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The Impact of Antenatal Exercise in Overweight and Obese Women on Maternal and Offspring Health

Sumudu Nimali Seneviratne

Abstract

Background

Overweight and obesity in pregnancy is associated with adverse health outcomes in both the mother and the offspring. It is not well established whether antenatal exercise can improve these outcomes.

Hypothesis

We hypothesized that antenatal exercise in overweight and obese women could improve offspring and maternal health and metabolic milieu, and protect offspring from adverse programming effects.

Methods/Design

A parallel two-arm randomised controlled trial was conducted in healthy non-smoking overweight and obese women (BMI≥25kg/m²) with a singleton pregnancy. Participants were randomised at 20 weeks of gestation to an intervention group (who underwent a home-based, moderate-intensity stationary cycling programme) or a control group (no exercise intervention). The primary trial outcome was birth weight and secondary outcomes included perinatal complications, neonatal body composition, maternal physical health (weight gain, fitness and body composition), quality of life, and pregnancy and delivery complications. Maternal and offspring (cord) blood metabolic markers were also measured. Primary analysis was based on intention-to-treat, using analysis of covariance regression models to evaluate differences between intervention and control groups, adjusting for pre-specified covariates.

Results

Seventy-five enrolled participants were randomised to intervention (n=38) or control (n=37) groups. Offspring birth weight was similar between groups (adjusted mean difference 104 grams, 95% CI -116 to 324, p=0.35).

Maternal aerobic fitness improved following the intervention but there were no differences in maternal weight gain, quality of life, pregnancy outcomes, or postnatal maternal body composition between groups. Exercise compliance ranged from 0-85 % (mean 33%).
Offspring neonatal adiposity and perinatal outcomes were similar. There was an increase in bone mineral content in offspring in the intervention group, and male offspring had increased adiposity compared to gender-matched controls.

There were no differences in maternal metabolic markers between groups. Offspring in the intervention group had lower cord blood interleukin-6 levels, and male offspring also had reduced insulin-like growth factor binding protein-1 levels, while other markers were similar between groups.

**Conclusions**

These study finding suggest that non-weight-bearing antenatal exercise does not appear to improve short term maternal and offspring outcomes. However, improvement in maternal fitness and differences in offspring body composition and metabolic markers indicate the potential for long-term health effects. This needs to be established by further research.
Acknowledgements

I would like to acknowledge and extend my heartfelt gratitude to my supervisor, Professor Paul Hofman, for providing me with this wonderful opportunity to embark on a research journey. I am very grateful for his encouragement, advice and support throughout these three years. I would also like to thank my co-supervisor Professor Wayne Cutfield for his guidance and wisdom, in times of need. I would also like to extend my gratitude to the study advisors/co-investigators including Professor Lesley McCoan, Dr Graham Parry and Dr Alec Ekeroma for their expert advice, guidance and support, especially when dealing with the intricacies of obstetric practice. A special thank you is due to Dr Yannan Jiang, for providing only not expert statistical advice and assistance, but also constant mentorship and support throughout this journey. I would also like to thank Dr Silmara Gusso, for her expertise and help in dealing with the exercise aspects of the study. I also extend my warm gratitude to Dr Jose Derrick for his expert help with editorial revisions and analysis during preparation of manuscripts for publication. I would also like to acknowledge Geovana Peres for her help with supervising the exercise intervention.

A very warm thank you is extended to Susan Craigie, Janene Biggs and Christine Brennan, for all the help given during study recruitment and coordination. Their willingness to lend a helping hand to share the seemingly endless tasks while running the trial was much appreciated. I am also extremely grateful to Raquel Rodrigues for all her help. Raquel was a ray of sunshine in this long journey, and I will always remember and value her sincere friendship and caring ways as well as the many valuable hours she spent voluntarily helping with dietary analysis. My fellow PhD colleagues Valentina Chiavaroli and Ben Albert also provided much needed comradeship and support over this time. I also acknowledge the friendly assistance provided by Jean Leonard, Tamara Gaitau, Prabha Hariswamy, Corazon Africa, Eric Thorstensen and Chris Keven at the Liggins Institute.

This study would not have been possible without the help and support of the midwife community in Auckland, and a special thank you is due to them. I am also greatly indebted to the wonderful study participants and their families. It was a joy and privilege getting to know each and every one of them and sharing this very special time of their lives.
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Finally, this journey would not have been possible without the love and support of my family. My husband Sanjeewa was a pillar of immense encouragement and support for me, even though he was doing his own doctoral studies during this time. My parents Helani and Susantha Jayasena and parents-in law were truly wonderful, making many sacrifices, to take turns to be with us in Auckland, and help us take care of our young family. My two beautiful children Senuka and Oneli, I am sorry for all the moments I missed sharing with you during these three years, but having you by my side and your unconditional love made everything possible.
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List of Publications

List of published and unpublished research papers included in this thesis


3. Sumudu N Seneviratne, Lesley M E McCowan, Graham K Parry, Yannan Jiang, José G B Derraik, Susan Craigie, Silmara Gusso, Geovana Peres, Alec Ekeroma, Wayne S Cutfield, Paul L Hofman. Effects of antenatal exercise on maternal health outcomes in overweight & obese pregnant women: a randomised controlled trial. *Submitted to Obstetrics & Gynecology*


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Chapter 3 Methods section "Antenatal exercise in overweight and obese women and its effects on offspring and maternal health design and rationale of the IMPROVE (Improving Maternal and Pregnancy Obesity Via Exercise) randomised controlled trial" BMC Pregnancy and Childbirth 2014, 14:148

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Chapter 4 Results section “Effects of antenatal exercise on maternal health outcomes in overweight & obese pregnant women: a randomised controlled trial” submitted to the journal ‘Obstetrics and Gynaecology’

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Chapter: Results section “The effects of antenatal exercise on the offspring of overweight and obese mothers: a randomized controlled trial.” International Journal of Obesity

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Chapter 5: Results section "The effects of antenatal exercise on the offspring of overweight and obese mothers: a randomized controlled trial" International Journal of Obesity

| Nature of contribution by PhD candidate | Study conception and design, ethics application, setting up and coordinating the trial, performance of tests, data collection and entry, writing the manuscript |
| Extent of contribution by PhD candidate (%) | 90% |

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Chapter 6: "Effects of antenatal exercise on metabolic markers in overweight and obese pregnant women and their new borns" submitting to the Journal of Clinical Endocrinology and Metabolism

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The Impact of Antenatal Exercise in Overweight and Obese Women on Maternal and Offspring Health

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### Abbreviations

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<td>ACOG</td>
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<td>ANZCTR</td>
<td>Australian New Zealand Clinical Trials Registry</td>
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<td>BIA</td>
<td>Bio-electrical impedance analysis</td>
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<td>BMC</td>
<td>Bone mineral content</td>
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<td>BMD</td>
<td>Bone mineral density</td>
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<td>BMI</td>
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<td>CRP</td>
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<td>Intensive care unit</td>
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<td>IGF</td>
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<td>Interleukin</td>
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<td>IMPROVE</td>
<td>Improving Maternal and Progeny Obesity Via Exercise</td>
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<td>IOM</td>
<td>Institute of Medicine</td>
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Chapter 1. General overview

1.1. Thesis organisation

This thesis commences with a general overview of this research work, and proceeds on to a review of the literature on the topic. In the literature review, a brief overview on obesity is followed by a section on the effects of overweight and obesity in pregnancy on maternal and offspring health outcomes, and on developmental programming of offspring obesity. The subsequent sections discuss the effects of antenatal exercise on maternal and offspring health, in-cooperating excerpts from the published manuscript “Exercise in pregnancies complicated by obesity: achieving benefits and overcoming barriers” (1). The methods section comprises of the second publication arising from this work “Antenatal exercise in overweight and obese women and its effects on offspring and maternal health: design and rationale of the IMPROVE (Improving Maternal and Progeny Obesity Via Exercise) randomised controlled trial” (2). This manuscript includes the trial protocol and discusses overall trial methodology. An additional section on neonatal body composition assessment is included subsequently. The next three chapters (chapters 4, 5 and 6) include trial results on maternal health outcomes, offspring health outcomes, and metabolic markers respectively. These chapters are written in the form of research papers submitted for publication. The methods sections in chapters 5 and 6 have been abbreviated to avoid duplication. The thesis concludes with a general discussion in chapter 7 on the overall trial results and implications, study strengths and limitations and directions for future research.

1.2. Statement of problem

The prevalence of overweight and obesity in women of reproductive age has risen rapidly over the last three decades (3). In certain regions of New Zealand, up to 65% of pregnant women are overweight or obese (4). Maternal overweight or obesity is associated with adverse outcomes during pregnancy, delivery and perinatal period for both mother and baby (5). Offspring of overweight/obese mothers have increased birth weight and adiposity as well as an increased risk of obesity and metabolic dysregulation throughout life (6-10). In utero exposure of the foetus to an abnormal metabolic milieu associated with maternal overweight and obesity is hypothesized to lead to adverse programming effects, thus affecting lifelong heath (10).
There is expert opinion that antenatal lifestyle interventions including maternal physical activity/exercise could potentially improve some of the negative consequences of maternal overweight and obesity on maternal and offspring health (5, 11, 12). However evidence of benefit from antenatal exercise on maternal and offspring health, in overweight and obese women in particular, is very limited (13-15).

1.3. Research approach

In this research work, we explored the effects of a moderate intensity non-weight bearing home-based antenatal exercise intervention in overweight and obese women, on maternal and offspring outcomes and metabolic dysregulation associated with obesity, by a randomised controlled clinical trial. The trial was based on a previous exercise trial conducted by the Liggins Institute, University of Auckland in leaner nulliparous pregnant women, where the intervention group achieved high exercise compliance and increased fitness, and their offspring had lower birth weight with lower insulin-like growth factor (IGF) I and II levels in cord blood (16).

1.4. Research aims/hypothesis

To determine if a moderate intensity antenatal exercise programme in the second half of pregnancy in overweight and obese women could lead to:

1. Improved offspring health via reduction in birth weight, neonatal adiposity and perinatal complications
2. Improved maternal health via reduction in gestational weight gain and pregnancy/delivery complications, and improvement in physical health and quality of life
3. Improved metabolic milieu via reduction in maternal and offspring insulin resistance/hyperinsulinaemia, adipocytokines / pro-inflammatory markers, and alterations in IGF axis and lipid profile

Thus, ultimately, protect offspring of overweight/obese mothers from adverse fetal programming effects and improve their long term health by reducing future risk of obesity and metabolic complications.
Chapter 2. Literature review

2.1. Obesity

2.1.1 Definitions

Overweight and obesity refer to abnormal or excessive accumulation of body fat that can impair health (17). Body mass index (BMI) is a common surrogate measure of fatness used to define overweight and obesity, and is calculated by dividing body weight (in kilograms) by the square of height (in meters). The World Health Organisation (WHO) defines overweight by a BMI $\geq$ 25 kg/m$^2$ and obesity by a BMI $\geq$ 30 kg/m$^2$ in adults, and recommends the use of this approach globally (17, 18). There can however, be a degree of mismatch between BMI and true degree of fatness, and its relationship with comorbidity can be influenced by other factors including age, gender, ethnicity, lifestyle and fat distribution (19, 20). While ethnic-specific BMI cut offs have also been proposed to define overweight and obesity, their use is still controversial (21, 22). In children, there are several classifications that can be used to define overweight and obesity (23). According to the WHO standards, in young children between 0 to 5 years, a BMI above +1 standard deviation (SD) for age and gender, is described as being at risk of overweight, above +2 SD as overweight, and above +3 SD as obese (24). In older children between 5 to 19 years of age, overweight is defined by a BMI $\geq$ +1 SD and obesity is defined by a BMI $\geq$ +2 SD according to age and gender (25).

2.1.2 Prevalence

Global situation

Obesity rates have increased globally in both adults and children over the last three decades (3, 26, 27). Obesity is now the most prevalent form of malnutrition in the developed world, and is also becoming rapidly prevalent in developing nations (26, 28, 29). The global prevalence of obesity has increased more than twofold between 1980 and 2014 (3, 26). According to the latest report in 2014 by the WHO, 1.9 billion adults (39% of the adult population) were overweight and 600 million adults (13%) were obese globally (17). Considering children and adolescents, combined overweight and obesity rates were 24% in developed countries and
13% in developing countries in 2013 (30). Further, 10% of the world’s children were overweight or obese, including 42 million below five years of age (17, 31).

**Local situation**

In New Zealand, according to the latest New Zealand Health Survey report in 2013/2014, nearly 30% of adults (1.1 million) were obese (32). In adults (18 years of age or above) obesity was defined by a BMI ≥ 30 kg/m², and overweight by a BMI between 25 -29.9 kg/m², and comparable age equivalent BMI cut-offs used in those < 18y. Obesity rates were highest in adults of Pacific origin (67%), and also high among Māori adults (46%). Further, 10% of children aged 2–14 years (79,000) were obese. Similar to adults, higher rates of childhood obesity were seen in Pacific (25%) and Māori (15%) children.

2.1.3 **Health and economic consequences**

Obesity increases morbidity and mortality in adults (33). Obesity is a major risk factor for non-communicable diseases including type 2 diabetes, hypertension, ischaemic heart disease, cerebrovascular accidents and certain malignancies such as colon and postmenopausal breast cancer (33, 34). Other health problems associated with obesity include non-alcoholic fatty liver disease, polycystic ovarian syndrome, gallbladder disease, obstructive sleep apnoea and social marginalisation (34). Obesity also leads to increased mortality mainly due to its association with cardiovascular disease as well as malignancy, diabetes and kidney disease (35). BMI demonstrates a linear relationship with morbidity and mortality, and a BMI between 21-23 kg/m² is associated with optimal life expectancy and disability free life (18, 33, 36). Increased BMI is the second leading risk factor associated with mortality, accounting for 3.4 million deaths globally (36). The distribution of adiposity is also associated with disease risk. Central obesity or excess abdominal fat, indicated by increased waist circumference or increased waist to hip ratio is linked to worse health consequences (37-40).

Childhood obesity has its own health complications (41-43). Obesity during childhood is associated with a higher risk of adult obesity (42, 44, 45). A review of epidemiologic data demonstrated that obesity in childhood increased the risk of adult obesity by at least twofold (44). Obese children have increased metabolic and cardiovascular complications similar to adults, including high blood pressure, dyslipidaemia, hyperinsulinaemia, insulin resistance and abnormalities in left ventricular and endothelial function (42, 46). They also show a higher predisposition to fatty liver disease, bronchial asthma, orthopaedic complications, obstructive
sleep apnoea and psychological problems (41, 42). Further, recent evidence associated overweight and obesity in childhood and adolescence with premature mortality and morbidity in adulthood (43).

Treatment of established obesity is difficult. Biological mechanisms operating to maintain body weight could account for the poor long-term efficacy of treatments for obesity (47). The treatment of obesity related disease however bears a substantial financial burden. Nearly 30 years ago, the annual cost of obesity related morbidity in the United States of America (USA) was US $ 39 billion (48). This figure increased to US $78 billion in 1998, and was estimated at US $147 billion in 2008 (49). Further, the per capita medical spending for an obese individual was estimated to be 42 % higher compared to an individual of normal weight (49). Similarly in Australia, compared to an individual with normal BMI, average annual health expenditure was 19% higher for an obese individual with a BMI between 30 and 35 kg/m2 and 51% higher for an individual with a BMI greater than 35 kg/m2 (50).

2.1.4 Aetiology

Obesity has a multifactorial aetiology, with complex interactions between genetics, environment and behaviour (19, 29). However, the fundamental cause of obesity is an imbalance between energy intake and energy expenditure (19). Societal and environmental changes associated with development are thought to be the main driving force behind the current obesity epidemic seen over the last three decades (17). The present generation are born to and live within an obesogenic postnatal environment. There is increased energy intake from high fat energy dense foods and reduced physical activity due to technological advancements, changes in modes of transportation and urbanisation (19, 29, 51). However, the maintenance of energy balance and body weight is regulated by biological systems which are established in early life (52, 53). Further, there is evidence that prenatal factors also play an important role in determining lifelong obesity risk (53-56). In recognition of this, the World Health Organisation now advocates a life-course approach to prevention and control of obesity and related co-morbidities, starting with preconception and antenatal maternal health (57). Maternal overweight and obesity during pregnancy is one such factor which is recognised to increase offspring obesity risk, possibly via in utero developmental programming effects (6, 53).
2.2. Maternal overweight and obesity during pregnancy

2.2.1 Prevalence

Concurrent with the global epidemic of obesity discussed above, there has been an increase in women of reproductive age who are overweight or obese worldwide (19, 58). In the USA, obesity rate in women aged between 20 to 40 years increased by 50% in less than two decades (59). This problem has now extended to developing countries as well (60). Further, in most countries obesity rates are higher in women than men (18). Therefore, this has led to an increasing number of women being overweight or obese during pregnancy. In Switzerland, the proportion of overweight and obese pregnant women increased from 16% to 30% between 1986 and 2004 (61). In the USA, data from nine states showed an increase in pre-pregnancy obesity from 13% to 22% between 1993 and 2003 (62). In England, up to 20% of pregnant females are obese (63).

New Zealand women have the second highest BMI among women in high income countries, surpassed only by the USA (3). Further, women in New Zealand, along with USA and Australia showed the greatest increase in BMI within high-income countries between 1980 and 2008 (3). According to recent health surveys, 29% of New Zealand women were obese (64). There was ethnic disparity in obesity prevalence, with 64% of Pacific and 45% of Maori women being obese in comparison to 26% of women of European or other descent (64). Further, between 2006 and 2012, there has been an increase in obesity rate in young adults from 14% to 20%, making young women more prone to obesity during their reproductive years (64). In certain areas of Auckland region in New Zealand, 65% of pregnant women delivering in a health facility were overweight or obese (86% Pacific, 69% Maori and 50% European/other) (4).

2.2.2 Effects on maternal health

Maternal overweight and obesity is associated with a multitude of adverse effects during pregnancy. Several large observational studies have reported on the adverse effects of increased maternal weight/ body mass index on maternal pregnancy outcomes (65-68) and perinatal outcomes (66-72). This has also led to an increased burden on maternity health services, with these women requiring a higher number of specialised antenatal visits and investigations, and longer hospital stay with increased hospitalization costs (73, 74).
Maternal mortality

Overweight and obesity during pregnancy appears to increase the risk of maternal mortality. The Confidential Enquiry into Maternal Deaths in the United Kingdom (UK) in 2006-2008 reported high rates of overweight and obesity in women dying from both direct (47% overweight, 30% obese) and indirect causes (50% overweight, 24% obese), compared to the general population (75).

Gestational weight gain and weight retention

Pregnancy is associated with changes in maternal body weight and body composition (76). However, changes in early pregnancy can differ according to pre-pregnancy weight status (76). While underweight and normal weight women increase weight by fat deposition (mainly in hip, back, and upper thigh regions) during this time, overweight and obese women show little or no additional fat accumulation, perhaps due to a reduced need for extra caloric reserves (76). At term, the additional weight of the foetus (3-4 kg) and supportive tissue (including uterus, placenta, amniotic fluid and mammary gland) add up to approximately 6.5 kg, while the remaining maternal weight gain is due to increase in maternal fat stores and blood and extravascular fluid (77).

It is recommended that overweight and obese women should gain less weight during pregnancy compared to normal weight women, to obtain optimum pregnancy outcomes for both mother and child (78, 79). According to the Institute of Medicine (IOM) revised gestational weight gain guidelines in 2009, the recommended gestational weight gain is 5–9 kg for obese women and 7–11.5 kg for overweight women, compared to 11.5–16 kg for normal weight women (79). Overweight and obese women whose weight gain was within guidelines, had less increase in fat mass during pregnancy (2.8 kg and -0.6 kg respectively) compared to those exceeding guidelines (4.2 and 3.1 kg respectively) (80). However, overweight and obese women are nearly twice as likely to exceed weight gain recommendations, compared to normal weight women (76). More than 60% of overweight and obese women show excessive weight gain in pregnancy (81).

The most consistent adverse outcome for mothers with excessive gestational weight gain is increased post-partum weight retention (82). Gestational weight gain is positively associated with maternal post-partum weight at 6 and 18 months (83). Post-partum weight retention can lead to higher risk of obesity-related complications in subsequent pregnancies (84). A nationwide Swedish study reported nearly doubling of odds of adverse pregnancy outcomes in
women who increased their BMI by 3 kg/m² between first and second pregnancies, compared to women whose BMI changed by less than 1 kg/m² [Odds ratios (OR) for pre-eclampsia 1.8 (95% confidence interval (CI) 1.5-2.1); gestational hypertension 1.8 (1.4-2.2); gestational diabetes 2.1 (1.7-2.6); caesarean delivery 1.3 (1.2-1.4); stillbirth 1.6 (1.2-2.2); and large for gestational age births 1.9 (1.7-2.1)] (84).

Further, pregnancy related fat gain tends to show a central distribution in overweight and obese women (85, 86). A small prospective longitudinal study showed that in lean and obese women gaining similar amounts of fat mass (4.7 versus 4.2 kg, p = 0.58) during pregnancy, obese women had more central fat deposition compared to lean women (85). A more central pattern of fat retention was also reported at 6 months postpartum in overweight and obese women compared to leaner women (86). Therefore excessive weight gain and postpartum fat retention can be more harmful for overweight and obese women, as central adiposity is more detrimental to long term health (37, 39).

**Pregnancy complications**

Overweight and obese women are at increased risk of pregnancy complications such as gestational diabetes and pre-eclampsia. Further, this risk increases with increasing maternal BMI (66, 67). A study analysing pregnancy data from more than 280,000 women in UK, reported that in comparison to women with a normal BMI, gestational diabetes mellitus and pre-eclampsia were more common in overweight and obese pregnant women (OR in overweight and obese women 1.7 (95% CI 1.5-1.8) and 3.6 (3.2-3.9) for gestational diabetes and 1.4 (1.3-1.6) and 2.1 (1.8-2.5)) for pre-eclampsia, respectively) (67). Among 22,658 pregnant women from San Francisco, higher rates of gestational diabetes and preeclampsia were found in obese women from all ethnic groups (65). Higher risks of gestational diabetes and pre-eclampsia in overweight/obese women have also been demonstrated by other studies in the USA and Australia (66, 68, 87). In 2007, a meta-analysis estimated that compared with women of normal weight, overweight, obesity and severe obesity increased the risk of developing gestational diabetes by twofold, fourfold and eightfold respectively (88). In 2009 another meta-analysis including 671,945 women reported similar patterns, with increased odds of developing gestational diabetes in overweight, moderately obese and morbidly obese women compared to women with normal BMI (OR 2.0 (95% CI 1.8 to 2.2), 3.0 (2.3 to 3.9) and 5.6 (4.3 to 7.2) respectively) (89). A strong positive association between maternal pre-pregnancy BMI and the risk of preeclampsia was also reported in a systematic review analysing data from 1.4 million women (90).
Pregnancy can be considered as “a metabolic stress test” for risk of developing long term metabolic complications (58). Although conditions such as gestational diabetes and pregnancy induced hypertension usually resolve after childbirth, these signify an increased risk of developing metabolic syndrome and cardiovascular disorders in later life (58, 84). For instance, the chance of developing type 2 diabetes is higher, following a diagnosis of gestational diabetes (91).

**Delivery complications**

There is an increase in risk of delivery complications with increasing maternal obesity. A meta-analysis looking at the impact of maternal BMI on delivery outcomes found that both maternal overweight and obesity were associated with increased rates of caesarean delivery emergency caesarean delivery and haemorrhage, while infection rate was increased threefold in obese women compared to women of normal weight (92). There was an increase in mean length of hospital stay from 2.4 days for women of normal BMI to 2.6 days for overweight, 2.7 days for obese and 3.3 days for morbidly obese (BMI > 40) women (92). An increased risk of caesarean delivery in overweight and obese women has also been reported by several large observational studies in the USA (65, 66, 68), UK (72) and Australia (87). Increased rates of induction of labour and postpartum haemorrhage were also found in overweight and obesity women compared to women with normal BMI (67). In USA, there was an increased duration of hospital stay for delivery among women who were overweight and obese, which was related to increased rates of caesarean delivery and obesity related high risk conditions (73).

The effects of overweight and obesity on timing of delivery are less clear. One meta-analysis showed increased odds of both post term and preterm delivery with increasing maternal BMI (92). However, another meta-analysis reported that the overall risk of preterm birth was not increased, but there was an increase in induced preterm birth in overweight and obese women attributed to increased maternal complications such as pre-eclampsia and gestational diabetes (93). An increased risk of preterm delivery with morbid maternal obesity has also been reported (94). A Swedish study reported that while the risk of very preterm delivery (≤32 weeks of gestation) was increased in nulliparous obese women, it was lower in parous obese women, compared to lean women (69). Therefore, the effects of obesity on risk of preterm delivery appear to be influenced by several factors, which could attribute to conflicting results.
The Impact of Antenatal Exercise in Overweight and Obese Women on Maternal and Offspring Health

Reduced breastfeeding rates

Maternal overweight and obesity is associated with reduced success in lactation (95). Overweight and obese mothers are less likely to be breast feeding at discharge from hospital following delivery, compared to normal weight (67). Further, overweight and obese mothers appear to breastfeed for a shorter duration than normal weight mothers, independent of socioeconomic and demographic characteristics (95, 96). Biological, psychological, behavioural and cultural reasons that may be responsible for reduced breastfeeding in obese women are explored in a recent systematic review (95).

Quality of life in pregnancy

Data on quality of life during pregnancy is limited, but there is some evidence that obese pregnant women have lowered quality of life compared to non-obese women. In 110 obese and 110 non-obese pregnant women from Mexico, who completed a generic quality of life questionnaire (12-item short-form health survey) in early and advanced pregnancy, the mental health component score was lower in obese women at both time points in pregnancy (97). The physical health component score decreased during pregnancy and was lower in obese than non-obese women in advanced pregnancy (97). Further, maternal BMI, weight gain, and complications during pregnancy showed negative associations with the physical health component score (97).

2.2.3 Effects on perinatal offspring health

Foetal mortality/stillbirths

Maternal overweight and obesity is associated with an increased risk of foetal mortality. In a retrospective analysis of 287,213 singleton pregnancies in UK, foetal deaths were higher among overweight (OR 1.1, 95% CI 0.9 to 1.3) and obese women (OR 1.4, 95% CI 1.1 to 1.7) compared to women with normal BMI (67). Among 54,505 pregnant women in the Danish National Birth Cohort, allowing for the effects of gestational age, weight gain, and maternal diseases in pregnancy, the risk of foetal death increased progressively through pregnancy in obese women compared with normal weight women, from early second trimester (adjusted hazard ratio (HR) 1.6, 95% CI 1.0 to 2.5) to 40 weeks of gestation (HR 4.6, 95% CI 1.6 to 13.4) (70). Overweight women also experienced an increasing risk of foetal death from 28
weeks up to 40 weeks of gestation (70). Risk of late (> 28 weeks of gestation) foetal stillbirths were partly attributed to inadequate placental function in overweight and obese women (70). Among 167,750 Swedish women too, late foetal deaths were increased among nulliparous overweight (OR 3.2, 95% CI 1.6 to 6.2); and obese women (OR 4.3, 95% CI 2.0 to 9.3) and among parous obese women (OR 2.0, 95% CI 1.2 - 3.3) compared to lean women (BMI>20) (69).

Overall, the risk of foetal death appears to increase progressively with advancing pregnancy, in association with maternal overweight and obesity, but the exact underlying reasons are uncertain (98). Possible reasons that have been suggested include diagnosed or undiagnosed maternal hypertensive disease and gestational diabetes, maternal hyperlipidaemia (causing reduced prostacyclin secretion and enhanced peroxidase production leading to vasoconstriction and platelet aggregation) and periods of maternal sleep apnoea (98), as well as placental dysfunction (70) in overweight and obese women. Further, reduced perception of decreased foetal movements by heavier women, may prevent more timely medical treatment (98).

