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## Maternal Physical Activity and Cardiorespiratory Fitness During Pregnancy and its Relation to Infant Size

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MATERNAL PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS  
DURING PREGNANCY AND ITS RELATION TO INFANT SIZE

by

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2017

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## DEDICATION

To the health of future pregnant women and their offspring.

## ACKNOWLEDGEMENTS

My dissertation would not have been possible without the support of several individuals. I would first like to thank my mentor, Dr. Pate and my committee members Dr. Sara Wilcox, Dr. Xuemei Sui and Dr. Jihong Liu. I would also like to thank Dr. Edward Archer and Dr. Andrew Ortaglia for their intellectual and statistical support through the development of this project and their superior collegueship. Lastly, a special acknowledgement to my family and friends whose love, encouragement and support undoubtedly aided in the success of this academic achievement.

## ABSTRACT

Recent evidence indicates that U.S.-born infants are larger today compared to 20 years ago. A strong determinant of neonatal size is maternal body mass, where larger mothers deliver larger infants. Consistent evidence indicates that higher levels of maternal physical activity (PA) during pregnancy reduce the risk of delivering a larger infant. However, this protective effect has only been demonstrated in normal weight pregnant women. Little is known about the relationship between maternal PA and neonatal size in overweight or obese pregnant women. Moreover, no studies have examined the association between maternal cardiorespiratory fitness (CRF), an indicator of habitual PA, on infant size in this pregnant subpopulation. Thus, the overall purpose of this dissertation was to determine if maternal PA moderates the association between maternal body mass and infant size and whether maternal PA and/or CRF are associated with neonatal size in overweight or obese pregnant women.

In study one, logistic regression analyses were performed to evaluate the moderating roles of maternal PA in the preconception and prenatal periods on the association between maternal body mass index (BMI) and the risk of delivering a macrosomic infant. Maternal BMI and physical activity served as the main predictor variables. Regression models were adjusted for maternal age and race/ethnicity, gestational age and weight gain, smoking and alcohol use, and infant sex. Overweight or obese pregnant women had increased odds of

delivering a macrosomic infant (OR = 1.69,  $p < 0.0001$ ; OR = 1.67,  $p = 0.003$ ). Neither maternal PA in the preconception nor prenatal periods modified the association between maternal BMI and the risk of delivering a macrosomic neonate (OR=0.98,  $p=0.34$ ; OR=1.00,  $p=0.13$ , respectively), after adjusting for covariates. The present study does not support the hypothesis that maternal PA prior to or during pregnancy alters the relationship between maternal BMI and infant size.

In study two, multiple linear regression models were constructed to determine the independent and joint associations of maternal PA and CRF with infant birthweight. Maternal PA and CRF were the main predictors and regression models were adjusted for gestational age, maternal age and weight gain, and group allocation. After adjusting for covariates, multiple linear regression analyses showed that maternal PA ( $\text{steps} \cdot \text{day}^{-1} \cdot \text{month}^{-1}$ ) ( $\beta = 0.03 \text{ g}$ , 95% CI: -0.03, 0.08g) and CRF ( $\text{ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) ( $\beta = -8.83 \text{ g}$ , 95%CI: -42.2, 24.5 g) were not independently nor jointly ( $\beta = 0.006 \text{ g}$ , 95%CI: -0.005, 0.005 g) associated with offspring birthweight. Contrary to hypotheses, maternal PA and CRF during pregnancy were not related to infant birthweight in overweight or obese pregnant women.

In study three, individual trajectories for maternal PA in the prenatal period were estimated via repeated measures analyses to represent the change in PA from mid (4<sup>th</sup> month) to late (8<sup>th</sup> month) pregnancy. Multiple linear regression models were then performed to determine the association between change in prenatal PA and birthweight. Change in maternal PA was the main predictor and

regression models were adjusted for gestational age, weight gain, maternal age and group allocation. PA declined from the 4<sup>th</sup> to the 8<sup>th</sup> month of pregnancy ( $-399.73 \pm 371.38$  steps·day<sup>-1</sup>·month<sup>-1</sup>). After adjusting for covariates, multiple linear regression analyses showed that the decline in prenatal PA ( $\beta = -0.28$  g, 95%CI: -0.70, 0.25 g,  $p=0.35$ ) was not associated with birthweight. In addition, CRF ( $\beta = 0.04$  g, 95%CI: -0.06 g, 0.14 g,  $p=0.697$ ) did not exhibit a moderating effect. Maternal physical activity declined in mid-to-late pregnancy, and contrary to hypotheses, the observed decrement was found to be unrelated to infant birthweight.

Overall, the findings from these studies demonstrate that higher levels of maternal physical activity prior to and during pregnancy do not modify the relationship between maternal body mass and neonatal size. In addition, these findings indicate that maternal physical activity and cardiorespiratory fitness do not independently or jointly associate with neonatal birthweight. These studies provide information about these relationships in an understudied subpopulation and contribute to this rapidly growing area of research. Several recommendations are suggested to address the limitations of these studies including sampling strategies that will increase variability in PA and CRF levels, more rigorous and precise measures of PA and infant anthropometry and the inclusion of metabolic biomarker assessments.



## TABLE OF CONTENTS

DEDICATION.....	iii
ACKNOWLEDGEMENTS.....	iv
ABSTRACT.....	v
LIST OF TABLES.....	xi
INTRODUCTION .....	1
CHAPTER 1: MODERATING EFFECTS OF MATERNAL PHYSICAL ACTIVITY PRIOR TO AND DURING PREGNANCY ON THE RELATIONSHIP BETWEEN MATERNAL ADIPOSITY AND INFANT MACROSOMIA.....	9
ABSTRACT .....	10
INTRODUCTION.....	11
METHODS .....	13
RESULTS.....	17
DISCUSSION.....	19
REFERENCES.....	25
CHAPTER 2: ASSOCIATIONS BETWEEN MATERNAL PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS DURING PREGNANCY AND INFANT BIRTHWEIGHT.....	32
ABSTRACT .....	33
INTRODUCTION.....	34
METHODS .....	37
RESULTS.....	42
DISCUSSION.....	44

REFERENCES.....	51
CHAPTER 3: ASSOCIATION BETWEEN CHANGE IN MATERNAL PHYSICAL ACTIVITY DURING PREGNANCY AND INFANT SIZE.....	59
ABSTRACT .....	60
INTRODUCTION.....	61
METHODS .....	63
RESULTS.....	69
DISCUSSION.....	70
REFERENCES.....	77
CHAPTER 4: OVERALL DISCUSSION .....	87
CHAPTER 5: PROPOSAL .....	101
INTRODUCTION.....	102
STATEMENT OF THE PROBLEM.....	103
AIMS .....	105
SCOPE.....	106
ASSUMPTIONS .....	107
LIMITATIONS.....	108
RELEVANCE OF THE PROPOSED STUDY .....	109
REVIEW OF LITERATURE.....	109
INFANT BIRTHWEIGHT .....	109
TRENDS IN INFANT BIRTHWEIGHT .....	110
TRENDS IN MACROSOMIA AND LARGE-FOR-GESTATIONAL AGE INFANTS.....	112

MATERNAL-FETAL AND NEONATAL CONSEQUENCES TO	
MACROSOMIA .....	117
MATERNAL ENVIRONMENT AND NUTRIENT SUPPLY .....	118
NUTRIENT SUPPLY AND FETAL OVERGROWTH.....	120
MATERNAL OBESITY AND FETAL GROWTH .....	122
MATERNAL RESOURCES HYPOTHESIS .....	124
PHYSICAL ACTIVITY AND NUTRIENT SUPPLY.....	125
IMPACT OF PHYSICAL INACTIVITY ON METABOLIC CONTROL AND FETAL GROWTH.....	126
PHYSICAL ACTIVITY OR EXERCISE AND FETAL GROWTH.....	131
PHYSICAL ACTIVITY IN PREGNANCY AND FETAL GROWTH .....	132
EXERCISE IN PREGNANCY AND FETAL GROWTH.....	135
PRENATAL CARDIORESPIRATORY FITNESS AND	
FETAL GROWTH.....	147
THE MODERATING ROLE OF PRENATAL PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS .....	149
SUMMARY .....	151
STUDY 1 .....	151
STUDY 2.....	159
STUDY 3.....	167
REFERENCES.....	176

