either by decreasing their physical activity level during the remaining time of the week [37] or by increasing their energy intake [38]. According to three recent meta-analyses [32,39,40], interventions combining physical activity and diet have proven effective in reducing GWG in overweight and obese women. We did not include any dietary advice or intervention in our study, and probably exercise training alone is not sufficient to reduce GWG in this population.

Changes in body composition throughout pregnancy might be an important determinant of glucose metabolism. Few studies have assessed body composition changes after exercise in pregnancy. Our findings of no significant differences between groups in body composition in late pregnancy are in line with a recent RCT on the effects of a 16-wk moderate intensity cycling program in overweight and obese pregnant women [33].

### Gestational Diabetes Mellitus

Our finding of an apparently lower incidence of GDM according to the WHO 2009 definition [27] among the women in the exercise group is in line with a recent meta-analysis of 13 RCTs [22] that concluded that structured moderate intensity exercise programs during pregnancy decrease the risk of GDM. However, two previous Cochrane reviews, one on exercise as the sole intervention [19] and one on both diet and exercise interventions [41], concluded that there is no clear GDM risk reduction after exercise training. Nobles et al. [42] randomized 251 women with increased risk of GDM to either exercise training or a comparison health and wellness group and found no reduction in GDM risk after exercise, in line with another previous review [20]. The recently published DALI Lifestyle Pilot study [43] found that women with BMI  $\geq 29$  kg/m<sup>2</sup> randomized to a healthy eating intervention had significantly lower fasting glucose and 2-h insulin concentrations than women in an exercise only group. In contrast to

the DALI study, our results indicate that exercise training alone may be sufficient to prevent glucose intolerance in overweight or obese pregnant women. An important difference between the DALI study and ours is that the exercise training was supervised in our study.

Using the WHO/IADPSG 2013 definition [28] of GDM in the ETIP study, the number of GDM cases increased in both groups, and there was no longer a significant difference between the groups. The WHO/IADPSG 2013 definition is mainly based on the HAPO study (2008) [44], which found strong associations between glucose levels below the WHO 2009 diagnostic definitions and adverse outcomes for both mother and child. However, a retrospective cohort study [45] that included 1,892 women diagnosed with GDM according to the WHO/IADPSG 2013 definition found a significantly higher risk for adverse pregnancy outcomes in those who also would be diagnosed as having GDM according to the WHO 2009 definition.

Despite the difference between the exercise and control groups in GDM incidence, we found no differences between the groups at late pregnancy in glucose levels, insulin, or HOMA2-IR. One possible reason for this finding is that women with high risk of GDM may respond differently to exercise training than women with lower risk [46], such that the average glucose and insulin levels are not sufficiently affected to obtain a difference between groups.

### Blood Pressure

We found a significantly lower systolic blood pressure among the women in the exercise group in late pregnancy, compared to the women in the control group. Diastolic blood pressure did not differ between groups in late pregnancy in the intention-to-treat analysis, but was significantly lower in the exercise group in the per protocol analysis. High blood pressure in pregnancy is associated with increased risk for preeclampsia [47] and thus is important to prevent. To our knowledge, only one previous RCT [33] has studied the effect of exercise training in pregnancy on exact blood pressure measurements among overweight/obese women. Seneviratne et al. [33] found no effect of exercise training on blood pressure in late pregnancy. Other studies that have assessed the effects of exercise on maternal hypertension risk have assessed hypertension as a dichotomous variable [34,35,39]. Some of these studies found no effect of exercise [17,34], but one study [35] found a reduced incidence of maternal hypertension after exercise training. The latter study included both normal weight, overweight, and obese women. Although fewer women in the exercise group than in the control group had hypertension in late pregnancy in our study, the difference was not statistically significant. Further studies are needed to ascertain whether exercise training can prevent hypertensive pregnancies in overweight/obese women.

### Generalizability

The ETIP study had few exclusion criteria, and the participants were representative of Norwegian women with BMI  $\geq 28$  kg/m<sup>2</sup> regarding age, parity, and education. However, participants had to have time available for the testing and training. The exercise group was offered training sessions at day and evening times. It is also possible that the participants volunteering for the ETIP study were extra aware of the possible beneficial effects of exercise training in pregnancy and thus were motivated to participate in our trial.

### Clinical Relevance

Obese women have elevated risk of GDM and maternal hypertension; thus, finding effective prevention strategies is highly relevant. The study revealed no adverse events related to moderate physical activity during pregnancy. The effect of exercise training to reduce

weight gain may most likely be improved with additional dietary interventions. During the study we experienced difficulties in motivating the women in the exercise group to adhere to the training program, despite supervised training sessions at St. Olavs Hospital, training sessions at different times during the week, and individually adjusted exercises. We think further studies should evaluate how supervised exercise programs for obese women can be implemented in the health care system, as well as how to obtain good adherence to such programs.

### Strengths

In our study, exercise training was the only intervention provided. This makes it easier to assess the isolated effects of exercise on pregnancy outcomes. The training program being standardized and supervised makes it easy to reproduce. Furthermore, we had thorough recording of exercise adherence as well as physical activity levels in the two groups. The primary outcome measure (GWG) was assessed by personnel blinded for group allocation. We also regard the assessment of body composition with the gold standard method of air displacement plethysmography as a strength.

### Limitations

The main limitation of the trial was the reduced statistical power because we were able to include only 2/3 of the 150 participants estimated in the power calculation. We analyzed 30 different secondary outcomes among a limited number of women, and thereby increased the risk for detecting differences between groups by chance, and making type 1 errors. Furthermore, only 50% of the participants in the exercise group performed the exercise training program per protocol, which makes it more difficult to detect possible effects of the intervention. However, adherence to exercise in the ETIP study was similar to that in most of the comparable clinical studies. Care must be taken in interpreting the results from the per protocol analysis. Such analyses could be selection biased if the reasons influencing compliance with the exercise training program are associated with prognostic factors [48].

### Conclusion

In this trial we did not observe a reduction of GWG or an improvement in body composition among overweight/obese women who were offered supervised exercise training during pregnancy. However, exercise training seemed to reduce the incidence of GDM as well as systolic blood pressure in late pregnancy. As exercise adherence is a major challenge in this population, there is a special need to find methods to reduce participant attrition in future studies.

### Supporting Information

**S1 Data. Participant characteristics and outcomes in late pregnancy.**  
(SAV)

**S2 Data. Physical activity in early pregnancy.** Part of a questionnaire.  
(SAV)

**S3 Data. Physical activity in late pregnancy.** Part of a questionnaire.  
(SAV)

**S1 Table. Outcome measurements comparing participants in the exercise group who adhered to the training protocol with the control group.** Supplementary material, per

protoco1. Secondary outcomes in late pregnancy and at delivery.  
(DOCX)

**S2 Table. Outcome measurements comparing participants in the exercise group who adhered to the training protocol with the control group—binary data.** Supplementary material, per protoco1. Secondary outcomes in late pregnancy and at delivery.  
(DOCX)

**S1 Text. Trial protocol.**  
(DOCX)

**S2 Text. CONSORT statement.**  
(DOC)

**S3 Text. Information given to the participants in the ETIP study.**  
(DOCX)

**S4 Text. Information given to the participants in the exercise group.**  
(DOC)

**S5 Text. Exercise recording form for training sessions at St. Olavs Hospital.**  
(DOC)

**S6 Text. Exercise program for training sessions at St. Olavs Hospital.**  
(DOC)

**S7 Text. Exercise recording form for training and physical activity at home.**  
(PDF)

**S8 Text. Home-based exercise program.**  
(DOC)

**S9 Text. Questionnaire regarding general physical activity at baseline.**  
(PDF)

**S10 Text. Questionnaire regarding general physical activity at late pregnancy.**  
(PDF)

**S11 Text. Funding: the Norwegian Fund for Post-Graduate Training in Physiotherapy.**  
(DOCX)

**S12 Text. Funding: the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU).**  
(PDF)

**S13 Text. Biobank approval.**  
(DOC)

**S14 Text. The Regional Committee for Medical and Health Research Ethics (REK midt) approval.**  
(PDF)

## Author Contributions

Conceived and designed the experiments: SM TM. Performed the experiments: KKG TM. Analyzed the data: KKG ØS. Contributed reagents/materials/analysis tools: TM KKG. Wrote the first draft of the manuscript: KKG. Contributed to the writing of the manuscript: KKG TM SM

ØS. Enrolled patients: KKG TM. Agree with the manuscript's results and conclusions: KKG TM SM ØS. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

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*SI Table. Supplementary material, per protocol. Primary and secondary outcomes in late pregnancy and at delivery. “Per protocol” model based analyses with baseline mean (all participants, final mean and 95% CI for the “per protocol” group and the control group, and comparison between groups presented by mean difference, 95% CI and p-value. Weight is calculated at delivery, the rest of the measurements are at gestational week 34-37.*

	Baseline mean	Per protocol Exercise group (n = 19)		Control group (n = 36)		Between-groups comparisons		
		Final mean	95% CI	Final mean	95% CI	Mean diff	95% CI	P
<i>Primary</i>								
Weight (kg)	96.3	106.2	102.2, 110.2	105.7	102.1, 109.4	0.52	-2.38, 3.42	0.73
Weight gain (kg)		9.9	7.5, 12.3	9.4	7.7, 11.1			
<i>Secondary</i>								
Body mass index (BMI)	34.6	37.4	36.1, 38.6	37.1	36.0, 38.2	0.28	-0.73, 1.29	0.59
<b>Body composition*</b>								
Fat mass kg	42.0	46.1	42.7, 49.5	44.9	41.9, 47.8	1.25	-1.80, 4.30	0.42
Fat mass %	44.1	43.0	41.4, 44.6	43.3	41.9, 44.8	-0.35	-1.64, 0.94	0.60
Fat free mass kg	52.5	58.5	56.4, 60.6	57.8	56.1, 59.6	0.65	-1.18, 2.48	0.49
Fat free mass %	55.9	57.0	55.4, 58.6	56.7	55.2, 58.1	0.35	-0.94, 1.64	0.60
<b>Skinfold thickness:</b>								
Biceps area	21.5	18.4	15.2, 21.5	18.4	15.8, 20.9	0.02	-3.32, 3.37	0.99
Triceps area	30.0	28.8	26.4, 31.3	29.8	27.8, 31.9	-1.00	-3.47, 1.47	0.43
Scapulae area	32.1	30.6	27.7, 33.6	31.3	28.9, 33.7	-0.64	-3.70, 2.42	0.68
<b>Blood pressure (BP)</b>								
Systolic BP (mmHg)	124.4	115.7	110.0, 121.5	128.1	123.6, 132.5	-12.4	-19.44, -5.25	0.001
Diastolic BP (mmHg)	76.0	75.1	71.6, 78.7	80.2	77.4, 82.9	-5.1	-9.39, -0.72	0.02
<b>Blood measurements</b>								
Fasting glucose (mmol/L)	4.8	4.5	4.2, 4.8	4.5	4.3, 4.8	-0.04	-0.42, 0.34	0.83
120 min glucose (mmol/L)	6.0	6.3	5.5, 7.1	5.8	5.3, 6.4	0.48	-0.50, 1.46	0.33
Insulin (pmol/L)	136.8	200.7	163.9, 237.5	205.6	177.1, 234.7	-4.9	-50.6, 40.8	0.83
HBA1c (%)	5.2	5.4	5.3, 5.5	5.4	5.3, 5.5	0.03	-0.21, 0.14	0.72
Insulin C-peptide (nmol/L)	0.6	0.9	0.7, 1.1	0.8	0.7, 1.0	0.04	-0.18, 0.27	0.71
Triglycerides (mmol/L)	1.4	2.8	2.4, 3.2	2.4	2.0, 2.7	0.41	0.13, 0.96	0.13
Ferritin (pmol/L)	117.3	25.8	0.45, 51.23	34.6	16.0, 53.3	-8.70	-40.20, 22.80	0.59
HDL cholesterol (mmol/L)	1.7	1.6	1.5, 1.8	1.7	1.6, 1.8	-0.09	-0.25, 0.07	0.29
LDL cholesterol (mmol/L)	2.9	3.5	3.1, 3.9	3.6	3.4, 3.9	-0.14	-0.58, 0.29	0.52
Cholesterol (mmol/L)	5.0	5.8	5.3, 6.3	6.4	6.0, 6.8	-0.64	-1.28, 0.00	0.05
Hemoglobin (g/L)	127.0	117.0	113.0, 120.0	117.0	114.0, 120.0	-0.1	-4.2, 4.3	0.97
High sensitive CRP (mg/L)	10.7	6.2	3.1, 9.4	6.5	4.2, 8.8	-0.29	-4.15, 3.57	0.88
HOMA2-IR	2.4	3.5	2.9, 4.1	3.6	3.2, 4.1	-0.19	-0.92, 0.53	0.60
<p><b>Missing:</b> Number of missing in the “per protocol” group varies between 0 and 5, in the control group between 0 and 3, except for body composition where there were 6 missing in the exercise group and 12 in the control group.</p> <p><b>Statistics:</b> The effect of treatment was assessed with linear mixed models. For the primary and secondary outcomes, the effect of time and treatment was taken as a fixed effect. Due to randomization, there are no systematic differences between groups at baseline. To account for repeated measurements, participant ID was included as a random effect.</p> <p><b>Abbreviations:</b> HDL: High density lipoprotein, LDL: Low density lipoprotein, HBA1c: Glycated hemoglobin, CRP: C-reactive protein, HOMA2IR: Homeostatic Model Assessment of insulin resistance.</p> <p>* Body composition was measured by air displacement plethysmography (BOD POD).</p>								

S2 Table. Supplementary material, per protocol. Secondary outcomes in late pregnancy and at delivery. “Per protocol” analysis based on observed data for the per protocol exercise and the control group and comparison between groups are presented in number of participants (N), percentage (%), odd ratio (OR), 95% confidence interval (CI), and p-value. Analyses of gestational diabetes mellitus and hypertension were done on basis of blood tests and blood pressure measurements at late pregnancy. Analyses of weight gain according to IOM recommendations were done one basis of weight measurements at delivery.

Outcomes late pregnancy/delivery	Per protocol Exercise group N = 19 n (%)	Control group N = 36 n (%)	Between groups comparisons		
			Odds Ratio	95% CI	P- value
Gestational diabetes mellitus					
WHO 2009*	1 (5.9)	9 (27.3)	0.1	0.007, 1.675	0.11
WHO/IADPSG 2013**	2 (13.9)	8 (27.3)	0.4	0.057, 2.597	0.33
Maternal hypertension	1 (11.1)	7 (21.2)	0.8	0.003, 2.294	0.14
>IOM recommendations	11 (57.9)	16 (44.4)	1.7	0.559, 1.529	0.40
<p><b>Missing:</b> Number of missing in the exercise varies between 0 and 2, in the control group between 0 and 3.  <b>Statistics:</b> Data were analyzed by Mixed logistic regression.  <b>Abbreviations:</b> WHO: World Health Organization. IADPSG: The International Association of the Diabetes and Pregnancy Study Groups, IOM: The Institute of Medicine recommendations for weight gain during pregnancy for overweight or obese women.  <b>*Definition:</b> Fasting plasma glucose <math>\geq 7.0</math> mmol/L, or 2 h concentration <math>\geq 7.8</math> mmol/L.  <b>**Definition:</b> Fasting plasma glucose <math>\geq 5.1</math> mmol/L, or 2 h <math>\geq 8.5</math> mmol/L.</p>					

## Paper II



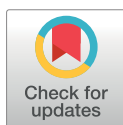
RESEARCH ARTICLE

# Effect of supervised exercise training during pregnancy on neonatal and maternal outcomes among overweight and obese women. Secondary analyses of the ETIP trial: A randomised controlled trial

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**Citation:** Garnæs KK, Nyrnes SA, Salvesen KÅ, Salvesen Ø, Mørkved S, Moholdt T (2017) Effect of supervised exercise training during pregnancy on neonatal and maternal outcomes among overweight and obese women. Secondary analyses of the ETIP trial: A randomised controlled trial. *PLoS ONE* 12(3): e0173937. <https://doi.org/10.1371/journal.pone.0173937>

**Editor:** Rebecca A. Krukowski, University of Tennessee Health Science Center, UNITED STATES

**Received:** December 22, 2016

**Accepted:** February 27, 2017

**Published:** March 21, 2017

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**Data Availability Statement:** All relevant data are within the paper and its Supporting Information files.

**Funding:** The present trial was supported by grants from The Liaison Committee between the Central Norway Regional Health Authority (RHA) (To author KKG, grant number: 46056728) and the Norwegian University of Science and Technology (NTNU), and The Norwegian Fund for Post-

## Abstract

### Background

Maternal obesity associates with complications during pregnancy and childbirth. Our aim was to investigate if exercise during pregnancy in overweight/obese women could influence birth weight or other neonatal and maternal outcomes at delivery.