**Congenital malformations**

Maternal obesity is associated with a higher risk of a range of foetal anomalies (99). These include neural tube defects, hydrocephaly, cardiovascular anomalies, cleft lip and palate, anorectal atresia and limb reduction anomalies (100). A meta-analysis demonstrated an increasing risk of neural tube defects seen among overweight, obese, and severely obese women compared with normal weight women (OR 1.2, 1.7 and 3.1 respectively) (101). Potential underlying reasons include increased diabetes, nutritional (especially folate) deficiencies and reduced antenatal detection of foetal anomalies (leading to reduced foetal terminations) in overweight and obese women (99).

**Perinatal complications**

Maternal overweight and obesity are also associated with increased perinatal complications in the offspring. These include an increased risk of birth trauma (OR 1.5, [95% CI 1.1-2.1]), obstructed labour/shoulder dystocia (2.9 [1.4-5.8]) and perinatal asphyxia compared to babies of normal weight women (99, 102). These babies are also more likely to be admitted to a neonatal unit (OR 1.5 [1.1-2.0]) with complications such as hypoglycaemia or respiratory distress (92, 99). Higher rates of respiratory distress are often due to transient tachypnoea following operative delivery, especially pre-labour caesarean delivery (99). It is likely that
increased offspring size at birth (discussed in the next section), increases the risk of birth trauma and perinatal asphyxia in these babies (103, 104). Further, increased maternal complications such as gestational diabetes and hypertensive disorders and increased risk of delivery by caesarean section may also attribute to increased perinatal complications in these babies. However, the increase risk of perinatal complications remains even after exclusion of babies with maternal diabetes or hypertensive disorders in pregnancy (99, 102).

Birth weight

Overweight and obese mothers are more prone to deliver babies with increased or abnormal birth weight. There are several terms used to define abnormal birth weight. Macrosomia refers to a birth weight > 4000g at birth, irrespective of gestational age, while large for gestational age (LGA) is defined as a birth weight > 90th percentile for gestational age at birth. On the other end of the spectrum, low birth weight refers to a birth weight < 2500g irrespective of gestational age, while small for gestational age (SGA) refers to a birth weight < 10th percentile for gestational age. Being born at either end of the birth weight spectrum is associated with poorer health outcomes in later life (55). Increased birth weight and extremes of birth weight are associated with a greater risk of obesity and metabolic complications in later life (105-108). In a meta-analysis, offspring of overweight and obese women had a mean increase in birth weight of 70.8 g (54.4 g to 87.2 g), compared to offspring of normal weight women (93). As well from being heavier at birth, offspring of overweight and obese women also have increased neonatal adiposity (109, 110).

When considering excessive birth weight, large for gestational age (LGA) births were significantly higher in both obese (16.8%) and overweight women (12.3%) compared to women with normal BMI (10.5%) (111). In two separate studies, compared to women with normal BMI, overweight women had a nearly twofold increased risk of giving birth to a LGA baby (OR 1.6 [95% CI 1.5-1.6] and 2.0 [1.2-3.4]), while obese women had a greater than twofold risk (OR 2.4 [2.2-2.5] and 2.6 [1.6-4.4]) (67, 112). Similarly, increased foetal macrosomia was also seen with increasing maternal weight (68, 72, 87). In Sweden, the risk of delivering a LGA baby increased by 23%, from 1992 to 2001. This was associated with increase in maternal BMI (and decrease in maternal smoking) over this period (71). Excessive gestational weight gain further increased the risk of LGA birth in both overweight and obese women (OR 3.6 [2.6-5.0] and 6.7 [4.8-9.3] respectively) (112).

High birth weight is associated with increased perinatal complications such as birth injury and perinatal asphyxia (103, 104). It is also associated with an increased risk of developing obesity.
in adulthood (107, 113, 114). Therefore increased maternal BMI can lead to high birth weight in the offspring, which can adversely affect both perinatal and long-term offspring health.

While the association of maternal overweight and obesity with excessive offspring birth weight is quite convincing, effects of maternal overweight and obesity on risk of SGA births and low birth weight (LBW) are less clear. According to a meta-analysis by McDonald et. al. overweight and obese women appeared to have reduced risk of having a LBW baby (0.84, [0.75 to 0.95]) as well as lower risk of SGA birth than women of normal weight (RR 0.8 [0.7 to 0.9]) (93). However, paradoxically, limited data also showed an increased risk of having an infant of very low birth weight (<1500 g) or extremely low birth weight (<1000 g) in obese women (93). Further, the beneficial effects of maternal overweight or obesity on LBW were higher in developing countries than developed countries, and the protective effect disappeared when publication bias was taken into account (93).

2.2.4 Effects on long term offspring health

Maternal overweight and obesity is also associated with long term offspring health, including a higher risk of obesity and metabolic dysregulation throughout life (6, 9). The influence of maternal obesity on risk of offspring obesity starts manifesting from early life (7, 115). Offspring of overweight and obese mothers show increased weight for age and length, in comparison to offspring of normal weight women as early as six months of age (115). The risk of obesity is increased twofold in pre-schoolers exposed to maternal obesity, compared to children whose mothers were not obese in pregnancy, even after controlling for birth weight and other confounding factors (RR 2.0 [95% CI 1.7-2.3] at 2 years of age and RR 2.3 [2.0-2.6] at 3-4 years of age) (7). Children exposed to maternal obesity also have a higher risk of developing metabolic syndrome in late childhood (OR 1.8 [95% CI 1.0–3.2]) (108). Data from the Motherwell birth cohort study from Scotland demonstrated that increased maternal BMI in pregnancy was an independent predictor of increased adiposity in the offspring at 30 years of age (8). These and other studies highlight the impact of maternal overweight and obesity during pregnancy on development of obesity and metabolic complications in the next generation (6, 116).
2.2.5 How maternal obesity could influence offspring obesity

The association between maternal and offspring obesity could be explained by several factors, all which could be interacting to bring about this association. These include shared genes, nurturing practices and behavioural factors such as food preferences and sedentary lifestyle (117-119). There is also emerging evidence that the in utero environment associated with maternal obesity could be contributing to this association via foetal programming effects (6, 55, 113).

Obesity runs in families (120-122). Garn et al. reported that offspring of two obese parents had three times greater skinfold thickness compared to offspring of two lean parents, by adolescence. (120). Whitaker et al. established that the risk of obesity in adulthood is influenced by both parental obesity and obesity in childhood (121). It is likely that genetics (123, 124) as well as nurturing patterns and shared behaviour within families (124-126) all play a role in this association. In a systematic review considering childhood and adolescent obesity from twin and adoption studies, twin studies demonstrated the role of genetic factors on variation in BMI, while adoption studies supported the role of family environment, with correlations between adoptees and adoptive parents (124). Other studies have reported similarity in dietary intake between parents and children (126) and familial aggregation of physical activity phenotype (125). However, the association between parental and offspring childhood obesity is stronger for maternal obesity compared to paternal obesity, suggesting that maternal obesity may play a greater role, acting via additional pathways to contribute towards offspring obesity (6, 116). It is now recognised that maternal obesity can influence offspring obesity risk via in utero developmental programming effects (10, 55, 127).
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2.3. Developmental programming of obesity

2.3.1 Concepts

The developmental origins of health and disease hypothesis proposes that early life environmental influences during sensitive periods of development such as the prenatal period can have lifelong effects on health (128). This occurs via ‘developmental plasticity’, a phenomenon by which an individual’s life history strategy is adjusted in response to environmental cues during early development (129). Developmental plasticity enables one genotype to give rise to different physiological or morphological states, in response to different environmental conditions during development. The resulting phenotype is therefore a product of both the genotype and environment (130). Therefore, modifying environmental metabolic cues during the phase of developmental plasticity can cause lasting adaptive changes in the offspring. The term 'programming' refers to the process in which a stimulus applied at a 'critical' or 'sensitive' period exerts long term effects (131). Such a stimulus may cause early life developmental programming in two ways: by inducing or impairing development of a somatic structure or by altering a physiological ‘set point’ or regulatory function, leading to potential lifelong effects (132). An adaptation is a change in a phenotype that occurs in response to a specific environmental signal, resulting in improved growth, survival or reproduction (129). It is presumed that there is a potential adaptive advantage for a particular phenotype in a specific environmental situation (129). However, exposure to certain environmental factors during the phase of developmental plasticity can also be disruptive, leading to adverse programming effects with negative long term health effects.

2.3.2 Developmental origins of obesity

The relatively short time period over which obesity rates have risen precludes genetic change as a major attributor, and it has been argued that post-natal lifestyle factors alone cannot fully explain the recent rapid increase in obesity (56, 133, 134). Further, the risk of developing obesity is now well recognised to be influenced by early life factors via developmental programming effects (128, 135, 136). The WHO has recently acknowledged this concept by advocating a life-course approach starting with maternal health (including preconception, antenatal and postnatal care and maternal nutrition) for the prevention and control of non-communicable diseases including obesity (57, 137).
Paradoxically, both a nutritionally limited or nutritionally excessive in utero environment can lead to later obesity and associated co-morbidities (127). Historically, the developmental origins of health and disease focussed on long term health consequences of foetal undernutrition including a higher risk of central obesity, diabetes, hypertension, coronary heart disease and stroke (11, 54, 129). Here, mismatch between a nutritionally restricted in utero life and plentiful post-natal environment was considered to lead to these adverse effects (136). However, given the worldwide epidemic of obesity, there is now wider attention on foetal overnutrition as a developmental pathway to obesity in later life (127, 138).

Foetal growth is influenced by the in utero environment, and there is a J or U shaped relationship between birth weight and future obesity risk (139). Parson demonstrated from longitudinal data from the 1958 British birth cohort study, that the relationship between birth weight and adult BMI was largely accounted for by maternal BMI in pregnancy (139). Maternal obesity, maternal diabetes and increased gestational weight gain during pregnancy all appear to increase both birth weight and offspring obesity risk (113).

The association between maternal and offspring obesity could be influenced by the abnormal ‘obesogenic’ metabolic environment the offspring is exposed to during foetal development (6, 10, 82). Catalano has hypothesised the existence of an obesity cycle where maternal obesity in conjunction with an abnormal metabolic milieu leads to foetal and neonatal obesity which continues to childhood and adulthood, propagating obesity in the next generation (Figure 1) (10). According to this hypothesis, the recent increase in overweight and obesity among women of reproductive age could be a potential modulator of the global obesity epidemic. Further, this vicious cycle could further propagate obesity in future generations, increasing the global obesity burden.
2.3.3 Maternal over nutrition and developmental programming of offspring obesity

Evidence

It is difficult to separate out the effects of in utero exposure from genetic and nurturing influences of maternal obesity in humans. However, animal studies provide evidence that exposure to an obese prenatal in utero environment increases offspring obesity risk (140-145). Levin demonstrated that rats genetically predisposed to obesity developed a greater adiposity with in utero exposure to maternal obesity (140). In another rodent study, maternal obesity was induced prior to conception by overfeeding, and the offspring of these obese dams were cross-fostered to lean dams, with ad libitum access to food, after delivery (141). Overfeeding prior to conception led to substantial increase in maternal body weight, adiposity, serum insulin, leptin, and insulin resistance in the dams (141). Although birth weight was not increased in offspring of obese dams, they gained increased body weight and higher percentage of body fat when fed a high fat diet compared to pups from lean dams (141). These studies therefore provide evidence that in utero exposure to maternal obesity per se further increases susceptibility to post-natal obesity, beyond genetics or nurturing practices associated with maternal obesity.
Mechanisms

The exact mechanisms by which maternal overweight and obesity during pregnancy cause in utero programming of offspring obesity is yet uncertain (127). It is proposed that the foetus ‘senses’ its future nutritional status via signals from the mother, and responds in ways which can establish lasting influences (129, 146). One hypothesis is that over nourished mothers provide excess nutrition to the foetus stimulating increased foetal insulin secretion, foetal overgrowth and increased adiposity(146). This increased tendency to fat mass accrual may then persist to childhood and adulthood (10). Also, the metabolic milieu of overweight/obese mothers differs from that of normal weight mothers (58, 147). Maternal obesity is associated with increased insulin resistance, increased levels of adipokines including leptin, IL-6 and TNF α and lipid abnormalities during pregnancy (58, 82, 147, 148). In utero exposure to this abnormal metabolic milieu is also implicated in foetal programming (10, 58, 82). It is proposed that foetal exposure to maternal obesity or gestational diabetes could lead to dysregulation of the adipoinesulin axis (leptin and insulin) in the offspring (6, 148) leading to alteration in central nervous system regulation of appetite, activity level and energy balance (6, 55, 149) and adipocyte metabolism (6, 149) (Figure 2). These factors are discussed in detail below.

Figure 2: Developmental programming effects of maternal obesity/maternal diabetes on the offspring (6).
**Increased nutrient transfer to the foetus**

Human foetal growth regulation is complex. In early gestation there is little variation in foetal growth, but by mid gestation, pre-natal environmental influences are superimposed onto the genetically determined development causing considerable variance in foetal growth and subsequent birth size (150). Nutrient transfer from the mother to the foetus is a dynamic process mediated via the placenta (151, 152). The provision of foetal nutrients also depends on a complex interplay between maternal lifestyle and behaviour (nutrition, energy expenditure), maternal metabolic and cardiovascular status, placental function and foetal endocrine status (151). The functional capacity of the placenta to supply nutrients to the foetus depends on its size, morphology, blood flow, transporter abundance and its rate of nutrient consumption (152). Maternal metabolism during pregnancy is regulated to allow for an adequate and continuous supply of nutrients to the developing foetus (153). However, there are differences in the metabolic milieu of the overweight or obese mother compared to leaner women, such as increased insulin resistance, leptin and obesity related pro-inflammatory markers, altered lipid metabolism and maternal/foetal IGF axis which can lead to perturbations in foetal nutrient supply (147, 151). Freinkel proposed that changes in maternal nutrients could affect developing foetal structures and lead to long term effects on offspring anthropometry behaviour and metabolic functions (154).

**Increased maternal insulin resistance**

Insulin resistance is a physiological change occurring in pregnancy, which is exacerbated in overweight and obese women (94). Maternal insulin resistance is positively correlated with both maternal BMI and leptin levels (155). In normal pregnancy, maternal insulin resistance increases with advancing pregnancy (156). Increased maternal insulin resistance reduces maternal uptake of glucose and amino acids, and increased lipolysis in maternal tissues, causing increased availability of nutrients for transfer to the foetus (55). The developing foetal pancreas responds to increased availability of glucose by producing insulin, which acts as a foetal growth hormone (55). In foetal life, insulin stimulates foetal secretion of IGF-1 and IGF-II, stimulating foetal growth and fat deposition (55, 157). Many studies have shown that increased maternal insulin resistance is positively related to birth weight and neonatal fat mass (100, 158-160). Maternal insulin resistance is associated with other metabolic factors in the circulation, showing a positive correlation with leptin and triglycerides, and a negative correlation with IGF binding protein-1 (IGFBP-I) (161).
As obesity increases insulin resistance, obese pregnant women are more insulin resistant than non-obese pregnant women from early pregnancy (94). This can cause excessive nutrient availability and transfer to the foetus, triggering foetal hyperinsulinaemia, foetal overgrowth and increased adiposity (159, 162, 163). This is supported by positive correlations between maternal BMI and cord blood insulin and C-peptide levels in the foetus, indicating that maternal obesity leads to hyperinsulinaemia in the offspring (164). Further, there is increased cord blood insulin and IGF-1 levels in macrosomic compared to normal weight newborns, suggesting that high insulin and IGF-I levels are associated with foetal overgrowth (165, 166).

Further evidence of effects of maternal insulin resistance on the offspring can be found when considering gestational diabetes, which represents the extreme of increased maternal insulin resistance during pregnancy (55). More than 60 years ago, Pedersen proposed the “hyperglycemia hyperinsulinism” pathway to explain the observation that offspring of diabetic mothers had higher birth weights (167). It is recognised that babies born to mothers with diabetes are at higher risk of macrosomia at birth, as well as obesity during both childhood and young adulthood (168). More recently, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated strong, continuous associations of maternal glucose levels, even below those diagnostic of diabetes, with increased birth weight and increased cord blood C-peptide levels (169). In this study, a total of 25,505 pregnant women in nine countries underwent 75 g oral glucose tolerance testing at 24 to 32 weeks of gestation. An increase of 1 SD in fasting, 1 hour and 2 hour plasma glucose levels were all independently associated with increased odds of delivering a LGA baby. Further, there was no threshold glucose value where the risk disappeared (169). This implies that even mildly impaired maternal glucose tolerance below levels associated with maternal diabetes, as can occur with maternal overweight and obesity, can lead to increased foetal growth.

**Alterations in the insulin-like growth factor (IGF) axis**

Maternal obesity also affects the insulin-like growth factor (IGF) axis expression in the mother during pregnancy. Maternal IGF-I level in pregnancy show a positive correlation with maternal BMI (170). Maternal IGF-I and IGF-II levels rise during pregnancy (171). Maternal IGF-I level is positively associated with birth weight (170). Further, increase in maternal IGF-I level from second to third trimester also positively correlates with birth weight, neonatal fat mass and placental mass (172). Increase in maternal IGF levels also occur in diabetes and may influence feto-placental growth by increasing the transfer of nutrients across the placenta (173). Based on animal research, several mechanisms via which maternal IGF-I and IGF-II
can enhance placental transport and nutrient supply to the foetus have been proposed (174). In animal models, chronic infusion of IGF-I in mid gestation is associated with an increased placental capacity to transport glucose at term. There is a negative correlation between maternal BMI and maternal IGFBP-I levels during pregnancy (161, 175). It is proposed that low serum IGFBP-I can represent a link between high BMI and increased foetal growth by increasing the bioavailability of IGF-I (175). Increased maternal IGF-I and reduced IGFBP-I seen in pregnancies complicated by maternal obesity could be potential mediators of increased foetal growth.

**Abnormalities in lipid metabolism**

Pregnancy is associated with hyperlipidaemia. Maternal triglyceride and cholesterol levels increase with gestation (176). Overweight and obesity pregnant women have differences in lipid profile compared to leaner pregnant women. In obese pregnant women hyperlipidaemia is exaggerated (147). Further, fasting triglyceride concentrations are higher and high-density lipoprotein (HDL) concentrations are lower in the obese women compared to lean women (147). Several studies have demonstrated associations between maternal lipid levels during pregnancy and birth weight (177, 178).

Maternal free fatty acids can transfer to the foetus and contribute to increased birth weight and adipose tissue in the foetus under normal conditions. Increased insulin resistance, with relative inability of insulin to suppress lipolysis leads to a marked increase in plasma free fatty acids in obese pregnant women (179). Several studies have found positive associations between maternal plasma fatty acid concentrations and offspring birth weight and neonatal adiposity (180).

Maternal triglyceride levels also correlate with birth weight. There is a positive correlation between maternal triglyceride levels at both mid and advanced pregnancy and birth weight (177, 178). Fasting maternal hypertriglyceridemia (over 259 mg/dl or 2.9 mmol/l) has been found to be an independent predictor of foetal macrosomia (177). Maternal serum triglycerides do not appear to cross the placenta (180). Hence there is speculation whether the relationship between birth weight and maternal hypertriglyceridemia could simply be reflecting increased maternal insulin resistance (177). There could however, be a direct relationship between birth weight and maternal triglyceride levels via hydrolysis to free fatty acids by placental lipases and transport to the foetus (180). However, there is controversy regarding the effects on birth weight at very high levels (177, 178, 180). It is reported that at maternal triglyceride levels
above the 85th to 90th percentile, there is reversal of this association with higher plasma triglyceride levels leading to lower birth weight (180).

Further, both maternal obesity and foetal macrosomia are associated with lipoprotein abnormalities consistent with high atherogenic risk (181). Obese mothers delivering macrosomic babies have higher serum triglyceride, very low density lipoprotein and apo B100 levels, and lower serum apo A-I and HDL 2 cholesterol concentrations compared to both non obese pregnant women and obese pregnant women with non macrosomic babies. Further, their babies also have higher cord blood levels of lipids and lipoproteins, apo B100, and apo A-I levels compared with other new-borns (181). However there are many unresolved issues regarding how altered maternal lipid metabolism in overweight and obese women affects foetal growth and adiposity as well as long term offspring health.

**Increased adipocytokines (leptin, tumour necrosis factor α, interleukin 6)**

Adipocytokines are adipocyte derived hormones. These include leptin, tumour necrosis factor α (TNF-α), interleukin 6 (IL-6) and adiponectin, as well as other newly discovered factors (resistin, visfatin, and apelin)(182). During pregnancy, adipocytokines are also secreted by the placenta. Adipokines are implicated in maternal insulin sensitivity, energy metabolism in pregnancy, and development of pregnancy complications (182). Potential effects of leptin, TNF-α and IL-6 on the foetus are discussed briefly.

Leptin is associated with increased body fat and influences satiety, and metabolism (183, 184). During pregnancy however, leptin is produced by maternal and foetal adipose tissues and placenta (183). Increased maternal leptin levels seen in pregnancy may result from increased placental production, increased secretion by adipose tissue, or low serum binding proteins (185). However, pregnancy also appears to induce a physiological leptin resistant state, because increased maternal energy intake and positive energy balance develop in late pregnancy despite increased leptin levels. Healthy obese women pregnant women have increased serum leptin levels compared to lean pregnant women during pregnancy (147, 148, 186). Maternal leptin levels correlate with maternal insulin resistance (161). Therefore maternal hyperleptinaemia may play a role in foetal growth and programming of obesity via modulation of insulin resistance.

TNF-α and IL-6 are pro-inflammatory cytokines generally produced by adipose tissue monocytes and macrophages, which are also implicated in development of insulin resistance (182). Increased TNF-α and IL-6 levels seen during pregnancy, probably of placental origin,
have been related to increased pregnancy associated insulin resistance (182, 187). Healthy obese pregnant women have increased levels of pro-inflammatory markers (IL-6 and C-reactive protein) compared to lean pregnant women (147, 148, 186), while higher TNF-α levels have been reported in women with impaired glucose tolerance (153). Therefore, increased adipocytokines can lead to increased maternal insulin resistance, and thus influence foetal development. Further, foetal exposure to increased pro-inflammatory markers and chronic inflammation in utero is also associated with enhanced adipogenesis in foetal life (188).

When considering the foetal circulation, higher cord blood levels of leptin and IL-6 have been reported in babies born to obese women (148). Leptin levels in cord blood correlate with birth weight and ponderal index (189-191), and are higher in asymmetrically large for gestational age babies (190). It has been suggested that cord blood leptin can be a marker of foetal fat mass in humans (185). Intrauterine exposure to maternal over nutrition increases offspring leptin expression in subcutaneous adipose tissue in animal models (143). There are positive associations between cord leptin and other hormones such as insulin and IGF-I (192). Further, leptin gene expression in adipose tissue appears to be regulated by circulating insulin in the foetus (193). Therefore it is difficult to determine if increased foetal leptin stimulates *in utero* growth, or simply reflects increased insulin levels in the foetal circulation and increased foetal adiposity (193).

However, increasing evidence suggest that leptin has physiological significance in foetal life (193). Widespread localisation of leptin receptors in the developing foetus, including bone and cartilage, suggests that leptin could be involved in the regulation of foetal growth (193). There is also evidence that leptin may increase foetal bone mass by decreasing bone resorption *in utero* (194). Leptin can also alter the structural and functional characteristics of developing adipocytes (195). Further, leptin exposure during critical windows of development in foetal life may also affect the hypothalamic development of appetite and energy balance regulation (149). Therefore, maternal adipokines may influence foetal growth by increasing maternal insulin resistance, and maternal obesity could also stimulate the synthesis and secretion of leptin in the foetus, which could play an important role in programming of future health.

**Foetal development of appetite and energy regulation**

Body weight is regulated centrally via regulation of appetite as well as energy expenditure and metabolism (34). In utero exposure to maternal over nutrition appears to influence several
aspects of offspring body weight regulation including appetite, metabolism and activity levels (76). Increased affinity to unhealthy food, and reduced energy expenditure have been reported in offspring of obese mothers (117, 196). Similar findings of reduced energy expenditure (142) and a greater affinity for unhealthy food (145) are also reported in animal models exposed to maternal over nutrition.

The importance of early life development on regulation of appetite and subsequent growth has been long recognised. In 1975 it was documented that “there is a critical point in development when the size of an animal, arising from its previous plane of nutrition, determines its appetite thereafter, and hence its rate of growth and dimensions at maturity” (197). It is now evident that satiety, food preference and even exercise capacity can have major developmental and biologically based determinants, which may be difficult to reverse once set points have been established in early life (137). Appetite and energy balance homeostasis are primarily regulated by the hypothalamus via nutrient, hormonal and neural signals from adipocytes, the pancreas, the gastrointestinal tract and other brain regions (149). Leptin acts via hypothalamic leptin receptors to regulate appetite via alterations in appetite regulatory neuropeptides (149). These include appetite stimulatory factors such as neuropeptide Y and agouti-related protein and inhibitory factors such as pro-opiomelanocortin and cocaine-and amphetamine-regulated transcript (149). Evidence from animal research further suggests that perinatal conditions may induce permanent changes in structure and function of the appetite regulation centres of the brain (55). In rat models, early life over nutrition and hyperinsulinaemia influenced hypothalamic development of appetite and energy balance via several pathways, including increased sensitivity to orexigenic neurotransmitters and decreased levels of satiety signals (198, 199). Similarly, sheep studies have shown that exposure to excessive in utero nutrition can alter the responses of the central appetite regulatory system to signals of increased adiposity, with reduced hypothalamic expression of the leptin receptor, and changes in expression of appetite regulating neuropeptides in offspring of overfed pregnant sheep compared to controls (144).

Modifying maternal over nutrition driven foetal programming of obesity

Despite a significant rise in obesity in recent years, prevention of foetal programming of obesity remains a relatively limited area of study (11, 200). However, foetal programming targets the earliest stages of development of obesity, and provides a novel paradigm to complement other strategies for lifelong prevention of obesity. Further, there is some evidence that maternal obesity driven offspring programming effects can be modified (201, 202).
Perhaps the best evidence available is the improvement in long term health outcomes in offspring born to severely obese women, after maternal weight loss from bariatric surgery (201, 202). A few studies have compared childhood outcomes between sibling offspring conceived before and after maternal weight loss from bariatric surgery (201, 202). One such study by Kral et al., compared the prevalence of obesity in children conceived to obese women after bilio-pancreatic bypass (bariatric) surgery, with age adjusted prevalence in siblings conceived before surgery, and with population standards. Rate of obesity in offspring born after surgery was 50% lower compared to offspring born before surgery, and similar to population levels (201). A similar study by Smith in 2009, demonstrated bariatric surgery resulted in significant maternal weight loss (36 ± 1.8% body weight), and offspring conceived following this, had lower birth weight and less macrosomia. These offspring also showed improvement in cardio-metabolic markers in childhood and adolescence, compared to siblings born before surgery, including a threefold lower prevalence of severe obesity, better insulin sensitivity, better lipid profile, lower leptin and lower C-reactive protein levels (202). Similarity, studies considering perinatal outcomes have reported lowered risk of LGA births and macrosomia following maternal bariatric surgery (203, 204). These findings confirm that pre-conceptional weight loss in severely obese mothers by bariatric surgery can improve offspring risk of obesity and metabolic complications. However, weight reduction by bariatric surgery is an extreme measure, not directly applicable to a majority of overweight and less obese women of reproductive age. Therefore it is necessary to look at other maternal interventions which could potentially benefit these offspring.

There is increasing expression of expert opinion, that antenatal lifestyle interventions in overweight and obese pregnant women could alter adverse foetal programming and improve offspring health (11, 12). It is postulated that modifying the obesogenic in utero environment by lifestyle changes such as increased antenatal physical activity or improved dietary intake during pregnancy could reduce harmful programming effects in the offspring (11). However, there is a scarcity of studies investigating lifestyle intervention strategies in overweight and obese mothers with the aim of attenuating offspring predisposition to obesity (200).