## LIST OF TABLES

Table 1.1. Maternal and infant sample characteristics, by analytic and excluded group.....	29
Table 1.2. Adjusted multiple logistic regression coefficients for the moderating effect of maternal physical activity in the preconception period on the relationship between maternal body mass index and the odds of delivering a macrosomic infant (>4,000g).....	30
Table 1.3. Adjusted multiple logistic regression coefficients for the moderating effect of maternal physical activity in the prenatal period (no. of months) on the relationship between maternal body mass index and the odds of delivering a macrosomic infant (>4,000g). ....	31
Table 2.1. Maternal and infant sample characteristics, by total and intervention group.....	55
Table 2.2. Adjusted linear regression coefficients assessing the independent association between CRF and birthweight (g) .....	56
Table 2.3. Adjusted linear regression coefficients assessing the independent association between average PA (steps/day) in pregnancy and birthweight (g) .	57
Table 2.4. Adjust linear regression coefficients assessing the joint association between average PA (steps/day) and CRF in pregnancy and birthweight (g).....	58
Table 3.1. Maternal and infant sample characteristics, by total and intervention group.....	82
Table 3.2. Maternal patterns of average physical activity (steps·day <sup>-1</sup> ) from mid-to-late pregnancy, by group .....	84
Table 3.3. Adjusted linear regression coefficients assessing the association between change in prenatal PA and infant birthweight, in grams. ....	85
Table 3.4. Adjusted linear regression coefficients assessing the modifying effect of CRF on the association between change in prenatal PA and infant birthweight, in grams .....	86

## INTRODUCTION

Compelling evidence indicates that higher levels of physical activity (PA) and cardiorespiratory fitness (CRF) are associated with numerous health benefits(4). These positive health outcomes are documented across various subpopulations(8, 21). Specifically, young adult women who participate in sufficient amounts of PA and develop healthy levels of CRF exhibit lower levels of body fat(19), and improved metabolic(10) and reproductive health(9). Moreover, research shows that pregnant women benefit from optimal levels of PA and CRF (17), with prenatal PA leading to increased perceptions of energy, and reduced feelings of fatigue(11), improved mood(16), and positive effects on gestational weight gain(13) and postpartum weight retention(14). Based on scientific evidence, women are encouraged to accumulate at least 150 minutes of moderate PA per week throughout the duration of their pregnancy(18, 20). While there are many well-documented maternal health benefits related to higher levels of PA in the prenatal period, much less is known about the effects of PA on the neonate.

Infant birthweight is a strong indicator of fetal development and well-being(24). Neonates born at either end of the birthweight distribution have increased risks of several morbidities and mortality(1, 2). While the birth of small and large neonates and their associated health outcomes are of equal public health importance, recent evidence indicates that over the past 20 years the

average birthweight of U.S.-born infants has increased(12). Consequently, these higher birthweights may lead to altered growth trajectories(25), and predispose neonates to overweight or obesity and the related adverse cardio-metabolic outcomes in childhood and adolescence(7). Importantly, a strong determinant of neonatal weight is maternal body mass index. That is, larger mothers tend to deliver larger infants(22). This is evidenced by the high rate of larger neonates among overweight or obese women(5). Considering the increasing prevalence of high body mass index among women of reproductive age(6), evaluating factors that may reduce the risk of the development of a larger neonate, especially in the overweight or obese population, is important to the long-term health of the infant.

Consistent evidence demonstrates that higher levels of maternal PA in pregnancy protects the fetus from overgrowth, thus promoting the delivery of a healthy-sized neonate(23). Unfortunately, the protective effect of maternal PA is only demonstrated among normal weight women. As such, little is known about the effects of maternal PA during pregnancy in overweight or obese pregnant women. Moreover, in normal weight and overweight or obese pregnant women, the effects of CRF, an indicator of habitual PA, on neonatal weight is unclear as studies assessing this relationship are inconsistent(3, 15) and non-existent in these subpopulations, respectively. Thus, the purpose of this dissertation project was to evaluate how maternal PA and CRF influence maternal adiposity and infant size during the prenatal period. This dissertation included three separate studies. The first study analyzed data from the National Maternal Infant Health

Survey of 1988 (NMIHS). The second and third study drew data from a previous randomized controlled exercise intervention trial(26, 27).

The aim of the first study was to determine if maternal PA in the preconception and prenatal periods modifies the association between maternal and infant weight status in a nationally representative sample of mothers delivering live-birth infants in 1988. Importantly, only one study to date has evaluated this relationship, however this study only considered the impact of maternal PA in the preconception period, failing to account for the potential influence of PA in the prenatal period. The aim of this study was to independently assess the moderating effects of maternal PA in both the preconception and prenatal periods on the association between maternal adiposity (i.e. body mass index) and infant size (i.e. birthweight, size for gestational age).

The second study determined the independent and joint associations between maternal PA and CRF and infant birthweight in a sample of overweight or obese pregnant women. Many studies evaluated the relationship between maternal PA in pregnancy and infant size. However, very few studies were conducted among overweight or obese women. Currently, no studies examined the relationship between maternal CRF and infant birthweight in this group. The aim of this study was addressed with three objectives. The first two objectives separately assessed the independent associations between maternal PA and CRF and infant birthweight. The third objective evaluated the joint association of maternal PA and CRF and infant birthweight.

The third study determined the influence of the change in maternal PA and CRF in the prenatal period and infant birthweight in a sample of overweight or obese women. Existing prospective studies evaluating the relationship between maternal physical activity and infant size primarily focused on the effects of the average level of physical activity across pregnancy or during specific trimesters on birthweight. Consequently, these studies failed to account for the naturally occurring changes in maternal physical activity. As such, the impacts of the changes in maternal physical activity across the prenatal period on infant size are largely unknown. The aim of this study was addressed with two objectives. The first objective examines the association between the change in maternal PA from mid-to-late pregnancy on infant birthweight. The second objective evaluated the potential moderating effect of maternal CRF on the association between change in maternal PA and infant birthweight.



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## CHAPTER 1

# MODERATING EFFECTS OF MATERNAL PHYSICAL ACTIVITY PRIOR TO AND DURING PREGNANCY ON THE RELATIONSHIP BETWEEN MATERNAL ADIPOSIITY AND INFANT MACROSOMIA

## **Abstract**

**Purpose:** Compelling evidence demonstrates that maternal pre-pregnancy body mass index is a significant determinant of infant size. Given the strong metabolic effects of physical activity (PA), it is unclear as to whether PA in the prenatal period may modify the association between maternal body mass and infant size. Therefore, the purpose of this study was to evaluate the modifying effect of maternal PA in the preconception and prenatal periods.

**Methods:** Data were from National Maternal and Infant Health Survey conducted in 1988. Women with singleton pregnancies, delivering term (37 to 44 weeks), live-birth infants (n=6,390). Macrosomia was defined as a birthweight greater than 4,000g. Maternal PA in the preconception and prenatal periods were self-reported by the mother. Multiple logistic regression models were performed to determine the moderating effects of maternal PA in the preconception and prenatal periods. Analyses were adjusted for maternal age, race/ethnicity, gestational age and weight gain, smoking and alcohol use, and infant sex.

**Results:** Mothers were on average 25 years of age and nearly 25% were overweight or obese. In the prenatal period, these women gained approximately 14 kg (30lbs) and delivered full-term ( $39.6 \pm 1.6$  weeks), live-birth infants weighing nearly 3300g (3.3kg; 7lbs 4 oz.). Maternal body mass was a significant, positive predictor of infant macrosomia (OR = 1.06,  $p < 0.0001$ ). After adjusting for covariates, neither maternal PA in the preconception (OR=0.98,  $p=0.34$ ) nor prenatal (OR=1.00,  $p=0.13$ ) periods were associated with offspring birthweight.

**Conclusions:** Maternal body mass was a significant, positive predictor of infant macrosomia. However, higher levels of maternal PA prior to and/or during pregnancy were unrelated to infant macrosomia or birthweight in a nationally representative sample of women delivering singleton, term infants. The use of more precise measurements of maternal PA and neonatal size are strongly recommended.