### Material and methods

This is a secondary analysis of a randomised controlled trial of exercise training in pregnancy for women with body mass index (BMI)  $\geq 28$  kg/m<sup>2</sup>. Ninety-one women (31.3  $\pm$  4.3 years, BMI 34.5  $\pm$  4.2 kg/m<sup>2</sup>) were allocated 1:1 to supervised exercise during pregnancy or to standard care. The exercise group was offered three weekly training sessions consisting of 35 minutes of moderate intensity walking/running followed by 25 minutes of strength training. Data from 74 women (exercise 38, control 36) were analysed at delivery.

### Results

Birth weight was 3719  $\pm$  695 g in the exercise group and 3912  $\pm$  413 g in the control group (CI -460.96, 74.89,  $p = 0.16$ ). Birth weight > 4000 g was 35% in the exercise group and 52% in the control group ( $p = 0.16$ ). Mean gestational age at delivery was 39.1 weeks in the exercise group and 39.5 weeks in the control group (CI -1.33, 0.43,  $p = 0.31$ ). No significant between-group differences were found in neonatal body size, skinfold thickness, placental weight ratio, or Apgar score. The prevalence of caesarean section was 24% in the exercise group and 17% in the control group (CI 0.20, 2.05,  $p = 0.57$ ). Mean length of hospital stay was 4.8 days in the exercise group and 4.5 days in the control group (CI -0.45, 1.00,  $p = 0.45$ ).

Graduate Training in Physiotherapy (To author SM, grant number: 7-370-00/08A). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

## Conclusions

Offering supervised exercise during pregnancy for overweight and obese women did not influence birth weight or other neonatal and maternal outcomes at delivery. However our trial was limited by low sample size and poor adherence to the exercise protocol, and further research is needed.

## Trial registration

ClinicalTrials.gov [NCT01243554](https://clinicaltrials.gov/ct2/show/study/NCT01243554)

## Introduction

The prevalence of maternal overweight and obesity is increasing [1] and has important consequences for the health of mother and child at delivery [2]. The World Health Organization (WHO) classifies overweight as body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>, and obesity as BMI  $\geq 30$  kg/m<sup>2</sup> [3]. Overweight and obesity in pregnancy is associated with adverse neonatal outcomes as high birth weight [4], preterm birth, perinatal death, congenital anomalies, birth trauma related to macrosomia, and transfer to neonatal intensive care unit (NICU) [5, 6]. Adverse outcomes for the mother at delivery include need for caesarean section and prolonged hospital stay [5, 7–9]. Furthermore, overweight and obese pregnant women are at increased risk for reduced insulin sensitivity and subsequently high levels of circulating glucose in the foetus [10–13]. This can lead to foetal overgrowth and macrosomia (birth weight  $\geq 4000$  g) and is associated with adverse obstetrical outcomes [14] childhood obesity, and cardiometabolic diseases later in life [10–13, 15, 16]. Long-term consequences of these adverse outcomes have led to an increased attention towards maternal obesity as a contributing factor to the developmental origins of health and disease [11, 17].

Previous studies have reported positive effects of lifestyle interventions combining diet and exercise on some delivery-related outcomes in normal weight women, including reduced risks of preeclampsia, shoulder dystocia and preterm birth [18]. However, the effect of lifestyle interventions in pregnancy on birth weight, gestational age, rates of caesarean section, and transfer to NICU are still unclear [18–21]. Wiebe et al. [22] found in a meta-analysis that supervised prenatal exercise reduced neonatal birth weight and caesarean delivery among women with BMI  $\leq 24.9$ . Previous studies have reported limited effect of lifestyle interventions on maternal or neonatal outcomes at delivery in overweight and obese women [19, 23–25].

We have previously published data from a randomised controlled trial of exercise training in pregnancy for women with BMI  $\geq 28$  kg/m<sup>2</sup>, addressing effects of regular exercise on gestational weight gain and several secondary outcomes in late pregnancy [26]. In the present paper we report secondary analyses of maternal and neonatal outcomes at delivery. We aimed to investigate the effect of regular exercise during pregnancy on birth weight, and hypothesised that the birth weight in the exercise group would be lower compared to the control group. In addition, we investigated possible effects of exercise training on neonatal outcomes such as body composition, Apgar score, placental weight ratio, preterm birth and admission to neonatal intensive care unit, and maternal outcomes such as mode of delivery, perineal tears and length of hospital stay.

## Materials and methods

### Trial design

The Exercise Training in Pregnancy (ETIP) trial was a single centre, parallel group randomised controlled trial. The trial included women with pre-pregnancy BMI  $\geq 28$  kg/m<sup>2</sup>. The trial was

carried out at The Norwegian University of Science and Technology, NTNU, and St. Olavs Hospital, University Hospital in Trondheim, Norway, with participant recruitment from September 2010 to March 2015. The trial was approved by the Regional Committee for Medical and Health Research Ethics (REK midt 2010/1522), and registered in ClinicalTrials.gov (NCT01243554). The protocol and the results from primary outcomes in the trial have been published previously [26, 27].

We made changes to the study protocol after commencement of the trial [26]. In November 2012 the criterion for maximum inclusion time gestational week 16 was changed to gestational week 18, and in March 2013 the inclusion criterion pre-pregnancy BMI  $\geq 30$  kg/m<sup>2</sup> was changed to BMI  $\geq 28$  kg/m<sup>2</sup>. The changes were done to accommodate slow recruitment in the trial, and the revised study protocol was approved by the Regional Committee for Medical and Health Research Ethics.

## Participants

Inclusion criteria were pre-pregnancy BMI  $\geq 28$  kg/m<sup>2</sup>, age  $\geq 18$  years, carrying a singleton viable foetus at 11–14 gestational weeks. Also, the women had to be able to visit St. Olavs Hospital for assessments and exercise sessions. Data on pre-pregnancy BMI was based on self-reported weight and height. Exclusion criteria were diseases affecting participation [28], high risk for preterm delivery [28], and regularly exercise training (twice or more weekly) in the period before inclusion. The procedures were in accordance to ethical standards of research and the Helsinki Declaration. Women were recruited through Google advertisements and by notices enclosed with invitations for routine ultrasound scans at St. Olavs Hospital. At the time of recruitment and before randomisation and participation, the women received written information and signed an informed consent.

## Intervention

All participants received standard maternity care, and women in the control group were not discouraged from physical activity. Women in the exercise group were offered supervised exercise sessions at St. Olavs Hospital three times weekly from early pregnancy until delivery. The exercise program was in accordance with the recommendations from the American College of Obstetricians and Gynaecologists [29]. The exercise sessions were supervised by a physical therapist and lasted for 60 min, and consisted of 35 min of walking/jogging on a treadmill for (endurance training), and 25 min of resistance training for large muscle groups and the pelvic floor muscles [26, 27]. The intensity of the endurance training was moderate, set to ~80% of maximal capacity (corresponding to Borg scale 12–15) [30]. The resistance training was with use of own body weight and consisted of squats, diagonal lifts on all fours, push-ups, oblique abdominal crunches and the “plank exercise”. Each exercise was performed as three sets of ten repetitions separated by a 1-min rest between sets; the “plank exercise” was performed in 30 sec. The pelvic floor exercises consisted of three sets of ten repetitions of pulling the pelvic floor up and holding the contraction for 6–8 s. The exercise program and load were individually adjusted when needed.

In addition to the supervised program women were asked to do a 50 minutes home exercise program twice weekly and to do pelvic floor muscle exercises every day. Adherence to the exercise program was registered in a training diary. The participants in the exercise group received a weight gain curve of recommended weight gain during pregnancy according to the 2009 Institute of Medicine recommendations [31]. The intervention group received no dietary advice, but both groups received a standard brochure at inclusion with information about healthy living during pregnancy.



## Outcomes

Baseline assessments were undertaken in gestational week 12–18 (early pregnancy). Neonatal and maternal outcomes in the current article were assessed at delivery and during the maternity stay at the hospital.

Birth weight was the principal outcome in this secondary analysis. Other neonatal outcomes were birth weight > 4000 g, head circumference, length, body surface area (BSA), skinfold thickness, abdominal and upper arm circumference, gestational age, Apgar score at 1 and 5 minutes, placental weight and placental weight ratio (PWR), and transfer to Neonatal Intensive Care Unit (NICU). Maternal outcomes were mode of delivery, preterm birth, preeclampsia, perineal tears, and duration of hospital stay.

Birth weight was measured at delivery by a Seca baby weight (Medema, Norway) by the birth attendants. We measured skinfold thickness by a Harpenden Skinfold Calliper (Holtain, Ltd, UK), on the right side of the body at the following sites; subscapularis; at the bottom of the angelus inferior scapula, triceps; at the middle between the olecranon and the humeral head. We used a measuring tape to measure abdominal and upper arm circumference. The abdomen was measured at the level of umbilicus and the upper arm at the middle between olecranon and humeral head. Skinfold thickness and circumference measurement were undertaken by the first author (KKG).

Mode of delivery, perineal tears, hospital stay, new-born length, head circumference, gestational age, Apgar score, placenta weight, and transfer to NICU were recorded in the hospital records. We calculated BMI of the newborn as weight in kilograms divided by the square of height in meters, and Body Surface Area (BSA, in m<sup>2</sup>) by the Mosteller Formula as (height (cm) x weight (kg) /3600)<sup>1/2</sup> [32]. We calculated the ratio of birth weight and placental weight (placental weight ratio, PWR) as placenta weight divided by birth weight. We defined preterm birth as delivery before gestational week 37.

## Sample size

We calculated the sample size in the ETIP trial based on the primary outcome; gestational weight gain from baseline to delivery [26]. We assumed a 6 kg mean difference between groups as clinically relevant [33, 34]. A two-sided independent sample *t*-test with a 5% level of significance, a standard deviation of 10, and a power of 0.9 gave a target study population of 59 in each group. We estimated the dropout to be 15% and aimed to include 150 women. We did not do an *a priori* sample size calculation for the outcomes reported in this paper, but we did a post-hoc power calculation on birth weight. Based on previous trials [35, 36], we considered a mean difference in birth weight 250 g clinically relevant, based on previous studies. With standard deviation of 430 g, alpha 0.05 and beta 0.2, we would have needed 94 participants in the trial to demonstrate a difference in birth weight between groups.

## Randomisation and allocation

Trial participants were randomised 1:1 to exercise or control groups after baseline assessments. We used a computer random number generator developed and administrated at the Unit for Applied Clinical Research at NTNU to generate the random allocation sequence, as previously detailed [26].

## Blinding

Birth attendants were blinded for group allocation. Measurements of skinfold thickness, abdominal circumference, and intervention administration were done non-blinded by the

investigators. The first author (KKG) was not blinded for group allocation as she supervised the exercise training. The statistician was blinded for group allocation.

## Statistical methods

The principal analyses were based on the intention to treat principle and all available data were used at all time points. Continuous data were tested for normality, and we used independent samples t-tests to assess the effect of the intervention. We used the Fisher's Exact Test or Pearson Chi Square Test to analyse effects of the intervention on dichotomous outcomes, with the exercise group as the reference group. Due to the randomisation model, we assumed no systematic differences between groups at baseline, however differences between groups at baseline were tested [26].

We performed supplementary analyses where we adjusted for gestational age and parity. We also analysed the association between BMI at early pregnancy and the variables birth weight and risk for caesarean delivery.

In addition to the primary analyses, we performed per protocol analyses where we compared women in the exercise group adhering to the exercise protocol with the control group [27]. Exercise per protocol was defined as one of the following: 1) attending  $\geq 42$  organized exercise sessions, 2) attending  $\geq 28$  exercise sessions + performing  $\geq 28$  home exercise sessions, or 3) performing  $\geq 60$  home exercise sessions. To count as a home session, the exercise had to be  $\geq 50$  minutes of either aerobic and/or strength training.

For the statistical analyses, we used IBM SPSS Statistics 23 for outcomes at delivery. Baseline demographic characteristics were analysed by Stata version 13.1. Supplementary analysis including adjustments and associations were analysed by R version 2.13.1. In comparison between groups we report mean values with 95% confidence intervals, for the continuous variables and odds ratios with 95% confidence intervals for dichotomous variables. We considered  $p$ -values  $< 0.05$  as significant.

## Results

Fig 1 shows the participant flow in the ETIP trial. Complete baseline data has been previously published [26]. No differences between groups at baseline were found, except from significant lower fasting glucose in the exercise group, 4.6 mmol/l vs 5.0 mmol/l,  $p = 0.02$  [26]. Mean pre-pregnancy (self-reported) BMI was  $33.9 \pm 3.8$  kg/m<sup>2</sup> in the exercise group, and  $35.1 \pm 4.6$  kg/m<sup>2</sup> in the control group. Mean gestational weight gain was 10.5 kg in the exercise group, and 9.2 kg in the control group ( $p = 0.35$ ). Fifty-eight percent of the women in the exercise group, and 44% of the women in the control group, gained more weight than recommended by the IOM guidelines.

Seventy-four women (exercise 38, control 36) were included in the analyses at delivery. Two women in the exercise group (BMI 29.7 and 28.3 kg/m<sup>2</sup>), and three women in the control group (BMI 29.4, 28.8 and 29.7 kg/m<sup>2</sup>), were classified as overweight at baseline. All other women had a pre-pregnancy BMI  $\geq 30$  kg/m<sup>2</sup>, and were classified as obese. Fifty percent of women in the exercise group and 38% in the control group were nulliparous ( $p = 0.18$ ). Women in the intervention group performed  $31.7 \pm 15.3$  (range 0–53) supervised sessions at the hospital and  $19.2 \pm 16.5$  (range 0–72) exercise sessions at home.

## Neonatal outcomes

We found no significant differences in birth weight or other neonatal outcomes at delivery between the exercise group and the control group (Table 1).

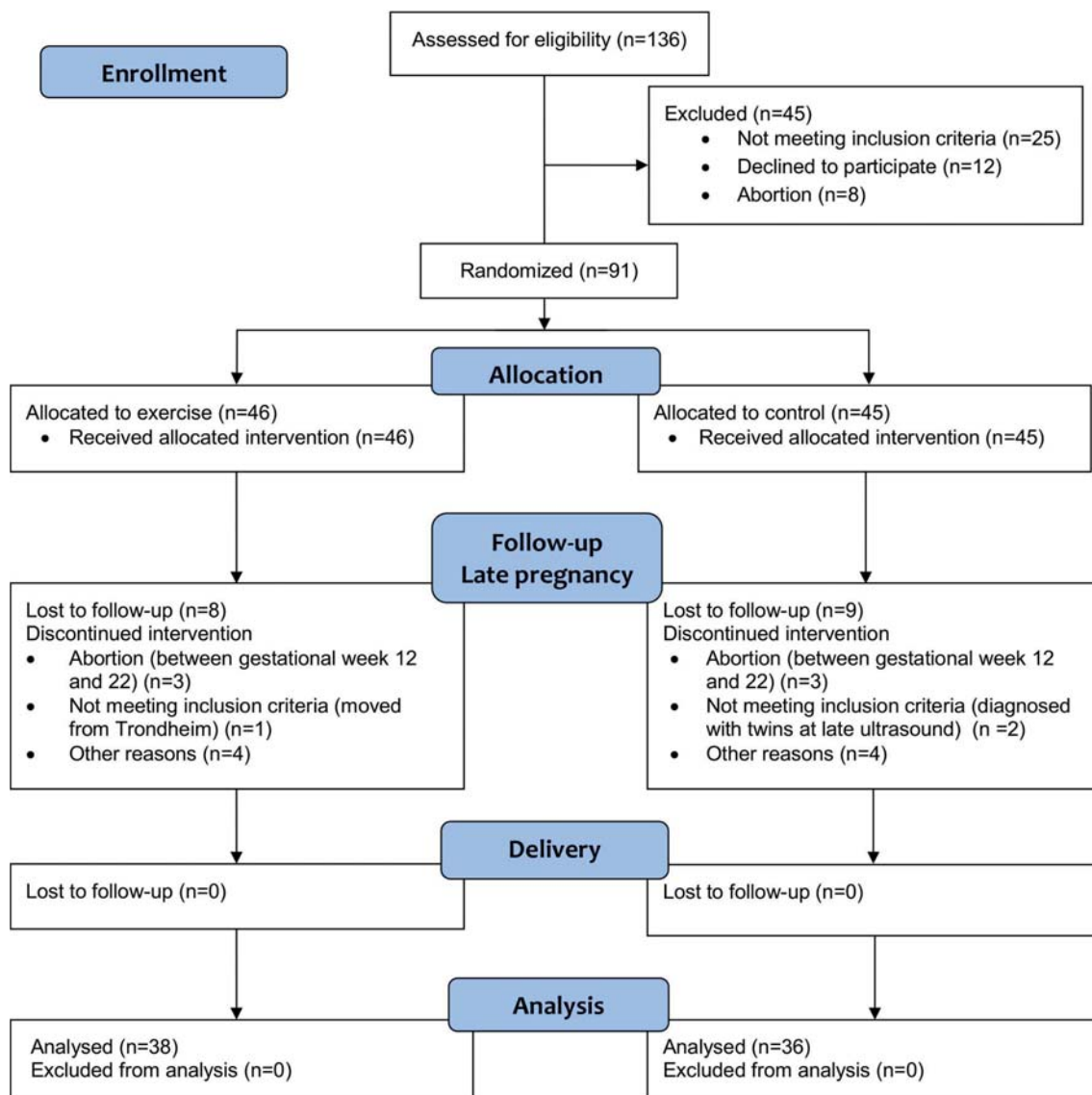


Fig 1. Flow chart of the ETIP trial (CONSORT flow diagram).