Maternal antenatal lifestyle interventions in overweight and obese women could potentially improve offspring health via several pathways. Limiting foetal over nutrition in utero could be potentially beneficial, and manifest as a reduction in birth weight and LGA births. Improvement in the unhealthy maternal metabolic milieu (demonstrated by increased insulin resistance, hyperinsulinaemia hyperglycaemia, hyperlipidaemia, and increased inflammatory
markers) may also help to combat the vicious cycle of maternal obesity and offspring obesity (10, 200). Other potential pathways by which offspring health could be improved by maternal lifestyle interventions include via reduction in excessive maternal gestational weight gain and reduction in pregnancy complications such as gestational diabetes (79, 168, 205). Gestational weight gain correlates positively with offspring birth weight (206), risk of foetal macrosomia (207) and new born adiposity in offspring of overweight/obese women (109). The IOM guidelines recommend diet and physical activity counselling to pregnant women to help achieve gestational weight gain within recommended limits (79). Gestational weight gain exceeding IOM guidelines, occurs in up to two thirds of overweight and obese pregnant women, and is associated with an increased risk of having a LGA birth (79, 81, 112). Limiting gestational weight gain may potentially reduce excessive birth weight and adiposity, leading to a healthier phenotype in offspring of overweight and obese women.

2.3.4 Early life indicators of offspring programming effects

Early life markers indicating potential adaptive responses in offspring of overweight and obese mothers by antenatal interventions have not been well delineated. Potential markers of reduced offspring obesity risk, identifiable at birth could include a reduction in excessive birth weight or LGA births, reduction in neonatal adiposity, and reduction in cord blood levels of metabolic markers associated with foetal over nutrition such as insulin, growth factors and leptin (55, 148, 162).

Birth weight

Excessive birth weight is associated with increased risk of obesity. Many recent studies looking at the association between birth weight and BMI in later life have found direct positive associations (55). A recent meta-analysis showed that having a birth weight above 4 kg was associated with a twofold increased risk of obesity in childhood and early adulthood compared to a birth weight below 4 kg (105). The longitudinal study involving the 1958 British birth cohort looked at the influence of birth weight on BMI and found a positive relationship between birth weight and BMI at 7, 11, 16, 23 and 33 years of age (139). However, the association between birth weight and BMI become more J shaped with increasing age, indicating that both extremes of birth weight were associated with adult obesity.

Given the positive correlation between birth weight and later life obesity, reduction of obesity risk could be manifest by reduction in birth weight in the generally heavier babies of
overweight and obese pregnant women. A modest reduction in birth weight, avoiding both extremes of birth weight (i.e., reducing LGA births without increasing SGA births) could potentially indicate better long term outcomes for these offspring (55, 208). Most factors that influence birth weight such as maternal age, height, parity and ethnicity and multiple pregnancy are non-modifiable, while maternal pre-pregnancy BMI, gestational weight gain and smoking are potentially modifiable factors (76). Maternal physical activity level is also suggested as a modifiable determinant of foetal macrosomia (209). There is need for further research to explore the underlying mechanisms by which a foetus achieves a given birth weight and how birth weight is associated with long term health (55, 132).

However, while birth weight is a readily available, and often reported surrogate measure of cumulative foetal growth, there are limitations in using birth weight as the sole measure of in utero growth (131). For instance a foetus growing continuously throughout gestation can have the same size at birth as a foetus whose growth was arrested for a period and then 'caught up'. Also different patterns of foetal growth could lead to different effects on foetal body composition, though overall birth weight may be the same. Furthermore, altered birth size is not an obligatory part of the pathway leading to increased disease risk. Oken et al., suggest that it is important for investigators to go “beyond birth weight” and assess other early life predictors of postnatal outcomes (55). Barker and colleagues have also stressed the importance of taking into account body proportions and adiposity to better reflect the environmental cues the foetus has been exposed to, and to prognosticate future health (210).

**Neonatal body composition**

When considering body composition, the human body is classically compartmentalized into fat and lean mass components, and the fat content reflects energy stores and substrate availability (158). Babies exposed to gestational diabetes and hyperglycaemia in late gestation have increased fat mass at birth. LGA babies also have higher body fat and lower lean body mass, which is further exaggerated by impaired maternal glucose tolerance (211). However, offspring of overweight and obese mothers are reported to have increased adiposity, even with normal maternal glucose tolerance.

Insulin resistance in the mother in early gestation also appears to be an important contributor to neonatal adiposity. Maternal insulin sensitivity before conception shows the best correlation with neonatal fat mass, while insulin sensitivity in late gestation shows strongest correlation with placental weight, neonatal birth weight and fat free mass (159). Further, elevated leptin
levels seen in maternal over nutrition, could also potentially be associated with decreased bone turnover and increased bone mass (194). Therefore both maternal obesity and the in utero metabolic environment can influence early life body composition.

In it possible that changes in early life body composition could affect long term health. Foetal hyperinsulinaemia may program foetal obesity through a lasting influence on adiposity in early life (55). Foetal adipose tissue undergoes extensive replication in the third trimester, and shows responsiveness to maternal nutrient supply. It is possible that alterations in adipocyte tissue cellularity established in foetal life may persist throughout life. The early nutritional milieu may stimulate cellular proliferation or adaptive clonal selection so that the quantity or proportion of cell populations in a tissue are permanently affected (132). Therefore, it is possible that an abundance of nutrients to the foetus causes more adipose cells to be laid down, promoting future obesity.

**Later life effects**

However, phenotypic effects of developmental programming may not be evident at birth, but can emerge later in life during periods of rapid growth or on exposure to postnatal environmental insults (129, 212). Foetal programming can affect offspring health via mechanisms such as alteration of appetite and energy regulation or gene expression (6, 11, 55). However alterations in appetite, food preferences and activity levels are difficult to identify in early life. Various aspects of developmental programming effects could manifest in the offspring at various stages in childhood and adulthood (129). Therefore, it appears that longitudinal follow up studies are necessary to identify the true extent of effects of early life interventions on offspring health. However, it has been highlighted that there is a scarcity of randomized clinical trials involving maternal interventions before or during pregnancy, where offspring are followed up longitudinally to identify lasting influences on offspring health (6, 200).
2.4. Exercise during pregnancy

2.4.1 Definitions

Physical activity is defined as any voluntary movement produced by skeletal muscles that results in energy expenditure, which includes sports and a range of recreational, occupational, and household activities (213). Exercise is defined as physical activity that is planned, structured, and repetitive, and where the final or intermediate objective is the improvement or maintenance of physical fitness (213).

2.4.2 Current recommendations for antenatal exercise

It is recommended that all pregnant women without medical or obstetric contraindications participate in regular moderate-intensity exercise during pregnancy (214-216). Current exercise recommendations by the American College of Obstetricians and Gynaecologists (ACOG) for healthy pregnant women are similar to those for non-pregnant individuals, and advocate 30 minutes or more of moderate intensity exercise on most, if not all days of the week for all pregnant women without any medical or obstetric complications (215). The Society of Obstetricians and Gynaecologists of Canada together with the Canadian Society for Exercise Physiology similarly encourages all women without contraindications to participate in aerobic and strength-conditioning exercises as part of a healthy lifestyle during their pregnancy (214). They advocate the second trimester as the most suitable time to initiate an exercise program in pregnancy, when the troublesome symptoms of the first trimester have subsided. According to these guidelines, previously sedentary women can start by exercising for 15 minutes daily three times a week and increase to 30 minutes, four times a week (214). They also recommend that all pregnant women should be educated that exercise is not associated with adverse pregnancy or neonatal outcomes. Validated target heart rate zones for exercise in overweight and obese pregnant women have recently been developed (217) and detailed guidelines specific to this group of women are also now available (218, 219).

2.4.3 Barriers to exercising during pregnancy

Despite above recommendations, participation in physical activity and exercise declines in pregnancy. Women in both developed and developing countries tend to engage in less physical
activity during pregnancy (167, 168). The decline in physical activity during pregnancy appears to be particularly marked among obese women (169, 170). Further, fewer women meet daily exercise recommendations during pregnancy compared to the non-pregnant state (171). In the USA, a retrospective survey was carried out in a selected group of women who exercised regularly and who volunteered to participate in the study through a national physical fitness conference. Although, the characteristics of the study population suggest that they would have higher tendency to exercise compared to the general population, and 83% of the subjects were aware of the ACOG guidelines, only 53% of the subjects reported adherence to the ACOG guidelines for exercise in pregnancy (172).

It is important to understand factors and perceptions leading to the decline in physical activity levels during pregnancy. There are a number of physiological changes of pregnancy that can make exercise more difficult and less acceptable to the pregnant women, such as an increased sense of breathlessness, change in centre of gravity with alteration of posture and balance, and ligamentous laxity (220, 221). Further, weight gain in pregnancy leads to an increase in the cardiorespiratory effort required to perform a given amount of physical activity (222).

Pregnant women also perceive a number of additional barriers to exercise such as tiredness, low motivation, and lack of enjoyment, and report concerns regarding pregnancy complications and foetal harm. In addition, there are practical reasons to avoid certain contact sports and other forms of exercise that involve an increased likelihood of falling or abdominal trauma, which may harm the foetus (214, 215). There are also a number of external factors including lack of childcare, lack of time, overly protective family members, lack of outdoor spaces to be active, and the cost of exercise facilities that also can play a role (223).

For overweight and obese pregnant women, there can be additional factors, accounting for reduced exercise levels in pregnancy. Poor self-image may be an extra hurdle, to exercising in public or in groups. One study showed that 45% of pregnant women were dissatisfied with their body size and shape, and these individuals were more likely to gain weight excessively in pregnancy (224). Another study revealed that although some obese women view limiting pregnancy weight gain as a motivator for exercising during pregnancy, many women prefer to postpone attempting weight control until after childbirth (225). Further, obese women have reported receiving very limited advice on safe and appropriate forms of antenatal exercise or being advised to be cautious and limit exercise during pregnancy (226, 227). They also perceived that their health care providers’ knowledge on appropriate exercise in pregnancy was limited (193) Conflicting advice about appropriateness of exercise during pregnancy may stem from outdated medical teaching when women used to be advised to reduce their exercise...
levels during pregnancy (214). Lack of access to correct information, support and advice on exercise during pregnancy are important modifiable factors that can be addressed via maternity care provision (223, 225, 226). However, while most women maintain frequent contact with their healthcare providers during pregnancy, adequate support for antenatal exercise does not appear to be readily available.

2.4.4 Prescribing antenatal exercise for overweight and obese pregnant women

Before advising women to exercise during pregnancy, it is important that contraindications to antenatal exercise are excluded. There are many absolute contraindications to antenatal exercise, including ruptured membranes, risk of preterm labour, hypertensive disorders of pregnancy, incompetent cervix, growth-restricted foetus, high order multiple gestation (triplets or above), placenta praevia after the second trimester, persistent second or third trimester bleeding, uncontrolled type I diabetes, uncontrolled thyroid disease and serious cardiovascular, respiratory, or systemic disorders (214, 215). It is also important that women receive adequate guidance on suitable types of antenatal exercise as well as exercise intensity, frequency and duration (218). Brisk walking, stationary cycling, swimming, and aqua aerobics cause less strain on ligaments and joints, and are preferable to high-impact exercises such as jogging and running during pregnancy (214). In overweight and obese women especially, non-weight-bearing exercises such as aqua aerobics and stationary cycling are likely to be more appropriate as pregnancy advances. It is important to encourage regular monitoring of exercise via self-reported measures combined with low-cost objective measures of physical activity whenever possible (228, 229). Heart rate monitors are useful tools to monitor compliance with prescribed exercise and to ensure women exercise at appropriate intensity (1). It is also important to consider pre-pregnancy activity level and modify the exercise prescription accordingly. We have proposed a series of steps for the prescription of exercise in pregnancies complicated by obesity (Table 1).
Table 1: Proposed steps for exercise prescription in pregnancies complicated by obesity.

<table>
<thead>
<tr>
<th>Steps</th>
<th>Notes</th>
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<tbody>
<tr>
<td>2. Information provision</td>
<td>Discuss potential benefits and risks of antenatal exercise and address any concerns. Recreational exercise and pregnancy (216) and PARmed-X for pregnancy (214) can be useful aids.</td>
</tr>
<tr>
<td>3. Personalised goals</td>
<td>It is important to personalise goals to maximize engagement (228). Decide on an exercise regime compatible with the patient's lifestyle and liking.</td>
</tr>
<tr>
<td>4. Timing of exercise initiation</td>
<td>If previously sedentary, the second trimester seems to be the best time to commence an exercise programme, once morning sickness has abated (214).</td>
</tr>
<tr>
<td>5. Type of exercise</td>
<td>Recommend low-impact aerobic exercises (brisk walking, stationary cycling, swimming, and water aerobics). Avoid activities involving a risk of loss of balance, falls, or abdominal trauma. Avoid the supine position after 16 weeks of pregnancy (214, 215).</td>
</tr>
<tr>
<td>6. Intensity of exercise</td>
<td>Avoid vigorous exercise. If already active, maintain moderate-intensity activities; if sedentary, start at low intensity and gradually increase to moderate-intensity. Validated heart rate ranges for overweight and obese pregnant women (217): Low intensity: 102-124 bpm (20-29 years of age); 101-120 (30-39 years of age) Moderate intensity: 125-147 bpm (20-29 years of age); 121-142 bpm (30-39 years of age) If heart rate cannot be monitored, the “talk test” can be utilised to ensure that exercise does not exceed moderate intensity. As the “talk test” implies, the woman is exercising at a comfortable intensity if she is able to maintain a conversation during exercise (214).</td>
</tr>
<tr>
<td>7. Duration of exercise</td>
<td>If previously sedentary, start with 15 minutes of moderate-intensity exercise, and increase in 5 minute increments up to 30 minutes (214). Include low-intensity warm-up and cool-down periods (214, 215).</td>
</tr>
</tbody>
</table>
8. Frequency of exercise
   If previously sedentary, start at 3 sessions per week on non-consecutive days, and increase up to 4 sessions or more per week (214, 215).

9. Behavioural change
   Employ behavioural changing techniques (228, 229):
   - Goal setting and planning – identify appropriate activities and set weekly/monthly exercise targets
   - Self-monitoring – use an exercise diary or a heart rate monitor
   - Feedback – inquire about exercise at each antenatal visit, address any new concerns, and continuously encourage patient

2.4.5 Methods to increase exercise in pregnancy

Pregnancy can be a powerful incentive to establish healthy lifestyle changes in overweight and obese women (230). In general, a more proactive approach by clinicians in promoting exercise is advocated, and merely inquiring how much a patient is exercising can be a good starting point (231, 232). Maternity health care providers can similarly encourage pregnant women to exercise with appropriate advice during initial antenatal care visits and utilize subsequent clinical visits for ongoing reinforcement.

However, more research is needed to establish the best methods of encouraging and sustaining exercise in pregnancy, especially in obese women. Two recent systematic reviews on behavioural interventions for improving physical activity in pregnant women provide some insight (228), (229). The review by Currie et al. concluded that while no specific technique can be recommended, healthcare professionals can help pregnant women to stay active by providing information on the importance of physical activity, discussing appropriate forms of exercise, emphasising personal goals, and planning during face-to-face encounters (228). Pearce et al concluded that little is known about the efficacy of interventions for physical activity during pregnancy, emphasising the need for more research in this area (229). Further, understanding the attitudes and cultural acceptability of exercise among pregnant women from diverse backgrounds is also important (233). Moreover, the community applicability and cost-effectiveness of providing opportunities for exercise need to be ascertained (234, 235). Considering the increasing number of obese women entering pregnancy and the health consequences for mother and baby, adequate education and support for exercise in pregnancy appears a timely need.
2.5. **Effects of antenatal exercise on maternal health**

There is expert consensus that antenatal exercise leads to positive effects on maternal and offspring health (12). Potential pathways via which antenatal exercise can improve maternal health include reduction in gestational weight gain and pregnancy/delivery complications and improvements in maternal cardiorespiratory fitness and metabolic milieu (Figure 3). Existing evidence that antenatal exercise in overweight/obese pregnant women can benefit maternal health is discussed below.

### 2.5.1 Effects on gestational weight gain, and pregnancy and delivery complications

Evidence from large observational studies considering pregnant women irrespective of weight status have suggested that exercise can be associated with reduced risk of excessive gestational weight gain (236), gestational diabetes (237) and pregnancy-induced hypertension/pre-eclampsia (238), reduced rates of caesarean section and instrumental delivery, and reduced length of hospital stay for childbirth (239, 240). Increased physical activity has also been associated with decreased risk of perineal lacerations and vaginal operative delivery (241). Results from several intervention studies also suggest that antenatal exercise can improve glucose tolerance (242), gestational weight gain (243, 244) and postpartum weight retention (245).

When considering higher grade of evidence of maternal benefits of antenatal exercise by systematic review and meta-analysis of randomised controlled trials however, there are some inconsistencies. For instance, Cochrane systematic reviews have not shown any benefits of antenatal aerobic exercise on gestational diabetes, pre-eclampsia or other pregnancy outcomes in the mother (246-248). One of the most comprehensive meta-analysis on the effects of lifestyle interventions during pregnancy conducted in 2012, included data from 44 trials, looked at a range of maternal and offspring pregnancy outcomes, and also conducted sub-analysis according to maternal BMI status, and type of intervention (dietary, physical activity or mixed interventions) (15). Overall, while all types of interventions were effective in reducing gestational weight gain (mean difference -1.4 kg, 95% CI -1.9 to -0.9), dietary interventions were the most effective (mean difference -3.8 kg, 95% CI -5.2 to -2.4). When considering the effects of physical activity only interventions (14 trials), there was a smaller but significant reduction in gestational weight gain (mean difference -0.7 kg, 95% CI -1.2 to -2.5), and no effect on rates of preterm delivery, caesarean section, or gestational age at
delivery. More recently, a modest reduction in gestational weight gain (mean difference 2.2 kg, 95% CI −3.14 to −1.3 kg and 0.6 kg, 95% CI -1.17 to 0.06) were demonstrated by two further meta-analysis including only antenatal exercise trials (249, 250). No effects were seen on postpartum weight loss or postpartum BMI (249). Another recent meta-analysis on risk of gestational diabetes, combining data from 10 antenatal exercise trials, reported a 28% reduced risk (95% CI 9 to 42 %) of gestational diabetes in the exercise groups compared with controls (251). Further, a systematic review and meta-analysis evaluating the effect on labour and delivery including data from 16 randomised controlled trials showed exercise groups had a significantly lower risk of caesarean delivery (relative risk 0.85, 95% CI 0.73 to 0.99), and gained significantly less weight than women in control groups (mean difference −1.13 kg, 95% CI−1.49 to −0.78), while risk of instrumental vaginal delivery was similar among groups.

Data on induction of labour, length of labour perineal tears, and use of epidural anaesthesia were insufficient to draw conclusions (252). So, overall, there is newly emerging evidence of conclusive benefits on antenatal exercise on maternal health. However, many studies involved pregnant women of any BMI, and were not specific to overweight and obese pregnant women.

The effects of antenatal exercise on maternal outcomes in overweight and obese women are less well studied. Recently however, a number of intervention studies (253-262), systematic reviews (13, 14, 223, 263) and meta-analysis (15, 264) have examined the effects of exercise and other lifestyle modifications on pregnancy outcomes in overweight and obese pregnant women. There is evidence from some intervention studies that exercise can be beneficial in improving maternal fitness (254, 259, 261), glucose tolerance (254, 264) and limiting weight gain (13, 255-257, 259, 264) in obese pregnant women, although other studies have not found positive effects (253, 258, 260, 262). Nonetheless, no negative effects have been reported (13).

When considering combined (dietary and/or physical activity) lifestyle interventions in overweight and obese women, a reduction in gestational weight gain has been found in some (14, 15, 264) but not all (263) meta-analysis. Further, no reduction in pregnancy and delivery complications such as gestational diabetes, preeclampsia and caesarean section have been shown by meta-analysis of combined lifestyle interventions in overweight/ obese women (263-265).

It is important to note that many of the recent intervention trials involving overweight and obese women such as the NELIP, LiP, LIMIT and UPBEAT studies (256, 258-260) included both dietary and physical activity interventions, making it difficult to discern out the effects of antenatal exercise per se on maternal health. Based on systematic reviews/ meta-analysis
considering purely exercise-only interventions (without a dietary intervention), the only potential benefit observed was a reduction in gestational weight gain (13). Therefore overall benefits of antenatal exercise intervention in overweight and obese women on maternal pregnancy outcomes remain unproven.

2.5.2 Effects on maternal cardiorespiratory fitness

Another potential advantage of antenatal exercise includes maintenance or improvement of maternal fitness (aerobic capacity) (246, 261), which may potentiate quicker return to pre-pregnancy activity levels after delivery, and help lose weight gained during pregnancy (266). During pregnancy, gestational weight gain causes an increase in the cardiorespiratory effort required to perform a given amount of work, leading to a ‘training effect’, unless a more sedentary lifestyle is adopted (222). Maximal aerobic power is well-preserved in pregnant women who remain physically active (267), and can even increase during pregnancy, possibly due to the “training effort” imposed by increasing weight (222). Controlled prospective studies have demonstrated that moderate prenatal exercise during the second and third trimesters is useful to improve aerobic fitness (267). Improvement in maternal fitness by aerobic exercise during pregnancy has been confirmed by a Cochrane review, despite no evidence of improvement in pregnancy outcomes (246). In overweight and obese pregnant women, there is evidence from a few intervention studies, that antenatal exercise can improve maternal fitness (254, 259, 261).

2.5.3 Effects on maternal metabolic milieu

Regular exercise with or without weight loss is associated with metabolic improvements, such as improved insulin sensitivity in the general population (268, 269). There is limited evidence that moderate intensity physical activity/exercise in obese women may reduce maternal insulin resistance and triglyceride levels (254, 270-272). The Lifestyle in Pregnancy (LiP) study was a randomized controlled trial involving 360 obese women (BMI 30–45 kg/m²) who were allocated in early pregnancy to lifestyle interventions with diet counselling and physical activities or to the control group (259). Women in the intervention group had improved fitness, lower gestational weight gain and lower increase in insulin resistance compared with control subjects (259). However, there were no changes in lipid profile between the groups (271). In
another recent prospective randomized controlled trial of aerobic exercise in 67 nulliparous pregnant, the experimental group completed a 3 month supervised exercise program including walking, aerobic exercise and stretching, commencing at 16 to 20 weeks of gestation. At the end of the intervention, maternal triglycerides were lower in the experimental group, although there was no difference in total cholesterol level and insulin resistance (272). Other antenatal exercise trials in overweight/obese women have reported a lack of improvement in maternal metabolic markers (253, 273). However, overall there appears to be potential for improving the in utero metabolic environment associated with maternal obesity via antenatal exercise.
2.6. Effects of antenatal exercise on offspring health

2.6.1 Safety of maternal exercise for the developing foetus

The safety of exercise during pregnancy for the foetus has been an issue of concern in the past, based on evidence of effects of strenuous antenatal exercise from animal research (274). Potential concerns included foetal malformations from exercise-induced hyperthermia in early gestation, foetal hypoxia and intrauterine growth retardation from redistribution of maternal blood flow and nutrients from utero-placental circulation to exercising muscle, and preterm delivery from increased uterine contractility (274). However over the last few decades no evidence has emerged that moderate maternal exercise adversely affects foetal well-being (274-276). Numerous studies on maternal antenatal exercise over the past 20 years have demonstrated that mild to moderate-intensity antenatal exercise in healthy well-nourished women exercise does not cause observable harm to the foetus (246, 277-279). This has led to a gradual change in opinion that moderate antenatal exercise is not only safe but may also be beneficial to offspring health (12, 277).

2.6.2 Potential benefits to offspring of overweight/obese women

Despite increasing rates of overweight and obesity and a view that antenatal exercise could be beneficial for maternal and offspring health, there is a paucity of intervention trials focussing on the effects of antenatal exercise on offspring of overweight and obese women (12, 13, 208). Pathways by which antenatal exercise could potentially improve the health of offspring of overweight and obese mothers include a reduction in excessive birth weight and LGA births, without increasing SGA births and alteration in offspring adiposity (55, 208). Reduction in excessive gestational weight gain, and improvement in the abnormal maternal and foetal metabolism associated with maternal obesity could also be potentially beneficial on offspring body composition and programming of energy homeostasis (6, 10, 148, 149, 280). Figure 3 shows potential pathways by which antenatal exercise could improve offspring and maternal health.
2.6.3 Effects on offspring birth outcomes

The effects of different regimes of antenatal exercise on birth weight and the mechanisms underlying these changes are complex (208, 281). In a recent meta-analysis on antenatal lifestyle interventions, physical activity interventions (14 trials) led to a modest reduction in birth weight (-60g, 95% CI -120 to -10g), as well as a trend towards reduction in LGA births (RR 0.5, 95% CI 0.3 to 1.1). In a Cochrane review, however, antenatal aerobic exercise in sedentary women had no significant effect on mean birth weight (237). Effects of antenatal exercise on foetal growth and birth weight are confounded by the many factors such as the intensity and frequency of exercise, and the time period during pregnancy in which it was performed (208, 281-283). This may partially explain conflicting reports on effects of antenatal exercise on birth weight. Beginning weight bearing exercise in early pregnancy can stimulate foeto-placental growth, and increase birth weight (284). Conversely, both weight bearing and non-weight bearing antenatal exercise in the second half of pregnancy appear to reduce birth weight (16, 208).

Exercise during pregnancy is associated with short term reduction in maternal blood glucose and insulin levels, suggesting more glucose is utilised by the mother during exercise via improved maternal insulin sensitivity and increased uptake by exercising muscle (285). This could potentially lead to a reduction in nutrient supply to the foetus, which if sustained, could alter foetal growth and development. In a randomised controlled trial of regular moderate intensity non-weight bearing exercise conducted in the second half of pregnancy by our research groups, offspring of exercisers had lower birth weight at birth (16). Maternal insulin sensitivity in late gestation was similar between groups, but there was a reduction in cord blood IGF-I and IGF-II in exercise offspring (16). As foetal IGF levels are regulated by nutrient supply, this suggests a down regulation of IGF by maternal exercise, potentially via reduced nutrient supply. However, similar effects have not yet been explored in offspring of overweight and obese pregnant women.

Individual studies (in non-obese women) have shown that regular moderate/vigorous maternal exercise in the latter half of pregnancy can cause a reduction in birth weight (within the normal birth weight range) ranging from 150 to 400 g (16, 281, 282). In one study however, vigorous exercise more than 5 times a week caused an increase in low birth weight (282), suggesting that exercise in pregnancy should be done in moderation. A meta-analysis considering the timing of maternal exercise during pregnancy, reported that women who continued to exercise vigorously at least 3 times a week into the third trimester had offspring
who were 200 g lighter at birth compared to active controls (reporting low or moderate levels of exercise less than 3 days per week) and 400 g lighter to those of sedentary controls (283). When considering extremes of birth weight, an observational study on nearly 80,000 Danish new-borns suggested that any form of maternal exercise during pregnancy decreased the risk of both LGA and SGA births (286).

Evidence on the effects of antenatal exercise on birth weight of offspring of overweight and obese mothers is limited. A systematic review on supervised antenatal exercise intervention in overweight and obese women included two trials reporting birth weight, with both studies showing no effect on birth weight (13, 261, 287). One trial included only overweight women (261), while the other included both overweight and obese women, and both interventions commenced in mid gestation and consisted of several types of exercise including walking and resistance exercise(261, 287). One study also reported no effect from the intervention on LGA and SGA births (287). A more recent trial (FitFor2 study), involving overweight and obese pregnant women at risk of gestational diabetes also reported no effect on birth weight or LGA births with an antenatal exercise regime (253). An trial of regular light intensity resistance training in the second and third trimesters of pregnancy, including women of all BMI categories however, showed an attenuation of high birth weight associated with increased maternal BMI in the intervention group (288).