## **Introduction**

The prevalence of infant macrosomia, defined as a birthweight greater than 4,000 g, has increased in US and other developed countries. (4, 14). Macrosomic infants are predisposed to altered growth trajectories and increased risk of obesity and the associated co-morbidities later in life(8, 24). Maternal body mass is a significant predictor of macrosomia (23), where larger mothers tend to deliver larger infants. The relationship between maternal body mass and infant macrosomia is thought to be a function of the mother's overall metabolic health, which is a strong determinant of the amount of energy reaching the fetus. Thus, because mothers with greater body mass often have poorer metabolic health(11), their fetuses are often exposed to excess energy resulting in the development of a larger infant (9, 16).

Considerable scientific evidence demonstrates that participation in sufficient levels of physical activity (PA) exerts strong effects on metabolic health. Given that maternal metabolic health underlies the relationship between maternal body mass and infant birthweight, higher levels of maternal PA prior to and/or during pregnancy may be necessary to prevent the development of an overgrown

infant, especially in larger mothers. This hypothesis is supported by the rigorous evidence demonstrating the effects of PA on several non-communicable diseases (NCDs) including non-alcoholic fatty liver and cardiovascular diseases, in non-pregnant populations(6, 15). Individuals participating in higher levels of PA exhibited reduced risks of several NCDs and specifically, metabolic diseases such as type II diabetes mellitus, regardless of weight status(7). As such, it is reasonable to suggest that the beneficial effects of PA on metabolic health found in non-pregnant populations, may exist in the preconception and/or prenatal periods. If so, mothers engaging in higher levels of PA prior to and/or during pregnancy may have improved metabolic health, controlling energy supply to their fetuses, and subsequently less likely to deliver a macrosomic infant, regardless of their body mass.

Evidence regarding maternal PA as a potential modifier of the relationship between maternal body mass and infant macrosomia is limited (13). To our knowledge only one study has evaluated this relationship and found that, for overweight or obese pregnant women, physical inactivity before pregnancy increased the risk of delivering a macrosomic infant compared to active women. A limitation of that study was that the authors did not evaluate PA in the prenatal period. It is possible that higher levels of maternal PA in the preconception and/or prenatal periods may affect infant macrosomia. As such, determining the influence of maternal PA prior to and during pregnancy on infant macrosomia is important, and these findings may better inform PA guidelines for pregnant and future pregnant women. To our knowledge, no studies have evaluated the



potential moderating effects of maternal PA in the preconception and prenatal periods on infant size. Therefore, the purpose of this study is to determine if maternal PA in both the preconception and prenatal periods moderate the association between maternal body mass index and the risk of delivering a macrosomic infant.

## **Methods**

### *Study Design & Sampling*

Data for the present study were from The National Maternal Infant Health Survey (NMIHS). The NMIHS was conducted by the National Center for Health Statistics in 1988 in order to identify factors that may be related to poor pregnancy outcomes(18). The NMIHS employed a follow-back survey design and sampled U.S. women who had a live birth, fetal death or infant death in 1988. To make inferences on a nationally representative sample, the NMIHS used a complex survey design that drew stratified samples of live-births, fetal and infant deaths identified via registered birth and death certificates. Black, very low (<1500g)- and moderately low- birthweight (2500-2499g) infants were oversampled. For the purposes of this study, only singleton, live-birth infants and their mothers were included in the analyses.

### *Study Population & Data Collection*

A total of 13,417 live-birth infants were sampled. To identify factors related to poor pregnancy outcomes, mothers of these infants were mailed a 35-page questionnaire that inquired about several maternal, paternal and infant characteristics during the preconception, prenatal and postnatal periods. The

average recall period, defined as the time between delivery of the infant and the receipt of the questionnaire, was 17 months. Of the 13, 417 mothers, 74.2% (n=9954) responded to the questionnaire. Some differences in the characteristics of mothers whom responded and did not respond to the questionnaire were observed. Mothers between the ages of 20 to 39 years, who were White, married, had fewer than four children, received early prenatal care, achieved more education, and resided in the Midwest region of the U.S. were more likely to respond to the questionnaire. Mothers of low-birthweight (<2500g) infants were less likely to respond to the questionnaire.

#### *Outcome Variable: Infant Macrosomia*

Infant macrosomia was the primary outcome variable in this study. Macrosomia was defined as a birthweight greater than 4,000g. Birthweight was defined as the weight of the infant, in grams, at the time of delivery. Birthweight and gestational age data were extracted from birth certificates. Birthweights less than 300 grams or greater than 9000 grams were considered implausible(19) and excluded from the analyses.

#### *Exposure Variables*

##### *Maternal Body Mass Index*

Maternal pre-pregnancy body mass index (BMI) was calculated using the standard equation:  $BMI = weight (kg) \div height (m^2)$ . Maternal pre-pregnancy height and weight were self-reported by the mother. In all analyses, maternal BMI was treated as a continuous variable.

### *Maternal Physical Activity*

Maternal PA in the preconception and prenatal periods were examined as potential moderating variables in this study. Pre-pregnancy PA was measured using the following question: *“Did you exercise or play sports at least three times a week before you got pregnant...include brisk walking for ½ hour or more, jogging, aerobic swimming etc.?”* The response was recorded as “yes” or “no.” Prenatal PA was assessed using two separate questions. First, mothers were asked the following question: *“Did you exercise or play sports at least three times a week after you got pregnant...include brisk walking for ½ hour or more, jogging, aerobic swimming etc.?”* the response was recorded as “yes” or “no.” Mothers answering ‘yes’ to this question answered the second PA question: *“How many months of this pregnancy did you engage in exercise or play sports at least three times a week?”* In this study, for mothers answering ‘no’ to participation in PA in the prenatal period, a value of 0 was entered for the second prenatal PA question.

### *Covariate Variables: Maternal and Infant*

Several maternal and infant characteristics were considered as potential covariates. Data were extracted from the mothers’ questionnaire and infant birth certificate. Maternal demographic characteristics that were considered potential covariates were: age (in years), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic and Other). Maternal pregnancy-related factors included as possible covariates were: gestational weight gain (GWG) and parity. GWG was calculated as the difference in weight (in pounds) at the time of

delivery and prior to pregnancy. Maternal behaviors that were considered potential covariates included: smoking status and alcohol use. For these behaviors, the mothers self-reported the use of cigarettes or consumption of alcohol in the last 12 months prior to delivery. Infant characteristics that acted as possible covariates included: sex (male or female) and gestational age (weeks). For live-birth infants, gestational ages less than 22 weeks or greater than 44 weeks were considered implausible(19).

### *Analytic Sample*

Of the 9,953 mothers, 9,146 women had singleton pregnancies. Of these women, 2,052 women delivered pre-term infants (22 to 36 weeks), and 6,390 women delivered a live-birth infant between 37 and 44 weeks gestation (i.e. full-term). In addition, of the women with singleton pregnancies (n=9,146), 264 women had implausible values for either gestational age (n=248) or infant birthweight (n=16), 455 women had missing data for either gestational age (n=448) or birthweight (n=7). The final sample size for this study was 6,390 women. Differences in several maternal and infant demographics and behavioral characteristics between the analytic and excluded samples are presented in Table 1.

### *Statistical Analyses*

To determine if maternal pre-pregnancy and-or prenatal PA moderate the association between maternal BMI and infant macrosomia, we performed multiple logistic regression analyses. First, we examined the unadjusted main effects of maternal BMI on infant macrosomia. Second, we separately assessed

the unadjusted main effects of pre-pregnancy PA and prenatal PA in conjunction with maternal BMI on infant macrosomia. Third, to determine the unadjusted moderating effects of pre-pregnancy PA and prenatal PA, we entered an interaction term between pre-pregnancy PA and maternal BMI and an interaction between prenatal PA and maternal BMI, in separate models. Lastly, we entered the maternal and infant covariates sequentially.

Because the NMIHS employed a complex survey design to make inferences on a nationally representative sample, weights were generated to account for non-response and study design and were included in all statistical analyses. All statistical analyses were performed in SAS statistical software version 9.4 (Cary, North Carolina). For the multiple logistic regression, with infant macrosomia as the outcome variable, odds ratios were estimated. For the multiple linear regression analyses, with infant birthweight (in grams) as the outcome variable mean regression coefficients were estimated. An alpha level of 0.05 was used to denote statistical significance for all analyses.