<https://doi.org/10.1371/journal.pone.0173937.g001>

There were two cases of preterm birth (pregnancy weeks 29 and 34) in the exercise group (Table 1), which represented two cases of neonatal birth weight < 2500 g. These women had their last exercise sessions 9 and 14 days prior to the preterm births. One woman in the exercise group chose to terminate the pregnancy at week 19+5 due to severe foetal malformations diagnosed at a routine second trimester ultrasound scan.

**Table 1. Neonatal outcomes at delivery for the exercise- and the control group.** Continuous data is presented as mean and standard deviation (SD) with comparison between groups as mean difference with 95% confidence interval (CI) and p-value. Dichotomous data is presented as number (n) and percent (%) and comparison between groups as odds ratio (OR), with 95% CI and p-value.

Neonatal outcomes	Exercise group N = 38		Control group N = 36		Between-group differences		
	n	Mean ± SD	n	Mean ± SD	Mean diff	95% CI	p-value <sup>a</sup>
Birth weight (g)	37	3719 ± 695	36	3912 ± 413	-193.04	-460.96, 74.89	0.16
Gestational age (weeks) <sup>b</sup>	37	39.1 ± 2.3	36	39.5 ± 1.3	-0.45	-1.33, 0.43	0.31
Length (cm)	34	50.7 ± 1.7	36	51.1 ± 1.9	-0.46	-1.32, 0.39	0.28
Head circumference (cm)	35	35.9 ± 1.5	36	35.8 ± 1.5	0.18	-0.53, 0.90	0.61
Abdominal circumference (cm)	32	32.1 ± 2.5	30	31.9 ± 2.1	0.12	-1.03, 1.28	0.83
Upper arm circumference (cm)	32	11.4 ± 2.1	31	11.4 ± 1.0	0.03	-0.79, 0.84	0.95
Body mass index at birth (kg/m <sup>2</sup> )	34	14.9 ± 1.3	36	15.0 ± 1.3	-0.06	-0.67, 0.56	0.86
Body surface area (m <sup>2</sup> )	34	0.23 ± 0.02	36	0.24 ± 0.02	-0.003	-0.011, 0.004	0.38
Skinfold thickness triceps	32	6.1 ± 2.0	30	6.3 ± 2.1	-0.25	-1.30, 0.79	0.63
Skinfold thickness subscapularis	32	5.4 ± 1.5	29	5.7 ± 1.9	-0.26	-1.13, 0.60	0.55
Apgar score 1 minute	36	8.4 ± 1.1	34	8.3 ± 1.7	0.15	-0.53, 0.83	0.66
Apgar score 5 minute	36	9.6 ± 0.5	34	9.4 ± 1.2	0.20	-0.24, 0.64	0.37
Placenta weight (g)	34	705.8 ± 165.4	32	666.7 ± 128.6	39.10	-34.07, 112.28	0.29
Placental weight ratio <sup>c</sup>	34	0.18 ± 0.02	32	0.17 ± 0.03	0.01	-0.001, 0.023	0.08
		n (%)		n (%)	OR	95% CI	p-value <sup>a</sup>
Birth weight > 4000 g	37	13 (35)	36	19 (53)	1.4	0.88, 2.36	0.16
Transfer to NICU <sup>d</sup>	37	3 (8)	34	3 (9)	1.0	0.46, 2.41	0.91
Preterm birth <sup>e</sup>	38	2 (5)	36	0 (0)	-	-	0.49

<sup>a</sup>Continuous variables were analysed by Independent Samples t-test. Dichotomous variables were analysed by Fisher's Exact Test and Pearson Chi-Square. Apgar score was analysed by Nonparametric Tests, Mann-Whitney U.

<sup>b</sup>Weeks between the first day of the mother's last menstrual period and the day of delivery.

<sup>c</sup>Placenta weight divided by birth weight.

<sup>d</sup>Neonatal Intensive Care Unit

<sup>e</sup>Delivery before gestational week 37.

<https://doi.org/10.1371/journal.pone.0173937.t001>

Three neonates in each group needed admission to the NICU after birth. In the exercise group, two neonates were admitted due to prematurity and one due to meconium aspiration. In the control group one neonate was transferred to NICU due to hypoglycaemia and infection, one due to asphyxia caused by shoulder dystocia, complicated by a humerus fracture, and one due to persistent pulmonary hypertension. Two women, one in each group, delivered their babies at other hospitals than St. Olavs Hospital, and we therefore have missing data on their outcomes.

### Maternal outcomes

No significant differences between groups were seen in length of hospital stay, mode of delivery, or perineal tears. Approximately 2/3 of the women in both groups had a normal delivery (Table 2). No women in the exercise group and two women in the control group had pre-eclampsia ( $p = 0.24$ ).

### Additional analyses

We did secondary analyses controlling for parity and gestational age and found no statistically significant difference between groups. We also analysed possible associations between BMI at

**Table 2. Maternal outcomes at delivery for the exercise- and the control group.** Continuous data is presented as mean and standard deviation (SD), with comparison between groups are as mean difference with 95% confidence interval (CI) and p-value. Dichotomous data is presented as number (n) and percent (%), with comparison between groups as odds ratio (OR), with 95% CI and p-value.

Maternal Outcomes	Exercise groupn = 38	Control groupn = 36	Between-group differences		
	n (%)	n (%)	OR	95% CI	p-value <sup>a</sup>
Mode of delivery <sup>b</sup>					
Normal vaginal delivery	22 (60)	24 (69)	1.2	0.77, 1.89	0.47
Operative vaginal delivery	7 (19)	5 (14)	0.9	0.50, 1.47	0.75
Caesarean section	9 (24)	6 (17)	0.8	0.50, 1.33	0.57
Perineal tears, grade 3–4 <sup>c</sup>	4 (18)	2 (10)	0.7	0.08, 2.91	0.66
	Mean ± SD	Mean ± SD	Mean diff	95% CI	p-value <sup>a</sup>
Length of hospital stay (days) <sup>d</sup>	4.8 ± 1.6	4.5 ± 1.5	0.28	-0.45, 1.00	0.45

<sup>a</sup>Continuous variables were analysed by Independent Samples t-test, dichotomous variables by Fisher’s Exact Test and Pearson Chi-Square.

<sup>b</sup>One missing in each group.

<sup>c</sup>Out of women with normal vaginal delivery. Three missing in the control group.

<sup>d</sup>Four missing in the exercise group and five in the control group.

<https://doi.org/10.1371/journal.pone.0173937.t002>

early pregnancy with birth weight and risk for caesarean delivery and found no statistically significant associations.

In secondary per protocol analyses we compared the control group to the women in the exercise group who adhered to the exercise protocol (n = 19, 50%). No significant differences in birth weight between exercise (3742 g ± 652) and control groups (3912 g ± 413), p = 0.24 were observed (S1 Table). There were no significant differences between groups in any other maternal and neonatal outcomes in the per protocol analysis (S1 and S2 Tables).

## Discussion

### Main findings

We found no effect of regular supervised exercise training during pregnancy on birth weight, body composition, or size of the neonate. Furthermore, we observed no between-group differences in any other maternal or neonatal outcomes at delivery.

### Neonatal outcomes

We found no difference between groups in neonatal birth weight, body surface area or body composition. This is in line with several other studies [18, 21, 37, 38] and confirmed by two recent systematic reviews [23, 24]. However, Barakat and colleagues [39] found a 2.5 times higher risk of macrosomia in women allocated to a control group compared to women who adhered to ≥ 80% to a supervised exercise program of three weekly sessions during pregnancy. In line with this, Hopkins et al. [36] observed significantly lower birth weight among babies born to women who exercised during pregnancy. Both these studies included women of all BMI categories. We observed a tendency of higher prevalence of children with birth weight > 4000 g in the control group, but the difference was not statistically significant. This finding is supported by a meta-analysis of 5278 newborns born to women in all BMI categories, in which a lower prevalence of macrosomia, despite no difference in birth weight, was observed in women who followed a lifestyle intervention program in pregnancy [40]. Of note, about 50% of the children born to women in the control group had birth weight > 4000 g. Babies with birth weight ≥ 4000 g are at increased risk for birth complications, childhood obesity, adult obesity, and future metabolic syndrome, compared to babies with birth weight 2500–4000 g [41].

Comparing the intervention protocol in the ETIP trial to exercise interventions in other randomised trials shows that many studies, as the ETIP trial, base their protocol on the American College of Obstetricians and Gynaecologists [29] recommendations for physical activity during pregnancy. Data from overweight and obese women in comparable RCTs of Barakat et al. [42] and Nascimento et al. [43], showed no effect on neonatal birth weight. Exercise interventions showing most effect on neonatal birth weight are characterized by including all weight classes [21, 42, 44, 45], and by including the participants early in pregnancy (gestational week 6–13) [42, 45], or by high frequency of exercise sessions (five times per week) [44]. Most RCTs on exercise training in pregnancy make use a combination of endurance training at light to moderate intensity, and resistance training, with duration of the sessions of 45–60 minutes two-three times per week until gestational week 36–38. The amount, intensity and duration of exercise in the ETIP trial are in line with several other randomised controlled trials on exercise in pregnancy, however, the mean inclusion time (gestational week) was higher (16.4) in the ETIP trial, and thus decreases the number of weeks of exercise during the pregnancy.

We observed a borderline statistically significant difference in PWR between groups ( $p = 0.08$ ), with means in both groups within the normal range of PWR [46]. We prefer not to speculate too much around a non-significant result, but placental weight is a measure that can reflect several aspects of foetal growth. Furthermore, both low and high PWR can predict adverse neonatal outcomes at delivery [47], and high PWR has been found to associate with increased risk of obesity and cardiovascular disease later in life [48–50].

We found no differences between groups in neonatal outcomes at delivery. This is in line with several other studies reporting no effects of exercise- or lifestyle (combining diet and exercise) interventions during pregnancy on Apgar score or head circumference [21, 37, 51]. Haakstad & Bø [21] observed higher mean Apgar scores at 1 minute, but not at 5 minutes, among newborns born to women allocated to training in a randomised controlled trial of 105 women. This was observed in a per protocol analysis and not in the intention-to-treat analysis, and Apgar score at 5 minutes is considered a better sign of newborn wellbeing than Apgar score at 1 minute [52, 53].

## Maternal outcomes

Most women had a normal vaginal delivery, and we observed no significant effect of exercise training on mode of delivery. A meta-analysis of 10 trials with a total of 3160 women found more normal deliveries among healthy regularly exercising pregnant women in all BMI categories [19]. However, a meta-analysis and systematic review of 6 RCTs ( $n = 2762$ ) of combined diet and exercise intervention during pregnancy among overweight and obese women found no effect on mode of delivery [23].

## Strengths

The exercise intervention in our trial included supervised training sessions. Supervised training sessions are important for compliance and effect of the intervention [54]. We used exercise as the only intervention, thereby enabling us to assess the isolated effects of exercise training on the reported outcomes. We included previously sedentary women with a BMI of 28 or more in the trial, hence our study population can be considered homogeneous. All data regarding delivery information was collected from patients' records at St. Olavs Hospital, and the records were assessed by personnel blinded for allocation. We also regard the additional measurements of skinfold thickness, body surface area and abdominal circumference as strengths to our study.

## Limitations

The main limitation of our trial is the small number of participants and hence the risk for statistical type 2 error. We planned to include 150 women in the ETIP trial [27], however ended up with 91 randomised women after a prolonged inclusion time. Furthermore, since only 50% of the women adhered to the training protocol, potential effects of the intervention may be undetected. However, the adherence to protocol was similar to other comparable trials on effects of lifestyle changes in pregnancy. When interpreting the per protocol analysis, care must be taken due to the risk of selection bias as compliance with the exercise program could be associated with other prognostic factors.

To accommodate slow recruitment to the trial, we prolonged the time limit for inclusion in the trial with two weeks (until pregnancy week 18). This reduced the time for training adaptations to occur, and may have reduced the chance for detecting effects of the intervention. In addition, we changed pre-pregnancy BMI limit from  $\geq 30.0$  to  $\geq 28.0$  kg/m<sup>2</sup>, and thereby including five overweight women in the analysis at delivery. This change to the protocol may have affected the homogeneity of the trial population, reduced the mean BMI in both groups, and thereby somewhat reduced the risk for adverse events. We argue, however, that including five women with a BMI between 28.0 and 30.0 kg/m<sup>2</sup> will not be of major importance for the interpretation of our results.

Further, the control group attended quite comprehensive health assessments during the pregnancy, and therefore may have increased their awareness of healthy living during the pregnancy.

We acknowledge that not providing any information regarding the participants' diet during the pregnancy is a limitation. Maternal nutrition may be a confounding factor due to its effect on both neonatal and maternal outcomes. We can assume that the women in the exercise group would be extra motivated for eating healthy as part of a more healthy lifestyle. On the other side, they could also compensate for the energy expended through exercise by eating more [55].

Measurement of neonatal skinfold thickness was non-blinded and may have introduced bias to the data on the effect of exercise on body composition. Interpretation must be done with caution.

## Generalisability

The ETIP trial had few exclusion criteria, and offered training sessions at different times of the day, indicating that a large proportion of pregnant women could volunteer for participation. We included about 10% of eligible women with BMI  $\geq 28$  in the area of St. Olavs Hospital, which is a similar inclusion rate as a previous RCT (TRIP trial) on exercise in pregnancy conducted in the same area a few years earlier [56]. These women were found to be representative for the population of pregnant women, and it is likely that this responds to the ETIP trial too. However, it is possible that the women recruited to the ETIP trial were extra aware of the possible benefits of lifestyle changes on maternal and neonatal health, and therefore more motivated to exercise during pregnancy compared to women who did not volunteer for this trial.

Comparison between the results from the current trial and data from large cohort studies [57–59] on women with pre-pregnancy obesity shows that the number of adverse outcomes in our control group was low and indicates that we had a quite healthy study population in the ETIP trial.

## Clinical relevance

The number of obese pregnant women is increasing. Thus, we urgently need to establish strategies to prevent associated risk factors. The intervention used in the ETIP trial was based on

recommendations for physical activity during pregnancy and involved an exercise program that can easily be performed individually or in groups, at home or supervised, without any equipment.

There were no adverse events in our trial related to the exercise intervention. Some previous studies have reported high risk of preterm delivery associated with exercise during pregnancy [60], but a recent meta-analysis did not find any association between aerobic exercise for 35–90 minutes 3–4 times per week and increased risk of preterm birth [61]. In the current trial two women in the exercise group had a preterm delivery, and we found no indication of this being related to participating in the exercise program. The majority of the women in this trial had a normal delivery, and the rate of caesarean delivery was relatively low.

## Conclusions

We found no effect of offering regularly supervised exercise training during pregnancy on birth weight or body size of neonates born to women with a pre-pregnancy body mass index of 28 kg/m<sup>2</sup> or more. The intervention program had no impact on other neonatal and maternal outcomes at delivery. Our trial was limited by small sample size and low adherence to the exercise protocol. We need larger, well-designed RCTs to further investigate the effect of exercise training on neonatal and maternal outcomes in this population.