Among overweight and obese women, meta-analysis of data from randomised controlled trials on antenatal lifestyle interventions (combining physical activity and nutritional interventions) showed no effect on mean birth weight or rate of LGA births (15, 263, 264). More recent trials including dietary and physical activity interventions, have demonstrated contradictory effects on mean birth weight and excessive birth weight in obese and overweight women. In the NELIP study, there was a reduction in excessive birth weight (between 4-4.5 kg) in overweight women, but a trend towards increase in obese women in the intervention arm (256). In the LiP (Lifestyle in Pregnancy) study, involving 360 obese pregnant women, offspring showed a trend towards increased risk of birth weight > 4kg although there was reduced gestational weight gain and improved physical fitness in mothers in the intervention arm (259). The authors have speculated on enhancement of placental function as a cause for increased birth weight in the intervention group. Offspring body composition was not assessed in these studies. Conversely, the recently concluded LIMIT study, a large randomised trial involving more than 2000 overweight and obese pregnant women, demonstrated a reduction in excessive birth weight (exceeding 4 kg and 4.5 kg) as well as reduction in respiratory distress syndrome, and shorter duration of hospital stay for offspring in the intervention arm (258,
There was no effect on mean birth weight or maternal gestational weight gain, and no increase in risk of low birth weight (258). The intervention mainly included advice and behavioural counselling on diet and physical activity (encouragement to increase walking and incidental activity). Hence overall, the effects from lifestyle interventions on birth weight of offspring of overweight and obese women are yet inconclusive.

### 2.6.4 Effects on offspring body composition

Antenatal exercise also appears to influence neonatal body composition (208). A recent prospective longitudinal study examined the relationship between self-reported maternal physical activity (using a pregnancy physical activity questionnaire) in early, mid and late pregnancy and neonatal body composition measured by air displacement plethysmography at birth (290). Increased maternal physical activity in late pregnancy was associated with reduced neonatal fat mass, but not with birth weight or fat free mass. There was no relationship between physical activity in early and mid-pregnancy and either neonatal body composition or birth weight.

The pattern and timing of exercise in relation to gestation appears to influence differential effects on offspring body composition (208, 291). A review by James Clapp, who has performed extensive research on the effects of antenatal exercise, elegantly demonstrates the complexities of the associations between maternal exercise and offspring body composition (291). Clapp’s studies suggest that a low to moderate exercise regime continued from early pregnancy throughout pregnancy can lead to an increase in birth weight due to increase in both lean and fat mass, while maintaining higher exercise volume throughout pregnancy can lead to a decrease in birth weight and fat mass (291). However, changes to the exercise regime in mid pregnancy can lead to additional effects. Decreasing a high volume weight bearing exercise regimen pregnancy in mid pregnancy can lead to an increase in birth weight with greater increase in fat compared to lean mass, while increasing exercise to a high level in mid pregnancy can lead to the opposite effects with reduced birth weight and fat mass (291).

Therefore, the above findings suggest that in order to achieve a reduction in offspring birth weight and adiposity, one should maintain a moderate to high exercise volume throughout pregnancy, and possibly increased exercise volume in latter pregnancy. Both reduction in exercise volume in mid pregnancy (increased birth weight and fat mass), and maintaining only a low exercise volume (increased birth weight) could be detrimental, if reduction in birth
weight and adiposity is the goal, as in offspring of overweight and obese women. However it is important to bear in mind that most of the studies involved lean physically active pregnant women, and therefore may not be directly relevant to offspring of overweight and obese pregnant women, who are the focus of this research.

2.6.5 Effects on long term offspring health

There is a dearth of data on the effects of maternal antenatal exercise on long term offspring health (208). Clapp demonstrated that regular vigorous antenatal exercise in 20 physically active lean women led to a reduction in offspring weight and subcutaneous fat at birth, and these offspring continued to have lower weight and subcutaneous fat compared to age matched controls at 5 years of age, as well as similar neurodevelopmental outcomes (292). In another study by Clapp, 52 infants of women who exercised during pregnancy were compared with matched controls at 1 year of age (293). Morphometric and neurodevelopmental outcomes were similar between groups, indicating normal development during the first year of life (293). More recently, offspring from the LiP randomised controlled trial in obese women (259)(which included antenatal dietary advice, coaching and exercise) were followed up for anthropometric, body composition and metabolic outcomes at 2.8 years of age (range 2.5–3.2) (294, 295). Children born to women with a normal BMI were included as a reference group. However, there were no differences between intervention, control and reference groups for BMI, body composition or rates of overweight and obesity (294). Further, metabolic markers including fasting glucose, insulin, triglycerides and HDL cholesterol were also similar between groups(295).

These appear to be the only published offspring follow up data available from clinical studies on maternal physical activity/exercise intervention in pregnancy. Thus, it is still far from established whether antenatal exercise could lead to improved long term health outcomes for offspring of overweight and obese women (12, 208). The need for antenatal interventional studies which follow up offspring long term to determine any persisting effects of offspring health has been highlighted (6, 291).

Overall, there is a dearth of data on the effects of antenatal exercise in overweight and obese women on offspring birth weight, early life body composition and metabolism and on long term health.
Figure 3: Potential pathways by which antenatal exercise could improve maternal and offspring health.
Chapter 3. Design and Methods

This chapter contains the trial protocol published in the journal BMC pregnancy and childbirth. The text has been modified to maintain consistency with the rest of the thesis. Additional information on assessment of neonatal body composition is provided in the subsequent section.
The Impact of Antenatal Exercise in Overweight and Obese Women on Maternal and Offspring Health
3.1. Trial protocol

Antenatal exercise in overweight and obese women and its effects on offspring and maternal health: design and rationale of the IMPROVE (Improving Maternal and Progeny Obesity Via Exercise) randomised controlled trial

Sumudu N Seneviratne, Graham K Parry, Lesley ME McCowan, Alec Ekeroma, Yannan Jiang, Silmara Gusso, Geovana Peres, Raquel O Rodrigues, Susan Craigie, Wayne S Cutfield, Paul L Hofman

Abstract

Background:

Obesity during pregnancy is associated with adverse outcomes for the offspring and mother. Lifestyle interventions in pregnancy such as antenatal exercise are proposed to improve both short- and long-term health of mother and child. We hypothesised that regular moderate-intensity exercise during the second half of pregnancy would result in improved maternal and offspring outcomes, including a reduction in birth weight and adiposity in the offspring, which could be protective against obesity in later life.

Methods/Design:

The IMPROVE (Improving Maternal and Progeny Risks of Obesity Via Exercise) study was a two-arm parallel randomised controlled clinical trial conducted in Auckland, New Zealand. Overweight and obese women (BMI ≥25 kg/m²) aged 18–40 years, with a singleton pregnancy of <20 weeks of gestation, from the Auckland region, were eligible for the trial.

Exclusion criteria were ongoing smoking or medical contra-indications to antenatal exercise. Participants were randomised with 1:1 allocation ratio to either intervention or control group, using computer-generated randomisation sequences in variable block sizes, stratified on ethnicity and parity, after completion of baseline assessments. The intervention consisted of a 16-week structured home-based moderate-intensity exercise programme utilising stationary cycles and heart rate monitors, commencing at 20 weeks of gestation. The control group did not receive any exercise intervention. Both groups underwent regular foetal ultrasonography.
and received standard antenatal care. Due to the nature of the intervention, participants were un-blinded to group assignment during the trial.

The primary outcome was offspring birth weight. Secondary offspring outcomes included neonatal body composition and anthropometry, neonatal complications and cord blood metabolic markers. Maternal outcomes include weight gain, pregnancy and delivery complications, aerobic fitness, quality of life, metabolic markers and post-partum body composition.

**Discussion:** The results of this trial provided valuable insights on the effects of antenatal exercise on health outcomes in overweight and obese mothers and their offspring.

**Trial registration:** Australian New Zealand Clinical Trial Registry ACTRN12612000932864
Background

The number of women entering pregnancy in an overweight or obese state has increased steadily in developed countries over the last three decades (61, 62, 296, 297), and is also increasing in developing nations (60). Maternal overweight and obesity are associated with adverse pregnancy outcomes, including higher risk of gestational diabetes, pre-eclampsia, operative delivery, foetal and perinatal mortality and morbidity, and excessive birth weight (66, 99). Maternal obesity can also result in long-term health problems for the offspring, secondary to perinatal problems and to intrauterine and postnatal programming effects (99, 298), including an increased obesity risk in childhood and adulthood (9).

However, it may be possible to alter programming of the offspring of obese women to a healthier phenotype by interventions in pregnancy (11). There is growing evidence to suggest the prenatal environment may play a role in programming obesity risk (113). The link between maternal and offspring obesity can be explained by the ‘early-life hyper nutrition’ pathway where exposure to over-nutrition during foetal or early postnatal life may lead to perturbations of adipogenesis and/or appetite control mechanisms, creating a propensity to later obesity (298). There is evidence from animal models that exposure to maternal obesity in utero can lead to offspring adiposity and cardiovascular and metabolic dysfunction, which may result from developmentally programmed hyperphagia, physical inactivity, and altered adipocyte metabolism (142). Catalano postulates the existence of a vicious cycle of obesity, whereby maternal obesity leads to foetal overgrowth and subsequently post-natal obesity. Overweight/obese children tend to become obese adults, and the females, when pregnant, will increase nutrient supply to the foetus leading in foetal overgrowth in the next generation (10, 58). Further, it is proposed that offspring obesity may be propagated and enhanced in early life because of the abnormal metabolic milieu in utero in overweight and obese women (10, 58). This raises the potential of in utero therapy to prevent downstream obesity and chronic disease obesity in the offspring, via lifestyle interventions targeting behaviours that lead to altered nutrient partitioning and foetal overgrowth (10, 11).

The effects of antenatal interventions on offspring outcome are difficult to establish. Birth weight is the most easily measured outcome assessing the impact of the intrauterine environment on foetal growth, (113). We hypothesized that a reduction in foetal over-nutrition would be reflected as lower birth weight in offspring of overweight and obese mothers. The association between birth weight and adult weight suggests that there are enduring effects on
later obesity risk (113), and we further postulated that reduction in birth weight would exert a protective effect on later obesity risk.

Antenatal exercise may play a positive role on both maternal and offspring health (277, 299), and may be especially beneficial to the offspring of overweight and obese women (208). While evidence on the effects of antenatal exercise on offspring outcomes (including birth weight) is inconsistent, there is no evidence of any adverse impact from moderate-intensity exercise (246, 277). Furthermore, the timing of antenatal exercise can be an important confounding factor leading to the varying effects of antenatal exercise on birth weight (208). There is evidence that antenatal exercise in the second half of gestation can reduce foetal over-nutrition, birth weight and adiposity in the offspring, and protect against future obesity. Barakat et al., found that resistance exercise during the second and third trimesters of pregnancy attenuated the effect of increased maternal weight on offspring birth weight (288). Clapp demonstrated that continuation of regular moderate to vigorous intensity antenatal exercise reduced offspring birth weight and subcutaneous fat mass at birth, with these potentially beneficial effects persisting up to 5 years of age (292), and that the maintenance of a high volume of exercise during mid and late pregnancy led to a reduction in foetal fat mass (281). In a recent randomised controlled trial, we showed that non-weight-bearing aerobic exercise during the second half of pregnancy in non-obese women led to a significant reduction in offspring birth weight and BMI, in association with a reduction in metabolic markers of foetal nutrition (16).

Despite many studies investigating the effects of exercise during pregnancy, the effects of antenatal exercise in overweight and obese women on both short- and long-term health of the offspring have remained largely uncertain. A recent systematic review of randomised controlled trials of antenatal exercise in overweight or obese women indicated that antenatal exercise may be beneficial in limiting gestational weight gain, but there is a lack of high-quality research evidence to assess the impact on offspring health (13). Thus, the main aims of this trial were to establish if regular moderate intensity, non-weight bearing exercise during the second half of pregnancy in overweight and obese women would reduce offspring birth weight and neonatal adiposity, and lead to long term beneficial changes such as reduced obesity risk in the offspring. Secondly, we explored the effects of antenatal exercise on maternal health including pregnancy outcomes, and maternal and cord blood metabolic and inflammatory markers.
Methods

The IMPROVE (Improving Maternal and Progeny Risks of Obesity Via Exercise) study was a two-arm parallel randomised controlled clinical trial conducted in Auckland, New Zealand. This study was approved by the Health and Disability Ethics Committee, (Ministry of Health, New Zealand; 12/NTB/24), and was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12612000932864). Locality approval was obtained from the research offices at Auckland, Counties Manukau, and Waitemata District Health Boards, as well as relevant Māori research committees within the Auckland region.

Participants

Pregnant women aged 18 to 40 years with a BMI ≥ 25 kg/m² who were carrying a singleton foetus less than 20 weeks gestation and resident in the Auckland region were eligible for the trial. Exclusion criteria included ongoing smoking during current pregnancy or contraindications to aerobic exercise in pregnancy as stated by the American College of Obstetricians and Gynaecologists (215).

Recruitment

The Auckland region has a population of approximately 1.4 million and approximately 21,000 births per year. Potential participants were recruited via maternity caregivers, posters and brochures in health care and community settings, and newspaper advertisements. All potential participants were supplied with detailed study information, and underwent an eligibility assessment. Eligible and willing participants were registered in the trial before completion of 20 weeks of gestation, and written informed consent was obtained at the baseline visit. Target rate of recruitment was 8 participants per month.

Randomisation

After completion of baseline assessments, participants were randomised in a 1:1 ratio to either intervention or control group, using stratified blocked randomisation with variable block sizes of 2 and 4. The two stratification factors considered were parity (nulliparous / parous) and ethnicity (Maori / Pacific / New Zealand European or other).

Computer generated randomisation sequences were provided by a biostatistician with no clinical involvement in the trial, and were stored securely in a password-protected computer.
Once a participant was registered to the trial a sequential study number was assigned to each participant by the recruitment coordinator. The recruitment coordinator did not have access to the randomisation tables. Group allocation was concealed until completion of baseline assessments.

**Intervention**

The intervention group followed a regular structured exercise regime between 20 to 36 weeks of gestation, similar in nature to a previous antenatal exercise intervention conducted in non-obese women at our research institute (16). The control group did not undergo any antenatal exercise intervention. Due to the nature of the intervention, participants were un-blinded to group assignment, following completion of baseline assessments.

The exercise regime consists of home-based stationary cycling. Magnetic exercycles (Sportop NB600/ NB800) and heart rate monitors (Polar S625X / Polar RS800) were provided to each participant in the exercise group at 20 weeks of gestation. Exercise intensity was prescribed using target heart rate zones developed and validated specifically for overweight and obese pregnant women (217). Participants received instructions on equipment use with a written exercise prescription with weekly exercise targets. The 16-week exercise regime consisted of 67 exercise sessions, comprising approximately 1500 minutes of moderate-intensity exercise. The frequency and duration of prescribed exercise varied over the intervention period. Participants are instructed to wear their heart rate monitors to record every prescribed exercise session they completed during the intervention period. This information was downloaded from each heart rate monitor to a computer, and compliance to prescribed exercise sessions was assessed at the end of the intervention period utilising Polar Precision Performance software (ProTrainer 5).

The intervention commenced with three exercise sessions per week and increased to five sessions per week. All exercise sessions commenced with a 5-minute warm-up on the stationary cycle at low intensity, maintaining heart rate below target rate, and concluded with a similar 5-minute cool down. The duration of moderate-intensity exercise at prescribed heart rate increased gradually from 15 minutes to 30 minutes per session and gradually decreases again from 33 weeks of gestation while maintaining the frequency at 5 sessions per week. A qualified exercise physiologist maintained regular contact with the exercising participants via phone, email, and home visits.
Over the duration of the intervention period, both groups were free to continue their normal exercise/physical activity routines, received standard antenatal care, and underwent similar study assessments. In addition, there are no dietary restrictions. Exercise participants developing obstetric contra-indications to exercise (215) discontinued the exercise intervention, but were included in the intention to treat analysis.

**Primary outcome**

Primary outcome was offspring birth weight, measured in grams (g) and standardized z-score (i.e. corrected for gestational age and gender)(300). As there are significant differences in birth weight between major ethnic groups in New Zealand, birth weight was also compared by customised centiles adjusting for maternal height, weight, parity, ethnic origin, gestational age at birth, and gender of the baby (301).

**Secondary outcomes**

Offspring outcomes included neonatal anthropometry and body composition, cord blood metabolic markers and new born complications including rates of large for gestational age (birth weight >90th centile) and small for gestational age (birth weight <10th centile) babies. Maternal outcomes included weight gain, aerobic fitness, quality of life, metabolic markers, post-partum weight and body composition, as well as pregnancy and delivery outcomes including timing and mode of delivery and length of hospital stay.

**Other aims and outcomes**

This study also aimed to establish a prospective mother-offspring cohort for follow up to determine the long term effects of antenatal exercise on anthropometry, body composition, and obesity risk.

**Clinical assessments/ Data collection**

Each participant visited the Maurice and Agnes Paykel Clinical Research Unit (Liggins Institute, Auckland) for three study assessments). The first visit for the baseline assessment occurred at 19 ± 1 weeks of gestation and the second visit at 36 ± 1 weeks of gestation. During the first visit, participants completed consent forms and filled in questionnaires on demographic, medical and obstetric history. The other procedures were similar for both first and second visits, where each participant’s weight, height, resting heart rate, resting blood
pressure, HbA1c, and aerobic capacity were assessed by a single investigator. Blood samples were collected and stored for metabolic testing. Participants completed a quality of life assessment questionnaire. At the second visit participants received a pack with instructions for collection of cord blood by delivery staff.

**Figure 4:** Timeline for IMPROVE study assessments

During the intervention period, participants in both groups were requested to maintain daily records of any exercise they engaged in, on exercise diaries provided by the study. Participants also completed 3-day food intake records and a physical activity questionnaire at baseline prior to randomisation and midway through the intervention when exercise prescription was maximal (32 weeks of gestation), to assess any group difference in these measures. These were posted out to participants beforehand and completed forms collected during study assessments.

The final study visit occurred at 14 ± 2 days after delivery. Maternal weight and neonatal anthropometry (weight, length and head circumference) were measured, and both mother and baby underwent body composition assessments by DXA scanning. Neonatal feeding history was obtained from the mother. Pregnancy, delivery and perinatal data were obtained from medical records.

**Antenatal measures**

Maternal body weight was measured to the nearest 0.1 kg using calibrated electronic scales (Tanita, USA). Maternal height was measured to the nearest millimetre using a fixed wall
Harpenden Stadiometer (Holtain Ltd., Crymych, UK). Resting heart rate and resting blood pressure were measured using standard protocols (302).

Aerobic fitness testing was carried out using a sub-maximal graded exercise test on an electronically-braked cycle ergometer (Schiller, Baar, Switzerland), with simultaneous breath-by-breath measurement of expired and inspired O₂ and CO₂ gas volumes (ParvoMedics TrueOne 2400 Metabolic Measurement System, Parvomedics, Sandy, Utah, USA) to a target heart rate of 150 beats per minute, as previously described (16). The test began with a workload of 30 W and increased by 10 W every minute until a target heart rate of 150 beats per minute was reached. Participants were instructed to maintain a constant cycling speed at 60 rpm throughout the test. Parameters of interest included time taken to reach the peak heart rate of 150 bpm, workload (W) when reaching peak heart rate, and peak VO₂.

Maternal quality of life was measured using a self-administered questionnaire, the WHO QOL-BREF version, which consists of a total of 26 questions in 4 domains (303). Maternal physical activity levels were measured using the Pregnancy Physical Activity Questionnaire (PPAQ). The PPAQ is self-administered and asks respondents to report the time spent participating in 32 activities, including household/caregiving, occupational, sports/exercise, transportation, and sedentary activities. It has been validated in an ethnically diverse pregnant population in the USA, and demonstrated high reproducibility and reasonable accuracy (304). The total weekly energy expenditure in MET-h/week is measured. Dietary data from 3-day food records completed at baseline and mid intervention were analysed using Foodworks 7 Professional edition (Xyris Software, Australia). Data was entered into the database by a single investigator blinded to group allocation, and analysed for total energy intake as well as % energy from protein, fat, and carbohydrate.

**Postnatal measures**

New born weight, length, and head circumference measured at birth were obtained from medical records. Data on Apgar scores at 1 and 5 minutes after birth, neonatal hypoglycaemia needing intravenous treatment, neonatal hyperbilirubinaemia requiring treatment, presence of birth injuries, congenital anomalies, admission to neonatal intensive care or special care units, and length of hospital stay following delivery were also collected. Neonatal anthropometry (weight, length, and head circumference) was measured by a single investigator at the Maurice and Agnes Paykel Clinical Research Unit at 14 ± 2 days after delivery. Neonatal weight was measured to the nearest 10 g using electronic scales (Tanita 1583, Tanita Corp). Neonatal
length was measured using a Holtain neonatometer. Occipito-frontal head circumference was obtained to the nearest millimetre using a flexible non-stretchable tape. BMI was calculated as weight/height^2 (kilograms/metre^2). Ponderal index was calculated as weight in grams x 100 divided by the cube of length in centimetres.

Maternal and neonatal body composition and bone density were evaluated at 14 ± 2 days after delivery by whole-body dual-energy absorptiometry (DXA, Lunar Prodigy 2000, General Electric, Maddison, Wisconsin, USA), by a single investigator at the Maurice and Agnes Paykel Clinical Research Unit. All scans were analysed by the same operator, utilising Encore 2007 software v.11.40.004 including paediatric software packages (GE Corp., Madison, WI, USA). Quality control checks were performed on a daily basis prior to scanning, using a standard block provided by the manufacturer.

**Metabolic markers**

Maternal blood samples collected at baseline and at the end of intervention were processed and stored at the Liggins institute. Venous cord blood was collected at delivery by the lead maternity carer, who was instructed beforehand on the procedure. Cord blood samples were processed within 3 hours of collection and stored at -80°C at hospital laboratories. All maternal and cord blood samples were analysed at the end of the study at the Liggins Institute. Parameters that were assessed included leptin, interleukin 6 (IL-6), tumour necrosis factor α (TNF α), sensitive C-reactive protein (CRP), triglycerides, total cholesterol, high density lipoprotein(HDL) cholesterol, low density lipoprotein (LDL) cholesterol, insulin-like growth factors I (IGF-I), IGF-II, insulin-like growth factor binding protein 1 (IGFBP-1) and IGFBP-3 in both maternal and cord blood, as well as maternal sex hormone binding globulin (SHBG) (measure of insulin resistance) and cord blood insulin.

**Statistical Considerations**

**Sample size**

Based on a previous exercise intervention performed by our research group in Auckland using similar methodology (16) and using birth weight as the primary outcome, it was estimated that a total sample size of 100 women (n=50 per group) would provide 80% power at 5% level of
significance (two-sided) to detect a group difference of 250 g or more, assuming a standard deviation of 430 g (16).

**Data analyses**

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc. Cary NC). All statistical tests were two-tailed and a 5% significance level maintained throughout the analyses. Study data were entered into an Excel database, and then imported into SAS for final analysis.

**Baseline characteristics**

Baseline characteristics were summarised using descriptive statistics with continuous variables described as mean and standard deviation and categorical variables described as frequencies and percentages, for the two treatment arms.

**Treatment effects**

Treatment evaluation was performed on the principle of intention to treat, using data collected from all randomised participants. Analysis of covariance regression models were used to evaluate the main treatment effect on the primary outcome between the two treatment groups, adjusting for maternal ethnicity and parity (i.e. randomisation factors), maternal BMI at study entry, gestational age at birth and offspring gender. For continuous secondary outcomes, a similar approach was used (adjustment factors are described in the methods section within each results paper). Model-adjusted means and their difference between two groups were estimated and tested. Logistic regression models were used for the analysis of binary outcomes, with associated odds ratio and 95% confidence interval. Reporting adhered to the CONSORT guidelines for reporting parallel group randomised trials (305, 306).

**Discussion**

This randomized controlled trial had several unique characteristics. First, it utilised a non-weight bearing home-based antenatal exercise intervention, previously applied to non-obese women (16). This would enable comparison of outcomes from a similar exercise intervention between obese and lean women. Secondly, the main focus of this antenatal exercise trial was on offspring health. While a number of randomised controlled trials of prescribed antenatal
exercise have been conducted over the last three decades, their primary focus has been on maternal health and there is a lack of robust evidence on the effects of antenatal exercise on offspring health (18, 23). Furthermore, while there is some evidence of positive long-term effects of antenatal exercise for offspring of lean mothers (20), long term effects on offspring of overweight or obese mothers appear to have received little attention. Therefore, this trial also aimed to establish a cohort of overweight/obese mothers and offspring with well-documented antenatal and perinatal data to be followed up to determine the long-term effects of antenatal exercise on offspring and maternal health. As a result, this study addressed the lack of prospective robust data on the effects of antenatal exercise on short- and long-term outcomes of mothers and their offspring (43).

Another feature of this trial was the use of methods to enhance and monitor compliance to prescribed exercise. Many antenatal exercise interventions, especially those involving overweight and obese women have encountered problems with compliance (261, 307). This can be partly attributed to the general tendency for physical activity levels to decline during pregnancy (308, 309), especially in mothers who are obese (310, 311). However, many previous exercise studies have also failed to report adequately on compliance with interventions (246). Previous studies have suggested that home-based exercise interventions can lead to increased compliance, as they enable exercise to be undertaken in a comfortable and familiar environment (16, 254). Therefore, a home-based intervention was chosen, to enhance feasibility of regular exercise, and improve compliance to the exercise protocol. Previous home-based stationary cycling interventions in non-obese (16) and obese (254) pregnant women have reported high acceptance and good compliance levels. Furthermore, during pregnancy, non-weight bearing exercises may be better tolerated, minimizing joint and musculoskeletal stress (214), and stationary cycling can be especially suitable for overweight or obese women, who are likely to continue to gain extra weight with advancing pregnancy. In addition, exercise prescription in our study was modified to suit sedentary overweight and obese pregnant women, with gradual progressive increase in frequency and duration in keeping with recommendations (214), while maintaining moderate intensity based on target heart rates specific for this group (217).

While this study was designed to optimise compliance, it remained essential to have objective assessment of compliance. This, unfortunately, has been absent from many exercise intervention trials. In this study, we used downloadable heart rate monitors, to obtain data on compliance with the exercise intervention (number of prescribed sessions completed) as well.
as the duration and intensity of exercise completed for each 4-weekly period during the 16-week intervention.

In summary, the study provided a platform to objectively assess a non-weight bearing exercise regime on overweight and obese women pregnant women, providing quantitative outcome data on them and their babies, and helping establish a mother-offspring cohort to be followed up to determine long term effects on health with the intervention.
3.2. Additional information on neonatal body composition assessment

3.2.1 Relevance of neonatal body composition assessment

The developmental origins of disease concept describes how early life influences via the intra-utero environment can lead to lasting effects on health. Birth weight is often taken as a proxy indicator of these effects. However, changes in foetal body composition with alteration of the in utero environment will not be adequately reflected by birth weight alone (55). Differences in birth weight defined more precisely as change in lean or fat foetal mass can assist in better understanding of these effects (153). Fat deposition increases exponentially over the second half of pregnancy and therefore provides a particularly sensitive measure of in utero nutrition during this time (312, 313). Further, alteration in fat deposition can account for substantial variation in birth weight at term (312). Neonatal body composition is influenced by gender, with female offspring having greater fat mass and percentage body fat and lower lean mass compared to male offspring (314). Increased neonatal adiposity (indicated by excessive BMI at 2 weeks of age) appears to be an independent risk factor associated with childhood overweight status up to 5 years of age (315). Therefore in this study, in addition to birth weight, early life body composition was also measured in the offspring.