## **Results**

The sample characteristics for the women included and excluded in the present analyses are documented in Table 1.1. Because the analysis was restricted to singleton, full-term pregnancies, differences in gestational age, maternal weight gain, maternal body mass index, and infant size were expected. No other meaningful significant differences were found.

For the analytic sample, mothers were, on average, 25 years of age and nearly 25% were overweight or obese. In the prenatal period, these women

gained approximately 14 kg (30lbs) and delivered full-term ( $39.6 \pm 1.6$  weeks), live-birth infants weighing nearly 3300g (3.3kg; 7lbs 4 oz.). The prevalence of infant macrosomia (9.3%) was slightly above the current U.S. prevalence estimate (8%) (14). Roughly 30% and 40% of mothers reported smoking and/or alcohol use in the 12 months prior to the birth of their child, respectively. In the *preconception* period, nearly 50% of mothers reported being active at least three times per week for at least 30 minutes. Forty-two percent of mothers reported being active at least three times per week for at least 30 minutes in the *prenatal* period. These mothers maintained this dose of PA for nearly three months ( $2.8 \pm 3.8$  months) of their pregnancy.

Preliminary analyses showed that maternal BMI was a significant positive predictor of infant size. Specifically, overweight or obese mothers had increased odds of delivering a macrosomic infant compared to normal weight mothers (OR = 1.69,  $p < 0.0001$ ; OR = 1.67,  $p = 0.0032$ , respectively). For the unadjusted *moderating effect* of maternal PA in the *preconception* period, our analyses revealed that participation in PA prior to pregnancy did not exhibit a *moderating effect* on the association between maternal BMI and the odds of delivering a macrosomic infant (OR = 0.97,  $p = 0.16$ ). Similarly, after adjusting for prenatal PA, gestational age and weight gain, maternal age and race/ethnicity, smoking and alcohol use, and infant sex, the *moderating effect* of maternal PA in the *preconception* period remained non-significant (OR=0.98,  $p = 0.34$ ) [see Table 1.2].

The unadjusted analysis for the moderating effect of maternal PA in the *prenatal* period showed that participation in PA during pregnancy significantly modified the association between maternal BMI and the odds of delivering a macrosomic infant (OR = 0.995, p=0.04). However, after controlling for preconception PA, gestational age and weight gain, maternal age and race/ethnicity, smoking and alcohol use, and infant sex, the *moderating effect* of PA in the *prenatal* period was no longer statistically significant (OR=1.00, p=0.13) [see Table 1.3].

Additional analyses were performed, using multiple linear regression, to evaluate the moderating effect of maternal PA prior to and during pregnancy on maternal BMI and infant birthweight. Similar to the logistic regression analyses, maternal BMI was a significant, positive predictor of infant birthweight ( $\beta = 14.55 \pm 1.70$  g,  $p < 0.0001$ ). Moreover, maternal engagement in PA *prior to* pregnancy did not *modify* the relationship between maternal BMI and neonatal birthweight in the unadjusted or adjusted regression models ( $\beta = -2.42 \pm 3.38$  g,  $p = 0.47$ ;  $\beta = -1.12 \pm 3.26$ ,  $p = 0.73$ , respectively). Correspondingly, maternal PA *during* pregnancy did not significantly *modify* the association between maternal BMI and infant birthweight in the unadjusted or adjusted regression models ( $\beta = -0.82 \pm 0.46$  g,  $p = 0.08$ ;  $\beta = -0.51 \pm 0.45$  g,  $p = 0.26$ , respectively).

## **Discussion**

The purpose of this study was to evaluate the moderating effect of maternal physical activity in both the preconception and prenatal periods on the relationship between maternal body mass and infant macrosomia. Consistent

with previous literature, our study found that maternal body mass was positively associated with the delivery of a macrosomic infant. However, there was no modifying effect of maternal PA in the preconception period on the association between maternal body mass and infant macrosomia. Similarly, in the prenatal period, maternal PA was not found to exert a modifying effect on this relationship. This present study was unique in that it was the first to evaluate the potential modifying effects of maternal PA both prior to and during pregnancy. Only one other study, to our knowledge, has evaluated this relationship, however that examination was restricted to the preconception period(13). Thus, this present study provides important information about the relationships between maternal PA and body mass and neonatal size.

Our observation that maternal PA in the *preconception* period does not modify the association between maternal body mass and infant macrosomia conflicts with the current literature. Only one other study has evaluated this relationship and these authors found that in overweight or obese women, low levels of maternal PA prior to pregnancy increased the risk of delivering a macrosomic neonate(13). The inconsistent findings between these studies may be consequent to non-differential misclassification as result of the measurement tool used to assess maternal PA. Both studies used a self-reported method to evaluate maternal prior to pregnancy, however, questions inquiring used varied greatly. In the Krogsgaard et al. (2013) study, women were asked to report the frequency, intensity and duration of the physical activities in which they participated in the preconception period. In the present study, women were



asked about their participation in a specific dose of PA (i.e. three times/week for 30 minutes). The specificity of the PA dose in this question may have led women to be inappropriately categorized as 'active' or 'inactive.' For example, if a woman participated in PA twice per week for 60 minutes, an equivalent dose of PA, she would have been classified as 'inactive' given she did not meet the three-day per week requirement. Consequently, this misclassification may have diluted the potential modifying effect of maternal PA, explaining our null observation(22). Thus, more open-ended questions or objective measurements of PA may provide information that more accurately reflects maternal PA behavior prior to pregnancy.

In the present study, maternal PA in the *prenatal* period exhibited no moderating effect on the relationship between maternal body mass and neonatal size. A possible explanation for this null observation is that the dose of PA these women engaged in was insufficient to impact maternal metabolic health and subsequently infant birthweight. In this study, women were considered 'active' if they participated in PA three times per week for at least 30 minutes. This amount of PA is less than the dose recommended by the United States Department of Health and Human Services and endorsed by the American Congress of Obstetricians and Gynecologists(20, 21). These entities encourage pregnant women to engage in at least 150 minutes of activity per week. In addition, it is likely that these women participated in less PA throughout the prenatal period as it is well-documented that maternal PA declines in pregnancy(10, 17). In support of this idea, women responding 'yes' to being physically active in pregnancy were

subsequently asked to report the number of months they maintained this behavior. On average, these women participated in this dose of PA for only three months of their pregnancy. This suggests that their PA declined, mostly likely in the final two trimesters, however we are unable to quantify the extent to which it decreased. Consequently, the lower dose and potential decline of maternal PA likely resulted in these women participating in levels of PA that were insufficient to impact maternal metabolic health, fetal nutrient supply and subsequently fetal growth and neonatal size. Currently, in the existing literature a dose of PA that is sufficient to regulate fetal nutrient supply and ultimately reduce the risk of infant macrosomia, has yet to be identified.

Another potential explanation for the null observation of maternal PA in the *prenatal* period as a modifier is non-differential misclassification of maternal PA behavior. The question evaluating maternal PA in the *prenatal* period was similar to the question assessing PA in the *preconception* period, as such, it suffers from the same limitations. The specificity of the dose of PA may have resulted in women being inappropriately classified as ‘active’ or ‘inactive.’ In addition to this, the extensive recall period may have also contributed to the misclassification. The average recall period, defined as the amount of time that lapsed between the delivery of the neonate and the receipt of the maternal questionnaire, was 17 months. As such, the ability of the mother to accurately recall her PA behavior during her pregnancy (or before pregnancy) may have been significantly diminished. Evidence demonstrates that there is an inverse relationship between length of the recall period and the ability of an individual to accurately recall their

behavior(2). Due to these considerable limitations of the measurement tool used to assess maternal PA, it is possible that our null observation is attributed to non-differential misclassification. As a result, the potential modifying effect of maternal PA in the prenatal period on the relationship between maternal body mass and infant size was possibly diluted(22).