## Supporting information

**S1 Table. Supplementary Table 1.** Neonatal outcomes at delivery for the per-protocol exercise group and the control group. Continuous data is presented as mean and standard deviation (SD) with comparison between groups as mean difference with 95% confidence interval (CI) and p-value. Dichotomous data is presented as number (n) and percent (%) and comparison between groups as odds ratio (OR), with 95% confidence interval (CI) and p-value. (DOCX)

**S2 Table. Supplementary Table 2.** Maternal outcomes at delivery for the per-protocol exercise group and the control group. Continuous data is presented as mean and standard deviation (SD), with comparison between groups as mean difference with 95% confidence interval (CI) and p-value. Dichotomous data is presented as number (n) and percent (%), with comparison between groups as odds ratio (OR), with 95% confidence interval (CI) and p-value. (DOCX)

**S3 Table. Supplementary Table 3.** Baseline characteristics of all women included in the ETIP study. (DOCX)

## Acknowledgments

### Competing interests

We declare that we have no conflicts of interest.

## Author Contributions

**Conceptualization:** SM TM KÅS.

**Formal analysis:** ØS KKG.

**Funding acquisition:** SM TM.



**Investigation:** KKG TM SAN SM.

**Methodology:** TM KKG SM SAN KÅS ØS.

**Project administration:** KKG TM SM SAN.

**Resources:** KKG TM SM ØS.

**Software:** ØS KKG TM.

**Supervision:** TM SM KÅS.

**Validation:** TM SM.

**Visualization:** KKG TM.

**Writing – original draft:** KKG.

**Writing – review & editing:** KKG TM SM SAN KÅS ØS.

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**Supplementary Table 1.** Neonatal outcomes at delivery for the per-protocol exercise group and the control group. Continuous data is presented as mean and standard deviation (SD) with comparison between groups as mean difference with 95% confidence interval (CI) and p-value. Dichotomous data is presented as number (n) and percent (%) and comparison between groups as odds ratio (OR), with 95% confidence interval (CI) and p-value.

Neonatal Outcomes	Exercise group n = 19	Control group n = 36	Between-group differences		
			Mean diff/ OR	95 % CI	p-value
	<i>Mean SD/ n (%)</i>	<i>Mean SD/ n (%)</i>			
Birth weight (g)	3742 ± 652	3912 ± 413	-170.04	-458.42, 118.43	0.24
Birth weight > 4000 g	7 (37)	19 (53)	1.9	0.61, 5.98	0.40
Gestational age (weeks)	39.1 ± 1.8	39.5 ± 1.3	-0.48	-1.32, 0.37	0.27
Length (cm)	50.7 ± 1.8	51.1 ± 1.9	-0.41	-1.51, 0.70	0.47
Head circumference (cm)	35.8 ± 1.7	35.8 ± 1.5	0.02	-0.89, 0.93	0.97
Abdominal circumference (cm)	31.9 ± 2.3	31.9 ± 2.1	0.08	-1.37, 1.22	0.91
Upper arm circumference (cm)	10.9 ± 0.9	11.4 ± 1.0	-0.52	-1.09, 0.05	0.07
BMI at birth (kg/m <sup>2</sup> )	14.8 ± 1.5	15.0 ± 1.3	-0.13	-0.94, 0.67	0.74
BSA (m <sup>2</sup> )	0.23 ± 0.02	0.24 ± 0.02	-0.003	-0.011, 0.004	0.38
Skinfold thickness triceps	6.1 ± 2.1	6.3 ± 2.1	-0.18	-1.46, 1.10	0.78
Skinfold thickness subscapularis	5.4 ± 1.6	5.7 ± 1.9	-0.24	-1.30, 0.82	0.65
Apgar score 1 minute	8.2 ± 1.3	8.3 ± 1.7	-0.12	-0.99, 0.78	0.43
Apgar score 5 minute	9.5 ± 0.6	9.4 ± 1.2	0.70	-0.47, 0.70	0.58
Placenta weight (g)	678.1 ± 175.9	666.7 ± 128.6	11.43	-77.00, 99.83	0.80
Placental weight ratio	0.18 ± 0.02	0.17 ± 0.03	0.01	-0.005, 0.02	0.19
Transfer to NICU	1 (0)	3 (9)	1.8	0.17, 18.64	1.00
Preterm birth	1 (5)	0 (0)	-	-	0.33
<p><i>Missing:</i> Differs between the variables and varies between 1 and 4 in the exercise group and between 4 and 11 in the control group.</p> <p><i>Statistics:</i> Continuous variables were analysed by Independent Samples t-test, dichotomous variables by Fisher's Exact Test and Pearson Chi-Square. Apgar-score were analysed by Nonparametric Tests, Mann-Whitney U.</p> <p><i>Abbreviations:</i> BMI: Body mass index. BSA: Body Surface Area. NICU: Neonatal Intensive Care Unit.</p> <p><i>Definitions:</i> Gestational age: Weeks between the first day of the mother's last menstrual period and the day of delivery. Placental weight ratio: Placenta weight divided on birth weight. Preterm birth: Delivery before gestational week 37.</p>					

**Supplementary table 2.** Maternal outcomes at delivery for the per-protocol exercise group and the control group. Continuous data is presented as mean and standard deviation (SD), with comparison between groups are as mean difference with 95% confidence interval (CI) and p-value. Dichotomous data is presented as number (*n*) and percent (%), with comparison between groups as odds ratio (OR), with 95% confidence interval (CI) and p-value.

Maternal Outcomes	Per-protocol exercise group n = 19	Control group n = 36	Between-group differences		
	<i>Mean SD/ n (%)</i>	<i>Mean SD/ n (%)</i>	<i>Mean diff/ OR</i>	<i>95 % CI</i>	<i>p-value</i>
Length of hospital stay (days)	5.1± 1.7	4.5 ± 1.5	0.55	-0.36, 1.46	0.45
<i>Mode of delivery:</i>					
Normal vaginal delivery	11 (58)	24 (69)	1.59	0.50, 5.01	0.55
Operative vaginal delivery	5 (26)	5 (14)	0.47	0.12, 1.88	0.30
Caesarean section	4 (21)	6 (17)	0.78	0.19, 3.18	0.73
Perineal tears, grade 3-4	2 (20)	2 (10)	0.42	-0.05, 3.53	0.58
Numbers less than n=19 in the exercise group and n=36 in the control groups were due to missing values. For mean length of hospital stay there were 4 missing in the exercise group and 5 in the control group.					
<i>Statistics:</i> Continuous variables were analysed by Independent Samples t-test, dichotomous variables by Fisher's Exact Test and Pearson Chi-Square.					



# Paper III





**Exercise training during pregnancy reduces circulating insulin levels in overweight/obese women postpartum. Secondary analysis of a randomised controlled trial (the ETIP trial).**

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Conflict of Interest statement: The authors declare no conflicts of interest.

## ABSTRACT

**Background/Objectives:** The primary aim was to investigate if supervised exercise training during pregnancy could reduce postpartum weight retention (PPWR) three months after delivery in overweight and obese women. We also measured circulating markers of cardiometabolic health, body composition, blood pressure, and physical activity level.

**Subjects/Methods:** This was a secondary analysis of a randomised controlled trial in which 91 women with BMI  $\geq 28$  were allocated 1:1 to an exercise program or a control group. Women in the exercise group were prescribed three weekly, supervised sessions of 35 minutes of moderate intensity walking/running followed by 25 minutes of resistance training. The control group received standard antenatal care. Assessments were undertaken in early pregnancy, late pregnancy, and three months postpartum. PPWR was defined as postpartum body weight minus early pregnancy weight.

**Results:** Seventy women participated three months after delivery, and PPWR was -0.8 kg in the exercise group (n=36) and -1.6 in the control group (n=34) (95% CI, -1.83, 3.84,  $p = 0.54$ ). Women in the exercise group had significantly lower circulating insulin concentration; 106.3 pmol/l compared to the control group; 141.4 pmol/l (95% CI, -62.78, -7.15,  $p = 0.01$ ), and showed a tendency towards lower homeostatic measurement of insulin resistance (HOMA2-IR) (3.5 vs. 5.0, 95% CI, -2.89, 0.01,  $p = 0.05$ ). No women in the exercise group compared to three women in the control group were diagnosed with type 2 diabetes postpartum ( $p = 0.19$ ). Of the women in the exercise group, 46.4% reported of exercising regularly, compared to 25.0% in the control group ( $p = 0.16$ ).

**Conclusions:** Offering supervised exercise training during pregnancy among overweight/obese women did not affect PPWR three months after delivery, but reduced

circulating insulin levels. This was probably due to a higher proportion of women being active postpartum in the exercise group.

## INTRODUCTION

Overweight and obesity among women in fertile age are associated with adverse health outcomes for mother and child, both during pregnancy and postpartum.<sup>1-11</sup> Overweight is defined as body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>, and obesity as BMI  $\geq 30$  kg/m<sup>2</sup> (according to the WHO classification system).<sup>12</sup> Pre-pregnancy overweight and obese women are at increased risk for high postpartum weight retention (PPWR).<sup>10,11</sup> Obese women are two times more likely than normal weight women to exceed the Institute of Medicine's (IOM) recommendations for gestational weight gain (GWG),<sup>13</sup> and half of the PPWR can be explained by GWG.<sup>14</sup> High PPWR is associated with reduced insulin sensitivity, hypertension, and later development of type 2 diabetes mellitus, and cardiovascular disorders.<sup>7,8,15,16</sup> High PPWR also predisposes for high pre-pregnancy BMI,<sup>7,8</sup> and further reduced maternal metabolic function in future pregnancies.<sup>17</sup>

Finding lifestyle interventions to limit GWG and thereby PPWR among overweight and obese women are important. Previous research investigating the effect of lifestyle programs during pregnancy targeting this group of women have demonstrated conflicting results on PPWR, glucose tolerance, and other cardiometabolic health variables.<sup>18-21</sup> Further, few trials have investigated the effect of regular exercise during pregnancy as the only intervention.

The primary aim of the Exercise Training in Pregnancy (ETIP) trial was to assess if offering supervised exercise training during pregnancy would reduce GWG in women with pre-pregnancy BMI of  $\geq 28.0$  kg/m<sup>2</sup>.<sup>22,23</sup> At delivery we found no difference in GWG between the groups, but we observed a lower incidence of gestational diabetes mellitus (GDM) and lower blood pressure in the exercise group.<sup>22</sup>

This is a secondary analysis of data from the ETIP trial where we assessed if providing a supervised exercise program during pregnancy could reduce PPWR three months after

delivery. Our *a priori* hypothesis was that the women in the exercise group would have a lower PPWR. We also investigated effects of the intervention during pregnancy on, body composition, blood pressure, physical activity level, and various circulating markers of cardiometabolic health, three months postpartum.

## **MATERIALS/SUBJECTS AND METHODS**

### **Trial design**

The ETIP trial was a single-centre, parallel-group randomised controlled trial (RCT) investigating effects of offering supervised regular exercise training during pregnancy compared to standard maternal care only, in overweight and obese women. The primary outcome measure in ETIP was GWG. The trial was performed between September 2010 and March 2015 at the Norwegian University of Science and Technology (NTNU) and St. Olavs Hospital, Trondheim University Hospital, Norway. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK-midt 2010/1522), registered in ClinicalTrials.gov (NCT01243554) and was in accordance with the Helsinki Declaration of 1975. The ETIP study protocol and primary findings of the trial have been published previously.<sup>22,23</sup>

We experienced slow recruitment and made changes to the study protocol after commencement of the trial, to accommodate the need for more participants.<sup>22</sup> The criterion for maximum inclusion time was originally 16 gestational weeks and was changed to 18 gestational weeks in November 2012. The inclusion criterion pre-pregnancy BMI was changed from  $\geq 30 \text{ kg/m}^2$  to  $\geq 28 \text{ kg/m}^2$  in March 2013.<sup>22</sup> The changes were approved by the Regional Committee for Medical and Health Research Ethics.

## **Participants**

Women were eligible if they had a pre-pregnancy BMI  $\geq 28$ , age  $\geq 18$  years, gestational week  $< 18$ , carrying one singleton live foetus at the 11-14-week ultrasound scan, and were able to attend assessments and exercise sessions at St. Olavs Hospital. Exclusion criteria were; habitual exercise training (twice or more weekly) in the period before pregnancy, high risk for preterm delivery, diseases that could interfere with participation, and contraindications in accordance to the ACOG recommendations for physical activity and exercise during pregnancy.<sup>24,25</sup> The women received written information and signed informed consent on behalf of themselves and their foetus before participation and randomization.

## **Intervention**

All participants received standard maternal care. In addition, women in the exercise group were offered supervised exercise sessions three times per week at the hospital from time of inclusion (at gestational week 12-18) until delivery.<sup>22</sup> The exercise program provided was in accordance with the recommendations from the American College of Obstetricians and Gynaecologists.<sup>26</sup> Women in the exercise group walked or ran on treadmills for 35 minutes at moderate intensity (65-80% of maximal capacity, estimated using a rate of perceived exertion of 12-15 on the Borg 6-20 scale<sup>27</sup>), followed by 25 minutes of resistance exercises for large muscle groups and a strength training program for the pelvic floor muscles. The strength training consisted of weight-bearing exercises such as squats, push-ups, diagonal lifts on all fours, oblique abdominal crunches, and pelvic floor muscle exercises, with three sets of ten repetitions of each exercise separated by a 1 minute rest between sets. In addition, the women also performed three sets of the “plank exercise” for 30 seconds. A physical therapist supervised all sessions and registered each woman’s adherence to the program. We also advised women in the exercise group to do 35 minutes of endurance exercise and 15 minutes of resistance exercise at home at least once weekly, as well as daily pelvic floor muscle

strengthening exercises. The participants registered their home-based exercise and general physical activities in a training diary. The women in the exercise group were informed of recommended weight gain during pregnancy, based on the guidelines of the Institute of Medicine (IOM).<sup>28</sup> They received an individually adjusted weight gain curve, where they weekly registered their weight measured at the hospital. The supervised exercise sessions were terminated at delivery. Women in the control group were informed about the recommended level of physical activity during pregnancy and were not discouraged from exercising on their own.

### **Outcomes**

The principal outcome of this secondary analysis was PPWR, defined as body weight at the postpartum visit minus body weight at early pregnancy. Weight was measured using a calibrated electronic scale (SECA 770, Medema, Norway). We also assessed the difference between postpartum weight and self-reported weight before pregnancy.

All participants underwent the same test protocol at early pregnancy (gestational week 12-18), in late pregnancy (gestational week 34-37), and three months postpartum. The participants underwent overnight fasting for  $\geq 10$  hours before doing an oral glucose tolerance test where they drank 75 g of glucose dissolved in 2.5 dl of water. We report the number of women who fulfilled the WHO definition of type 2 diabetes; fasting plasma glucose  $\geq 7.0$  mmol/l, and/or 2 hour concentration  $\geq 11.1$  mmol/l.<sup>29</sup> We measured plasma insulin by enzyme immunoassay (ELISA, IBL-International, Germany), using a DS2 ELISA processing system (Dynex Technologies, USA), according to the manufacturer's procedures. As a measure of insulin resistance, we used the homeostatic assessment of insulin resistance (HOMA2-IR), calculated as  $[\text{glucose} \cdot \text{insulin}] / 22.5$ .<sup>30</sup> All other blood measurements were analysed by Roche Modular P-system (Roche, Switzerland).



Blood pressure measurements were taken three times at two-minute intervals, and the average was used in the analysis. Hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg and/or a diastolic blood pressure  $\geq 90$  mmHg. We used a Harpenden Caliper (Holtain Ltd, UK) to measure subscapular-, biceps-, and triceps skinfold thickness. Body composition was additionally measured with air displacement plethysmography (BOD POD, COSMED The Metabolic Company, Italy). We measured waist circumference at the postpartum visit, using measuring tape at the level of the umbilicus at normal expiration. Assessments were undertaken by principal investigators (KKG and TM), trained nurses and biomechanical laboratory personnel. For a more detailed description of outcome measures, see Garnæs et al.<sup>22</sup>

The participants answered questionnaires about their physical activity and exercise training. They were asked if they adhered to the recommendations of  $\geq 150$  minutes of moderate intensity physical activity per week, and about their amount and intensity of exercise training. Women were also asked about breastfeeding at the time of the postpartum visit; whether they were exclusively breastfeeding and the number of meals per 24 hours.

### **Sample size**

The sample size calculation in the ETIP-trial was based on a primary outcome of gestational weight gain from baseline to delivery.<sup>22,23</sup> To detect a 6 kg clinically significant difference in weight gain between the groups, we needed a minimum of 118 participants (with alpha 0.05, beta 0.90). We did not do a separate power calculation for the analyses presented in this report.

### **Randomization and blinding**

After early pregnancy assessments were undertaken, we allocated participants 1:1 to exercise or control groups, using a computer random number generator. For details about the randomization procedure, see Garnæs et al.<sup>22</sup> The personnel measuring weight at birth and

undertaking blood analyses, and the statistician were blinded for group allocation. All other measurements were unmasked.