3.2.2 Procedure for body composition assessment by DXA scanning

DXA scanning has been shown to be a safe, reliable and precise method for both whole body and regional body composition assessment in young subjects (316-318). However, attention to detail and consistency in scanning procedure is important, especially in younger subjects, in order to obtain accurate data (319, 320). Incorrect positioning, variation in the amount of covering, and movement artefacts can affect the measures obtained (317, 320). Therefore extra measures were taken to maintain a standard protocol when performing neonatal scans. As pre-instructed, babies were brought for assessment clothed in lightweight indoor clothing not containing metal. The scans were performed with the neonate asleep/settled, following a feed, and adequate time and a quiet environment was provided for the baby to be fed and put to sleep by the mother, before the scan was done. The neonates were placed in the centre of the scanning platform, in a supine position and wrapped in a standard lightweight cotton blanket with arms by the sides, and legs extended, and positioned as symmetrically as possible, without disturbing the baby. A quiet warm environment was maintained. In very occasional cases where a neonate showed signs of movement, the scanning procedure was
discontinued and a new scan performed when the baby settled. All postnatal assessments were performed by a single investigator, using the same fan beam DXA scanner, and analysed using the same paediatric software package. In neonates, total body fat mass, lean mass, bone mineral content (BMC), percentage body fat (fat mass per 100g body weight), bone mineral density (BMD) and regional fat (percentage fat in arms, legs and trunk) were obtained directly from the software. The lines demarcating body regions were adjusted in a consistent manner to ensure correct placement, prior to obtaining regional body composition measures. Fat mass index (fat mass (kg)/ body length (m)$^2$) was also calculated as an additional marker of adiposity.

Similarly, a standard procedure was followed for maternal body composition assessment. Participants were positioned symmetrically in the midline of the scanning field, in the supine position, with the head end positioned approximately 3 cm below the horizontal edge of the scanning field with arms by the side of the body, with palms facing downwards, and legs extended. Metal objects were removed prior to scanning, and participants were instructed to remain motionless until the scanning arm of the DXA passed over their body to avoid artefact effects. Maternal post-natal total body fat mass, lean mass and percentage body fat was obtained and fat mass index calculated.

3.2.3 Methods of assessing neonatal body composition

Neonatal body composition can be assessed using a number of indirect and direct and methods. The simplest methods include anthropometric measures such as BMI and ponderal index (153). These measures have limited accuracy, with poor discrimination between lean and fat mass (321), but can be used as proxy measures when other measures are not easily accessible or feasible. Measurement of skin fold thickness, is another technique which can be employed, where percentage fat mass is estimated using validated equations (322, 323). However extensive training and meticulous care is needed to ensure accuracy and reproducibility of skinfold measurement between observers (323).

Other techniques of measuring neonatal adiposity and body composition, which are safe and appropriate for use in neonates, include dual energy X-ray absorptiometry (DXA), bio electrical impedance analysis (BIA) and air displacement plethysmography. They utilise the body composition models dividing body weight into two compartments: fat mass and fat-free
mass. However, DXA can further differentiate fat free mass as lean mass (skeletal muscle and organ tissue) and bone mineral content (bone mass)(324).

Dual energy X-ray absorptiometry utilises two low-intensity collimated X-ray beams at two energies to scan the whole body or the region of interest (325). When the X-ray or photon source is placed on one side of an object, the intensity of the beam obtained on the opposite side of the object is related to its thickness, density, and chemical composition (326). Attenuation of the beam through bone, lean tissue and fat is different, reflecting differences in densities and chemical composition (326). This principle is utilised to measure body composition. DXA provides accurate and precise estimates of neonatal body composition (327). Advantages of DXA for body composition assessment include short measurement time, minimal radiation dose and immediate availability of results (324, 326). The effective dose of radiation by total body DXA scan of a neonate is approximately 1 μSv (317), which is lower than the effective dose from daily background radiation which is approximately 8 μSv per day (328). Software allowing delineation of specific anatomical areas of the body (upper limbs, lower limbs, trunk and head region) also enables regional body composition assessment from a whole body scan, which is an added advantage (318). A limitation with this method, especially in young subjects, is that if the subject moves during the scan, image artefacts can be produced (53). Thus, infants are scanned while asleep or tightly swaddled in a blanket. DXA results can be dependent on both the DXA instrument and software used (324, 325).

In BIA, a weak alternating electrical current is passed through the body, and the body’s resistance to the current is measured (325). For this measurement, electrodes are usually attached at the foot and hand on the same side of the body. This measure is inversely proportional to hydrated tissue mass, and is converted to an estimate of fat free mass, and used in a two compartment model to calculate fat mass (325). Advantages of BIA include relatively low cost and portability of the instruments. However, studies in infants have not shown any significant advantage over basic anthropometric measurements (329).

The principle of air displacement plethysmography is utilised by the PEA POD instrument for measuring body composition in infants. PEA POD measurements are easy to perform, and do not require the infant to be restrained during the rapid (2 minute) procedure (330). This technique has been validated in infants, and appears to be accurate and increasing in use (330, 331). However, it cannot differentiate between lean and bone mass, and can be less accurate than DXA in differentiating between fat mass and fat free mass (332). Further, its use is limited by the weight of the subject, and can only be used in infancy (329). This makes this
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method inappropriate for studies where follow up in early childhood is required. An adult-sized instrument, the BOD POD, can be used in children starting from 5 years of age (325).

More advanced multiple compartment models enable further differentiation into various body components (325). CT and MRI are more accurate direct methods of assessing body composition. Importantly, they enable separation of fat mass into subcutaneous and visceral compartments (326). However, they are costly, and CT involves exposure to a high dose of radiation making it inappropriate for body composition assessments in neonates (326).
Chapter 4. Effects of antenatal exercise on maternal health outcomes in overweight & obese pregnant women: a randomised controlled trial

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Abstract

Background:
The benefits of antenatal exercise on maternal health are not well established, particularly in overweight/obese pregnant women. We hypothesized that antenatal exercise would improve physical health, quality of life, and pregnancy outcomes in overweight/obese women.

Methods:
A two-arm parallel randomised controlled trial was conducted in pregnant women of BMI \( \geq 25 \) kg/m\(^2\). Participants were randomised to a 16-week home-based moderate-intensity stationary cycling programme from 20 weeks of gestation, or to a control group with no exercise intervention. The primary outcome was offspring birth weight. Maternal outcomes included weight gain, aerobic fitness, quality of life, pregnancy outcomes, and postnatal body composition measured by whole-body dual energy X-ray absorptiometry. Exercise compliance was recorded with heart rate monitors.

Results:
75 participants were randomised in the study (intervention 38, control 37). Aerobic fitness improved in the intervention group compared to controls (48.0 sec improvement in test time to target heart rate; \( p=0.019 \)). There was no difference in weight gain, quality of life, pregnancy outcomes, or postnatal maternal body composition between groups. However, compliance with exercise protocol was poor, with an average of 33% of exercise sessions completed. Sensitivity analyses showed that greater compliance was associated with improved fitness [increased test time (\( p=0.002 \)), greater VO\(_2\) peak (\( p=0.015 \)), and lower resting heart rate.
(p=0.014)], reduced postnatal adiposity [reduced fat mass (p=0.007) and BMI (p=0.035)], and better physical quality of life (p=0.034).

**Conclusions:**

Maternal non weight-bearing moderate intensity exercise in the second half of pregnancy was associated with improved fitness, but had no observed effects on clinical outcomes.

**Précis:**

Non-weight-bearing moderate-intensity exercise in the second half of pregnancy was associated with improved fitness in overweight/obese women, but had no observed effects on clinical outcomes.
**Introduction**

There has been a global increase in rates of overweight and obesity among women of reproductive age. As a result, the number of women entering pregnancy in an overweight or obese state has nearly doubled over the last three decades, now affecting more than a third of pregnancies in some nations (61, 62, 297, 333). Overweight and obesity are associated with many pregnancy complications, including a two-to threefold increase in the risk of gestational diabetes, pregnancy induced hypertension, and pre-eclampsia, as well as increased risk of caesarean section, induction of labour, and longer hospital stay (1). The associated reduction in physical health and quality of life during pregnancy are also important issues (334-336).

Regular exercise can be beneficial, leading to improved physical and mental health (337). Daily moderate-intensity physical activity of 30 minutes or more during pregnancy is advocated by at least 11 guidelines worldwide (215, 229). However, the effects of antenatal exercise in overweight and obese women remain unclear (1). Meta-analysis and systematic reviews focusing on antenatal physical activity interventions in overweight/obese women have reported a modest reduction in gestational weight gain, but no impact on other clinical outcomes (13, 14).

Yet, pregnancy can be a powerful time to initiate lifestyle interventions (230). Further, there are a number of ways to encourage and maintain exercise in overweight and obese pregnant women (1). Home-based exercise in particular, may be more acceptable than exercising in groups for these women (who often have poor body image), while non-weight-bearing exercise is likely to cause less strain on ligaments and joints (1, 224). To our knowledge, no randomised clinical trial has yet assessed the effects of home-based non-weight-bearing antenatal exercise on quality of life or maternal body composition in overweight/obese women. The aims of this randomised controlled trial were to assess the effects of a home-based antenatal stationary cycling exercise intervention on maternal and offspring health (2). We hypothesised that the exercise intervention would lead to a reduction in maternal weight gain and improvements in other maternal health outcomes (fitness, quality of life, body composition, and pregnancy outcomes).
Methods

Study design

The IMPROVE (Improving Maternal and Progeny Obesity Via Exercise) study was a parallel two-arm randomised controlled trial on antenatal exercise, with 1:1 allocation ratio to intervention or control group (2). It was conducted in Auckland (New Zealand) between March 2013 and October 2014. Ethics approval for the trial was obtained from the Health and Disability Ethics Committee, Ministry of Health, New Zealand. Written and verbal informed consent was obtained from all participants. This trial was performed in accordance with all appropriate institutional and international guidelines and regulations for medical research, in line with the principles of the Declaration of Helsinki. The trial protocol has been published previously (2).

Participants

Pregnant women aged 18–40 years with a body mass index (BMI) ≥ 25 kg/m² and a singleton pregnancy less than 20 weeks of gestation were eligible for the study. Exclusion criteria were ongoing smoking, multiple pregnancy, pre-existing contraindications to antenatal exercise, or living outside the Auckland Region (215). Participants were recruited via newspaper advertisements, posters, and brochures, as well as via referral from maternity carers in the region.

Randomisation

Participants were allocated into intervention or control groups using computer-generated randomisation sequences in variable block sizes, stratified on ethnicity (Maori/Pacific Islander/New Zealand European/other) and parity (nulliparous/parous). These sequences were generated by a biostatistician with no clinical involvement in the trial, stored securely with password protection, and used sequentially according to order of enrolment. The recruitment coordinator, responsible for order of enrolment did not have access to the randomisation tables at any time during the study, thus maintaining allocation concealment. Group allocation was revealed to participants after completion of baseline assessments, by a separate investigator.
**Intervention**

The intervention group participated in a structured home-based moderate-intensity antenatal exercise programme utilising magnetic stationary bicycles (Sportop NB600/NB800) from 20 to 35 weeks of gestation. Participants received a written programme prescribing frequency and duration of weekly exercises. Participants were also provided with heart rate monitors (Polar S625/Polar RS800, Polar Electro Oy, Kempele, Finland) to wear during all cycling sessions, and given target heart rates to maintain exercise sessions at moderate intensity (40-59% VO₂ reserve) (2, 217). Each exercise session included a 5-minute warm-up and cool-down period at low intensity. A total of 67 sessions were prescribed (frequency varying between 3 to 5 sessions per week, and duration of moderate-intensity exercise between 15-30 minutes per session, according to stage of pregnancy). Each participant was visited at home at the beginning of the intervention by an exercise physiologist, who was available for help with any exercise-related problems the participants encountered during the intervention period. The number of sessions completed, as well as duration and intensity of stationary cycling undertaken was obtained at the end of the intervention period by heart rate monitor data (using Polar Pro Trainer 5 software, Polar Electro Oy). The control group was neither prescribed an exercise intervention nor provided with heart rate monitors.

Due to the nature of the intervention, participants were un-blinded to group allocation after completion of baseline assessments. They continued routine antenatal and delivery care with their chosen maternity carers. Participants in both groups were able to continue their routine physical activity and diet without restriction.

**Outcomes**

The primary outcome of the trial is offspring birth weight. In this paper, we report pre-specified maternal outcomes, while offspring health outcomes (including the primary trial outcome, birth weight) are reported elsewhere.

**Pregnancy outcomes**

These data were obtained from clinical records. Gestation at delivery was based on an early dating scan at <16 weeks of gestation (or on the last menstrual period where a scan was not available). Total gestational weight gain was obtained by subtracting the weight at the booking antenatal clinic visit from the last antenatal weight (measured after 36 weeks of gestation).
Duration of hospital stay for childbirth was recorded as the time between admission to maternity unit for childbirth and discharge home following delivery. Gestational diabetes mellitus was diagnosed by a standard 75 g oral glucose tolerance, based on a fasting plasma glucose ≥5.5 mmol/l and/or a 2-hour post-test plasma glucose ≥9.0 mmol/l. Pregnancy-induced hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, on at least two occasions after 20 weeks of gestation without proteinuria; pre-eclampsia as pregnancy-induced hypertension with proteinuria; preterm delivery as childbirth <37 weeks of gestation; severe post-partum haemorrhage as blood loss >1000 ml following delivery; perineal tears as spontaneous lacerations of any degree occurring during labour; and early initiation of breast feeding as new born put to the breast within one hour of birth.

**Physical health outcomes**

Participants underwent three assessments at the Maurice and Agnes Paykel Clinical Research Unit (Liggins Institute): 1) at baseline (19 weeks of gestation), 2) at the end of the intervention (36 weeks of gestation), and 3) post-natally (approximately 2 weeks after delivery). Socio-demographic and past medical/obstetric data were collected at the first assessment. Height was measured to the nearest millimetre using a Harpenden Stadiometer (Holtain Ltd., Crymych, UK), while weight was measured to the nearest 0.1 kg using the same calibrated electronic scale (Model 1582, Tanita, USA) during all assessments. BMI was consequently calculated as per standard formula. Difference in weight between assessments 1 and 2 was taken as weight change during intervention, and between assessments 2 and 3 as weight loss at follow-up.

Aerobic capacity was assessed on all participants by a single investigator using a sub-maximal graded exercise test on an electronically-braked cycle ergometer (Schiller, Baar, Switzerland), with simultaneous breath-by-breath measurement of expired and inspired O₂ and CO₂ volumes (ParvoMedics TrueOne 2400, Parvomedics, Sandy, Utah, USA) (16). Tests were performed as previously described (2). Parameters of interest were the time taken to reach the target heart rate of 150 bpm, workload when reaching target heart rate, and submaximal peak VO₂ achieved. An increase in test time to reach the target heart rate and the work load tolerated would indicate an improvement in fitness. Resting heart rate and resting blood pressure (seated position) were measured prior to the fitness test by an automated blood pressure measuring device (Dinamap Pro Care 100, GE Healthcare, UK) using an appropriately-sized cuff.
Results

**Post-natal body composition**

Maternal body composition was measured by whole body dual energy X-ray absorptiometry (Lunar Prodigy 2000, General Electric, Maddison, Wisconsin, USA) approximately two weeks after delivery. Total body fat mass, lean mass, percentage body fat, and bone mineral density were obtained using Encore 2007 software v.11.40.004 (General Electric). Maternal fat mass index (fat mass (kg)/ body length (m)) was subsequently calculated.

**Quality of life**

Participants completed a self-administered generic health-related quality of life assessment questionnaire (WHO QOL-BREF) (303) at baseline and at the end of the intervention period. The WHO QOL-BREF consists of a total of 26 questions in four domains: physical health, psychological, social relationships, and environmental. Each of the domains was scored as per guidelines and transformed to a 0–100 scale, with values closer to 100 indicating better quality of life. An overall score was obtained by averaging the four individual domain scores. Note that a generic quality of life questionnaire was used due to lack of pre-validated questionnaires specific to pregnancy (338).

**Statistical analysis**

Treatment evaluation was performed on the principle of intention to treat. Analysis of covariance regression models were used to evaluate the main treatment effect on continuous maternal outcomes, adjusting for maternal ethnicity and parity (i.e. stratification factors), as well as baseline value (except for postnatal body composition and pregnancy outcomes, for which baseline BMI was used as a proxy measure instead). Logistic regression models were used for the analysis of binary outcomes, with associated odds ratios and 95% confidence intervals. Possible associations between compliance with study protocol (expressed as percentage of prescribed exercise sessions completed) and maternal outcomes in the intervention group were initially assessed using Spearman's rank correlations. Subsequently, sensitivity analyses were carried out with multiple regression models constructed as described above; treating compliance as a linear predictor to test its association with maternal outcomes using the $\beta$-coefficient and associated p-value. Statistical analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Minitab v.16 (Pennsylvania State University, State College, PA, USA). All statistical tests were two-tailed and maintained at a
5% significance level. Missing data were not imputed. No adjustment has been made for multiple testing.

**Results**

Between March 2013 and April 2014, a total of 195 women were assessed for eligibility, and 75 participants were enrolled in the trial (intervention n=38, control n=37) (Figure 5). As rate of recruitment was slower than anticipated, the recruitment period was extended from the original 12 month period, by 2 months. Baseline characteristics in intervention and control groups were similar (Table 2), as were baseline fitness levels (Figure 6) and quality of life scores. Follow up of trial participants continued until October 2014, when all pre-determined assessments were completed. Three participants developed medical contraindications to antenatal exercise and discontinued the intervention, but outcome data were collected and included in the intention-to-treat analysis (Figure 5). One participant (intervention group) withdrew from the study during the intervention period, and outcome data were not collected at her request (Figure 5). A total of 37 participants per group were included in the outcome analysis, in accordance to their original group assignment.
**Figure 5:** CONSORT diagram describing flow of participants in the IMPROVE study.
Table 2: Characteristics of study participants at baseline (19 weeks of gestation). Continuous variables are summarised as means ± SD, and categorical variables as n (%). Note that there were no statistically significant differences between groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.6 ± 4.6</td>
<td>31.1 ± 5.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.7 ± 14.1</td>
<td>93.6 ± 17.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.0 ± 6.7</td>
<td>165.5 ± 5.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.1 ± 4.4</td>
<td>34.1 ± 5.9</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>9 (24%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>11 (29%)</td>
<td>11 (29%)</td>
</tr>
<tr>
<td>Maori</td>
<td>5 (13%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>New Zealand European or other</td>
<td>22 (58%)</td>
<td>21 (57%)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>26 (68%)</td>
<td>17 (46%)</td>
</tr>
<tr>
<td>Part-time</td>
<td>5 (13%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Not employed</td>
<td>7 (19%)</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>Annual household income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ$ 50,000 or less</td>
<td>8 (21%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Greater than 50,000</td>
<td>25 (66%)</td>
<td>19 (51%)</td>
</tr>
<tr>
<td>Declined to answer/did not know</td>
<td>5 (13%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Number of years in education</td>
<td>15.1 ± 2.9</td>
<td>14.8 ± 2.2</td>
</tr>
<tr>
<td>Pregnancy data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Availability of dating scan</td>
<td>36 (95%)</td>
<td>36 (97%)</td>
</tr>
<tr>
<td>Previous gestational diabetes</td>
<td>3 (8%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Previous gestational hypertension/pre-eclampsia</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Previous caesarean section</td>
<td>9 (24%)</td>
<td>7 (19%)</td>
</tr>
</tbody>
</table>
**Table 3:** Maternal health outcomes in participants in intervention (n=37) and control (n=37) groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>Estimated difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Pregnancy and birth outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestation at delivery (d)</td>
<td>274 ± 12</td>
<td>278 ± 10</td>
<td>-3.3</td>
<td>-8.3, 1.7</td>
<td>0.196</td>
</tr>
<tr>
<td>Gestational weight gain (kg)</td>
<td>12.0 ± 5.3</td>
<td>13.2 ± 5.8</td>
<td>-1.2</td>
<td>-3.9, 1.6</td>
<td>0.397</td>
</tr>
<tr>
<td>Length of hospital stay (h)</td>
<td>61 ± 41</td>
<td>80 ± 107</td>
<td>-20.2</td>
<td>-61.3, 20.9</td>
<td>0.329</td>
</tr>
<tr>
<td>Gestational diabetes mellitus</td>
<td>4 (11%)</td>
<td>2 (5%)</td>
<td>2.1</td>
<td>0.3, 12.8</td>
<td>0.432</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>1 (3%)</td>
<td></td>
<td>0.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>1.8</td>
<td>0.1, 40.1</td>
<td>0.726</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
<td>2.3</td>
<td>0.2, 29.6</td>
<td>0.511</td>
</tr>
<tr>
<td>Induction of labour*</td>
<td>5 (19%)</td>
<td>8 (28%)</td>
<td>0.9</td>
<td>0.2, 3.9</td>
<td>0.935</td>
</tr>
<tr>
<td>Augmentation of labour*</td>
<td>7 (26%)</td>
<td>10 (35%)</td>
<td>0.9</td>
<td>0.2, 3.4</td>
<td>0.846</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>18 (47%)</td>
<td>13 (35%)</td>
<td>1.7</td>
<td>0.6, 4.5</td>
<td>0.293</td>
</tr>
<tr>
<td>Severe postpartum haemorrhage</td>
<td>3 (8%)</td>
<td>5 (14%)</td>
<td>0.6</td>
<td>0.1, 2.9</td>
<td>0.509</td>
</tr>
<tr>
<td>Perineal tears*</td>
<td>6 (22%)</td>
<td>10 (35%)</td>
<td>0.2</td>
<td>0.1, 1.1</td>
<td>0.061</td>
</tr>
<tr>
<td>Early initiation of lactation</td>
<td>25 (66%)</td>
<td>28 (76%)</td>
<td>0.8</td>
<td>0.2, 3.2</td>
<td>0.796</td>
</tr>
<tr>
<td><strong>Antenatal physical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ fitness test time (sec)</td>
<td>31.6 ± 88.4</td>
<td>-12.6 ± 69.1</td>
<td>48.0</td>
<td>8.3, 87.6</td>
<td>0.019</td>
</tr>
<tr>
<td>Δ test work load (W)</td>
<td>4.6 ± 15.3</td>
<td>-3.6 ± 12.2</td>
<td>8.8</td>
<td>1.5, 16.0</td>
<td>0.019</td>
</tr>
<tr>
<td>Δ peak VO₂ (ml/kg/min)</td>
<td>0.24 ± 2.1</td>
<td>-0.71 ± 2.6</td>
<td>0.67</td>
<td>-0.5, 1.88</td>
<td>0.267</td>
</tr>
<tr>
<td>Δ weight over intervention period (kg)</td>
<td>8.3 ± 3.7</td>
<td>8.8 ± 4.0</td>
<td>-0.6</td>
<td>-2.3, 1.2</td>
<td>0.512</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mmHg)</td>
<td>113.2 ± 12.2</td>
<td>118.5 ± 9.8</td>
<td>-3.1</td>
<td>-8.6, 2.3</td>
<td>0.249</td>
</tr>
<tr>
<td>Resting diastolic blood pressure (mmHg)</td>
<td>67.8 ± 8.3</td>
<td>70.0 ± 8.7</td>
<td>-0.8</td>
<td>-4.8, 3.1</td>
<td>0.675</td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>82.0 ± 8.4</td>
<td>85.0 ± 11.3</td>
<td>-3.7</td>
<td>-8.9, 1.4</td>
<td>0.151</td>
</tr>
<tr>
<td><strong>Postnatal physical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss at follow-up (kg)</td>
<td>8.1 ± 2.6</td>
<td>7.5 ± 2.5</td>
<td>0.8</td>
<td>-0.5, 2.2</td>
<td>0.234</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32.4 ± 4.6</td>
<td>34.5 ± 6.2</td>
<td>-0.3</td>
<td>-1.2, 0.5</td>
<td>0.410</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>46.0 ± 7.0</td>
<td>47.1 ± 6.9</td>
<td>0.3</td>
<td>-2.3, 2.9</td>
<td>0.836</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>38.7 ± 9.1</td>
<td>43.1 ± 11.7</td>
<td>-1.5</td>
<td>-4.2, 1.2</td>
<td>0.277</td>
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<tr>
<td>Total body fat (%)</td>
<td>45.3 ± 4.8</td>
<td>47.3 ± 4.6</td>
<td>-1.0</td>
<td>-2.9, 1.0</td>
<td>0.304</td>
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<tr>
<td>Fat mass index</td>
<td>14.1 ± 3.2</td>
<td>15.8 ± 4.1</td>
<td>-0.5</td>
<td>-1.3, 0.2</td>
<td>0.163</td>
</tr>
<tr>
<td><strong>Post-intervention quality of life</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>61.0 ± 18.0</td>
<td>64.1 ± 14.1</td>
<td>-2.4</td>
<td>-12.0, 7.2</td>
<td>0.617</td>
</tr>
<tr>
<td>Psychological</td>
<td>72.6 ± 13.7</td>
<td>71.6 ± 9.5</td>
<td>1.6</td>
<td>-4.6, 7.8</td>
<td>0.599</td>
</tr>
<tr>
<td>Social</td>
<td>69.0 ± 15.9</td>
<td>74.2 ± 16.2</td>
<td>-5.2</td>
<td>-13.5, 3.2</td>
<td>0.221</td>
</tr>
<tr>
<td>Environmental</td>
<td>78.8 ± 10.1</td>
<td>78.2 ± 9.3</td>
<td>-0.6</td>
<td>-6.2, 5.0</td>
<td>0.839</td>
</tr>
<tr>
<td>Overall</td>
<td>70.2 ± 10.7</td>
<td>72.2 ± 9.3</td>
<td>-1.8</td>
<td>-7.7, 4.2</td>
<td>0.545</td>
</tr>
</tbody>
</table>

* Only including participants without pre-labour Caesarean section (intervention n=27, control n=29)

[The difference in means is provided for continuous variables and in odds ratios for categorical variables, as well as the associated 95% confidence intervals (CI). Data are adjusted for maternal ethnicity, parity, and baseline value (except for postnatal body composition and pregnancy outcomes, for which baseline BMI was used as a proxy measure instead). P-values statistically significant at p<0.05 are shown in bold.]
Physical health outcomes

Women in the intervention group improved their aerobic fitness with intervention, increasing the test time taken to reach the target heart rate of 150 bpm in comparison to controls (+48.0 sec; p=0.019) (Table 3; Figure 6). Women who exercised also increased their peak work load compared to control women (+8.8 W; p=0.019) (Table 3). There were no differences in other physical health outcomes between groups, including weight gain over the intervention period, postpartum weight and adiposity (Table 3).

Quality of life

There were no differences in post-intervention quality of life scores between groups (Table 3).

Exercise and compliance

Compliance with the cycling intervention (as objectively measured by heart rate monitor data) was highly variable, with an average of 33% of exercise sessions completed (range 0–85%). Only a third of participants in the intervention group completed more than 30 of the 67 prescribed sessions. Further, compliance with study protocol progressively decreased with advancing pregnancy. The average total duration of cycling per participant was 556 minutes (range 0–1788 minutes), 52% of which were at moderate intensity, 40% at low intensity, and 8% at high intensity.

Effects of compliance

Compliance with study protocol was correlated with changes in test time (ρ=0.49; p=0.013), work load (ρ=0.64; p=0.001), resting heart rate (ρ=−0.49; p=0.008), and in weight gain over the intervention period (ρ=−0.48; p=0.010). Improved compliance was also correlated with lower postnatal fat mass (ρ=−0.53; p=0.002), lower total body fat percentage (ρ=−0.40; p=0.030), and lower BMI (ρ=−0.43; p=0.015).

As a result, sensitivity analyses were conducted, showing that greater compliance was associated with increased fitness and reduced postnatal adiposity (Table 4). Specifically, greater compliance was associated with increased test time, greater VO₂ peak, increased work load, and lower resting heart rate, reduced fat mass and lower postnatal BMI (Table 4). Further, compliance was associated with better post-intervention physical quality of life (β=0.265; p=0.034).
Figure 6: Aerobic fitness (expressed as the time taken to reach the target heart rate of 150 bpm) in intervention (grey) and control (black) groups at baseline and post-intervention. Higher values represent greater fitness. Data are means ± SEM. * p=0.019 for the comparison between groups post-intervention.