This study has strengths and limitations. Foremost, this was the first study to evaluate maternal PA in the preconception and prenatal periods as a modifier of the relationship between maternal body mass and neonatal size. Second, this study was conducted using a large, diverse, nationally representative sample of women delivering singleton, full-term, live-birth infants in the United States. As such, our findings can be generalized to a large sample of women. However, the present study also has limitations. First, maternal PA and body mass were measured via self-reporting methods. This type of assessment is notorious for producing less accurate estimates of behavior compared to more objective assessments(1, 5). Consequently, the use of these imprecise and error-prone tools may have led to biased, misestimated associations(3). Second, we did not consider other potential health behaviors that have been documented to influence infant size, including maternal diet (26). Third, although infant birthweight is the most widely used metric for infant size, it has limitations. This metric is unable to capture vital details about infant size including tissue composition (i.e. fat and fat-free mass) that are key to future health risks of these neonates(8). Lastly, macrosomia is poorly defined in the current literature. The

birthweight thresholds that define macrosomia vary greatly (i.e. > 4000, > 45000, > 5000g) (12, 25). As such, it is possible that we misclassified classified infants.

In conclusion, the present study observed that maternal PA in the preconception and prenatal periods did not exhibit a modifying effect on the relationship between maternal body mass and infant size. This was the first study to evaluate this relationship and thus, provides important information about these relationships and contributes to the rapidly growing field of maternal-child health. Future studies should address the limitations of the present study. First, more precise assessments of maternal PA behavior and maternal and infant anthropometrics are necessary. Second, future researchers should include the assessment of metabolic biomarkers, such as serum glucose and lipids. These factors are posited to be the mechanisms that underlie these relationships, however are often ignored in studies. In conclusion, the findings of this study provide no evidence that higher levels of maternal PA in the preconception or prenatal periods modify the association between maternal body mass and neonatal size.

### **Conflicts of Interests**

The authors have no conflicts of interests to disclose.

### **Acknowledgements**

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**Table 1.1** Maternal and infant sample characteristics

Sample Characteristics	Analytic Group			Excluded Group		
	N	Mean	SD	N	Mean	SD
<b>Maternal <sup>a</sup></b>						
<b>Age (y)**</b>	6393	25.8	5.7	3388	25.4	6.0
<b>Race/Ethnicity (%)***</b>	6393			3388		
NH White	2745	42.9	-----	1151	34.0	-----
NH Black	2868	44.9	-----	1842	54.4	-----
Hispanic	566	8.9	-----	307	9.1	-----
Other.	214	3.4	-----	88	2.6	-----
<b>Body Mass Index (kg/m<sup>2</sup>)***</b>	6393	23.1	4.6	3388	23.0	4.9
Underweight (%)	623	9.8	-----	435	12.8	
Normal Weight (%)	4181	65.4	-----	2110	62.3	
Overweight (%)	489	17.2	-----	546	16.1	
Obese (%)	1100	7.7	-----	297	8.8	
<b>Prenatal Behaviors</b>						
Smoking <sup>†***</sup>	6393	28.4	-----	3388	33.2	-----
Drinking <sup>†</sup>	6393	38.7	-----	3388	37.8	-----
Preconception PA <sup>†***</sup>	6393	48.5	-----	3388	45.6	-----
Prenatal PA <sup>†**</sup>	6393	42.4	-----	3380	36.9	-----
Prenatal PA <sup>***</sup> (# of months)	6393	2.8	3.6	3388	2.1	3.0
<b>Infant<sup>***</sup></b>						
Gestational age	6393	39.6	1.6	2877	31.8	5.1
Gestational weight gain	6393	13.9	8.1	3388	11.1	9.3
Birthweight (g)	6390	3293.5	595.6	3384	1974.2	999.6
Macrosomia (%)	6393	9.31	-----	3388	1.6	-----
Sex (%)						
Male	6393	51.0	-----	3388	50.2	-----

Note: \*p<0.05; \*\*p<0.01 \*\*\*p<0.0001. The analytic sample was defined as women delivering full-term (37 to 44 weeks), live-birth infants in 1988. The excluded sample was defined as women delivering non-full-term infants (<37 weeks), or those with implausible gestational ages for live-births (<22 or >44 weeks). †'No' is the referent group. These values correspond to the raw data from the women sampled in the NMIHS survey, sample weights were not applied to account for the complex survey design.

**Table 1.2.** Adjusted multiple logistic regression coefficients<sup>a</sup> for the moderating effect of maternal physical activity in the preconception period on the relationship between maternal body mass index and the odds of delivering a macrosomic infant (>4,000g).

Predictors	Parameter Estimates			
	$\beta$	SE	OR	p-value
<b>Primary Exposures</b>				
BMI (kg/m <sup>2</sup> ) <sup>†</sup>	0.09	0.01	1.09	<0.0001
Preconception PA <sup>§</sup>	0.39	0.50	1.48	0.44
BMI * Preconception PA <sup>§</sup>	-0.02	0.02	0.980	0.34
<b>Covariates</b>				
Prenatal PA (no. of months)	-0.001	0.02	0.98	0.95
Gestational Age (weeks)	0.21	0.03	1.24	<0.0001
Gestational weight gain	0.05	0.01	1.06	<0.0001
Smoking*	-0.76	0.13	0.47	<0.0001
Drinking*	0.07	0.11	1.08	0.5101
Infant Sex**	0.58	0.11	1.78	<0.0001
Maternal Age	0.03	0.01	1.03	0.0013
Maternal Race/Ethnicity***				
NH Black	-0.88	0.11	0.41	<0.0001
Other	-1.30	0.39	0.27	0.0009
Hispanic	-0.27	0.18	0.77	0.13

<sup>a</sup> Referent group for the outcome variable = average-for-gestational age (AGA).

Only regression coefficients for large-for-gestational age are displayed. OR =

odds ratio. <sup>†</sup>BMI is calculated from pre-pregnancy weight and height self-

reported by the mother. <sup>§</sup> 'No' is the referent group. \* 'No' is the referent group.

\*\* 'Female' is the referent group. \*\*\*NH = Non-Hispanic, NH White is the referent

group. Sample weights were applied to account for non-response and study

design.

**Table 1.3.** Adjusted multiple logistic regression coefficients<sup>a</sup> for the moderating effect of maternal physical activity in the prenatal period (no. of months) on the relationship between maternal body mass index and the odds of delivering a macrosomic infant (>4,000g).

Predictors	Parameter Estimates			
	$\beta$	SE	OR	p-value
<b>Primary Exposures</b>				
BMI (kg/m <sup>2</sup> ) <sup>†</sup>	0.09	0.01	1.10	<0.0001
Prenatal PA	0.10	0.07	1.11	0.13
BMI * Prenatal PA	-0.004	0.003	1.00	0.13
<b>Covariates</b>				
Preconception PA <sup>§</sup>	-0.08	0.13	0.93	0.55
Gestational Age (weeks)	0.21	0.03	1.24	<0.0001
Gestational weight gain	0.05	0.01	1.06	<0.0001
Smoking*	-0.76	0.13	0.47	<0.0001
Drinking*	0.07	0.11	1.07	0.52
Infant Sex**	0.58	0.11	1.78	<0.0001
Maternal Age	0.03	0.01	1.03	0.0010
Maternal Race/Ethnicity***				
NH Black	-0.89	0.11	0.41	<0.0001
Other	-1.30	0.39	0.27	0.0010
Hispanic	-0.27	0.18	0.77	0.13

<sup>a</sup> Referent group for the outcome variable = average-for-gestational age (AGA).

Only regression coefficients for large-for-gestational age are displayed. OR = odds ratio. †BMI is calculated from pre-pregnancy weight and height self-

reported by the mother. § 'No' is the referent group. \* 'No' is the referent group.

\*\* 'Female' is the referent group. \*\*\*NH = Non-Hispanic, NH White is the referent group. Sample weights were applied to account for non-response and study design.

## CHAPTER 2

# ASSOCIATIONS BETWEEN MATERNAL PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS DURING PREGNANCY AND INFANT BIRTHWEIGHT

## **Abstract**

**Purpose:** Significant evidence demonstrates that physical activity (PA) during pregnancy reduces the risk of delivering heavier infants. However, this relationship is restricted to normal-weight pregnant women. In addition, the evidence on the impact of maternal cardiorespiratory fitness (CRF), an objective indicator of habitual PA, on offspring birthweight is equivocal. Therefore, the purpose of this study was to evaluate the relationship between maternal PA and CRF during pregnancy and offspring birthweight in a sample of overweight or obese pregnant women.