### **Statistical methods**

Analyses were done according to the “intention to treat” principle. All available data were used at all time points. Baseline data (early pregnancy) were tested for normality and comparison between groups analysed by an independent samples t-test and Fisher’s Exact Test. The effect of treatment on the continuous postpartum outcomes was assessed with mixed linear models. The effect of time and treatment was specified as a fixed effect having the levels 'baseline', 'training late pregnancy', 'control late pregnancy', 'training postpartum' and 'control postpartum'. No systematic differences between groups at baseline were assumed due to randomization. Participant ID was included as a random effect to account for repeated measurements. To account for apparent variance heterogeneity across time, the covariance structure for the error term was specified as diagonal. The effect of treatment on dichotomous postpartum outcomes was analysed using exact logistic regression adjusting for the baseline (early pregnancy) outcome when available, with the exercise group as the reference group.

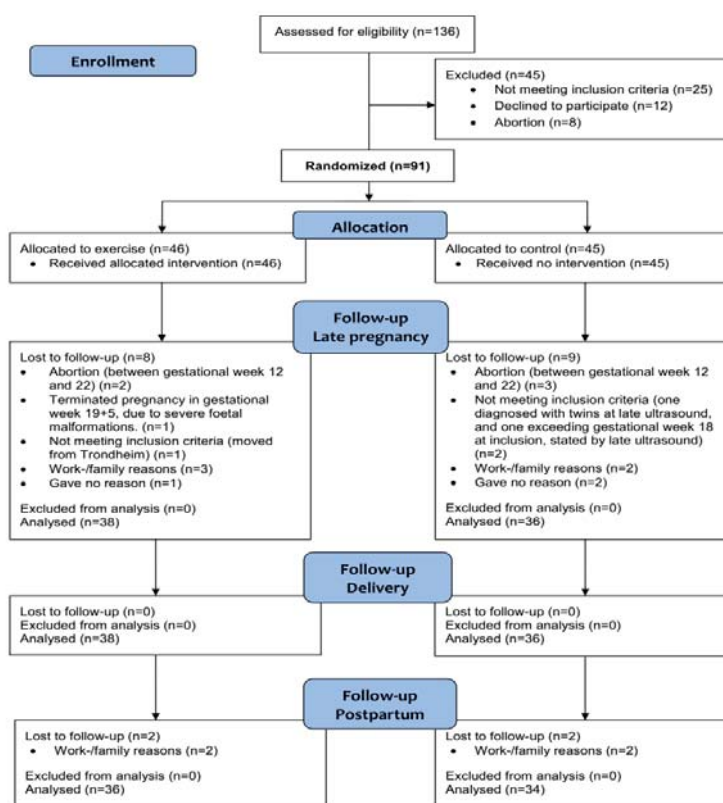
Analyses were performed using IBM SPSS Statistics 22 for baseline values, R version 2.13.1 for continuous outcome data, and Stata version 13.1 for dichotomous outcome data. All results are given as mean values with 95% confidence intervals and p-values < 0.05 were considered as significant.

We did supplementary mixed model analyses of PPWR where we adjusted for the number of days since delivery, lactation and physical activity. We also investigated association between PPWR and gestational weight gain, lactation and physical activity. We performed, as described in the protocol,<sup>23</sup> per protocol analyses of women in the exercise group adhering to the exercise protocol. In these analyses we included women in the exercise group who undertook one of the following: 1) attending  $\geq 42$  organized exercise sessions, 2)

attending  $\geq 28$  exercise sessions + performing  $\geq 28$  home exercise sessions, 3) performing  $\geq 60$  home exercise sessions. The exercise had to be  $\geq 50$  minutes of either aerobic and/or strength training to count as a home session.

## RESULTS

The trial was conducted between September 2010 and March 2015, and enrolment was ended due to prolonged time for inclusion and fewer eligible participants than expected. Figure 1 outlines the flow of participants during the trial. Seventy (77%) of 91 women included in the ETIP trial were assessed at three months postpartum and two women in each group dropped out from late pregnancy/delivery until the postpartum visit (Figure 1).



**Figure 1.** Flow chart of the ETIP trial.

Two of the women in the exercise group included in the postpartum analysis were classified as overweight pre-pregnancy (BMI 28.3 and 29.7) compared with three women in the control group (BMI 28.8, 29.4, and 29.7). All other women had pre-pregnancy BMI  $\geq 30$  and were classified as obese. Of the women in the exercise group included in the postpartum analyses, 54.3% adhered to the training protocol. The mean time for postpartum testing was  $99.8 \pm 10.2$  days after delivery in the exercise group and  $95.7 \pm 10.4$  days in the control group. Apart from a lower fasting glucose in the exercise group ( $p = 0.02$ ), baseline (early pregnancy) characteristics did not differ between groups. The women in the exercise group performed (in mean)  $31.7 \pm 15.3$  (Range 0-53) supervised sessions at the hospital, and  $19.2 \pm 16.5$  (Range 0-72) exercise sessions at home.

Mean gestational weight gain during pregnancy was  $10.5 \pm 4.6$  kg in the exercise group and  $9.7 \pm 6.9$  kg in the control group ( $p = 0.55$ ). Among women in the exercise group, 58% gained more weight during pregnancy than recommended by the IOM guidelines compared with 44% in the control group.<sup>22</sup> Table 1 presents model-based outcomes at baseline (means for all participants) and at the postpartum visit.

**Table 1.** Outcomes at three months postpartum. “Intention to treat” model based analyses with early pregnancy (baseline) mean for all participants, and comparison between groups are presented as mean, 95% confidence interval (CI) and p-value. Weight retention is estimated based both on the difference between postpartum weight and early pregnancy (baseline) weight, and between postpartum weight and pre-pregnancy weight.

	Baseline	Exercise Group (n = 36)		Control Group (n = 34)		Between-Group Comparison		
		Mean	95% CI	Mean	95% CI	Mean Diff	95% CI	p-value
<b>Weight (kg)</b>	96.8	96.0	92.7, 99.3	95.2	91.9, 98.5	0.82	-1.83, 3.46	0.54
<b>PPWR<sup>1</sup> (kg)*</b>		-0.8	-2.7, 1.1	-1.6	-3.5, 0.3	0.82	-1.83, 3.84	0.54
<b>PPWR<sup>2</sup> (kg)**</b>		1.52	-0.73, 3.78	0.52	-1.82, 2.86	1.0	-2.15, 4.16	0.53
<b>BMI (kg/m<sup>2</sup>)</b>	34.5	34.2	33.2, 35.3	33.9	32.9, 35.0	0.29	-0.67, 1.25	0.55
<b>Waist circumference (cm)</b>	107.5	105.0	101.7, 108.2	102.9	99.6, 106.2	2.06	-1.34, 5.47	0.24
<b>Body composition***</b>								
Fat mass (kg)	43.1	42.1	39.6, 44.6	42.0	39.5, 44.5	0.11	-2.05, 0.92	0.92
Fat mass (%)	44.6	44.2	43.0, 45.5	43.9	42.7, 45.2	0.28	-0.83, 1.38	0.62
Fat-free mass (kg)	52.7	52.1	50.4, 53.7	53.0	51.4, 54.7	-0.96	-2.83, 0.92	0.32
Fat-free mass (%)	55.4	55.7	54.4, 57.1	56.4	55.1, 57.7	-0.65	-1.97, 0.67	0.33
<b>Skinfold thickness</b>								
Biceps area (mm)	21.1	16.7	14.7, 18.7	17.5	15.5, 19.6	-0.85	-3.15, 1.44	0.47
Triceps area (mm)	30.0	26.4	24.4, 28.4	26.8	24.8, 28.8	-0.43	-2.67, 1.82	0.71
Subscapular area (mm)	31.8	28.5	26.3, 30.8	30.0	27.7-32.3	-1.44	-4.03, 1.16	0.28
<b>Blood pressure</b>								
Systolic BP (mm/Hg)	124.5	120.6	117.5, 123.8	124.02	120.7, 127.4	-3.40	-7.70, -0.99	0.13
Diastolic BP (mm/Hg)	76.0	75.8	73.3, 78.4	78.4	75.7, 81.1	-2.61	-6.19, 0.96	0.15
<b>Blood measurements</b>								
Fasting glucose (mmol/l)	4.7	5.1	4.9, 5.3	5.1	4.8, 5.26	0.02	-0.24, 0.27	0.91
120-min glucose (mmol/l)	5.9	5.2	4.7, 5.8	5.8	5.3, 6.4	-0.60	-0.60, 1.31	0.10
Insulin (pmol/l)	139.6	106.3	83.3, 129.2	141.4	118.1, 164.6	-35.10	-62.78, -7.15	0.01
HbA1c (%)	5.2	5.3	5.2, 5.4	5.4	5.3, 5.5	-0.10	-0.25, 0.04	0.17
Insulin C-peptide (nmol/l)	0.6	0.7	0.6, 0.8	0.7	0.6, 0.8	-0.01	-0.14, 0.11	0.82
Triglycerides (mmol/l)	1.4	0.8	0.6, 1.0	1.0	0.8, 1.2	-0.21	-0.47, 0.05	0.12
Ferritin (pmol/l)	127.0	69.9	56.0, 83.6	64.5	49.7, 79.1	5.46	-14.81, 25.71	0.60
HDL cholesterol (mmol/l)	1.7	1.5	1.5, 1.6	1.5	1.4, 1.6	-0.02	-0.14, 0.11	0.81
LDL cholesterol (mmol/l)	2.8	3.1	2.8, 3.4	3.2	2.8, 3.5	-0.08	-0.51, 0.34	0.71
Total cholesterol (mmol/l)	5.0	4.9	4.5, 5.2	5.1	4.7, 5.4	-0.23	-0.71, 0.25	0.34
Haemoglobin (g/l)	126.7	128.4	125.4, 131.5	129.7	126.5, 132.9	-1.30	-5.50, 2.90	0.56
High-sensitive CRP (mg/l)	10.7	4.2	2.9, 5.6	4.8	3.4, 6.2	-0.58	-2.50, 1.34	0.55
HOMA2-IR	2.5	3.5	2.5, 4.6	5.0	3.9, 6.0	-1.44	-2.89, 0.01	0.05

**Missing:** The number of missing in the exercise group varied between 1 and 5, in the control group between 1 and 3.

**Statistics:** The effect of treatment was assessed with linear mixed models. For the primary and secondary outcomes, the effect of time and treatment was taken as a fixed effect. Due to randomization, no systematic differences between groups at baseline were assumed.

**Abbreviations:** PPWR, postpartum weight retention. BMI, Body mass index. BP, blood pressure. HbA1c, Glycated Haemoglobin. HDL, High-density lipoprotein. LDL, Low-density lipoprotein. CRP, C-reactive protein, HOMA2-IR, homeostatic assessment of insulin resistance.

\*PPWR<sup>1</sup>, postpartum weight minus weight at early pregnancy (baseline).

\*\*PPWR<sup>2</sup>, postpartum weight minus pre-pregnancy weight. Weight at pre-pregnancy was based on self-reported data. Mean pre-pregnancy weight for all participants were 94.4 kg.

\*\*\*Body composition was measured by air displacement plethysmography (BOD POD).

### **Postpartum weight retention**

PPWR was not significantly different between groups, with -0.8 kg in the exercise group and -1.6 kg in the control group ( $p = 0.54$ ) (Table 1). Women in both groups had returned to their early pregnancy body weight three months postpartum. We observed no association between PPWR and gestational weight gain ( $p = 0.79$ ), PPWR and lactation ( $p = 0.63$ ), or between PPWR and fulfilling recommendations of 30 minutes of physical activity per day ( $p = 0.20$ ).

**Table 2.** Outcomes at three months postpartum. “Intention to treat” analysis, observed data, for the exercise and the control group and comparison between groups are presented in number of participants (N), percentage (%), odds ratio (OR), 95% confidence interval (CI), and p-value.

	Exercise group	Control group	Between-Group Comparison		
	n = 36	n = 34	Odds Ratio	95% CI	p - value
	<i>n (%)</i>	<i>n (%)</i>			
Type 2 diabetes	0 (0)	3 (9.1)	4.96	0.46, ∞	0.19
Hypertension	3 (8.8)	3 (10.0)	1.17	0.15, 9.30	1.00
Physical activity ≥ 150 minutes/week*	21 (72.4)	22 (78.6)	1.17	0.68, 2.02	0.76
Exercise training**	13 (46.4)	7 (25.0)	0.39	0.12, 1.19	0.16
Exclusively breastfeeding	18 (60.0)	21 (77.8)	1.44	0.90, 2.31	0.17
Breastfeeding 3-4 meals/24h	4 (13.3)	1 (3.7)	0.63	0.37, 1.05	0.36

**Missing:** Type 2 diabetes: Exercise group 1 missing, control group 1 missing. Hypertension: Exercise group 1 missing, control group 4 missing. Physical activity questionnaire: Exercise group 7 missing, control group 6 missing. Lactating questionnaire: Exercise group 6 missing, control group 7 missing.

**Statistics:** Type 2 diabetes and hypertension were analysed by exact logistic regression Model. Data on physical activity and breastfeeding are based on a self-reported questionnaire and were analysed by Fisher's Exact test.

**Definitions:** Type 2 diabetes: Fasting plasma glucose ≥ 7.0 mmol/l or 2 h concentration ≥ 11.1 mmol/l, according to the definition of the World Health Organization (WHO). Hypertension: Systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90.

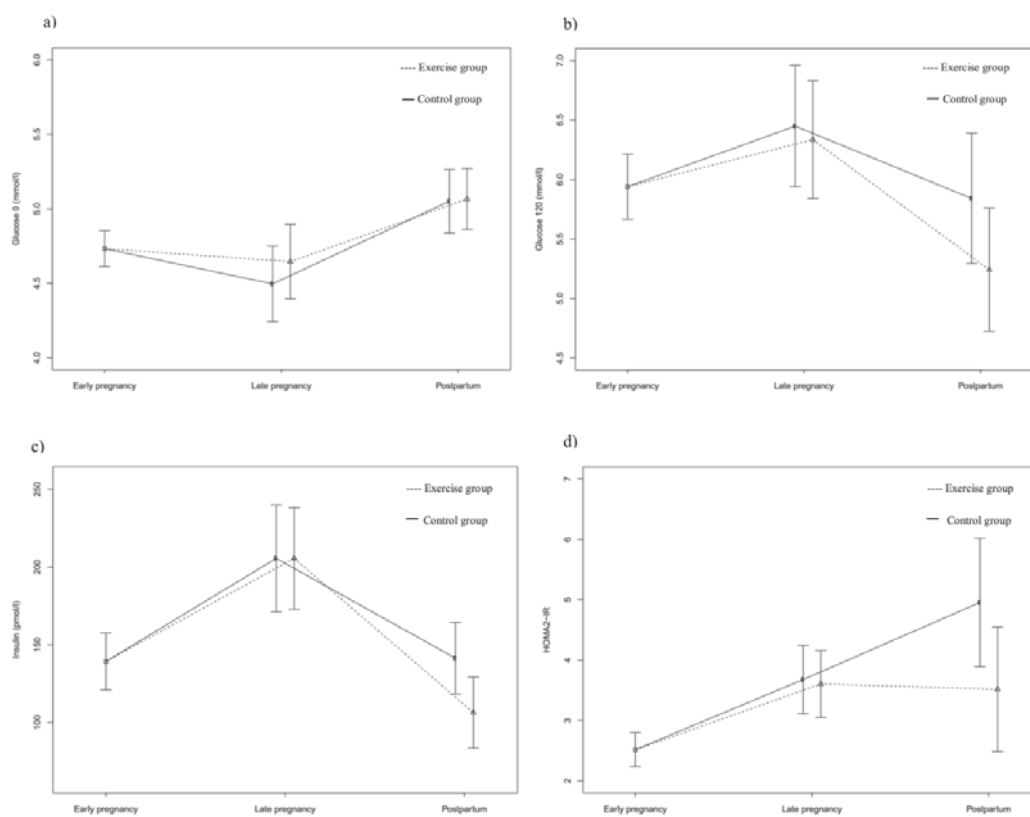
\* Physical activity ≥ 150 minutes/week: 30 minutes of daily physical activity.

\*\* Exercise training ≥ 90 min with moderate intensity and/or ≥ 45 min with high intensity per week

### Other outcome measures

Fasting glucose was equal between groups at the postpartum visit (Figure 3a), but we observed a tendency towards lower 120 min glucose in the exercise group compared to the control group (5.2 mmol/l vs 5.8 mmol/l,  $p = 0.10$ ) (Figure 2b). The insulin concentration was significantly lower in the exercise group compared to the control group ( $p = 0.01$ ) (Table 1). Figure 2c outlines the insulin levels at baseline, in late pregnancy, and postpartum. HOMA2-IR (insulin resistance) was lower in the exercise group, but the group difference was not statistically significant (Figure 2d). No women in the exercise group compared to three women in the control group fulfilled the diagnostic criteria for type 2 diabetes postpartum ( $p = 0.19$ , Table 2). All three women were diagnosed with GDM in late pregnancy, and none had diabetes before pregnancy. We also observed a trend towards lower systolic and diastolic blood pressure in the exercise group (Table 1).