Table 4: The association between exercise compliance and maternal physical health outcomes at antenatal (36 weeks of gestation) and post-natal (approximately 2 weeks after delivery) assessments among the intervention group (n=37).

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antenatal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ fitness test time (sec)</td>
<td>1.534</td>
<td>0.628, 2.441</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Δ test work load (W)</td>
<td>0.336</td>
<td>0.172, 0.501</td>
<td><strong>0.0004</strong></td>
</tr>
<tr>
<td>Δ peak VO₂ (ml/kg/min)</td>
<td>0.044</td>
<td>0.010, 0.079</td>
<td><strong>0.015</strong></td>
</tr>
<tr>
<td>Δ resting systolic blood pressure (mmHg)</td>
<td>-0.020</td>
<td>-0.219, 0.179</td>
<td>0.838</td>
</tr>
<tr>
<td>Δ resting diastolic blood pressure (mmHg)</td>
<td>0.006</td>
<td>-0.121, 0.133</td>
<td>0.927</td>
</tr>
<tr>
<td>Δ resting heart rate (bpm)</td>
<td>-0.169</td>
<td>-0.301, -0.038</td>
<td><strong>0.014</strong></td>
</tr>
<tr>
<td>Δ weight over intervention period (kg)</td>
<td>-0.041</td>
<td>-0.099, 0.018</td>
<td>0.161</td>
</tr>
<tr>
<td><strong>Post-natal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>-0.031</td>
<td>-0.059, -0.002</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>-125</td>
<td>-213, -38</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>-0.067</td>
<td>-0.137, 0.004</td>
<td>0.065</td>
</tr>
</tbody>
</table>

Compliance was defined as the percentage of prescribed exercised session completed. Statistical models have adjusted for ethnicity, parity, and baseline value (or baseline BMI for postnatal body composition). P-values statistically significant at p<0.05 are shown in bold.
Adverse events

There were no adverse effects reported in association with the exercise intervention.

Discussion

This study showed that a 16-week programme of moderate-intensity non-weight-bearing antenatal exercise led to an improvement in aerobic fitness in overweight and obese women in the second half of pregnancy. Nonetheless, the exercise intervention did not lead to any observed effects on maternal weight gain or pregnancy outcomes.

These results align with a Cochrane review showing improvement in fitness but lack of evidence of other benefits or risks to pregnant women of any BMI with aerobic antenatal exercise (246). Similar results with improvement in aerobic fitness, but no effect on maternal pregnancy outcomes, were demonstrated with the same intervention, in leaner nulliparous pregnant women, by our research unit previously (16). The trend towards reduced perineal tears in the intervention group is consistent with a report of reduction in perineal lacerations with increased physical activity during pregnancy in a prospective cohort (241). Meta-analysis of antenatal exercise trials in pregnant women of any BMI (15, 250) and specific to overweight/obese pregnant women (13, 14) have also demonstrated a lack of benefit on pregnancy outcomes other than a modest (0.4-0.9 kg) reduction in gestational weight gain. There is no compelling data to confirm that a reduction in gestational weight gain will benefit pregnancy and labour complications (339).

Data on quality of life during pregnancy in relation to exercise are limited. A lack of effect of exercise on quality of life in advanced pregnancy was previously reported in obese women following a light to moderate intensity exercise program (group sessions and walking at home), utilising the WHOQOL- BREF questionnaire (287). Other trials of antenatal exercise, not specifically targeting overweight/obese women, and using a variety of generic questionnaires, have reported conflicting results (340-342). The unavailability of a validated questionnaire specific to pregnancy (338) and the timing of the evaluation in relation to childbirth, could contribute to differences between studies. However, most studies have shown a reduction in physical quality of life with advancing pregnancy, and the association between increased compliance and improved physical quality of life shown in this trial suggests that regular exercise maybe beneficial in improving this component.
One of the study limitations was the small sample size involving 75 participants. The sample size was determined by primary trial outcome (birth weight) (2), and could have low power to detect differences in maternal pregnancy outcomes between groups. Despite its relatively small sample size however, this study is still one of the largest randomised controlled trials on a home-based antenatal exercise intervention in overweight/obese women conducted to date (13, 14). While there are several recent larger trials in overweight/obese women such as the LIMIT and UPBEAT trials (258, 343), their interventions include a major dietary component and exercise prescription is less specific, making it very difficult to discern the effects of antenatal exercise *per se* on outcomes. For instance, a greater reduction in weight gain is observed with interventions including a dietary component in addition to exercise (14, 15).

Another major limitation of this trial was low compliance with the exercise protocol. Poor compliance has been a problem common to other studies, especially those involving overweight and obese pregnant subjects (260). Although this intervention incorporated several measures to improve exercise compliance, including the use of a home based intervention, non-weight bearing type of exercise and guidance from an exercise physiologist, compliance was still unsatisfactory. The same intervention previously reached higher compliance rates (75%) in leaner (BMI 25.5 kg/m²) women (16), emphasizing the difficulty in motivating heavier women to exercise. However, unlike many other studies, we have quantified compliance objectively with heart rate monitoring throughout the intervention period (15). Further, sensitivity analysis showed that within the intervention group, increased compliance was associated with improved fitness, reduced postnatal adiposity, and better physical quality of life. This indicates that women who exercised more, where able to achieve benefits on physical health.

This study included a multi ethnic group of healthy non-smoking overweight and obese pregnant women from the Auckland region. Generalizability of results to the community, were improved by not limiting participation to women attending a single maternity care institution, as has been the case in some previous trials. However, it is possible that the women opting to participate in this trial were more motivated to undergo antenatal lifestyle modification than the general population.

The positive impact of antenatal exercise on maternal fitness in overweight and obese women was demonstrated by this trial. Improved fitness, while not appearing to benefit pregnancy and postnatal outcomes, could have long term beneficial effects, if maintained. Improved fitness may reduce later risk of diabetes and other obesity related complications including
hypertension and dyslipidaemia (344). This can be especially beneficial in overweight/obese women, who are at increased risk of chronic obesity related morbidity. Improvement in cardiorespiratory fitness is also associated with a lower risk of mortality from all-causes and cardiovascular deaths in women, and appears to attenuate the higher risk of death associated with obesity (345). Further, there was also evidence of reduction in maternal adiposity when exercise compliance was high. Follow-up of study participants is planned to look at impact on long-term health.

Overall, the potential beneficial effects of non-weight bearing antenatal exercise in overweight and obese women on maternal health outcomes, other than improved fitness, remain unproven. However, data from this study indicate that low exercise compliance could potentially account for the lack of demonstrable effects on pregnancy outcomes. Novel strategies to improve exercise compliance may need to be considered in this group who appear relatively resistant to complying with prescribed antenatal exercise in the second half of pregnancy. There may also be greater benefit by starting in early pregnancy or prior to conception. Nonetheless, further studies are needed to determine if such an approach is feasible and of greater benefit.
Chapter 5. The effects of antenatal exercise on the offspring of overweight and obese mothers: a randomized controlled trial
Sumudu N Seneviratne, Yannan Jiang, José G B Derraik, Raquel Rodrigues, Janene Biggs, Lesley M E McCowan, Graham K Parry, Silmara Gusso, Alec Ekeroma, Wayne S Cutfield, Paul L Hofman

Abstract

Objectives:
We aimed to assess whether antenatal exercise would reduce birth weight and adiposity and improve health outcomes in the offspring of overweight/obese mothers.

Study design:
A parallel two-arm randomised controlled trial was conducted in non-smoking healthy overweight/obese women (BMI >25 kg/m²) with singleton pregnancies, who were randomised at 20 weeks of gestation to a 16-week home-based moderate-intensity stationary cycling programme or control arm with no intervention. Exercise compliance was assessed by heart rate monitors. Primary outcome was birth weight; secondary outcomes included offspring perinatal outcomes and postnatal (approximately 2 weeks) body composition. Primary analysis was done on the intention-to-treat basis.

Results:
75 participants were randomised in the study (intervention 38, control 37). Compliance with exercise intervention was on average 33%. Offspring birth weight (adjusted mean difference (MD) 104 g; p=0.347), postnatal adiposity, and perinatal outcomes were similar between groups. Overall, the only change in body composition was an increase in bone mineral content in intervention offspring (MD 9.1 g; p=0.010). In sex-specific analyses, male offspring in the exercise intervention arm had increased adiposity compared to controls, including greater fat mass (MD 110 g; p=0.017) and increased body fat percentage (MD 1.6%; p=0.044). In contrast, girls in the intervention group had increased bone mass compared to gender-matched controls (MD 8.3 g; p=0.046).
Conclusions: Non-weight-bearing exercise in the second half of pregnancy in overweight/obese women did not alter offspring birth weight, perinatal complication rates, or postnatal adiposity. Gender-specific alterations in body composition in the offspring of exercising mothers suggest that antenatal exercise may have potential implications for offspring health, which require further investigation.
Introduction

Rates of overweight and obesity have increased rapidly among both adults and children worldwide over the last three decades (30). Consequently, the number of women entering pregnancy in an overweight/obese state has also increased (61, 62). Offspring born to overweight/obese women tend to be heavier and fatter at birth, and also are at higher risk of perinatal complications (99, 109). Further, they are at increased risk of obesity, metabolic complications, and cardiovascular events in later life, as well as premature mortality (8, 9, 346, 347). It is hypothesised that the abnormal \textit{in utero} environment associated with maternal obesity leads to foetal over-nutrition. As a result, there is adverse foetal programming that is thought to lead to increased susceptibility to obesity and associated complications later in life (10). Birth weight and postnatal body composition are proxy measures of the foetal \textit{in utero} environment, as well as markers of long-term obesity risk (55). Interestingly, reducing maternal obesity status by bariatric surgery prior to pregnancy has been associated with improved offspring health (201, 202). These include a reduction in excessive birth weight, and lower rates of obesity and better metabolic health in childhood (201, 202). This suggests that interventions targeting maternal obesity can potentially improve the short- and long-term health of these offspring.

A number of prenatal and antenatal lifestyle interventions are being investigated to improve maternal and foetal health (11). There is expert consensus that physical activity before and/or during pregnancy can improve long-term offspring health (12). A recent meta-analysis reported that antenatal physical activity in women of any body mass index (BMI) led to a small reduction in offspring birth weight (15). It is possible that this modest reduction in birth weight in offspring of overweight/obese women may be beneficial in the long-term, for example reducing obesity risk (1, 208).

However, there is limited evidence from clinical trials showing benefits of antenatal exercise in offspring of overweight/obese women (1), as shown by two recent systematic reviews (13, 14). The limited data available have shown no effect of physical activity on birth weight and perinatal outcomes (253, 261, 287). Moreover, to our knowledge, no study to date has assessed the effects of antenatal exercise on directly measured body composition of babies of overweight/obese women, which may better reflect subtle changes resulting from an altered \textit{in utero} environment (55). Therefore, we aimed to determine the effects of a home-based non-weight-bearing antenatal exercise intervention in overweight/obese women on offspring birth weight, perinatal outcomes, and body composition. Based on a previous study using the same
methodology in leaner women (16), we hypothesised that the intervention would lead to a reduction in offspring birth weight (2).

Methods

(Study design, participants, randomisation and intervention as given in Chapter 4.)

Outcomes

The primary outcome was birth weight, with secondary outcomes including perinatal complications and offspring post-natal body composition. Data on maternal outcomes, foetal growth, and metabolic markers are being reported separately.

Maternal and paternal socio–demographic data were obtained, and maternal weight and height measured at baseline (19 weeks of gestation). At baseline and mid-intervention (32 weeks of gestation), maternal habitual physical activity was assessed by the Pregnancy Physical Activity Questionnaire (PPAQ) (304), while dietary intake was evaluated using 3-day food intake records, and analysed using Foodworks software (Xyris Software Pvt Ltd, Australia).

Birth weight and other perinatal outcomes were obtained from clinical records. Gestation at delivery was based on an early dating scan at <16 weeks of gestation (or on the last menstrual period where a scan was not available). Placental weight was measured untrimmed by delivery staff. Perinatal outcomes were defined as follows: large for gestational age (LGA) – birth weight >90th centile; small for gestational age (SGA) – birth weight <10th centile for gestational age (348); perinatal asphyxia – 5-minute Apgar score <7; hypoglycaemia – blood glucose less than 2.5 mmol/l, requiring therapy other than supplemental feeding; respiratory distress – any non-specific respiratory distress needing respiratory support/oxygen therapy. Length of postnatal hospital stay was defined the time between delivery and home discharge. Other parameters calculated were standardized birth weight z-score (adjusting for gestational age and gender) (300), offspring BMI and ponderal index. Customised birth weight centiles (adjusting for maternal ethnicity, parity, height, weight and offspring gender and gestational age using New Zealand population data) (301) were also obtained.
Postnatal body composition

The offspring were assessed by research staff at approximately 2 weeks of age at the Maurice and Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Body composition was measured by whole-body dual-energy absorptiometry (DXA) scanning (Lunar Prodigy 2000, General Electric, and Maddison, Wisconsin, USA), which has been previously shown to be safe and reliable for assessments in neonates (317). To minimize artefact effects, scans were performed with the neonate asleep/settled and in lightweight indoor clothing. Postnatal feeding history was obtained and neonatal weight and length measured as pre-specified. All scans were performed and analysed by a single investigator, using Encore 2007 software v.11.40.004 including paediatric software packages (GE Corp., Madison, WI, USA).

Data analyses

Treatment evaluation was performed on an intention-to-treat basis. Analysis of covariance regression models were used to evaluate the main treatment effect on the primary outcome and other birth measures between the two treatment groups, adjusting for maternal BMI at study entry, maternal ethnicity and parity (i.e. stratification factors), gestational age at birth and offspring gender. A similar approach was used for post-natal body composition, additionally adjusting for postnatal age at assessment (349). Perinatal complications were adjusted for maternal BMI, ethnicity and parity. Model-adjusted means and the mean difference between two groups (MD) were estimated and tested. Logistic regression model was used for the analysis of binary outcomes, with associated odds ratio and 95% confidence interval provided. Subgroup analysis was undertaken to determine any gender specific effects on birth weight and postnatal body composition (316, 350). Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided at 5% significance level. Missing data were not imputed. No adjustment has been made for multiple testing.
Results

A total of 195 women were assessed for eligibility; 75 eligible consenting participants completed baseline assessments and were subsequently randomised into the trial (intervention n=38, control n=37) (Figure 5). Three participants developed medical contraindications to antenatal exercise and discontinued the intervention, but included in the intention-to-treat analysis (Figure 5). One participant (intervention group) withdrew from the study during the intervention period, and outcome data were not collected at her request (Figure 5). Baseline participant (maternal) and paternal characteristics are presented in Table 5, and there were no observed differences between groups.

Table 5: Baseline maternal and paternal characteristics (19 weeks of gestation) Continuous variables are summarised as means ± SD, and categorical variables as n (%).

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td><strong>Maternal characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.6 ± 4.6</td>
<td>31.1 ± 5.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.7 ± 14.1</td>
<td>93.6 ± 17.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.1 ± 4.4</td>
<td>34.1 ± 5.9</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>9 (24%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>11 (29%)</td>
<td>11 (29%)</td>
</tr>
<tr>
<td>Maori</td>
<td>5 (13%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>NZ European or other</td>
<td>22 (58%)</td>
<td>21 (57%)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>26 (68%)</td>
<td>17 (46%)</td>
</tr>
<tr>
<td>Part-time</td>
<td>5 (13%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Not employed</td>
<td>7 (19%)</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.1 ± 2.9</td>
<td>14.8 ± 2.2</td>
</tr>
<tr>
<td><strong>Paternal characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.8 ± 6.3</td>
<td>32.8 ± 5.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.1 ± 5.5</td>
<td>31.6 ± 6.5</td>
</tr>
<tr>
<td><strong>Annual household income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZS 50,000 or less</td>
<td>8 (21%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Greater than NZS 50,000</td>
<td>25 (66%)</td>
<td>19 (51%)</td>
</tr>
<tr>
<td>No answer/did not know</td>
<td>5 (13%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td><strong>Pregnancy data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Availability of dating scan</td>
<td>36 (95%)</td>
<td>36 (97%)</td>
</tr>
</tbody>
</table>
**Results**

A total of 37 participants per group were included in the birth outcome analysis, in accordance to their original group assignment. Offspring birth weight was similar in the intervention and control groups (p=0.35), as were other parameters measured at birth (Table 6). Customised birth weight centiles between intervention and control groups were also similar (52 ± 33% vs 43 ± 26%, respectively; p=0.12). There were no group differences for other birth outcomes and perinatal complications (Table 6). The total number of male (n=38) and female (n=36) offspring were similar, but there was unequal gender distribution between groups, with fewer male offspring in the intervention group (n=13, 34%), compared to control group (n=25, 68%). There was one perinatal death in each group due to reasons unrelated to the exercise intervention (cord tightly wrapped around neck at birth and listeriosis diagnosed on histology).

**Table 6:** Birth outcomes in the intervention (n=37) and control (n=37) groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>Difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (d)</td>
<td>274 ± 12</td>
<td>278 ± 10</td>
<td>-3.28</td>
<td>-8.30, 1.73</td>
<td>0.196</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3578 ± 630</td>
<td>3594 ± 469</td>
<td>104</td>
<td>-116, 324</td>
<td>0.347</td>
</tr>
<tr>
<td>Birth weight z-score</td>
<td>0.65 ± 1.12</td>
<td>0.38 ± 0.86</td>
<td>0.21</td>
<td>-0.26, 0.68</td>
<td>0.380</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>51.2 ± 2.6</td>
<td>51.8 ± 2.5</td>
<td>0.06</td>
<td>-0.99, 1.09</td>
<td>0.923</td>
</tr>
<tr>
<td>Occipito-frontal circumferences</td>
<td>35.1 ± 1.6</td>
<td>35.1 ± 1.4</td>
<td>0.28</td>
<td>-0.40, 0.95</td>
<td>0.416</td>
</tr>
<tr>
<td>Ponderal index (g/cm³)</td>
<td>26.5 ± 2.8</td>
<td>25.8 ± 2.4</td>
<td>0.53</td>
<td>-0.70, 1.76</td>
<td>0.392</td>
</tr>
<tr>
<td>BMI at birth (kg/m²)</td>
<td>13.6 ± 1.6</td>
<td>13.4 ± 1.2</td>
<td>0.31</td>
<td>-0.30, 0.92</td>
<td>0.318</td>
</tr>
<tr>
<td>Placental weight (g)</td>
<td>665 ± 192</td>
<td>670 ± 135</td>
<td>-0.77</td>
<td>-96, 91</td>
<td>0.953</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
<td>8.3 ± 1.6</td>
<td>8.0 ± 2.3</td>
<td>0.35</td>
<td>-0.61, 1.32</td>
<td>0.465</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>9.2 ± 1.7</td>
<td>9.1 ± 2.1</td>
<td>0.08</td>
<td>-0.85, 1.01</td>
<td>0.869</td>
</tr>
<tr>
<td>Length of hospital stay (h)</td>
<td>61 ± 41</td>
<td>80 ± 107</td>
<td>-20</td>
<td>-61, 21</td>
<td>0.329</td>
</tr>
<tr>
<td>LGA</td>
<td>9 (24%)</td>
<td>4 (11%)</td>
<td>2.52</td>
<td>0.67, 9.38</td>
<td>0.170</td>
</tr>
<tr>
<td>SGA</td>
<td>4 (11%)</td>
<td>3 (8%)</td>
<td>1.34</td>
<td>0.23, 7.96</td>
<td>0.745</td>
</tr>
<tr>
<td>Birth weight &gt;4 kg</td>
<td>10 (26%)</td>
<td>7 (19%)</td>
<td>1.59</td>
<td>0.50, 5.04</td>
<td>0.429</td>
</tr>
<tr>
<td>Birth weight &lt;2.5 kg</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0.75</td>
<td>0.03, 17.71</td>
<td>0.860</td>
</tr>
<tr>
<td>Foetal death in utero</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0.93</td>
<td>0.05, 17.23</td>
<td>0.959</td>
</tr>
<tr>
<td>Admission to HDU/ICU³</td>
<td>3 (8%)</td>
<td>3 (8%)</td>
<td>0.91</td>
<td>0.16, 5.28</td>
<td>0.915</td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td>0.44</td>
<td>0.04, 5.41</td>
<td>0.521</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>4 (11%)</td>
<td>3 (8%)</td>
<td>1.31</td>
<td>0.26, 6.63</td>
<td>0.743</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>5 (13%)</td>
<td>2 (5%)</td>
<td>2.62</td>
<td>0.45, 15.32</td>
<td>0.284</td>
</tr>
</tbody>
</table>

³HDU/ICU high dependency unit/ intensive care unit

[Continuous variables are summarised as means ± SD, and categorical variables as n (%). The estimated differences in means are provided for continuous variables and in odds ratios for categorical variables, as well as the associated 95% confidence intervals (CI). Data are adjusted for maternal ethnicity, parity, and baseline BMI; continuous birth parameters (except birth weight z-score) are also adjusted for gestational age and gender.]
Postnatal outcomes

Postnatal body composition was assessed in 66 babies born at term (intervention n=32, control n=34). Reasons for non-assessment were: death in utero (n=2), not discharged from hospital due to prematurity/perinatal asphyxia (n=2), and loss to follow-up (n=4). The median age at postnatal assessment was 14 days in both groups. Feeding patterns in intervention and control groups (exclusive breast feeding rate 50 vs 51%, respectively; p=0.90) and weight gain from birth were similar (Table 7). Adjusted postnatal adiposity (fat mass, total body fat percentage, and fat mass index) and lean mass were similar between groups (Table 7), as was regional fat distribution (percentage of fat in trunk and limbs). Offspring in the intervention arm had increased bone mineral content compared to controls (Table 7).

Table 7: Postnatal outcomes at approximately 2 weeks of age in the intervention (n=32) and control (n=34) groups.

<table>
<thead>
<tr>
<th>Postnatal outcomes</th>
<th>Intervention Mean</th>
<th>Intervention SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Differencea</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean mass, g</td>
<td>3599</td>
<td>556</td>
<td>3575</td>
<td>437</td>
<td>153.4</td>
<td>0.159</td>
</tr>
<tr>
<td>Fat mass, g</td>
<td>343</td>
<td>136</td>
<td>283</td>
<td>111</td>
<td>50.9</td>
<td>0.129</td>
</tr>
<tr>
<td>Bone mineral content, g</td>
<td>50</td>
<td>15</td>
<td>46</td>
<td>15</td>
<td>9.1</td>
<td>0.010</td>
</tr>
<tr>
<td>Bone mineral density, g/cm²</td>
<td>0.48</td>
<td>0.03</td>
<td>0.48</td>
<td>0.02</td>
<td>0.00</td>
<td>0.961</td>
</tr>
<tr>
<td>Total body fat, %</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>0.7</td>
<td>0.260</td>
</tr>
<tr>
<td>Arm percentage fat, %</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>4</td>
<td>0.7</td>
<td>0.545</td>
</tr>
<tr>
<td>Leg percentage fat, %</td>
<td>15</td>
<td>5</td>
<td>12</td>
<td>5</td>
<td>1.1</td>
<td>0.493</td>
</tr>
<tr>
<td>Trunk percentage fat, %</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>-0.1</td>
<td>0.904</td>
</tr>
<tr>
<td>Fat mass index, kg/m2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.2</td>
<td>0.140</td>
</tr>
<tr>
<td>Post-natal weight, g</td>
<td>3927</td>
<td>618</td>
<td>3890</td>
<td>502</td>
<td>178.1</td>
<td>0.153</td>
</tr>
<tr>
<td>Post-natal length, cm</td>
<td>53</td>
<td>2</td>
<td>54</td>
<td>2</td>
<td>0.2</td>
<td>0.676</td>
</tr>
<tr>
<td>Post-natal BMI kg/m2</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>0.5</td>
<td>0.134</td>
</tr>
<tr>
<td>Post-natal ponderal index, g/cm³</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0.1</td>
<td>0.215</td>
</tr>
<tr>
<td>Change in weight from birth, g</td>
<td>281</td>
<td>315</td>
<td>285</td>
<td>252</td>
<td>-8.8</td>
<td>0.881</td>
</tr>
</tbody>
</table>

aAll models have adjusted for maternal ethnicity, parity, baseline BMI, gestational age, offspring gender and postnatal age and analysed using linear regression.
Results

Post hoc analyses by gender

Male offspring in the intervention group had similar birth weight, but showed increased postnatal adiposity compared to male controls (increased fat mass, percentage body fat and fat mass index; Table 8). Of note, adiposity appeared to be increased peripherally (percentage fat in legs MD 4.1%, p=0.045; in arms MD 2.8%, p=0.070) rather than centrally (trunk MD 1.2%, p=0.378) in comparison to male controls. Amongst female offspring, there were no observed differences for adjusted birth weight, adiposity, or lean mass (Table 8). However, there was an increase in bone mineral content in female offspring the intervention group compared to control offspring (Table 8).

Table 8: Sex-specific birth and postnatal outcomes in the intervention and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>MD</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys</strong> Birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>13</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (g)</td>
<td>3447 ± 852</td>
<td>3688 ± 420</td>
<td>233</td>
<td>-123, 589</td>
<td>0.191</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>13.1 ± 1.9</td>
<td>13.4 ± 1.1</td>
<td>0.84</td>
<td>-0.03, 1.71</td>
<td>0.059</td>
</tr>
<tr>
<td>Ponderal index (g/cm³)</td>
<td>25.8 ± 2.8</td>
<td>25.5 ± 2.4</td>
<td>1.61</td>
<td>-0.21, 3.45</td>
<td>0.081</td>
</tr>
<tr>
<td>Postnatal N</td>
<td>11</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean mass (g)</td>
<td>3775 ± 67</td>
<td>3644 ± 405</td>
<td>354</td>
<td>-14.4, 722</td>
<td>0.059</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>338 ± 149</td>
<td>264 ± 92</td>
<td>110</td>
<td>21, 199</td>
<td>0.017</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>7.9 ± 2.0</td>
<td>6.6 ± 1.8</td>
<td>1.6</td>
<td>0.00, 3.20</td>
<td>0.044</td>
</tr>
<tr>
<td>Fat mass index (kg/m²)</td>
<td>1.14 ± 0.41</td>
<td>0.89 ± 0.28</td>
<td>0.3</td>
<td>0.06, 0.60</td>
<td>0.017</td>
</tr>
<tr>
<td>Bone mineral content (g)</td>
<td>51.0 ± 18.6</td>
<td>49.0 ± 15.1</td>
<td>11.3</td>
<td>-1.3, 23.9</td>
<td>0.077</td>
</tr>
<tr>
<td><strong>Girls</strong> Birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>24</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (g)</td>
<td>3648 ± 78</td>
<td>3399 ± 524</td>
<td>71</td>
<td>-254, 396</td>
<td>0.658</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>13.8 ± 1.4</td>
<td>13.3 ± 1.4</td>
<td>0.23</td>
<td>-0.77, 1.22</td>
<td>0.644</td>
</tr>
<tr>
<td>Ponderal index (g/cm³)</td>
<td>26.8 ± 2.9</td>
<td>26.4 ± 2.6</td>
<td>0.40</td>
<td>-1.51, 2.30</td>
<td>0.673</td>
</tr>
<tr>
<td>Postnatal N</td>
<td>21</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean mass (g)</td>
<td>3507 ± 99</td>
<td>3409 ± 489</td>
<td>-12</td>
<td>-284, 260</td>
<td>0.928</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>346 ± 133</td>
<td>328 ± 142</td>
<td>2.2</td>
<td>-113, 118</td>
<td>0.969</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>8.8 ± 2.5</td>
<td>8.6 ± 3.1</td>
<td>-0.1</td>
<td>-2.5, 2.3</td>
<td>0.937</td>
</tr>
<tr>
<td>Fat mass index (kg/m²)</td>
<td>1.22 ± 0.44</td>
<td>1.17 ± 0.45</td>
<td>0.01</td>
<td>-0.38, 0.39</td>
<td>0.973</td>
</tr>
<tr>
<td>Bone mineral content (g)</td>
<td>49.1 ± 12.4</td>
<td>39.9 ± 12.0</td>
<td>8.3</td>
<td>0.14, 16.4</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Data are means ± SD, with estimated mean differences (MD) and associated 95% confidence intervals (CI). Data are adjusted for maternal ethnicity, parity, and baseline BMI, gestational age, and gender (as well as age at assessment for postnatal outcomes).