**Methods:** This study employed a prospective design using data from a randomized controlled exercise intervention trial in sedentary, overweight or obese pregnant women with a history of preeclampsia. Women with complete data (n=89) on infant birthweight, peak oxygen consumption (at 17 weeks), and daily PA measured via a pedometer (17 weeks to delivery) were eligible for analyses. Multiple linear regression models were performed to determine the independent and joint associations of PA and CRF with offspring birthweight. Gestational age, weight gain, and group allocation were considered as covariates.

**Results:** On average, participants were 32 years old, overweight/obese (BMI  $29.97 \pm 7.14 \text{ kg/m}^2$ ), unfit ( $\text{VO}_{2\text{peak}}$ :  $19.85 \pm 3.35 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), and led low active lifestyles ( $6,579.91 \pm 2379.17 \text{ steps/day}$ ). After adjusting for covariates, multiple linear regression analyses showed that maternal PA ( $\text{steps} \cdot \text{day}^{-1} \cdot \text{month}^{-1}$ ) ( $\beta = 0.03 \text{ g}$ , 95% CI: -0.03, 0.08g) and CRF ( $\text{ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) ( $\beta = -8.8 \text{ g}$ , 95%CI: -42.2,

24.5 g) were not independently nor jointly ( $\beta = 0.006\text{g}$ , 95%CI: -0.005, 0.02 g) associated with offspring birthweight.

**Conclusions:** Maternal PA and CRF during pregnancy were not related to infant birthweight in overweight or obese pregnant women with a history of preeclampsia. Our findings conflict with the inverse relationships found among normal weight women. The limited variability in maternal PA and CRF in pregnancy, likely consequent to the low active lifestyle led by these women, may explain the null findings of this study. Further research is recommended given the paucity of studies examining these relationships in overweight or obese pregnant women.

## **Introduction**

The average birthweight of US-born infants has increased in the U.S, over the past 20 years(9). Higher birthweight is associated with altered growth trajectories that predispose neonates to obesity and the associated cardio-metabolic morbidities throughout their lives (3). Intrauterine energy supply is considered the strongest predictor of fetal growth, and in excess, leads to higher infant birthweights (10). Maternal metabolic health, defined as control of circulating levels of blood sugars and lipids, is a major determinant of the energy supplied to the fetus. Any loss in metabolic control results in the delivery of increased energy supply and fetal overgrowth (5). Importantly, it is also well established that maternal body mass is strongly and positively related to offspring birth weight and adiposity (15). Specifically, overweight or obese mothers are more likely to deliver larger infants. This relationship is posited to be a function of

reduced maternal metabolic health leading to augmented fetal energy supply and subsequent higher birthweight infants. Nearly 50% of women of reproductive age are overweight or obese (4); as such, the exploration of modifiable factors enabling these women to control the amount of nutrients supplied to the fetus is critical to the health of her offspring.

Among non-pregnant populations, considerable scientific evidence demonstrates that physical activity (PA) and cardiorespiratory fitness (CRF) exhibit protective effects on several cardio-metabolic health outcomes (1). This is consequent to the improvements in metabolic health (e.g., insulin sensitivity) via adaptations to habitual PA (14). Notably, these strong effects persist in the presence of excess adiposity. This suggests that the increased prevalence of adverse cardio-metabolic health outcomes among overweight or obese persons (8) may not be a result of their excess adiposity per se, but rather their lower levels of CRF and PA. It is reasonable to suggest that this same phenomenon operates in pregnancy, whereby the lower levels of maternal PA and CRF in pregnancy, especially among the overweight or obese women, reduce metabolic health, augment energy supply, and result in a larger neonate. Collectively, this suggests that adequate levels of maternal PA and CRF may have the potential to 'normalize' the amount nutrients available to the fetus thereby promoting optimal fetal growth.

Many studies have assessed maternal PA and CRF in the prenatal period on various maternal-infant health outcomes. Several studies assessed the effects of PA on fetal growth, with a recent review of exercise intervention trials

concluding a significant protective effect of PA on birthweight (16). Yet, this finding was restricted to normal-weight pregnant women, with null effects found among their overweight or obese counterparts. The latter finding may be largely due to a small number of rigorous intervention studies implemented among this subpopulation. Conversely, fewer studies have assessed the effects of maternal CRF on offspring growth during infancy. The focus of the existing studies was on changes in maternal CRF with advancing gestation (2) and in response to exercise training (11). As such, the scientific evidence regarding the impact of CRF on birthweight is rather limited and equivocal; previous studies yielded reports of positive, negative or null findings (7, 12, 17). Importantly, no studies examining this relationship were conducted among obese pregnant women. Taken together, the impact of CRF and PA on birthweight in overweight and obese pregnant women is extremely limited, warranting further exploration.

Thus, the overall purpose of this study was to investigate the relationships between maternal physical activity and cardiorespiratory fitness in the prenatal period and infant birthweight. We addressed the purpose of this study by evaluating the independent and joint associations of physical activity and cardiorespiratory fitness on birthweight. We conducted a secondary data analysis using data from a randomized exercise intervention trial implemented in a sample of overweight or obese pregnant women.



## **Methods**

### *Study Design*

The present study employed a prospective design using data drawn from a randomized exercise comparative trial conducted between November 2001 and July 2006. Briefly, the primary purpose of the trial was to examine the effects of moderate intensity exercise during pregnancy on the incidence of preeclampsia and the pathophysiological progress of preeclampsia (e.g. oxidative stress). Secondary outcomes included maternal weight gain and birth outcomes(18).

### *Participant Eligibility & Recruitment*

Pregnant women were recruited from nine prenatal clinics under two medical care systems in Michigan. Women were eligible to participate in the exercise trial if they were: 1) less than 14 weeks gestation, 2) diagnosed with preeclampsia in a previous pregnancy, 3) had a peak oxygen consumption  $\leq 50^{\text{th}}$  percentile of women in their respective age-group, and 4) participated in a sedentary lifestyle or had a self-reported PA energy expenditure of  $< 840$  kcals per day. Exclusion criteria for the exercise trial were: 1) a diagnosis of chronic hypertension or pre-gestational diabetes, 2) presence medical or physical limitations preventing the participation in exercise, 3) physician instructions prohibiting the engagement of prenatal exercise or 4) low mental acuity or language barrier preventing effective communication with research staff.

### *Randomization and Intervention Groups*

Two hundred and ten women agreed to participate in the study and 41% (n=86) of these women did not meet the eligibility criteria. The remaining 124

eligible participants were randomly allocated to the intervention group (n= 64) or comparative group (n=60). The intervention group consisted of a walking exercise program. Participants in this group were instructed to walk for 40 minutes, five times per week at a moderate intensity (55-69% maximum heart rate). In the comparative group, participants engaged in a stretching program of equivalent frequency and duration as compared to the exercising group, however the women were instructed not to exceed a 10% increase in resting heart rate. Women also performed stretching movements via videotape. All participants wore Polar S810 heart rate monitors and wristwatch devices to validate their adherence to the exercise or stretching programs. Further details on the intervention and comparative groups can be found elsewhere (19). For the purposes of this study, the data were collapsed across both groups and group allocation was controlled for in the analyses.

*Outcome Variable: Infant Birthweight*

Infant weight was the dependent variable in this study and was expressed as birthweight in grams. Infant birthweight was defined as the weight of the neonate at the time of delivery. Data on birthweight were extracted from the mother's medical records.

*Exposure Variables: Physical Activity and Cardiorespiratory Fitness*

Daily PA was measured using a pedometer (Digiwalker SW200) attached to an elastic belt and worn on the participants' waist. The participants were instructed to wear the pedometer during waking hours and to remove them during sleep and any water-based activities (e.g., showering). Additionally, the

participants were asked to keep a log of their total daily step counts. The pedometers were distributed to the participants at 18 weeks of gestation and were retrieved at the end of pregnancy (prior to delivery). For the purposes of this study, total daily steps counts were averaged across all the available days for each participant to provide an estimate of the average daily PA (steps per day) during pregnancy.