Approximately 75% of the total study population fulfilled the recommended amount of weekly general physical activity three months postpartum (Table 2). Twice as many women in the exercise group reported regular exercise (defined as  $\geq 90$  min with moderate intensity and/or  $\geq 45$  min with high intensity per week), but the between-group difference was not statistically significant. The number of women exclusively breastfeeding at the postpartum visit was not significantly different between groups (Table 2).



**Figure 2.** a) Fasting glucose at early pregnancy, late pregnancy, and postpartum. b) 120 min glucose after oral glucose tolerance test at early pregnancy, late pregnancy, and postpartum. c) insulin at early pregnancy, late pregnancy, and postpartum. d) homeostatic measurement of insulin resistance (HOMA2-IR) at early pregnancy, late pregnancy, and postpartum.



### **Additional analyses**

We analysed PPWR in both groups adjusted for number of days from birth to postpartum test and observed no significant effect on postpartum weight ( $p = 0.76$ ) or PPWR ( $p = 0.32$ ). The effect estimate of weight loss per day was  $-0.016$  kg. We found no effect of adjusting for lactation and physical activity.

Half of the exercising women included in the postpartum analysis ( $n = 19$ ) fulfilled the training intervention during pregnancy as described in the study protocol.<sup>23</sup> Detailed data are presented in Supplementary File 1 and Supplementary File 2. We found no difference in PPWR (postpartum minus early pregnancy) between the per protocol exercise group ( $-0.1$  kg, 95% CI,  $-2.7, 1.1$ ) and the control group ( $-1.7$  kg, 95% CI,  $-3.5, 0.3$ ) ( $p = 0.35$ ), and no difference in PPWR when using self-reported pre-pregnancy weight between the per protocol exercise group ( $2.5$  kg, 95% CI,  $-0.7, 3.8$ ) and the control group ( $0.2$  kg, 95% CI,  $-1.8, 2.9$ ) ( $p = 0.28$ ). At postpartum, there was no difference in mean weight between the exercise group ( $95.9$  kg) and the control group ( $94.8$  kg) ( $p = 0.47$ ) (Supplemental File 1). Women in the per protocol exercise group had significantly lower resting systolic and diastolic blood pressure compared to the control group, ( $117.0/73.1$  mmHg vs.  $124.0/78.4$  mmHg) (systolic BP,  $p = 0.01$ , diastolic BP,  $p < 0.01$ ), and they had lower insulin levels ( $14.1$  mmol/l vs  $19.7$  mmol/l,  $p = 0.04$ ) (Supplementary File 1).

No harmful, unintended or adverse events were reported.

### **DISCUSSION**

Offering supervised regular exercise during pregnancy for overweight and obese women did not lower PPWR compared to women receiving standard maternal care. Both groups regained the pre-pregnancy weight three months after delivery. However, we found a significantly lower blood insulin concentration and a tendency towards lower homeostatic

measurement of insulin resistance in the exercise group compared to the control group. This may imply a reduced risk for developing type 2 diabetes in the exercising women. Among women who adhered to the training protocol during pregnancy, we also found significantly lower systolic and diastolic blood pressure three months postpartum.

Pre-pregnancy BMI is a strong predictor of PPWR with higher weight retention in overweight and obese women.<sup>31,32</sup> We have found no RCTs assessing the isolated effects of exercise training in pregnancy on PPWR in exclusively overweight and obese women. Previous studies have combined different types of intervention, such as diet and exercise, and/or included participants of all BMI categories. Those RCTs have shown divergent results; some have found no effect,<sup>33-36</sup> whereas others have found lower PPWR in the intervention group.<sup>32,37</sup> Phelan and colleagues,<sup>32</sup> found lower PPWR in normal weight and overweight women after a lifestyle intervention program, but not among obese women. According to one meta-analysis, studies reporting lower PPWR have included women in all BMI categories and included both supervised exercise training and intensive dietary interventions.<sup>21</sup> Among studies providing ancillary analyses, some have suggested positive effects of exercise on PPWR among women adhering to the intervention protocol.<sup>32,33,35,38</sup> We did not show any differences in PPWR between groups using early pregnancy weight measurement, self-reported weight pre-pregnancy, or analysing women who exercised per protocol. However, women in both groups had almost regained their pre-pregnancy and early pregnancy weight at the postpartum visit. Our trial included supervised exercise training from early in pregnancy and throughout the pregnancy, but the results indicate that the amount or intensity of the exercise ought to be higher or combined with dietary intervention to improve outcomes. Adherence to the training protocol was low, and may have reduced the difference between groups. Low adherence to the training protocol is a common challenge in trials including obese pregnant women.

Obese women have an increased risk for high insulin values and for developing diabetes mellitus type 2 postpartum.<sup>39</sup> We found significantly lower concentration of insulin in the exercise- compared to the control group. During pregnancy the insulin resistance increases, especially in obese women.<sup>40,41</sup> To compensate, increased insulin secretion is needed.<sup>40</sup> Lower insulin and trends towards lower 120 minutes glucose level and lower HOMA2-IR among women in the exercise group, may indicate lower risk of developing type 2 diabetes. The difference between groups in incidence of type 2 diabetes was not significant, but our results may have been affected by a small sample size.

Obese women are at increased risk for high blood pressure during pregnancy and postpartum.<sup>42-44</sup> We observed significantly lower systolic and diastolic blood pressure among women who adhered to the prescribed exercise, compared to the control group. We are not aware of any previous trials assessing the effect of exercise training during pregnancy on postpartum blood pressure. However, exercise has been shown to lower resting blood pressure among obese, non-pregnant subjects.<sup>45,46</sup>

Women are recommended to be physically active during pregnancy and postpartum to maintain a healthy weight and to prevent negative health outcomes.<sup>12,47</sup> However, physical activity tends to decrease significantly during these periods, especially among women with high BMI.<sup>48</sup> Approximately 75% of women in our study reported fulfilling the recommendations of minimum 150 minutes of weekly moderate intensity physical activity at three months postpartum. A higher proportion of women in the exercise group (46% vs 25%) reported regular exercise postpartum. In conjunction with the inclusion criteria “not exercising regularly pre-pregnancy”, these numbers reveal an increase in exercise training for both groups postpartum compared to before pregnancy. The statistical comparison is likely hampered by a low number of participants in each group.

GWG and lactation have been found to be important factors for PPWR.<sup>32,49</sup> In the present study, we found no associations between GWG and PPWR or between lactation and PPWR.

### **Study strength and limitations**

The ETIP trial was the randomised, controlled study design. The exercise program was described in detail and should be easy to reproduce. Previous research has found supervised exercise to be important for adherence to the exercise protocol, for motivation, and for the safety of the participant, and to be more effective than general guidance.<sup>18</sup> We measured weight objectively at study entry and at postpartum, and we only included sedentary overweight/obese women in the trial. We measured skinfold thickness and body composition in addition to weight, and provided information on potential confounding factors such as lactation and GWG. Our intervention included the exercise program only, and no diet. Thus, we could assess the effect of exercise alone in contrast to previous trials with mixed interventions.

The main limitation was a small study sample. We did not recruit as many participants as originally planned and experienced additional drop-outs during the intervention period. This affected the power of the study and decreased the possibility of detecting true effects of the intervention. The proportion of drop-outs was, however, equally distributed between groups, and we had only two drop-outs in each group after delivery. In addition, only 50% of women in the exercise program adhered to the protocol. We prolonged the time limit for inclusion in the trial from gestational week 16 to 18, which reduced the mean number of weeks of exercise before delivery, and thus the effect of the intervention. Our change in inclusion criteria BMI from  $\geq 30$  to  $\geq 28$ , may have reduced the homogeneity of the trial population, but only five women in the postpartum analysis had a pre-pregnancy BMI below 30.

The current trial did not provide any information on diet and possible changes in eating habits in the groups. The control group underwent comprehensive health assessments during pregnancy and after delivery and this may have motivated also women in the control group to undertake lifestyle changes.

### **Generalisability**

The participants were recruited from Google advertisement and through an information letter to all pregnant women in Trondheim. There is a risk for over-representation of highly motivated women in the trial. This may influence the external validity (generalizability) of the trial, but not the internal validity (comparisons between groups).

### **Clinical relevance**

The exercise intervention in the current trial was based on the ACOG recommendations for physical activity and exercise during pregnancy. The program provides no equipment and consisted of exercises that could easily be implemented by women themselves at home. The findings are relevant for sedentary overweight and obese pregnant women. The finding of lower concentration of insulin in the exercise group is clinically important as this may reduce the risk of future type 2 diabetes.<sup>50</sup> The blood pressure was lower in the women who reported to exercise per protocol during pregnancy and imply a reduced risk for developing cardiovascular diseases. This highlights the need of increasing adherence to exercise training in pregnancy for this population. No adverse events related to exercise occurred, and the findings in the current trial support the recommendations for exercise training during pregnancy.

### **CONCLUSION**

Offering supervised exercise during pregnancy among overweight and obese women did not affect PPWR three months after delivery compared to standard antenatal care. Both groups

had regained their early pregnancy weight three months postpartum. We observed lower circulating insulin among the women in the exercise group, as well as lower blood pressure in those who adhered to the exercise protocol. This may decrease the risk for developing both type 2 diabetes and cardiovascular diseases in later life. Further studies are needed to assess if supervised exercise during pregnancy can reduce the risk for development of type 2 diabetes and hypertension postpartum.

## AKNOWLEDGEMENTS

### **Funding**

The presents study was supported by grants from The Norwegian Fund for Post-Graduate Training in Physiotherapy, The Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU).

### **Prior publications of the study:**

Exercise Training in Pregnancy for obese women (ETIP): study protocol for a randomised controlled trial. Moholdt TT, Salvesen K, Ingul CB, Vik T, Oken E, Mørkved S. *Trials*. 2011 Jun 17;**12**:154. doi: 10.1186/1745-6215-12-154.

Exercise Training and Weight Gain in Obese Pregnant Women: A Randomised Controlled Trial (ETIP Trial). Garnæs KK, Mørkved S, Salvesen Ø, Moholdt T. *PLoS Med*. 2016 Jul **26**;13:e1002079. doi: 10.1371/journal.pmed.1002079.

### **CONFLICT OF INTEREST**

The authors declare no conflicts of interest.

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**Table 1.** Outcomes at three months postpartum. “Per protocol” model based analyses with baseline mean (all participants at early pregnancy) and comparison between groups are presented as mean, 95% confidence interval (CI) and p-value. Weight retention is estimated based both on the difference between postpartum weight and early pregnancy weight, and between postpartum weight and pre-pregnancy weight.

	Baseline Mean	Per protocol Exercise Group (n = 19)		Control Group (n = 34)		Between-Group Comparison		
		Final Mean	95% CI	Final Mean	95% CI	Mean Diff	95% CI	p-Value
<b>Weight (kg)</b>	96.3	95.9	91.8, 100.1	94.8	91.0, 98.5	1.18	-2.05, 4.42	0.47
<b>PPWR<sup>1</sup> (kg)*</b>		-0.1	-3.0, 2.2	-1.7	-3.5, 0.4	1.64	-1.82, 5.11	0.35
<b>PPWR<sup>2</sup> (kg)**</b>		2.5	-1.5, 4.8	0.2	-1.8, 3.1	2.32	-1.98, 6.61	0.28
<b>BMI (kg/m<sup>2</sup>)</b>	34.6	34.5	33.1, 35.8	34.0	32.8, 35.2	0.48	-0.70, 1.66	0.42
<b>Waist circumference (cm)</b>	106.5	99.3	95.6, 103.1	104.4	99.9, 109.0	-5.10	-11.66, 1.46	0.13
<b>Body composition***</b>								
Fat mass (kg)	43.1	42.3	39.1, 44.9	42.0	39.2, 44.9	0.28	-2.46, 3.01	0.84
Fat mass (%)	44.8	44.3	42.7, 45.9	44.08	42.7, 45.5	0.22	-1.15, 1.59	0.76
Fat-free mass (kg)	52.3	51.9	49.8, 54.0	52.6	50.9, 54.4	-0.74	-2.89, 1.41	0.50
Fat-free mass (%)	55.3	55.6	53.9, 57.4	56.3	54.7, 57.8	-0.61	-2.29, 1.06	0.47
<b>Skinfold thickness</b>								
Biceps area (mm)	21.2	16.4	13.9, 18.9	17.6	15.5, 19.8	-1.21	-3.77, 1.36	0.36
Triceps area (mm)	30.0	26.6	24.0, 29.2	26.9	24.7, 29.1	-0.31	-3.04, 2.42	0.82
Subscapular area (mm)	32.1	27.9	25.1, 30.8	30.2	27.8–32.6	-1.29	-5.335, 0.78	0.14
<b>Blood pressure</b>								
Systolic BP (mm/Hg)	124.4	117.0	112.6, 121.4	124.0	120.5, 127.5	-6.98	-12.39, -1.56	0.01
Diastolic BP (mm/Hg)	76.0	73.1	69.8, 76.3	78.4	75.8, 81.0	-5.37	-9.29, -1.44	<0.01
<b>Blood measurements</b>								
Fasting glucose (mmol/l)	4.8	5.0	4.8, 5.3	5.1	4.8, 5.3	-0.04	-0.336, 0.29	0.83
120-min glucose (mmol/l)	6.0	5.3	4.6, 6.0	5.9	5.3, 6.5	-0.56	-1.44, 1.32	0.21
Insulin (pmol/l)	134.0	97.9	66.7, 129.2	136.8	112.5, 161.8	-39.31	-75.70, -2.85	0.04
HbA1c (%)	5.2	5.3	5.2, 5.55	5.4	5.3, 5.5	-0.09	-0.27, 0.10	0.35
Insulin C-peptide (nmol/l)	0.6	0.7	0.6, 0.8	0.7	0.6, 0.8	-0.00	-0.12, 0.12	0.99
Triglycerides (mmol/l)	1.4	0.9	0.6, 1.2	1.0	0.8, 1.2	-0.12	-0.47, 0.23	0.51
Ferritin (pmol/l)	116.8	62.0	44.9, 79.3	63.8	50.6, 77.7	-1.71	-23.30, 19.91	0.88
HDL cholesterol (mmol/l)	1.7	1.5	1.3, 1.6	1.5	1.4, 1.6	-0.02	-0.18, 0.14	0.81
LDL cholesterol (mmol/l)	2.9	3.2	2.8, 3.7	3.2	2.8, 3.5	-0.07	-0.47, 0.61	0.80
Total cholesterol (mmol/l)	5.0	5.0	4.5, 5.5	5.1	4.7, 5.5	-0.12	-0.72, 0.48	0.69
Hemoglobin (g/l)	126.6	127.4	122.9, 131.9	129.5	126.0, 130.0	-2.10	-7.60, 3.30	0.44

High-sensitivity CRP (mg/l)	10.7	4.3	2.4, 6.2	4.8	3.3, 6.2	-0.49	-2.86, 1.88	0.69
HOMA2-IR	2.5	3.1	2.2, 4.1	4.9	3.3, 6.5	-1.76	-3.90, 0.37	0.06

**Missing:** The number of missing in the exercise and the control group varied between 1 and 3.

**Statistics:** The effect of treatment was assessed with linear mixed models. For the primary and secondary outcomes, the effect of time and treatment was taken as a fixed effect. Due to randomization, no systematic differences between groups at baseline were assumed.

**Abbreviations:** PPWR, postpartum weight retention. BMI, Body mass index. BP, blood pressure. HbA1c, Glycated Hemoglobin. HDL, High-density lipoprotein. LDL, Low-density lipoprotein. CRP, C-reactive protein, HOMA2-IR, homeostatic assessment of insulin resistance.

\*PPWR<sup>1</sup>, postpartum weight minus weight at early pregnancy.

\*\*PPWR<sup>2</sup>, postpartum weight minus pre-pregnancy weight. Weight at pre-pregnancy was based on self-reported data. Mean pre-pregnancy weight for all participants were 94.4 kg.

\*\*\*Body composition was measured by air displacement plethysmography (BOD POD).

**Table 2.** Outcomes at three months postpartum, per protocol. Analysis for the exercise per protocol group and the control group and comparison between groups are presented in number of participants (N), percentage (%), odds ratio (OR), 95% confidence interval (CI), and p-value.