Compliance

Compliance with the exercise intervention (measured by heart rate monitor data) was highly variable, with an average of 33% of exercise sessions completed (range 0–85%). Only 9 (24%) participants completed at least 50% of prescribed sessions. Notably, there was a steady decline...
in compliance with the exercise protocol as pregnancies progressed (Figure 7A). Compliance was greater in participants of European descent than in those of Maori or Pacific Island ethnicity (44%, 23% and 13% respectively). Maternal compliance was unaffected by the gender of the foetus (p=0.99). Total duration of cycling throughout the intervention was on average 572 minutes per participant, with 40% at low intensity, 52% at moderate intensity, and 8% at high intensity (Figure 7B).

**Figure 7:** Compliance with prescribed exercise sessions, and duration and intensity of stationary cycling undertaken by the intervention group during the 16-week intervention period; A) Box and whisker plot showing the percentage of exercise sessions completed out of the total (67) prescribed; B) mean duration of cycling activity according to exercise intensity over the 4-week periods of intervention.

---

**Adverse events**

There were no adverse effects reported in association with the exercise intervention.
**Routine physical activity and dietary intake**

Total dietary energy intake at baseline and mid-intervention was similar between groups, as were the percentages of energy intake from carbohydrate, fat, or protein (Table 9). Energy expenditure in household/caregiving, and occupational activities were also similar in both groups at baseline and mid-intervention (Table 10).

**Table 9:** Average daily dietary energy intake in trial participants at baseline and mid-intervention

<table>
<thead>
<tr>
<th>Average daily dietary intake^b</th>
<th>Intervention (N=38)</th>
<th>Control (N=37)</th>
<th>Test of Group Difference ^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily energy intake (kcal)</td>
<td>2113</td>
<td>570</td>
<td>2005</td>
</tr>
<tr>
<td>% energy from carbohydrates</td>
<td>46</td>
<td>7</td>
<td>46</td>
</tr>
<tr>
<td>% energy from fat</td>
<td>35</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>% energy from protein</td>
<td>17</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td><strong>Mid-intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily energy intake (kcal)</td>
<td>1998</td>
<td>661</td>
<td>2106</td>
</tr>
<tr>
<td>% energy from carbohydrates</td>
<td>44</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>% energy from fat</td>
<td>36</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>% energy from protein</td>
<td>18</td>
<td>5</td>
<td>19</td>
</tr>
</tbody>
</table>

^a Two sample t-test, ^b self-reported by participants on 3-day dietary records at baseline (19 weeks of gestation) and mid-intervention (32 weeks of gestation), and nutrient content analysed by Foodworks software.

**Table 10:** Average weekly energy expenditure on habitual physical activity in trial participants at baseline and mid-intervention

<table>
<thead>
<tr>
<th>Average weekly energy expenditure (MET-h/week)^b</th>
<th>Intervention (N=38)</th>
<th>Control (N=37)</th>
<th>Test of Group Difference ^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total physical activity</td>
<td>292</td>
<td>164</td>
<td>281</td>
</tr>
<tr>
<td>Household/Caregiving activity</td>
<td>108</td>
<td>69</td>
<td>125</td>
</tr>
<tr>
<td>Occupational activity</td>
<td>102</td>
<td>96</td>
<td>72</td>
</tr>
<tr>
<td><strong>Mid intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total physical activity</td>
<td>261</td>
<td>101</td>
<td>259</td>
</tr>
<tr>
<td>Household/Caregiving activity</td>
<td>103</td>
<td>64</td>
<td>110</td>
</tr>
<tr>
<td>Occupational activity</td>
<td>83</td>
<td>77</td>
<td>77</td>
</tr>
</tbody>
</table>

^a Two sample t-test, ^b self-reported by participants on pregnancy physical activity questionnaires (PPAQ) at baseline (19 weeks of gestation) and mid intervention (32 weeks of gestation).
Discussion

Non-weight-bearing exercise in the second half of pregnancy in overweight/obese women did not alter offspring birth weight, perinatal complication rates, or postnatal adiposity. However, low compliance with the exercise intervention might have contributed to the lack of effect. Nonetheless, there were gender-specific alterations in body composition in the offspring of exercising mothers, with boys having increased adiposity and girls increased bone mass compared to gender-matched controls.

There is a paucity of data on the effects of antenatal exercise on offspring of overweight/obese women (13). Excluding studies with concomitant dietary interventions, only a few clinical trials in overweight/obese women have examined the effects of antenatal exercise on offspring health (253, 261, 287). These trials also reported low compliance with the intervention, and similarly reported no changes in birth weight or perinatal outcomes (253, 261, 287). However, offspring body composition was not assessed.

This study appears to provide the first observation from a clinical trial that antenatal exercise in overweight/obese women is associated with gender-specific changes in offspring body composition. We observed increased bone mass in girls born to mothers in the exercise group. In lean women, observational studies have linked increased self-reported vigorous physical activity to reduced neonatal offspring bone mass (351, 352). More pronounced effects of maternal exercise on male offspring were also noted when this intervention was studied in leaner nulliparous women, although the effects were in contrast to the present findings, with boys of the intervention group showing a reduction in BMI and ponderal index (208). However, increased adiposity in male offspring with antenatal exercise has been previously demonstrated in a rat model, where voluntary exercise in pregnant Wister rats resulted in increased fat mass percentage only in male pups (353).

Gender differences in foetal developmental programming have been recognised in both humans and animal models (354-356), and while placental and epigenetic changes are implicated, the exact underlying mechanisms are still unclear (354, 356). Modulation of offspring body composition by factors in the intra-uterine environment (e.g. maternal body composition, inflammatory metabolic factors, antenatal exercise) in a gender-specific manner has been previously described (350, 355, 357). In particular, data from animal research suggest that male offspring appear more susceptible to effects of both maternal obesity and antenatal exercise, compared to female offspring (355). In rodent models, diet induced maternal obesity
increased offspring leptin, triglycerides and fat mass in male but not female offspring, and maternal exercise prevented the rise in leptin in male offspring (358). Further in offspring of non-obese controls, maternal exercise reduced insulin resistance in male offspring (358). Therefore gender specific alterations in foetal metabolism by antenatal exercise may play a role.

The pattern and timing of exercise during pregnancy can lead to differential effects on offspring size and body composition at birth (208, 281). For example, Clapp et al. found that a reduction in exercise in mid-pregnancy led to an increase in offspring birth weight and fat mass, which was attributed to stimulation of placental growth at the terminal villous level when exercise volume decreased (281). It is therefore possible that reduction in exercise in advanced pregnancy in our intervention group might have triggered a similar phenomenon (albeit at a later gestation). Alternatively obese pregnant women have placental and metabolic abnormalities (increased pro-inflammatory cytokines, increased muscularity of placental vessel walls, and endothelial dysfunction), which can affect foetal nutrient transfer (147, 359-361). Antenatal aerobic exercise has the potential to reduce pro-inflammatory adipocytokines, and improve endothelial dysfunction and placental blood flow regulation (361, 362). Such changes could potentially alter foetal nutrient transfer and influence offspring body composition and metabolism.

We acknowledge that this study has some limitations. The pre-specified sample size of 50 participants per group was not achieved as the recruitment rate was slower than anticipated. However, this issue was counter-balanced by a high follow-up rate, with birth outcomes available on 99% of participants. Nonetheless, the study was likely underpowered to detect changes in secondary outcomes (such as perinatal complications) with relatively low occurrence rates.

Importantly, poor compliance with the exercise protocol might have attenuated or altered the impact of the intervention. Low compliance with antenatal physical activity interventions is a problem common to most studies involving overweight/obese pregnant women (253, 363). Previous researchers have pointed out that attending group sessions was a barrier to compliance with intervention protocols (253, 363). In this trial, we adopted a home-based approach that enabled participants to exercise within the privacy of their own home, at times most convenient to them, but compliance was still somewhat low at 33%. Previously, leaner nulliparous pregnant women showed much higher compliance (80%) with the same intervention (16), highlighting the difficulties in motivating overweight/obese women to
exercise in pregnancy. We also observed lower exercise volume during pregnancy and greater reduction in exercise levels between mid and late gestation in the overweight/obese women compared to the previous cohort of leaner women (16). This reflects documented differences in general physical activity levels during pregnancy (using pedometers) between lean and obese women (310, 311). Commencing exercise prior to conception has shown promising results for the offspring in animal models (355, 364), and may be a strategy worth exploring. Nonetheless, additional measures to improve motivation and maintain compliance need to be considered in future studies (1, 229).

Of note, objective and detailed monitoring of exercise compliance (including intensity and duration) was a strength that has often been lacking in previous antenatal exercise trials (15). It is important that trial outcomes are assessed based on the actual intervention put in practice rather than that prescribed by the study protocol. In addition, maternal dietary intake and non-interventional exercise were also monitored both prior to and during the intervention, ensuring that these factors would not significantly affect trial outcomes.

The time lapse between birth and assessment of body composition (approximately 14 days) might have resulted in some influence of the postnatal environment on the outcomes measured. However, this gap was pre-specified, avoiding the potential confounding effects of varying degrees of weight loss during the first 10 days of life, and allowing for the establishment of regular feeding and sleeping patterns. Offspring growth and feeding patterns from birth to time of assessment were assessed and found to be similar between groups, and adjustments were done for postnatal age at assessment; thus, confounding effects were unlikely to account for observed differences.

Although antenatal exercise did not alter offspring birth weight, changes in postnatal body composition suggest that there may be lasting effects on offspring health. Indeed, measures of body composition early in life may be better markers of in utero programming effects on long-term health than birth weight (55). Observational studies show that increased early life adiposity is associated with an increased risk of childhood overweight (15), which in turn tracks to adult obesity (10, 365). As the offspring of overweight and obese mothers are already recognised to be at high risk of later life obesity, increased neonatal adiposity in male offspring requires further follow-up. However, the increase in male neonatal adiposity was distributed peripherally rather than centrally. This may be less harmful in the long term, as an adverse metabolic profile is more closely associated with central (abdominal) rather than peripheral adiposity (37). Nonetheless, data on long-term health implications of regional
distribution of neonatal adiposity are lacking. Although not a main trial outcome, the increase in bone mineral content in female offspring following antenatal exercise is also relevant, since an increase in early life bone mass may be protective against future osteoporosis (366).

Long-term follow up of this cohort was pre-planned (2), and will help determine the impact of these early life body composition changes on offspring long-term health. We also recommend that other researchers undertaking antenatal exercise interventions assess gender-specific effects on offspring body composition (354, 367). Reverse translational research (mimicking present study conditions in animal models) may also be helpful to elicit the mechanisms underlying the observed findings (368).
Chapter 6. Effects of antenatal exercise on metabolic markers in overweight and obese pregnant women and their new-borns

Sumudu N Seneviratne, José G B Derraik, Yannan Jiang, Raquel O Rodrigues, Janene Biggs, Christine Brennen, Graham K Parry, Lesley M E McCowan, Wayne S Cutfield, Paul L Hofman

Abstract

Context:
Obese and overweight pregnant women are at higher risk of metabolic perturbations, which may alter placental function and foetal growth. The effects of antenatal exercise on maternal and offspring metabolism are unknown.

Objective:
To determine the effects of antenatal exercise in overweight and obese pregnant women on pre-specified metabolic markers in maternal and cord blood.

Design:
A parallel two-arm randomised controlled trial.

Participants:
75 non-smoking overweight/obese women (BMI >25 kg/m²) with a singleton pregnancy <20 weeks of gestation randomised to intervention (n=38) or control (n=37) groups.

Intervention:
A 16-week home-based moderate-intensity stationary cycling program starting at 20 weeks of gestation, with exercise compliance monitored by heart rate monitors

Main outcome measures:
Maternal and cord blood metabolic markers.
Results:

There were no differences in maternal metabolic markers post-intervention between groups. Offspring in the intervention arm had reduced cord blood IL-6 levels compared to controls (adjusted mean difference -13.97 pg/ml; p=0.026). Post hoc analyses also showed that male offspring in the intervention group had lower IGFBP-1 levels than male controls (adjusted mean difference -59.2 ng/ml; p=0.030).

Conclusions:

Non-weight-bearing exercise in the second half of pregnancy in overweight/obese women did not alter maternal metabolic markers, but led to alterations in offspring metabolic markers at birth. However, the long-term effects of the observed alterations are uncertain, and need to be determined by follow-up of these children.
Introduction

Obese and overweight pregnant women have metabolic dysregulation in pregnancy, including hyper-insulinaemia, dyslipidaemia, hyperleptinaemia, and higher levels of inflammatory markers (147). During pregnancy, metabolic dysregulation can adversely affect not only the mother, but also cause adverse programming effects in the offspring (6, 10, 148). Offspring of overweight/obese women have an increased risk of obesity and metabolic dysregulation throughout their life cycle (9, 127), but metabolic dysregulation can manifest as early as the neonatal period (148).

There is expert consensus that regular moderate-intensity exercise during pregnancy may improve long-term health outcomes in both mother and offspring (12) and antenatal exercise is recommended for all women without medical contraindications (215). Exercise has been associated with improvements in obesity-related chronic inflammation (369), insulin resistance (370, 371) and lipid profile (372) in obese women. However, there is limited evidence on the effects of antenatal exercise on metabolic health of the mother (373). Further, to our knowledge, the effects of antenatal exercise on metabolic markers in offspring of overweight/obese women early in life have not been previously described.

The IMPROVE (Improving Maternal and Progeny Obesity Via Exercise) randomised controlled trial aimed to determine the effects on maternal and offspring health of home-based non-weight-bearing antenatal exercise in the second half of pregnancy in overweight and obese women (2). In this study, we assessed the effects of the exercise intervention on pre-specified maternal and cord blood metabolic markers. We hypothesized that antenatal exercise would improve the metabolic milieu of both mother and offspring.

Methods

(Study design, participants, randomisation and intervention as given in Chapter 4.)

Study assessments

Trial participants completed three study assessments: at baseline (19 weeks of gestation); post-intervention (36 weeks of gestation), and at follow-up (approximately 2 weeks after delivery). The primary outcome was birth weight. Maternal weight and fitness level (measured by a
submaximal exercise test) were assessed at baseline and post intervention as previously
described (2). Birth outcomes were obtained from clinical records, and neonatal and maternal
body composition was measured by whole body dual energy X ray absorptiometry,
approximately two weeks after delivery (2).

Maternal venous blood was collected at baseline (19 weeks of gestation) and post-intervention
(36 weeks of gestation) in a non-fasting, resting state during scheduled study assessments.
Cord blood was collected at birth by delivery staff. All maternal and cord blood samples were
centrifuged and separated within 3 hours of collection, and stored below -20°C until laboratory
analysis.

Pre-specified metabolic markers measured in maternal and cord blood included adipokines and
inflammatory markers (leptin, interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α) and
highly-sensitive C-reactive protein (hs-CRP)), total cholesterol, low-density lipoprotein
cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, insulin-like
growth factor I (IGF-I), IGF-II, insulin-like growth factor binding protein 1 (IGFBP-1), and
IGFBP-3. Maternal chronic glycaemia was assessed by glycated haemoglobin (HbA1c), while
maternal sex hormone binding globulin (SHBG) was used as a surrogate measure of insulin
resistance (374). SHBG exhibits minimal diurnal variability, as well as minimal variability
between fasting and postprandial states, making it a useful marker of insulin resistance in
obstetric care (375). Plasma insulin was measured in cord blood.

Serum adipokines, IGFs, and IGFBPs were measured in duplicate using a laser-based
fluorescent analytical test instrumentation (MAGPIX 4.2, Luminex Corporation, Austin, TX,
USA) and customised commercially available MILLIPLEX® map magnetic bead-based
multianalyte panels (Human Adipokine Magnetic Bead Panel #HADK2MAG-61K; Human
IGF-I, II Magnetic Bead Panel # HIGFMAG-52K; and Human IGF Binding Protein Magnetic
Bead Panel #HIGFBMAG-53K) (Millipore Corporation, Billerica, MA, USA) respectively,
according to manufacturer instructions. Inter-assay coefficients of variation (CV) were <20%
and intra-assay CVs were <10% for all assays (Appendix 1).

Maternal HbA1c was measured on venous whole blood at time of venepuncture, using a
glycohaemoglobin analyser (Seimens/Bayer DCA 2000+ analyser). hs-CRP was measured by
particle-enhanced immunoturbidimetric assay and plasma lipids by colorimetric enzymatic
analysis using an automated clinical chemistry analyser (Roche Hitachi 902, Roche
Diagnostics, Germany). Maternal plasma SHBG and cord plasma insulin were measured by an
automated electro-chemiluminescence immune-analyser (Elecsys 2010 immuno-analyser, Roche Diagnostics, Germany). Inter-assay CVs were <4% for all assays (Appendix 2).

**Data analyses**

Clinical characteristics of trial participants and their offspring were summarised as mean and standard deviation for continuous variables and number and percentage for categorical variables. Treatment evaluation was performed on the principle of intention-to-treat. Analysis of covariance regression models were used to evaluate main treatment effects on maternal and cord metabolic markers, adjusting for maternal ethnicity and parity (i.e. stratification factors) and baseline outcome value (maternal markers) or offspring gender (cord blood markers). Sex-specific post hoc analyses were also carried out due to observed alterations in offspring adiposity following the intervention (Seneviratne et al., unpublished data). Model-adjusted means and their differences between two groups were estimated and tested. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-tailed and maintained at a 5% significance level. Missing data were not imputed. No adjustment has been made for multiple testing.

**Results**

195 women were assessed for eligibility and 75 participants were randomised into the trial; birth outcomes were available for 74 participants (37 per group) due to one study withdrawal (Figure 5, page 73). There were no differences in baseline characteristics between groups (Table 5, page 86) and pregnancy outcomes and birth parameters were also observed to be similar (Seneviratne et al., unpublished data) (Table 3, page 75 and Table 6, page 87). However, the intervention led to an improvement in maternal fitness (Seneviratne et al., unpublished data) (Table 3), with post hoc analyses showing an increase in neonatal adiposity in male offspring (Seneviratne et al., unpublished data) (Table 8, page 89).

**Maternal blood**

Maternal metabolic markers in intervention and control groups are shown in Table 11. There were no observed differences between groups.
Table 11: Post-intervention (36 weeks of gestation) maternal metabolic outcomes in intervention (n=37) and control (n=37) groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>MD</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adipokines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>37.4 ± 23.5</td>
<td>37.8 ± 20.7</td>
<td>-0.32</td>
<td>-6.25, 5.61</td>
<td>0.915</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin-6 (pg/ml)</td>
<td>2.93 ± 2.45</td>
<td>3.37 ± 3.25</td>
<td>-0.96</td>
<td>-2.81, 0.88</td>
<td>0.295</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>4.54 ± 1.94</td>
<td>4.39 ± 1.78</td>
<td>0.13</td>
<td>-0.53, 0.79</td>
<td>0.700</td>
</tr>
<tr>
<td>hs-CRP (mg/l)</td>
<td>4.68 ± 4.66</td>
<td>6.11 ± 4.69</td>
<td>-0.56</td>
<td>-2.90, 1.70</td>
<td>0.629</td>
</tr>
<tr>
<td><strong>Glucose homeostasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>412 ± 92</td>
<td>418 ± 115</td>
<td>-5.69</td>
<td>-30, 19</td>
<td>0.644</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.44 ± 0.25</td>
<td>5.46 ± 0.35</td>
<td>0.08</td>
<td>-0.04, 0.19</td>
<td>0.186</td>
</tr>
<tr>
<td><strong>IGF axis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>129 ± 20</td>
<td>125 ± 23</td>
<td>-1.0</td>
<td>-9.6, 7.7</td>
<td>0.826</td>
</tr>
<tr>
<td>IGF-II (ng/ml)</td>
<td>485.6 ± 161.4</td>
<td>452.5 ± 151.8</td>
<td>35.6</td>
<td>-40, 111</td>
<td>0.348</td>
</tr>
<tr>
<td>IGFBP-1 (ng/ml)</td>
<td>8.48 ± 3.63</td>
<td>9.73 ± 5.17</td>
<td>-0.88</td>
<td>-3.17, 1.41</td>
<td>0.442</td>
</tr>
<tr>
<td>IGFBP-3 (ng/ml)</td>
<td>1622 ± 517</td>
<td>1398 ± 555</td>
<td>203</td>
<td>-84, 490</td>
<td>0.161</td>
</tr>
<tr>
<td><strong>Lipid profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.20 ± 1.27</td>
<td>6.26 ± 1.48</td>
<td>-0.03</td>
<td>-0.41, 0.36</td>
<td>0.885</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>3.60 ± 1.28</td>
<td>3.55 ± 1.37</td>
<td>-0.04</td>
<td>-0.44, 0.37</td>
<td>0.858</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.46 ± 0.33</td>
<td>1.59 ± 0.42</td>
<td>-0.06</td>
<td>-0.17, 0.04</td>
<td>0.239</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>3.16 ± 1.35</td>
<td>2.97 ± 0.94</td>
<td>0.13</td>
<td>-0.33, 0.59</td>
<td>0.570</td>
</tr>
</tbody>
</table>

Data are means ± SD; differences in means (MD) are provided with the associated 95% confidence intervals (CI), adjusted for stratification factors (maternal ethnicity and parity) and baseline value (at 20 weeks of gestation).

**Cord blood**

Cord blood was collected and analysed in 56 healthy term offspring (intervention n=25, control n=31), excluding babies with intrauterine death or severe birth asphyxia (n=3), or born prematurely (n=3) (Table 12). IL-6 levels in cord blood were reduced in the intervention offspring compared to controls (adjusted mean difference (MD) -13.97 pg/ml; p=0.026). All other metabolic markers were similar in both groups.

Sex-specific analyses showed a reduction in IGFBP-1 concentrations in male offspring in the intervention group (24.8 vs 85.7 ng/ml; MD -59.2 ng/ml (95% CI -112.3, -6.1); p=0.030). However, this was not observed in females (41.3 vs 41.5 ng/ml; MD 11.45 ng/ml (95% CI -41.7, 64.59); p=0.658).
Table 12: Metabolic markers in offspring cord blood for intervention (n=25) and control (n=31) groups.

<table>
<thead>
<tr>
<th>Metabolic Markers</th>
<th>Intervention</th>
<th>Control</th>
<th>MD</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipokines/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>28.7 ± 22.4</td>
<td>27.9 ± 32.1</td>
<td>-1.73</td>
<td>-18.3, 14.8</td>
<td>0.835</td>
</tr>
<tr>
<td>Interleukin-6 (pg/ml)</td>
<td>4.36 ± 3.59</td>
<td>19.0 ± 29.4</td>
<td>-14.0</td>
<td>-26.2, -1.71</td>
<td>0.026</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>5.95 ± 3.44</td>
<td>5.56 ± 2.81</td>
<td>0.52</td>
<td>-1.36, 2.40</td>
<td>0.580</td>
</tr>
<tr>
<td>Glucose homeostasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (uU/ml)</td>
<td>8.57 ± 4.89</td>
<td>8.92 ± 5.49</td>
<td>-0.54</td>
<td>-3.65, 2.57</td>
<td>0.731</td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>61.1 ± 32.1</td>
<td>53.1 ± 29.0</td>
<td>1.64</td>
<td>-15.8, 19.1</td>
<td>0.851</td>
</tr>
<tr>
<td>IGF-II (ng/ml)</td>
<td>327 ± 128</td>
<td>284 ± 122</td>
<td>24</td>
<td>-47, 96</td>
<td>0.497</td>
</tr>
<tr>
<td>IGFBP-1 (ng/ml)</td>
<td>34.7 ± 41.0</td>
<td>71.5 ± 80.5</td>
<td>-25.3</td>
<td>-62.0, 11.6</td>
<td>0.174</td>
</tr>
<tr>
<td>IGFBP-3 (ng/ml)</td>
<td>773 ± 236</td>
<td>760 ± 275</td>
<td>-2.3</td>
<td>-158, 153</td>
<td>0.976</td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>1.85 ± 0.52</td>
<td>1.75 ± 0.50</td>
<td>0.01</td>
<td>-0.27, 0.28</td>
<td>0.953</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>0.65 ± 0.26</td>
<td>0.59 ± 0.29</td>
<td>0.01</td>
<td>-0.15, 0.16</td>
<td>0.941</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>0.78 ± 0.26</td>
<td>0.72 ± 0.28</td>
<td>0.01</td>
<td>-0.15, 0.16</td>
<td>0.925</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.47 ± 0.25</td>
<td>0.51 ± 0.24</td>
<td>-0.02</td>
<td>-0.16, 0.11</td>
<td>0.755</td>
</tr>
</tbody>
</table>

Data are means ± SD; differences in means (MD) are provided with the associated 95% confidence intervals (CI), adjusted for stratification factors (maternal ethnicity and parity) and offspring gender.

Compliance

As previously reported, compliance with the exercise protocol was poor (Seneviratne et al. unpublished data) (Figure 7). On average, the number of cycling sessions completed was 22 from a total of 67 prescribed sessions (33%; range 0-85%). There were no reports of any major adverse effects from the intervention.

Discussion

We observed that non-weight-bearing exercise in the second half of pregnancy in overweight/obese women did not alter metabolic markers in the mother. However, this antenatal exercise intervention led to a reduction in IL-6 levels in offspring cord blood.

A recent study highlighted that maternal obesity during pregnancy could adversely affect offspring metabolism at birth, with higher levels of cord blood IL-6, leptin, and insulin in offspring of obese women compared to offspring of lean women (148). In utero exposure to elevated levels of insulin, leptin, and adipocytokines such IL-6 and TNF has been implicated in adverse programing effects on the foetus. These include alterations in appetite regulation and adipocyte metabolism, and insulin resistance, potentially contributing to higher risk of obesity and metabolic syndrome in offspring of obese mothers in later life (149, 376-378). IL-6 in particular, can stimulate leptin expression, as well as modulate hepatic and skeletal muscle insulin signalling (379). In a rodent study, pre-natal exposure to high IL-6 resulted in
decreased insulin sensitivity in male rats and increased fat depots in both male and female in adult life (376). Therefore, the lower cord blood IL-6 level observed in the offspring of the intervention group is a promising sign. We speculate that these lower IL-6 levels could be associated with a lower future risk of obesity and metabolic complications in the offspring of obese mothers who exercised during pregnancy.

The exact mechanisms underlying the reduction in cord blood IL-6 concentrations with exercise are uncertain. In adult life, circulating IL-6 levels are increased in obese subjects, and are associated with increased insulin resistance (380). However, the offspring in the exercise group were not leaner than controls (Seneviratne et al., unpublished data, Chapter 5), so that changes in adiposity cannot account for the reduced cord IL-6 levels. In addition to secretion by adipose tissue, the other potential source of IL-6 in the foetal circulation is placental inflammation (381, 382). In obese women, there is an increased inflammatory response suggestive of chronic villitis in the placenta, with accumulation of macrophages and increased production of pro-inflammatory mediators, including IL-6 (360). Further, there is some evidence of trans-placental transfer of IL-6 to the foetal circulation (383). Therefore, we speculate that lower foetal cord IL-6 levels in offspring of overweight/obese mothers who exercised may indicate a reduction in placental inflammation. However, this could not be confirmed by histological examination of the placenta, since placental sampling was not performed in this study.

In post hoc sex-specific analyses, male offspring in the intervention group displayed lower cord blood IGFBP-1 levels. In both children and adults, obesity is associated with decreased IGFBP-1 (384, 385). Thus, the lower IGFBP-1 levels were consistent with the increased fat mass observed in male offspring in the intervention arm compared to male controls (Seneviratne et al. unpublished data). The implications of these findings for long-term health are unclear. Our findings nonetheless add to the body of evidence showing sex-specific effects in association with alterations in the early life environment (386, 387).