Cardiorespiratory fitness was defined as peak oxygen consumption ( $\dot{V}O_{2\text{peak}}$ ) and estimated via a submaximal treadmill test at 17 and 28 weeks of gestation. The exercise testing followed the Cornell Exercise Protocol. This protocol consisted of walking on a treadmill for eight, two-minute stages with progressive increments in speed and grade. Prior to the initiation and throughout the exercise test, heart rate, blood pressure, fatigue, oxygen consumption, carbon dioxide production and minute ventilation were continuously monitored. The metabolic and respiratory markers were assessed using a portable indirect calorimeter (VO2000, Medical Graphics Corporation, Minneapolis, MN), that was previously validated in a sample of sedentary pregnant women (20). Heart rate, blood pressure and fatigue were assessed throughout the exercise-testing period.  $\dot{V}O_{2\text{peak}}$  was determined by the highest amount of oxygen consumed during the exercise test.  $\dot{V}O_{2\text{peak}}$  was expressed relative to participants' body weight as milliliters of oxygen per kilogram per minute ( $\text{mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Despite the evidence in the literature that CRF remains constant across pregnancy when expressed relative to weight gain, in this sample of pregnant women there appeared to be considerable variability in the change in CRF from

17 to 28 weeks of gestation. As such, for the purposes of this study, CRF at weeks 17 gestation were used to provide an estimate of the average level of CRF in early pregnancy.

*Covariate Variables: Maternal and Infant Characteristics*

Maternal and infant characteristics considered potential covariates included: maternal age, gestational weight gain (GWG), gestational age and group allocation. Maternal age and gestational age were extracted from the participants' medical records. Gestational weight gain was calculated using the participants' objectively-measured weight at weeks 17 and 28 weeks of gestation ( $\text{Weight}_{28 \text{ weeks}} - \text{Weight}_{17 \text{ weeks}}$ ). This non-traditional expression of gestational weight gain was used as nearly 40% of the data necessary to provide the standard expression of gestational weight gain (weight at delivery - pre-pregnancy weight) was missing. Given the difficulty of women to accurately report their pre-pregnancy weight (13) and the assumption that minimal weight is gained in the first trimester (6), we created an additional GWG variable using the objectively-measured weight at 17 weeks and weight at delivery ( $\text{Weight}_{\text{delivery}} - \text{Weight}_{17 \text{ weeks}}$ ). For the significant missing data for 'weight at delivery' we performed multiple imputation. We then compared the results between both expressions of GWG (data not shown), for all analyses performed we found each expression exerted a similar impact on the regression coefficients and standard errors. As such, we elected to use the objectively-measured weight gained during 17 and 28 weeks gestation. Group allocation was also considered a potential covariate given the exposure of this intervention trial was exercise which may

influence some of the independent variables and the outcome variable of interest.

### *Statistical Analysis*

The demographic, pregnancy-related and behavioral characteristics of this sample were determined using Student's t-tests and Pearson's Chi-Square test. For our analytical approach, we carried out three separate analyses using multiple linear regression. In this study, we attempted to determine the following: 1) the independent association of PA and infant birthweight, 2) the independent association of CRF and infant birthweight and 3) the joint associations of PA and CRF on infant birthweight.

For each analysis, the outcome variable was birthweight, expressed in grams. The steps to building each of these regression models were identical. We first assessed the assumptions of linear regression and all were reasonably satisfied. Bivariate associations between all the independent (primary and covariates) and dependent variable were performed. To assess the independent associations of PA and CRF on infant birthweight, the main effects were first added to the model. Next, covariates were sequentially added. To examine the joint association of PA and CRF, we used an interaction term between PA and CRF. We first evaluated the joint association in an unadjusted model. Following this, covariates were sequentially added to the model. The following variables were expressed continuously: CRF ( $\text{ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), PA (steps per day), gestational weight gain (kg), age (y), and gestational age (weeks). Group

allocation was treated as a categorical variable. All analyses were conducted in SAS 9.4 (Cary, North Carolina) and the significance level was set at 0.05.

### *Missing Data*

For the purposes of this study, only women with complete data on infant birthweight were included in the analyses. As a result, only 89 of the 124 women participating in the study were eligible for the final analyses. To determine the potential effects of selection bias, we tested the differences of select maternal characteristics (age, gestational age, BMI, and gestational weight gain) between women with complete and missing infant birthweight data. We found there to be no significant differences, thereby providing some evidence that excluding women without complete data on birthweight may not result in biased results. Thus, the final sample size for the analyses of this study was 89 pregnant women.

### **Results**

The sample characteristics, inclusive of maternal, pregnancy and behavior-related factors are provided in Table 2.1. At 17 weeks of gestation, the average pregnant woman was 32 years old with a BMI classified as overweight/obese (BMI:  $29.97 \pm 7.14 \text{ kg/m}^2$ ). In addition, these women, on average, delivered full-term, normal weight infants (gestational age:  $38.64 \pm 1.88$  weeks; birthweight:  $3477.48 \pm 577.48\text{g}$ ) and gained approximately 6.5 kilograms in mid-pregnancy (17 to 28 weeks). The prevalence of macrosomia in this sample was 14%, nearly double the current prevalence estimate of macrosomia the United States (~8%). Only 4% of infants delivered were low-birthweight

(<2500 g). The cardiorespiratory fitness levels of the pregnant women were low ( $VO_{2peak}: 19.85 \pm 3.35 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), and considered 'unfit' ( $VO_{2peak}: \leq 21.0 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) compared to CRF levels of similar pregnant women established by Mottola et al. Similarly, on average, this sample accumulated 6600 steps per day, suggesting a 'low active' level of daily physical activity (Tudor-Locke and Bassett, 2004). Nearly all characteristics between intervention conditions were similar with the exception of daily PA, where the exercise condition accrued more steps per day compared to the stretching condition ( $7718.19 \pm 2223.78$  vs  $5185.53 \pm 1750.39$  steps/day;  $p < 0.0001$ ).

The adjusted linear regression coefficients for the independent associations between CRF, PA and infant birthweight are presented in Tables 2.2 and 2.3, respectively. The independent association between CRF at 17 weeks gestation and infant birthweight did not reach statistical significance ( $\beta = -8.83 \text{ g}$ , 95%CI: -42.2, 24.5 g), after adjusting for gestational age and weight gain, and group allocation. Similarly, the relationship between daily PA, expressed in steps per day, and infant birthweight (Table 2.3), was not statistically significant ( $\beta = 0.03 \text{ g}$ , 95%CI: -0.03, 0.08g), after controlling gestational age and weight gain, and group allocation.

The adjusted linear regression coefficients for the joint relationship between CRF and PA, and infant birthweight are depicted in Table 2.4. The joint association was assessed via an interaction between CRF and PA, and was found to not be significantly associated with infant birthweight ( $\beta = 0.006 \text{ g}$ ,

95%CI: -0.005, 0.017 g), after adjusting for gestational age and weight gain, and group allocation.

## **Discussion**

Considerable evidence indicates that maternal physical activity during pregnancy exerts a protective effect on infant birthweight. In a recent systematic review, Wiebe et al (2015) examined the effects of 28 PA interventions during the prenatal period on infant birth size. The conclusion of this review was that women participating in higher levels of maternal PA delivered lighter infants. These protective effects however, occurred only in normal weight pregnant women (22). Because nearly 50% of women of reproductive age are overweight or obese (7) and possess the greatest risk of delivering heavier infants (6), we thought it important to determine if a protective effect existed in overweight or obese pregnant women. Thus, in the present study, we examined the association between maternal PA in pregnancy and infant birthweight in a sample of overweight or obese pregnant women. The major finding of this study was that, in overweight and obese pregnant women, PA was not associated with infant birthweight.

Our observation that maternal physical activity was not associated with infant birthweight in overweight or obese pregnant women is consistent with the limited number of previous studies assessing this relationship in this group (14, 16, 18). For example, Nascimiento et al. (2012) examined the effects of a weekly supervised, light-to-moderate intensity exercise program on several maternal-infant outcomes including infant birthweight. Similarly, Oostdam et al. (2012)



assessed the effects of a bi-weekly moderate intensity aerobic and strength-training exercise program on maternal metabolic health (i.e. blood glucose and insulin sensitivity) and infant birthweight. Lastly, Ruiz et al. (2013) examined the effects of a light-to-moderate intensity exercise program consisting of aerobic and strength exercises, performed three times per week. Collectively, these studies found that maternal physical activity was not associated with infant birthweight. This conflicts with the established inverse relationship found in normal weight pregnant women. A possible explanation for the conflicting evidence between these subpopulations is that the dose of PA was insufficient to influence infant birthweight. An obvious difference in these studies is the fact that overweight or obese women possess more fat mass. Consequently, increased adiposity and elevated blood lipids are posited to be one of the mechanisms leading to greater nutrient supply to the fetus, resulting in higher birthweights (8, 12). Strong evidence indicates that physical activity inversely associates with blood lipid levels (1, 10). As such, the amount of PA necessary to affect these levels in overweight or obese pregnant women, and thereby significantly impact infant birthweight, may be considerably higher than the levels of PA exhibited in this sample and those in previous studies.