	<b>Per protocol Exercise group (n = 19)</b>	<b>Control group (n = 34)</b>	<b>Between-Group Comparison</b>		
	<i>n (%)</i>	<i>n (%)</i>	<i>Odds Ratio</i>	<i>95% CI</i>	<i>p - value</i>
Type 2 diabetes	0 (0)	3 (9.1)	0.63*	0.50, 0.78	0.54
Hypertension	1 (5.6)	3 (10.0)	1.9	0.18, 19.7	1.00
Physical activity $\geq$ 150 minutes/week**	12 (80.0)	22 (78.6)	0.92	0.19, 4.34	1.00
Exercise training***	7 (46.7)	7 (25.9)	0.40	0.11, 1.51	0.19
Exclusively breastfeeding	8 (50.0)	21 (77.8)	3.50	0.92, 13.3	0.93
Breastfeeding 3-4 meals/24h	3 (18.8)	1 (3.7)	0.17	0.12, 1.76	0.14
<p><b>Missing:</b> Type 2 diabetes: Exercise group 1 missing, control group 1 missing. Hypertension: Exercise group 1 missing, control group 4 missing. Physical activity questionnaire: Exercise group 4 missing, control group 6 missing. Lactating questionnaire: Exercise group 3 missing, control group 7 missing.</p> <p><b>Statistics:</b> The data were analyzed by Fisher's Exact test.</p> <p><b>Definitions:</b> Type 2 diabetes: Fasting plasma glucose <math>\geq</math> 7.0 mmol/l or 2 h concentration <math>\geq</math> 11.1 mmol/l, according to the definition of the World Health Organization (WHO). Hypertension: Systolic blood pressure <math>\geq</math> 140, diastolic blood pressure <math>\geq</math> 90.</p> <p>* For cohort control group.</p> <p>**Physical activity <math>\geq</math> 150 minutes/week: 30 minutes of daily physical activity.</p> <p>*** Exercise training <math>\geq</math> 90 min with moderate intensity and/or <math>\geq</math> 45 min with high intensity per week</p>					

## Appendix 1. Information sheet



## Appendix 1

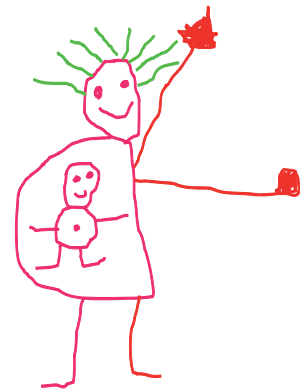
Forespørsel om å delta i en vitenskapelig undersøkelse

# TRENING I SVANGERSKAPET

**En randomisert klinisk studie av trening av gravide med en kroppsmasseindeks  $\geq 28$**



Studien er et samarbeidsprosjekt mellom NTNU og Kvinneklinikken ved St. Olavs Hospital





### Bakgrunn og målsetting

I perioden 2010-2015 gjennomføres et forskningsprosjekt ved St. Olavs Hospital, med målsettingen å øke kunnskapen om helsen hos gravide med kroppsmasseindeks  $\geq 28$ . Undersøkelsen tar sikte på å finne ut mer om effekter av trening under svangerskapet, i forebygging og behandling av svangerskapsrelatert sykdom (svangerskapsdiabetes, høyt blodtrykk, rygg- og/eller bekkenrelaterte smerter, urin- og/eller avføringslekkasje). Vi vil også undersøke om treningen påvirker fødselen.

### Hvem kan delta, og hva innebærer deltakelse

Gravide kvinner ( $\geq 18$  år) med kroppsmasseindeks\*  $\geq 28$  inviteres til å delta. For at vi skal få vite mer om helsetilstanden generelt, og om helsen i svangerskapet spesielt, ber vi om å få ta blodprøver av alle deltakerne i prosjektet, og at alle svarer på spørreskjema og gjennomfører enkelte tester. Testingen foregår ved St. Olavs Hospital hovedsakelig i svangerskapsuke 14 (12-18) og 37, samt tre måneder etter fødselen. Testingen vil foregå over to dager, og den ene dagen må du være på sykehuset i ca tre timer fordi det skal gjøres en sukkerbelastningstest, der blodprøvene skal tas med to timers mellomrom. Du møter fastende denne dagen og vil bli tilbudt mat etterpå. Vi vil også se på blodårene dine med ultralyd, registrere vekt og gjøre målinger av kroppssammensetning, teste utholdenhet (kondisjon), og gjøre noen tester av bekkenbunns-funksjon og bekkensmerter. Dessuten ber vi om at vi får benytte informasjon om vekt og blodtrykk fra svangerskapsjournalen, og opplysninger om fødselsforløpet og barnets vekt, lengde samt rutine barnelegeundersøkelse fra fødselsjournalen. Vi ber også om å få ta blodprøve fra navlestrengen like etter fødsel, og på barselavdelingen vil barnets kroppssammensetning beregnes.

Når det gjelder trening under svangerskapet, vet man ennå ikke sikkert om svangerskapsproblemer kan behandles og forebygges, og eventuelt hvilke tiltak som har best effekt. Deltakerne i denne undersøkelsen blir derfor tilfeldig fordelt i to grupper. En datamaskin avgjør ved loddtrekning (randomisering) hvilken behandling du skal ha. Du får et tilfeldig nummer i databasen, og bare prosjektkoordinator kjenner koblingen mellom nummeret i databasen og din identitet. Deltakerne i den ene gruppen får den informasjonen som nå gis rutinemessig til gravide. Den andre gruppen er en treningsgruppe, hvor deltakerne skal delta i en times trening to-tre ganger i uka ved St. Olavs hospital. I tillegg skal et hjemmetreningsprogram på 45 minutter gjennomføres minst en gang i uka. Treningen gjennomføres fra oppstart i studien og til tester i uke 37, eventuelt helt til fødsel hvis du orker. Treningen tilpasses din fysiske form.

\*

#### Kroppsmasseindeks beregnes ved:

$$\frac{\text{Vekt (kg)}}{\text{Høyde (m)} \times \text{høyde (m)}}$$

Høyde (m) x høyde (m)

Eksempel:  $84\text{kg}/1,65\text{ m} \times 1,65\text{ m} = 31$

Du må kunne møte til testing på dagtid. Hvis du kommer i treningsgruppa, kan du få velge mellom trening på dag- eller kveldstid. Alle deltakerne vil få en pakke med barnemat til en verdi av ca 500 kroner som takk for at de deltar.

Etter at forskningsprosjektet er avsluttet, vil alle deltakere få skriftlig informasjon om resultatene. Hvis trening viser seg å ha god effekt som behandling og forebygging, vil deltakerne i kontrollgruppen få informasjon om treningsprogrammet etter at prosjektet er avsluttet. For å kunne undersøke langtidsvirkningen av trening under svangerskapet, ber vi om samtykke til at data oppbevares i 20 år, slik at vi kan kontakte deltakerne igjen for eventuelle oppfølgingsstudier på din og barnets helse i årene etter fødselen.

#### **Frivillighet og samtykke**

- Deltakelse i prosjektet er frivillig.
- Alle deltakere i prosjektet har rett til å trekke seg fra prosjektet når de måtte ønske, uten at dette får konsekvenser for videre oppfølging og behandling. All informasjon deltakerne gir i forbindelse med prosjektet, behandles konfidensielt, og data aidentifiseres. Alle som skal ha kontakt med de innsamlede data, er underlagt taushetsplikt i henhold til Forvaltningslovens § 13 og Helsepersonellovens § 21.
- Deltakerne er dekket av Pasientskadeerstatningsordningen.

#### **Etisk og faglig vurdering**

- Prosjektet er vurdert av Regional komite for medisinsk forskningsetikk, Region Midt-Norge, og komiteen har godkjent at prosjektet gjennomføres.

Ansvarlige prosjektledere er Kjell Åsmund Salvesen, overlege ved Kvinneklubben, St. Olavs Hospital, Siv Mørkved, Forskningsjef ved St. Olavs hospital, og Trine Moholdt, post doktor ved Institutt for samfunnsmedisin, NTNU.

HVIS DU ØNSKER Å DELTA, ELLER HAR SPØRSMÅL OM PROSJEKTET, BES DU KONTAKTE:

Prosjektleder: Trine Moholdt, tlf: 97 09 85 94, e-post: [trine.moholdt@ntnu.no](mailto:trine.moholdt@ntnu.no)

Eller:

Kirsti Krohn Garnæs, e-post: [kirsti.k.garnas@ntnu.no](mailto:kirsti.k.garnas@ntnu.no)

ID-nummer:

*(fylles ut av ..)*

Hvis du ønsker å delta må du fylle ut dette samtykkeformularet. Samtykkeformularet leveres til prosjektkoordinator ved oppmøte for første test.

## **SAMTYKKEERKLÆRING FOR PROSJEKTET "TRENING I SVANGERSKAPET"**

Jeg har lest informasjonsskrivet og har hatt anledning til å stille spørsmål. Jeg er også informert om at journalopplysninger fra det aktuelle svangerskap og fødsel vil bli gjennomgått og registrert og samtykker i å delta i studien.

Sted og dato, .....

-----  
Underskrift

## Appendix 2. Exercise program, Hospital



**Appendix 2.**

## TRENINGSPROGRAM

**Dette programmet utføres på fellestreninger på St. Olavs Hospital**

Hvorfor	Tid	Hva	Beskrivelse
Oppvarming	10 min	Gange på tredemølle	Du skal bli god og varm, og lett andpusten. Borgs skala:12-13
Utholdenhet	25 min	Gange på tredemølle	Du skal kjenne at du trener, men klare å snakke litt underveis. Borgs skala: 13-15
Bevegelighet	2-3 min	Lette tøyninger	Tøy ut på baksida og forsida av lår, bakside legger.
Styrke bein	2-3 min	Knebøy	Stå med hoftebreddes avstand mellom beina og bøy ned så langt du klarer i knærne. 10 repetisjoner x 3
Bekkenbunn	3 min	Stående løft	10 repetisjoner (hold 6-8 sek + raske løft mot slutten av holdeperioden)
Styrke rygg + mage	5 min	Diagonal-løft + Planken	Stå på alle fire og løft motsatt arm og ben. 10 repetisjoner hver side x 3 + Knær eller tær og underarmer i gulvet. Rett linje fra skulder til kne eller ankel. Hold i 30 sek.
Bekkenbunn	3 min	Firefotstående	10 repetisjoner (hold 6-8 sek + raske løft mot slutten av holdeperioden)
Styrke overkropp	3 min	Armheving	Knær eller tær i gulvet. Strak rygg. 10 repetisjoner x 3
Styrke mage	3 min	Skrå sit-ups*	Ryggliggende: skulder mot motsatt kne. 10 repetisjoner på hver side, x 3. Trekk sammen bekkenbunnsmuskler før løft av overkroppen.
Bekkenbunn	3 min	Sittende	10 repetisjoner (hold 6-8 sek + raske løft mot slutten av holdeperioden)

Totalt 60 min

\* Kan være ubehagelig for noen pga avklemming av vena cava – da utføres øvelsen i sittende (skredderstilling, motstand mot rotasjon annenhver side). Hvis ubehaglig nedtrykksfølelse i bekkenet / underlivet – IKKE gjør øvelsen.



## Appendix 3. Home-based exercise





### Appendix 3.

## EGENTRENING

Egentreningsprogrammet består av to deler, både utholdenhetstrening (30 min) og styrketrening (ca 15 min).

Utholdenhetstreningen kan oppnås på ulike måter, men det er viktig at du finner en treningsform som passer deg. Du kan gå rask tur, jogge, sykle, svømme eller annet. Det viktigste er at du får økt puls over lengre tid (30 min). Intensiteten skal være såpass at det oppleves *litt anstrengende*, det vil si at du skal bli varm og svett.

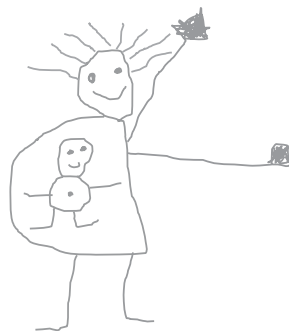
Styrketreningen har til hensikt å styrke ben, armer, rygg, mage og bekkenbunnsmuskler. Det er viktig at du prøver deg litt fram og finner den utgangsstillingen som passer best for deg. Spør gjerne personen som leder gruppetreningen om hjelp til dette. Det vil være naturlig at en utgangsstilling som passer deg bra i begynnelsen av treningsperioden, passer mindre bra mot slutten av treningsperioden enten fordi magen har blitt større, du har blitt sterkere eller noe oppleves ubehagelig. Da kan du bytte til en annen utgangsstilling.

Du skal ta **10 repetisjoner x 3**

Underveis eller etter treningen skal du ikke ha noe ubehag. Det er naturlig å være litt støl i etterkant av treningen, spesielt i oppstartsfasen, men du skal ikke ha smerter. Ta kontakt dersom noe medfører ubehag.

Hjemmetreningsprogrammet skal gjøres minst **to dager i uka** i tillegg til treninga på sykehuset. Det er fint om du er så aktiv som mulig i hverdagen utover denne treninga også.

OBS! Husk å registrere treninga i treningsdagboka!



## Styrketrening

### KNEBØY



Stå med hoftebreddes avstand med føttene. Bøy ned i hofte- og kneledd med ”knær over tær”, og rumpa ut bak som om du skal sette deg på en stol. Stram setet og strekk opp igjen til stående stilling. Varier tyngden med hvor langt du bøyer ned.

10 repetisjoner x 3

### ”PLANKEN” (gjøres tre ganger)



#### Alternativ A)

Stå på alle fire (knær og strake armer) med ryggen i nøytral stilling. Trekk navlen inn mot ryggen (nedre del av magen) og hold posisjonen i 30 sek.



#### Alternativ B)

Stå på knær og strake armer, eller ha underarmer i gulvet. Hold kroppen strak og ryggen i nøytral stilling. Trekk navlen inn mot ryggen (nedre del av magen) og hold posisjonen i 30 sek.



#### Alternativ C)

Stå på tærne og albue, hold kroppen strak og ryggen i nøytral stilling. Trekk navlen inn mot ryggen (nedre del av magen) og finn stillingen som bildet viser: Hold posisjonen i 30 sek.

### **OBS!**

**Pust godt mens du gjør øvelsen (ikke hold pusten)!**

**Dersom du ikke klarer å holde posisjonen må du gå bytte til en enklere utgangsstilling eller korte ned holdetiden!**

## Exercise Training in Pregnancy

### ARMHEVINGER



#### Alternativ A)

Stå med føttene i skulderbreddes avstand et stykke ut fra veggen. Len deg mot veggen på strake armer med strak kropp. Trekk navlen inn mot ryggen (nedre del av magen, se ”Plankeøvelsen”). Gjør armhevinger mot veggen. Varier tyngden med å stå nærmere veggen (lettere) eller lenger fra veggen (tyngre).

10 repetisjoner x 3



#### Alternativ B)

Stå på knær og strake armer. Trekk navlen inn mot ryggen (nedre del av magen, se ”Plankeøvelsen”). Gjør armhevinger med knærne i gulvet og strak kropp.



#### Alternativ C)

Stå på tær og strake armer. Trekk navlen inn mot ryggen (nedre del av magen, se ”Plankeøvelsen”). Gjør armhevinger med tærne i gulvet og strak kropp.

### DIAGONALLØFT



#### Alternativ A)

Stå på knær og strake armer med hodet i nøytral stilling. Trekk navlen inn mot ryggen (nedre del av magen, se ”Plankeøvelsen”). Løft diagonalt arm og ben til vannrett stilling.

10 repetisjoner x 3

#### Alternativ ved smerter:



#### Alternativ B)

Stå på knær og strake armer med hodet i nøytral stilling. Trekk navlen inn mot ryggen (nedre del av magen, se ”Plankeøvelsen”). Løft en og en arm strakt frem.

## Exercise Training in Pregnancy



Alternativ C)

Stå på knær og strake armer eller på albue med hodet i nøytral stilling. Trekk navlen inn mot ryggen (nedre del av magen, se ”Plankeøvelsen”). Strekk et og et ben vannrett bakover.

### BEKKENBUNNENS MUSKLER

Løft opp og inn rundt urinrør, skjede og endetarm uten å spenne mage, sete og lår. Ta i så hardt du kan under hver sammentrekning og forsøk å holde i 6-8 sekunder før du slipper rolig ned. Pust rolig ut og inn, både under og mellom muskelsammentrekningene. Velg en eller flere av disse utgangstilningene:



Alternativ A)

Sitt med bena fra hverandre i skredderstilling med rett rygg. Trekk sammen rundt åpningene i bekkenbunnen.