Increased insulin resistance, inflammatory up-regulation and metabolic dysregulation are seen in overweight obese women in advanced pregnancy (58, 147, 148). However, we did not observe any alterations in maternal metabolic markers with the antenatal exercise intervention. These findings are consistent with those from another recent trial in obese pregnant women, which found no alteration in maternal fasting insulin, glucose, triglycerides, cholesterol or leptin levels following an antenatal exercise intervention (273). Previous research by our group (using a similar exercise intervention but in leaner pregnant women) also failed to show
any effects on maternal insulin resistance or maternal IGF axis, although an increase in maternal leptin levels was observed in mothers who exercised (16, 388). A recent observational study exploring the effects of maternal physical activity during pregnancy (measured by accelerometers) also failed to show any impact of moderate to vigorous activity on maternal insulin resistance IGF-I, IGFBP-3, or leptin levels (389).

Despite these negative findings, there is some evidence that antenatal exercise can alter the maternal metabolic milieu. A recent review suggested that increased physical activity could lower maternal total cholesterol, triglyceride and TNF-α levels in pregnancy (373). Exercise also caused a transient reduction in TNF-α and leptin levels in women who exercised at least four times a week during pregnancy (390). However, when these women stopped exercising, concentrations of both parameters rose at rates comparable to those in the control group (390). Further, exercise-induced changes in IGF-I and IGFBP-1 levels can be transient and disappear within a week following exercise cessation (391).

The main limitation in this study was the poor compliance with the prescribed exercise protocol shown by the women in the intervention group. This might have possibly masked some findings. Of note, there was a marked reduction in compliance during the last weeks of the intervention, prior to metabolic assessment (Seneviratne et al., unpublished data, Figure 7), which could have contributed to the negative findings in maternal and offspring metabolic markers. Our previous study showed that leaner nulliparous pregnant women had much higher compliance (80%) with the same intervention (16), which illustrates the challenges to motivate overweight and obese women to exercise during pregnancy.

In conclusion, an antenatal exercise intervention commencing in mid gestation did not alter the maternal metabolic milieu of overweight and obese pregnant women. This could have reflected low exercise compliance in advanced pregnancy, when metabolic testing was conducted. However, there were changes in metabolic markers in the offspring, with lower cord blood IL-6 levels in the intervention arm, as well as lower IGFBP-1 levels in male offspring compared to controls. These results suggest that maternal antenatal exercise alters the metabolic milieu in the offspring, and may possibly alter long-term health outcomes. Further studies are required to confirm these results, and follow-up of these offspring are important to determine whether exercise in these women is associated with long-term effects (2).
Chapter 7. Discussion and Conclusions

7.1. Summary of findings

Main trial outcomes

The main aim of this research was to determine if overweight/obese pregnant women could improve offspring and maternal health by participating in an antenatal exercise intervention. Specifically we hypothesized that the antenatal exercise intervention would lead to a reduction in offspring birth weight and neonatal adiposity, potentially indicating improved long term health. However, the trial results did not show lower birth weight or adiposity in offspring in the intervention group, refuting this hypothesis. Extremes of birth weight and perinatal complication rates were also similar between groups. Further, there was no reduction in cord insulin and leptin with the intervention. Thus overall, there was no indication that the intervention was successful in reducing foetal programming of obesity.

The only positive findings on offspring health were higher neonatal bone mass and lower cord blood IL-6 levels in offspring in the exercise group. Although not main trial outcomes, these factors could still potentially benefit long term offspring health. Inflammatory adipocytokines including IL-6 can exert an inhibitory effect on bone formation (3). Therefore the higher bone mass seen in offspring in the exercise group could have resulted from lower IL-6 levels in the foetal circulation. Further, increased bone formation in early life could be beneficial in reducing future osteoporosis (3). In animal models, pre-natal exposure to high IL-6 levels causes decreased insulin sensitivity in male offspring and increased adiposity in both male and female offspring in adult life (376). Therefore, it is possible that lower cord blood IL-6 levels seen in offspring in the intervention arm could be associated with improved long term health. In view of the limited data available in this area, follow up will be important to determine if these observed changes lead to clinically significant long term effects.

When considering maternal health, despite an improvement in maternal fitness following the intervention, we did not find any short term benefits on pregnancy weight gain, pregnancy outcomes, body composition or metabolic markers in the mother. However, if the intervention results in continuation of exercise and maintenance of fitness in participants in the exercise group, it could benefit long term health (344, 345, 392).
Therefore a home-based non-weight bearing antenatal exercise programme commencing in mid gestation in overweight and obese women did not improve short term health outcomes in both mother and offspring. Secondary changes observed in mothers and offspring following the intervention including higher maternal fitness, higher offspring bone mass and lower IL-6 in the foetal circulation at birth could potentially signify long term benefits, but will need exploration and confirmation by follow up studies.

**Compliance with the exercise intervention**

Objective monitoring of exercise compliance in intervention participants throughout the intervention period using heart rate monitors enabled reliable assessment of the amount of exercise actually performed. Overall compliance with exercise intervention was low (mean 33%, range 0-85 %), and decreased with advancing gestation. This could potentially have reduced the magnitude of change from the intervention on outcome measures, and contributed to a lack of statistical significant differences between groups. Further, decline in exercise volume during the latter stage of pregnancy could have influenced trial results further. Foetal weight and adiposity show greatest increase during advanced pregnancy, with adiposity increasing exponentially from 30 weeks of gestation (312, 313). Decline in exercise during this period could therefore have accounted for a lack of difference in adiposity between groups. Further, lowering of exercise prior to maternal metabolic testing could also have accounted for the lack of demonstrable effects, as changes in some metabolic markers can disappear within weeks of reducing exercise (390, 391). When considering the effects of varying compliance on maternal health outcomes, exercise compliance showed positive associations with adjusted post-intervention fitness, physical quality of life and postnatal adiposity, suggesting improvement in these outcomes with higher exercise compliance.

Additionally, low exercise compliance could potentially explain the difference in results between the present study, and a similar trial previously conducted by our research group, upon which this study was based (16). In the previous study involving leaner nulliparous women, exercise compliance was high (80%) up to 36 weeks of gestation, and offspring in the intervention group had reduced birth weight, accompanied by reduced cord blood IGF-I and II levels (16). An observational study recently reported that increased maternal physical activity in late pregnancy was associated with lower neonatal adiposity, but no association was found for mid pregnancy maternal physical activity (290). These findings imply that antenatal
Discussion and Conclusions

exercise may only reduce birth weight and adiposity if exercise is continued during advanced pregnancy, which did not happen in the present study.

Further, engaging in a lower amount of exercise than prescribed, and lowering of compliance midway through the intervention (Figure 7) could even have led to changes completely opposite to that hypothesized in some intervention offspring, depending on the individual pattern of maternal exercise. As discussed in two previous reviews, maternal exercise can influence foetal growth and body composition in opposing ways, depending on the timing, amount, intensity, and changes in the pattern of exercise performed (208, 281, 291). This may partially explain why male offspring in the intervention group had higher adiposity compared to controls.

Overall, objective monitoring of exercise enabled the actual pattern of exercise implemented by the intervention to be accurately described and appraised against observed outcomes. The present findings reinforce the importance of objective compliance assessment in trials of this nature.

Gender-specific changes in offspring body composition

Gender differences in foetal developmental programming effects are recognised in both humans and animal models (354-356). Further, there is evidence of gender specificity in foetal programming effects from both maternal obesity, and antenatal interventions (350, 355, 357). The mechanisms underlying these differential effects are yet unclear (354, 356). However, male offspring appear to be more susceptible to maternal antenatal exercise effects compared to female offspring (355, 393). In the previous antenatal exercise study using similar methodology, male offspring showed greater susceptibility to change with maternal antenatal exercise, showing greater reduction in birth weight than female offspring (394). This was the rationale for conducting gender based sub-analysis for offspring outcomes (birth weight, body composition and cord blood metabolic markers) in the present study.

In the gender-specific subgroup analysis, we found that male offspring in the exercise group had higher adiposity (fat mass, percentage body fat and fat mass index), and lower cord blood IGFBP-1. Conversely, female offspring in the intervention group only showed higher bone mass. Differing exercise compliance was unlikely to have led to this effect, as exercise compliance was similar in participants giving birth to male and female offspring. A study in rats similarly showed that moderate maternal exercise during pregnancy led to lasting gender-
specific changes in offspring body composition, with an increase in adiposity in male but not female offspring (353). Further, this change was observed in mature male offspring, indicating a persistent effect, although the underlying mechanism was not apparent (353).

It is unclear why maternal exercise led to increased fat mass in male offspring and increased bone mass in female offspring in the present study. There are complex associations between adipose and bone tissue formation, with leptin playing a key role (395, 396). Moreover, adipocytes and osteoblasts arise from a common precursor cell, and this differentiation, can be influenced by hormonal and environmental factors (397). Increased male adiposity could either have been influenced by, or led to reduced cord blood IGFBP-1 (384, 385, 398-402). However, further research is needed to confirm these findings and clarify the mechanisms underlying these gender specific alterations observed with maternal exercise.

Gender specific effects on offspring outcomes by maternal antenatal exercise or lifestyle interventions have not received much attention in clinical studies. This is an important area of research that needs to be explored by future clinical trials. The post hoc gender-based findings from this study highlight the importance of exploring changes in offspring outcomes according to gender, rather than just controlling for this, especially in the field of developmental programming (354).
7.2. Implications of findings

Although antenatal exercise is proposed to improve maternal and offspring health (12), we did not find evidence of any improvement in pregnancy outcomes, with this 16 week antenatal exercise intervention commencing in mid pregnancy. Further, there is no evidence from previous trials in overweight and obese women to indicate that antenatal exercise per se could improve offspring outcomes (13, 15, 261, 287). While the recently concluded LIMIT study, one of the largest antenatal lifestyle intervention trials in overweight and obese women to date, reported a reduction in high birth weight and improvement in some perinatal outcomes (258, 289), it is not possible to discern whether changes in dietary habits or physical activity following the intervention led to this improvement (403). Further, the authors postulate that dietary change may have played a key role (404). Therefore benefits from maternal antenatal exercise on offspring of overweight and obese women remain unproven.

It is important to bear in mind that low compliance with exercise, especially in advanced pregnancy, can be a key factor why no benefits from antenatal exercise on maternal or offspring health have been demonstrated in overweight and obese women. However, it remains unclear what measures will make it feasible for this group of women to continue exercising into latter stages of pregnancy, where potentially maximal offspring benefits can be achieved. Our trial participants were volunteers, making them more likely to be motivated to exercise, compared to the general population. Despite this, average compliance with prescribed sessions was less than 50%. It is noteworthy however, that there was objective evidence of improvement in fitness even at this level.

Low exercise compliance, as seen this study, has been a problem common to many lifestyle intervention trials involving overweight and obese pregnant women (260, 262, 363). In view of this, additional strategies to improve exercise compliance in pregnancy should be considered. We used a home based antenatal exercise intervention to increase accessibility, minimise disruption to daily routine, and increase acceptability to pregnant overweight/obese participants, who may dislike exercising in groups (2, 224, 363). We also hoped that using a non-weight bearing type of exercise would permit continuation of exercise up to latter stages of pregnancy, regardless of increasing body weight. However, exercise compliance reduced with advancing pregnancy in the third trimester. In the previous study in leaner nulliparous women, decline in exercise compliance was observed at a later stage from 35-36 weeks of pregnancy. The reasons given for low compliance by participants in the present study included tiredness and pelvic discomfort with increase in size of baby, as pregnancy advanced. This is
an important consideration, given that overweight and obese women have heavier babies. It is possible use of other types of non-weight-bearing exercise such as water aerobics might help better support the weight of the baby and improve exercise compliance in advanced gestation. However, two previous trials employing this method found no benefit on offspring outcomes, and also reported problems with compliance (405, 406).

In the present study, women of Pacific Island ethnicity showed lowest exercise compliance. This is an important consideration, given the higher prevalence of obesity, and higher risk of offspring obesity within this community (64, 407). Cultural reasons could have contributed to low exercise compliance, as activities involving the whole family within community settings are commonplace, rather than solitary home-based activity in the Pacific community (408). Previous lifestyle intervention studies for obese and diabetic participants from these communities have successfully utilised community based exercise programmes (408, 409). Therefore, feasibility of group exercise with involvement of other members of the family/community in community settings could be considered in future studies involving this group of pregnant women.

The other important implication arising from study findings is the gender specific nature of effects on offspring following maternal exercise. Definite conclusions cannot be based solely on the post-hoc gender specific analysis from the present study. However, these findings, along with observations from others, indicate that offspring gender may well play a role in determining the effects of maternal antenatal interventions on foetal growth, body composition and metabolism (350, 355, 357). It is noteworthy that male offspring in the exercise group in the present study showed increased neonatal adiposity, and a similar effect has been noted in male offspring in later life by animal research (353). This raises an important question whether commencing a moderate intensity exercise intervention in mid–gestation could potentially be harmful to long term offspring health, specifically for male offspring. Due to paucity of literature in this research area, this question can only be answered by following up the present study cohort.
7.3. Generalizability of results

The present trial was open to overweight/obese pregnant women of any ethnicity and parity excluding those at extremes of age, multiple pregnancy or smoking during current pregnancy (factors which can substantially affect birth weight) and contraindications to antenatal exercise. Therefore, these study findings are applicable to a majority of healthy pregnant overweight or obese women. Baseline data indicated that participants in both groups came from a similarly wide range of socio-economic and cultural back groups, increasing generalizability of results to the community. However, as effects of antenatal exercise on offspring outcomes differ according to timing, volume and intensity of exercise, these study findings pertain to low volume moderate intensity non-weight bearing exercise from mid-gestation.

Further, study outcomes on biological/physiological factors such as maternal fitness, anthropometry and metabolic markers are likely to be generalizable to other populations. Recent findings of the New born Cross-Sectional Study of the INTERGROWTH-21st Project’ indicate than new born anthropometry is similar across diverse populations, where mothers are healthy and well-nourished (410). However health care related outcomes such as delivery complications can be influenced by standard clinical practice within different settings (410). Similarly, acceptability and compliance with antenatal exercise can be influenced by cultural and social beliefs (233). Therefore applicability of results to other settings will need to be interpreted within these contexts. Further, as final trial participants were volunteers, there could be a bias towards women motivated or interested in a healthy lifestyle in pregnancy in this study.
7.4. Study strengths

Study design

A main strength of this study was the study design being a parallel arm randomised controlled trial, providing the best level of evidence possible from a single study. Further, the trial was designed and reported in accordance to the CONSORT (Consolidated Standards of Reporting Trials) guidelines in keeping with internationally endorsed standards (305). The study was registered prospectively with a clinical trial registry and the study protocol was published at an early stage of the trial (2), ensuring consistency and transparency of study methods from the start of the study. The primary trial end point was defined as birth weight and sample size calculation done accordingly.

Recruitment from the community

Trial participants were recruited from the community using advertisements and referrals from maternity carers within the region, rather than limiting participation to pregnant women attending selected health care institutions. Recruitment was open to eligible women of any ethnicity and parity and utilising any type of maternity care within the three district health boards in Auckland region, including private or state funded care. Exclusion criteria were limited to factors which could substantially influence/confound birth weight (smoking in pregnancy, multiple pregnancy, extremes of maternal age below 18 years or above 40 years), or prevent implementation of the intervention (contraindications to antenatal exercise as stated by the American College of Obstetricians and Gynaecologists ) (215). These factors helped increase generalizability of study results to the community.

Randomisation of participants to intervention and control arms

Standard randomisation techniques were employed to allocate participants to intervention or control group. Proper randomisation enables both known and unknown prognostic factors to be balanced between randomised groups (305). We used an unpredictable allocation sequence which was concealed from the recruiting investigator throughout the trial, to minimise selection bias at trial entry. Additionally the use of stratified block sampling for maternal ethnicity and parity ensured similar representation between the two groups. This was
important as Auckland has a multi-ethnic community, and birth weight (primary trial outcome) varies substantially according to maternal ethnicity and parity (411, 412).

**Home based exercise intervention**

A home-based approach was used to increase exercise compliance, providing participants the opportunity to exercise at times most convenient to them, with minimal disruption to daily routine. This approach addressed factors known to impair compliance in pregnancy, such as lower acceptability of exercising in groups, difficulty in traveling to exercise sessions at specified times, and overlapping work and childcare commitments (262, 363). Participants in the present study appreciated the ease this provided. Further some women also reported using the opportunity to exercise during times of the day, when individual pregnancy symptoms (such as nausea or tiredness) were minimal. However, exercise compliance declined with advancing pregnancy mainly due to physical discomfort associated with advancing gestation.

**Objective monitoring of exercise compliance**

The importance of objective measurement of exercise compliance has been previously highlighted (2, 251). This study is among a few antenatal trials which have measured exercise compliance objectively (16, 307). While the use of a home based intervention meant that constant supervision was not possible, the use of heart rate monitors enabled objective evaluation of the number of sessions completed, as well as duration and intensity of exercise throughout the intervention period enabling accurate quantification of the actual amount of exercise undertaken. This also enabled sensitivity analysis according to exercise compliance within the intervention group.

**Monitoring diet and physical activity**

Many lifestyle intervention trials in overweight and obese women have incorporated both dietary and physical activity interventions (256, 258, 307, 339). In this study, we used only an exercise intervention, to discern the effects of exercise *per se* on outcomes. Therefore, no dietary advice or counselling was provided outside of routine antenatal care, and neither was
caloric restriction emphasized in the study. However, there could potentially be indirect effects from exercise on routine physical activity, appetite and dietary intake (413). Therefore we assessed dietary intake and routine physical activity between intervention and control groups not only at baseline, but also midway through the intervention. Group comparisons ensured that dietary intake and habitual physical activity were similar between groups at both time points (Appendices 1 & 2), and did not exert confounding effects on outcomes.

**Body composition assessments**

Although a number of studies have assessed the effect of exercise on birth weight and pregnancy outcomes, effects on maternal and neonatal body composition have received limited attention (15, 55). A few studies have reported on maternal or neonatal body composition using indirect anthropometry based measures (14, 289), which are less accurate. (20, 321, 323, 414). In this study we used whole body DXA scanning, which is safe and reliable after delivery, to determine offspring as well as maternal body composition, enabling differentiation between fat, lean and bone mass (316, 317). Use of DXA scanning provides an additional benefit, enabling comparison of body composition outcomes with a previous study, as discussed below (2, 16).

**Metabolic assays**

In this study, we performed concurrent assessment of metabolic markers in mothers and offspring as well as clinical outcomes. The metabolic milieu is implicated in the adverse foetal programming effects with maternal obesity, as well as foetal overgrowth (6, 10, 148). Therefore it was important to assess for changes in the metabolic milieu as well as early life anthropometric and body composition outcomes in the offspring. This allows for exploration of possible mechanistic pathways by which antenatal exercise could have influenced clinical outcomes, as discussed in the next section.
Data analysis

Primary data analysis was conducted as pre-specified on an intention-to-treat basis, including primary outcome data on 99% of randomised participants, and maintaining original group assignment irrespective of adherence to the protocol, as is recommended (305). Group comparisons for primary and secondary endpoints were done using analysis of covariance regression models adjusting for pre-specified factors, and both effect size and its precision (95% CI) reported, in keeping with standard protocol (305).
7.5. Study limitations

Sample size

A sample size of 100 participants (50 participants per group) was anticipated based on initial sample size calculation. We targeted a recruitment rate of 2 participants per week, enabling the desired sample size to be reached within a 12-month period. However, there were difficulties in maintaining this recruitment rate. Although the recruitment period was extended by 2 months, further extension was limited by funding restrictions. Therefore only 75 participants were recruited in total. However, we achieved a high participant retention rate. The initial sample size was estimated enabling 80% power to detect a difference in birth weight of 250 g or more between groups, maintaining a significance level of 0.05. With the final sample size achieved (37 per group), a difference in birth weight of 280 g or more between groups was needed to achieve significance at the same level. However, the small difference in birth weight observed between groups suggests low likelihood that the primary outcome would have achieved statistical significance between groups, even with the initial sample size. Therefore, rejection of the hypothesis that antenatal exercise would alter birth weight appears reasonable, under these circumstances.

Exercise compliance

Although we utilised several measure to increase exercise compliance, Physical discomforts associated with increasing foetal size and weight gain prevented many women from continuing exercise into the third trimester. Nevertheless, the intervention group participated in some exercise, and demonstrated an increase in fitness level following the intervention, indicating that a difference between groups was established, although it did not translate to differences in clinical outcomes.

Lack of blinding

Due to the nature of the intervention and limited staff resources, it was not possible to blind participants or outcome assessor to group allocation, after randomisation. However all baseline assessments were completed before revealing group allocation, and most outcomes were objective measures, minimising any undue effects from lack of blinding.
Multiple outcomes

In addition to the primary outcome, we assessed a range of secondary outcomes related to maternal and offspring health. These outcomes were pre-specified in the study protocol, and there were several reasons to include multiple outcomes. This is a relatively new area of research with limited data, and lack of definite consensus as to which offspring parameters best indicate improved long term health (55, 208). Further, we wanted to examine the effectiveness of the intervention on improving maternal health and metabolic markers in overweight obese pregnant women which in turn, could also be mediators of improved offspring health. These are recognised reasons leading to assessment of multiple outcomes in clinical trials (415). As pre-specified in the protocol, we conducted separate testing of each individual outcome, without adjusting for multiple testing, which is a commonly used approach (2, 415). This approach however, increases the likelihood of obtaining significant results due to chance (type-I error) (415).

Post hoc exploratory analysis

In addition to the pre-specified primary analysis, additional (gender based) subgroup analyses of offspring outcomes and sensitivity analyses of maternal outcomes (based on exercise compliance in intervention group) were performed. Subgroup analysis is useful when there are important differences in pathophysiology that might influence the effects of the intervention (416). Evidence of gender specificity in foetal programming effects from maternal obesity and antenatal interventions therefore, justifies this decision (350, 355, 357). However, the post hoc nature of the subgroup analysis reduces the acceptability of results, compared to pre-specified analysis (305). While observations from post hoc sub group analyses are not always invalid, they are generally under-powered and considered reliable only after replication by other studies, irrespective of plausibility or significance (416-418). Sensitivity analysis is useful to explore the effects on trial results, by protocol deviations, such as varying levels of compliance with the intervention (418). Although pre-specification of sensitivity analysis is preferred it is recognised that issues relevant for sensitivity analysis cannot always be pre-specified and are often identified following initial data analysis, when the individual characteristics of the study are identified (418).
7.6. Directions for further research

In utero growth, body composition and metabolism of offspring of overweight and obese women and the impact of antenatal interventions on these measures are areas of research with limited data (6, 11). It would be pertinent therefore, to explore the data generated from this trial further, to identify associations between offspring growth, body composition and metabolic markers, as well as moderators and mediators of antenatal exercise on offspring outcomes (419). Identification of moderators would help establish on whom and under what circumstances the intervention led to different effects, while mediators would determine how the intervention instituted these effects (419). Such analyses are recommended following primary analysis of randomised controlled trials (419). In this study, initial sensitivity analysis indicated that exercise compliance and offspring gender appeared to be moderating the effects of maternal antenatal exercise on maternal and offspring outcomes respectively. Therefore further analysis is anticipated, in collaboration with the department of biostatistics, to determine potential moderating and mediating factors of antenatal exercise on outcomes, using an analytic framework described by Kraemer et. al. (419).

While gender-specific effects on offspring health and developmental programming, is well described in animal models, it has hereto received limited attention in human studies (367). In view of the gender-specific changes in offspring body composition and metabolic markers observed in this study, we suggest that future antenatal intervention trials should include pre-planned gender-specific offspring outcome analysis. Meta-analysis of offspring data from antenatal trials based on offspring gender could also be helpful to identify gender specific programming and other health effects on the offspring.

Further, there is a scarcity of studies comparing the effects of antenatal exercise on offspring and maternal outcomes between normal weight and overweight/obese women. However there are substantial biological and behavioural differences between these two groups of women, which can potentially moderate the effects of antenatal exercise, including differences in placental function, metabolic milieu and physical activity patterns during pregnancy (147, 310, 420). Therefore, it is planned to combine data from the current study and a previous study (in leaner nulliparous women) which involved similar trial methodology (16), and determine the impact of antenatal exercise for similarly assessed outcomes (birth weight, neonatal body composition, maternal fitness, weight gain and post-natal body composition), according to maternal weight status ( normal weight vs overweight / obese). Sub-analysis of offspring outcomes (according to gender) is more acceptable on pooled trial data, and is planned (416).
Perhaps most importantly, a follow up study of this mother-offspring cohort is planned (2). This trial has helped establish a mother-offspring cohort with extensive early life data including socio-demographic and pregnancy data, maternal diet and physical activity during pregnancy, early life offspring anthropometry and body composition, and metabolic markers. This study will hopefully serve as a starting point to facilitate follow up studies to establish if lasting changes are instituted on offspring and maternal health with antenatal exercise. This will help bridge the current research gap on effects of antenatal exercise in overweight and obese women on long term health offspring and maternal health (6, 12, 200, 208).
Appendices

Appendix 1

Coefficient of variability (CV) values for assays performed using magnetic bead-based multianalyte panels

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Inter assay % CV</th>
<th>Intra assay % CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>6.2</td>
<td>2.6</td>
</tr>
<tr>
<td>IL-6</td>
<td>4.6</td>
<td>2.9</td>
</tr>
<tr>
<td>TNF-α</td>
<td>8.0</td>
<td>5.1</td>
</tr>
<tr>
<td>IGF-I</td>
<td>15.5</td>
<td>2.9</td>
</tr>
<tr>
<td>IGF-II</td>
<td>16.0</td>
<td>7.6</td>
</tr>
<tr>
<td>IGFBP-1</td>
<td>15.6</td>
<td>3.7</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>16.8</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Appendix 2

Coefficient of variability (CV) values for assays performed using auto-analysers

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Inter-run % CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>2.3</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>3.9</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.4</td>
</tr>
<tr>
<td>HDL-C</td>
<td>2.9</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.6</td>
</tr>
<tr>
<td>SHBG</td>
<td>4.4</td>
</tr>
<tr>
<td>Insulin</td>
<td>2.5</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Appendix 3 – Ethics approval

Health and Disability Ethics Committees
Ministry of Health
1 the Terrace
PO Box 5013
Wellington
6011
0800 4 ETHICS
hdecs@moh.govt.nz

16 October 2012

Dr Paul Hofman
Liggins Institute, University of Auckland, Private Bag 92019, Auckland Mail Centre
Auckland mail centre
Private Bag 92019
Auckland 1142

Dear Dr Hofman

Re: Ethics ref: 12/NTB/24
Study title: Can lifestyle changes during pregnancy improve pregnancy outcomes and protect offspring from the effects of an obesogenic environment

I am pleased to advise that this application has been approved by the Northern B Health and Disability Ethics Committee. This decision was made through the HDEC-Expedited Review pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study’s sponsor, to ensure that these conditions are met. No further review by the Northern B Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at any locality in New Zealand, all relevant regulatory approvals must be obtained.

2. Before the study commences at any locality in New Zealand, it must be registered in a WHO-approved clinical trials registry (such as the Australia New Zealand Clinical Trials Registry, www.anzctr.org.au).

3. Before the study commences at a given locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

After HDEC review

Please refer to the Standard Operating Procedures for Health and Disability Ethics Committees (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.
Participant access to ACC

The Northern B Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don’t hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

[Signature]

Raevyn Sporle
Charperson
Northern B Health and Disability Ethics Committee

End: appendix A: documents submitted
appendix B: statement of compliance and list of members
References


64. Ministry of Health. The Health of New Zealand Adults 2011/12: Key findings of the New Zealand Health Survey. Wellington 2012.


The Impact of Antenatal Exercise in Overweight and Obese Women on Maternal and Offspring Health


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