Alternativ B)

Stå med bena fra hverandre, kjenn etter at du er slapp i setemusklene mens du trekker sammen i bekkenbunnsmusklene.

## Exercise Training in Pregnancy



Alternativ C)

Stå på alle fire med knærne ut til siden og føttene sammen. Hev bekkenbunnen opp og innover.

## SKRÅ MAGEMUSKLER



Alternativ A)

Skrå sit-ups i sittende. Sitt i skredderstilling med rett rygg. Press motsatt arm og kne mot hverandre. Bruk strak arm og press diagonalt.

10 repetisjoner til hver side, x 3



Alt. b)

Skrå sit-ups i ryggliggende. Ligg på ryggen med bøyde ben og korsryggen i kontakt med gulvet. Løft overkroppen litt opp fra underlaget slik at skulder peker mot motsatt kne.

**OBS!**

**Noen gravide kan bli uvel eller svimmel av å ligge på ryggen. Dersom det gjelder deg bør du trene de skrå bukmusklene i utgangsstilling a.**

Trekk sammen bekkenbunnsmusklene samtidig som du gjør skrå sit-ups.



## Appendix 4. Exercise registration at Hospital









## Appendix 5. Physical activity registration at home

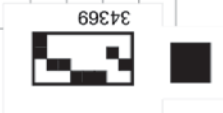


# Appendix 5.

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ID-nummer

Uke	Aktiviteter	Intensitet		Tidsbruk (i minutter)													
		Litt anstreng ende	Anstreng ende	Meget anstreng ende	0-10 min	10-20 min	20-30 min	30-40 min	40-50 min	50-60 min	60-70 min	70-80 min	80-90 min	90-100 min	100-120 min	over120 min	
Mandag	<input type="checkbox"/> Gå <input type="checkbox"/> Jogge/løpe <input type="checkbox"/> BBT <input type="checkbox"/> Sykle <input type="checkbox"/> Svømme <input type="checkbox"/> Styrke <input type="checkbox"/> Annet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tirsdag	<input type="checkbox"/> Gå <input type="checkbox"/> Jogge/løpe <input type="checkbox"/> BBT <input type="checkbox"/> Sykle <input type="checkbox"/> Svømme <input type="checkbox"/> Styrke <input type="checkbox"/> Annet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Onsdag	<input type="checkbox"/> Gå <input type="checkbox"/> Jogge/løpe <input type="checkbox"/> BBT <input type="checkbox"/> Sykle <input type="checkbox"/> Svømme <input type="checkbox"/> Styrke <input type="checkbox"/> Annet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Torsdag	<input type="checkbox"/> Gå <input type="checkbox"/> Jogge/løpe <input type="checkbox"/> BBT <input type="checkbox"/> Sykle <input type="checkbox"/> Svømme <input type="checkbox"/> Styrke <input type="checkbox"/> Annet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



ID-nummer

Aktiviteter	Intensitet			Tidsbruk (i minutter)											
	Litt anstreng ende	Anstreng ende	Meget anstreng ende	0-10 min	10-20 min	20-30 min	30-40 min	40-50 min	50-60 min	60-70 min	70-80 min	80-90 min	90-100 min	100-120 min	over 120 min
Fredag <input type="checkbox"/> Gå <input type="checkbox"/> Jogge/løpe <input type="checkbox"/> BBT <input type="checkbox"/> Sykle <input type="checkbox"/> Svømme <input type="checkbox"/> Styrke <input type="checkbox"/> Annet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Søndag <input type="checkbox"/> Gå <input type="checkbox"/> Jogge/løpe <input type="checkbox"/> BBT <input type="checkbox"/> Sykle <input type="checkbox"/> Svømme <input type="checkbox"/> Styrke <input type="checkbox"/> Annet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## Appendix 6. Questionnaire, physical activity and exercise early pregnancy





## Appendix 6.

### FYSISK AKTIVITET OG TRENING

Statens råd for ernæring og fysisk aktivitet skiller mellom fysisk aktivitet og trening. Vennligst forhold deg til definisjonene nedenfor når du besvarer de neste spørsmålene.

Fysisk aktivitet defineres som "all kroppslig bevegelse produsert av skjelettmuskulatur som resulterer i en vesentlig økning i energiforbruket utover hvilenivå".

**30) Sosial- og helsedirektoratet anbefaler voksne å være i fysisk aktivitet 30 minutter daglig for å oppnå helsegevinst. Oppfyller du dette daglig?**

- Ja
- Nei

Trening defineres som "fysisk aktivitet i fritiden som gjentas regelmessig over tid med målsetting å forbedre for eksempel form, prestasjon eller helse".

**31) Trente du regelmessig siste året før du ble gravid?**

- Ja
- Nei (gå videre til spørsmål 30)

**32) Hvis ja, hvor mange dager i uken trente du gjennomsnittlig det siste året før dette svangerskapet?**

- 1 dag
- 2 dager
- 3 dager
- 4 dager
- 5 eller flere dager

**33) Hvor lenge trente du vanligvis per økt?**

- 0-30 min
- 30-60 min
- 60-90 min
- >90 min

**34) På hvilken intensitet trente du vanligvis?**

- Uten å bli svett eller andpusten (oppleves litt anstrengende)
- Ble svett og litt andpusten (oppleves anstrengende)
- Ble veldig svett og pustet tungt (oppleves svært anstrengende)

**35) Trener du regelmessig nå som du er gravid?**

- Ja
- Nei (gå til spørsmål 36)

**36) Hvis ja, hvor mange dager i uken trener du gjennomsnittlig?**

- 1 dag
- 2 dager
- 3 dager
- 4 dager
- 5 eller flere dager

**37) Hvor lenge trener du vanligvis per økt nå?**

- 0-30 min  30-60 min  60-90 min  >90 min

**38) På hvilken intensitet trener du vanligvis?**

- Uten å bli svett eller andpusten (oppleves litt anstrengende)  
 Blir svett og litt andpusten (oppleves anstrengende)  
 Blir veldig svett og puster tungt (oppleves svært anstrengende)

**39) Har du opprettholdt samme treningsnivå som før graviditeten?**

- Jeg var mer aktiv før graviditeten  
 Jeg er like aktiv som før graviditeten  
 Jeg er mer aktiv nå enn før graviditeten

**40) Hvilken form for trening bedriver du nå? (sett ett eller flere kryss)**

- Spesiell gymnastikk/aerobic for gravide  Aerobic/gymnastikk/dans uten hopp og løp  Aerobic/gymnastikk/dans med hopp og løp
- Folkedans/rock/swing  Sykling  Rask gange/turgange
- Løping/jogging/orientering/skigåing  Ballspill/nettballspill  Svømming
- Helsestudio/styrketrening  Yoga/Pilates  Kampsport
- Annet: \_\_\_\_\_

**41) Hvor ofte gjør du hjemmeøvelser for disse muskelgrupper?**

	Aldri	1x/uke	2x/uke	3x/uke	>3x/uke
Magemuskler	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ryggmuskler	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bekkenbunnsuskler (innvendig muskler rundt skjede, urinrør og endetarm)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**42) Hvor mange minutter bruker du hver dag på å sykle/gå/jogge til og fra arbeid?**

(legg sammen tiden til og fra arbeidet)

- Ingen  20 - 30 min  30 - 60 min  >60 min

Appendix 7. Questionnaire, physical activity and exercise late pregnancy



## Appendix 7.

**FYSISK AKTIVITET OG TRENING**

Statens råd for ernæring og fysisk aktivitet skiller mellom fysisk aktivitet og trening. Vennligst forhold deg til definisjonene nedenfor når du besvarer de neste spørsmålene.

***Fysisk aktivitet*** defineres som "all kroppslig bevegelse produsert av skjelettmuskulatur som resulterer i en vesentlig økning i energiforbruket utover hvilenivå".

**14) Sosial- og helsedirektoratet anbefaler voksne å være i fysisk aktivitet 30 minutter daglig for å oppnå helsegevinst. Oppfyller du dette daglig?**

- Ja  Nei

***Trening*** defineres som "fysisk aktivitet i fritiden som gjentas regelmessig over tid med målsetting å forbedre for eksempel form, prestasjon eller helse".

**15) Trener du regelmessig nå?**

- Ja  Nei (gå til spørsmål 20)

**16) Hvis ja, hvor mange dager i uken trener du?**

- 1 dag  
 2 dager  
 3 dager  
 4 dager  
 5 eller flere dager

**17) Hvor lenge trener du vanligvis per økt nå?**

- 0-30 min  30-60 min  60-90 min  >90 min

**18) På hvilken intensitet trener du vanligvis?**

- Uten å bli svett eller andpusten (oppleves lite anstrengende)  
 Blir svett og litt andpusten (oppleves anstrengende)  
 Blir veldig svett og puster tungt (oppleves svært anstrengende)

**19) Hvilken form for trening bedriver du? (sett ett eller flere kryss)**

- |  |   |   |
|--|---|---|
| <input type="checkbox"/> Spesiell gymnastikk/<br>aerobic for gravide | <input type="checkbox"/> Aerobics /gymnastikk/<br>dans uten hopp og løp | <input type="checkbox"/> Aerobic / gymnastikk<br>dans med løp og hopp |
| <input type="checkbox"/> Folkedans /rock /swing                      | <input type="checkbox"/> Sykling  | <input type="checkbox"/> Rask gange /turgange                         |
| <input type="checkbox"/> Løping /jogging/<br>orientering /skigåing   | <input type="checkbox"/> Ballspill /netballspill                        | <input type="checkbox"/> Svømming                                     |
| <input type="checkbox"/> Helsestudio /styrketrening                  | <input type="checkbox"/> Yoga /Pilates                                  | <input type="checkbox"/> Kampsport                                    |
| <input type="checkbox"/> Annet: _____                                |   |   |

TRENING I SVANGERSKAPET – TEST 2

Initialer  ID-nummer

**20) Hvor ofte gjør du hjemmeøvelser for disse muskelgrupper?**

	<b>Aldri</b>	<b>1x/uke</b>	<b>2x/uke</b>	<b>3x/uke</b>	<b>&gt;3x/uke</b>
Magemuskler	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ryggmuskler	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bekkenbunnsuskler (innvendige muskler rundt skjede, urinrør og endetarm)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**21) Hvor mange minutter bruker du hver dag på å sykle /gå /jogge til og fra arbeidet?**

*(legg sammen tiden til og fra arbeidet)*

Ingen       20 - 30 min       30 - 60 min       >60 min

Appendix 8. Questionnaire, physical activity and exercise postpartum





## Appendix 8.

### FYSISK AKTIVITET OG TRENING

Statens råd for ernæring og fysisk aktivitet skiller mellom fysisk aktivitet og trening. Vennligst forhold deg til definisjonene nedenfor når du besvarer de neste spørsmålene.

***Fysisk aktivitet*** defineres som "all kroppslig bevegelse produsert av skjelettmuskulatur som resulterer i en vesentlig økning i energiforbruket utover hvilenivå".

**52) Sosial- og helsedirektoratet anbefaler voksne å være i fysisk aktivitet 30 minutter daglig for å oppnå helsegevinst. Oppfyller du dette daglig?**

- Ja  Nei

**Trening** defineres som "fysisk aktivitet i fritiden som gjentas regelmessig over tid med målsetting å forbedre for eksempel form, prestasjon eller helse".

**53) Trener du regelmessig NÅ?**

- Ja  Nei (gå til spørsmål 60)

**54) Hvis ja, hvor mange dager i uken trener du?**

- 1 dag  
 2 dager  
 3 dager  
 4 dager  
 5 eller flere dager

**55) Når startet du med trening etter fødselen?**  uker etter fødselen

**56) Hvor lenge trener du vanligvis per økt nå?**

- 0-30 min  30-60 min  60-90 min  >90 min

**57) På hvilken intensitet trener du vanligvis?**

- Uten å bli svett eller andpusten (oppleves lite anstrengende)  
 Blir svett og lett andpusten (oppleves anstrengende)  
 Blir veldig svett og puster tungt (oppleves svært anstrengende)

**58) Har du opprettholdt samme treningsnivå som før graviditeten?**

- Jeg var mer aktiv før graviditeten  
 Jeg er like aktiv som før graviditeten  
 Jeg er mer aktiv nå enn før graviditeten

TRENING I SVANGERSKAPET – TEST 3 Initialer  ID-nummer

**59) Hvilken form for trening bedriver du? (flere kryss mulig)**

- Spesiell gymnastikk/  
barseltrening       Aerobics /gymnastikk/  
dans uten hopp og løp       Aerobic / gymnastikk  
dans med løp og hopp
- Folkedans /rock /swing       Sykling       Rask gange /turgange
- Løping /jogging/  
orientering /skigåing       Ballspill /nettballs spill       Svømming
- Helsestudio /styrketrening       Yoga /Pilates       Kampsport
- Annet: \_\_\_\_\_

**60) Hvor ofte gjør du hjemmeøvelser for disse muskelgruppene?**

	Aldri	1x/uke	2x/uke	3x/uke	>3x/uke
Magemuskler	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ryggmuskler	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bekkenbunns­muskler (innvendige muskler rundt skjede, urinrør og endetarm)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**61) Dersom du trener bekkenbunns­muskler, hvor mange ”knip” (sammentrekninger av**

**bekkenbunns­muskle­ne) gjør du per dag?**  knip

**62) Har du fått informasjon om bekkenbunnstrening etter fødselen?**

- Ja, fra: (flere kryss mulig)
- Barselavdelingen
  - Jordmor / helsesøster / lege
  - Brosjyrer / bøker / internett
  - Muntlig informasjon fra andre: \_\_\_\_\_
- Nei

**63) Hvor mange dager i uka går du tur nå?**

- 1     2     3     4     5     6     7

**64) Hvor lenge går du per gang (i gjennomsnitt)?**

- Under 5 min
- 5-9 min
- 10-19 min
- 20-29 min
- 30-44 min
- 45-59 min
- 1-1,5 t
- 1,5-2 t
- Over 2 t

TRENING I SVANGERSKAPET – TEST 3 Initialer  ID-nummer

**65) Når du går tur; i hvilket tempo går du (i gjennomsnitt)?**

- Sakte tempo - Uten å bli svett og andpusten (oppleves lite anstrengende)
- Moderat tempo - Blir svett og lett andpusten (oppleves anstrengende)
- Raskt tempo - Blir veldig svett og puster tungt (oppleves svært anstrengende)



## Appendix 9. Questionnaire, breastfeeding postpartum



**Appendix 9.****AMMING OG BARNETS HELSE****18) Da du kom hjem fra fødeklubben, hvor mye ammet du da?**

- Alle måltider (fullammet)
- 3-4 måltider per døgn
- Ca. 2 måltider per døgn
- Færre enn 2 måltider per døgn
- Ammet ikke

**19) Hvor mye ammer du nå?**

- Alle måltider (fullammer)
- 3-4 måltider per døgn
- Ca. 2 måltider per døgn
- Færre enn 2 måltider per døgn
- Ammer ikke

**20) Dersom du fullammet tidligere, men ikke fullammer nå, hvor mange uker etter fødselen sluttet du å fullamme?**

Jeg sluttet å fullamme  uker etter fødselen

**21) Dersom du ikke fullammer nå, hvorfor gjør du ikke det?**

- Jeg har ikke nok melk
- Jeg synes det er upraktisk
- Barnet suger ikke tilstrekkelig
- Ammeproblemer (såre bryster osv.)
- Annet, vennligst spesifiser: \_\_\_\_\_

**22) Dersom du ammet tidligere, men har sluttet helt, hvor mange uker etter fødselen sluttet du helt å amme?**

Jeg sluttet helt å amme  uker etter fødselen

**23) Dersom du ikke ammer nå, hvorfor sluttet du?**

- Melken tok slutt
- Jeg synes det var upraktisk
- Barnet sugde ikke tilstrekkelig
- Ammeproblemer (såre bryster osv.)
- Annet, vennligst spesifiser: \_\_\_\_\_

**24) Har du søkt profesjonell hjelp (jordmor, helsesøster, sykepleier, lege, Ammehjelpen) for ammeproblemer?**

- Aldri
- En gang
- 2-4 ganger
- Mer enn 4 ganger

**25) Dersom du har søkt hjelp for amming, hva var problemet? (mer enn et svar mulig)**



TRENING I SVANGERSKAPET – TEST 3 Initialer  ID-nummer

- Såre brystvorter
- Lite/manglende melk
- Barnet sugde dårlig
- Annet, vennligst spesifiser: \_\_\_\_\_

**26) Får barnet morsmelkerstatning nå?**

- Ja, barnet får:
  - Collett
  - NAN
  - Nutramigen
  - Soyamelk
  - Annet: \_\_\_\_\_
- Nei