Currently, the U.S. Physical Activity Guidelines, with concurrence from the American College of Obstetricians and Gynecologists (4, 20), recommend that pregnant women engage in 150 minutes per week of moderate-intensity aerobic and strength-training activities throughout pregnancy. Given the low amount of physical activity achieved by the pregnant women in this sample, it is likely they

did not meet the current recommendations. However, the physical activity prescribed in the aforementioned studies (14, 16, 18) appears to exceed this recommendation yet, infant birthweight remained unaffected across all studies. From these findings, two important observations can be made. First, the doses of physical activity levels in the current and other studies may have been insufficient to impact birthweight, suggesting that a higher dose of PA may be required. Second, given that the dose of PA prescribed in these studies exceeded the current PA guidelines, revised recommendations specific to overweight or obese pregnant women may be necessary. However, given the paucity of studies conducted in this population, more research assessing the effect of various doses of PA on infant size are essential to ascertain the existence of an effect.

Another possible explanation for the null association found in this present study is low variability in PA levels. In this study, the average daily steps accumulated was 6579.91 steps with a SD of 2379.17 steps. While the variability in daily PA in this study is higher compared to previous studies (9), this amount may have been insufficient to detect an effect. Limited variability in the independent variable may result in a loss of power, thus reducing the likelihood of finding a statistically significant association (17). The reduced variability in PA found in this sample, may be result of strict eligibility criteria imposed during participant recruitment. Specifically, these women had a history of preeclampsia, which affects between 3 and 10% of all pregnancies (21). Common characteristics of women with preeclampsia are overweight or obesity and sedentarism (11, 15). Given the selective population from which these women

were drawn, it is not surprising that their daily PA patterns were similar, consequently reducing variability in this behavior. In addition, the small sample size in this study likely reduced our statistical power, potentially explaining our null findings.

This study was novel in that it was the first to examine the association between maternal cardiorespiratory fitness and birthweight in a sample of overweight or obese pregnant women. The scientific knowledge on this relationship is non-existent in this group as previous studies limited their samples to normal weight pregnant women and reported conflicting effects on infant birthweight. Based on the strong metabolic effects of physical activity and posited influence on fetal nutrient supply (2), we hypothesized that maternal cardiorespiratory fitness, an indicator of habitual physical activity, would inversely associate with birthweight. However, the findings of this study demonstrated that maternal CRF appears not to influence infant birthweight. A potential explanation for the lack of an association demonstrated in this study may be limited variability in the levels of CRF in the study sample. Few studies have assessed CRF in overweight or obese pregnant women. Collectively, these studies have indicated reduced variability in the levels of CRF in this group. Mottola et al. (2006) measured CRF among an anthropometrically diverse sample of pregnant women (13). The average CRF, expressed as peak oxygen consumption, was  $23.7 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  with a standard error (SE) of  $5.0 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . In a similar study, Davenport et al. (2008), assessed the CRF of overweight and obese pregnant women (5). Compared to CRF values found in the former study, lower levels of

CRF ( $21.6 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and reduced variability (SE:  $3.8 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) were found among overweight and obese pregnant women. The lower levels of CRF found in the latter study are similar to those found in our study with an average CRF of  $19.85 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and SE of  $3.35 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . While low variability may be inherent in this specific subpopulation (i.e. history of preeclampsia, sedentarism), the additional requirement of a low fitness level (< 50<sup>th</sup> percentile) likely further reduced the variability in cardiorespiratory fitness levels. Consequently, the limited variability potentially precluded our ability to ascertain an effect through a loss in statistical power.

This study has strengths and limitations. First, to our knowledge, this is the first study to address the independent and joint associations between maternal PA and CRF and infant birthweight, in a sample of overweight or obese pregnant women. Given the well-documented health benefits of CRF and PA, the investigation of its potential influence on maternal-fetal health was warranted. Second, objective measures of PA and CRF were used in this study, thus reducing biases associated with subjective assessments (e.g. self-report) (3). In addition to these significant strengths and the aforementioned limitations (i.e. limited variability, poor adherence/compliance), this study has other limitations. First, while our sample is one of the largest available that includes measures of PA, CRF and birthweight (i.e.,  $n=89$ ), it may have been too small to detect an association. The recruitment and retention of pregnant women, especially the overweight or obese subpopulation, is a considerable challenge in this field; poor study adherence is common. Second, we did not consider other potential health

behaviors that have been documented to influence infant size, including maternal diet (23). Third, the use of birthweight as a measure of fetal growth may have resulted in our inability to capture important changes in tissue composition and future health risks (2). Evidence indicated that PA and exercise may yield significant differences in tissue composition with no differences found in birthweight (19).

In conclusion, the scientific evidence regarding the relationships between PA, CRF and birthweight is limited, especially among overweight and obese pregnant women. This study is the first provide important information regarding these relationships and contributes to this rapidly advancing area of research. Nonetheless, before any definitive conclusions are drawn from the findings of this study, further research is warranted. To address the aforementioned limitations of this study, future investigators should consider employing sampling strategies (e.g. purposive sampling) that may increase variability in the levels of maternal PA and CRF. Additionally, the development of novel strategies to enhance recruitment and retention should be encouraged given the established issues with the overweight and especially the obese subpopulations. Lastly, the underlying mechanisms that are posited to explain the relationships between physical activity and cardiorespiratory fitness and birthweight, such as maternal metabolic health and the associated biomarkers, are often neglected in these studies. Accordingly, we strongly recommend that future researchers collect data on the metabolic profiles of their study population. In closing, this study provide evidence that neither maternal PA nor CRF in the prenatal period are associated

with birthweight. However, given the established inverse relationship between PA and birthweight in normal weight pregnant women, we recommend further investigation into these potential relationships in overweight or obese pregnant women.

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### **Conflict of Interest**

The authors have no conflicts to disclose.

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**Table 2.1.** Maternal and infant sample characteristics, by total and intervention group

Sample Characteristics	Total (n=90)			Exercise (n=49)			Stretching (n=41)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
<b>Maternal <sup>a</sup></b>									
Age (y)	90	32.3	4.7	49	32.5	21.5	41	32.1	4.9
Weight (kg)	90	80.4	18.7	49	79.9	19.1	41	81.0	18.4
Height (m)	90	1.6	0.1	49	1.6	0.1	41	1.6	0.1
Body Mass Index (kg/m <sup>2</sup> )	90	30.0	7.1	49	29.7	7.5	41	30.3	6.8
Gestational Weight Gain *	90	6.45	3.6	49	6.0	2.9	41	7.0	4.2
CRF (ml O <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup> ) <sup>b</sup>	90	19.9	3.4	49	20.0	3.1	41	19.7	3.6
Physical Activity (steps/day)	89	6579.9	2379.2	49	7718.2**	2223.8	40	5185.5	1750.4
No. Days Monitored	89	114.2	32.6	49	114.6	32.6	40	113.6	33.0
<b>Infant</b>									
Gestational Age (weeks)	90	38.64	1.9	49	38.5	2.0	41	38.8	1.7
Birthweight (g)	90	3477.48	577.5	49	3475.5	613.4	41	3479.9	538.6
Macrosomia (%)	90	14.44	-----	49	7.8	-----	41	6.7	-----

Note: <sup>a</sup> Demographic characteristics (age, weight, height, and body mass index) are reported at 17 weeks gestation.

\*Gestational weight gain represents weight gain during 17 weeks and 28 weeks of gestation (corresponding to

participant laboratory visits). \*\*denotes significant between-group differences (p<0.0001). \*\*For all behavioral

characteristics (cardiorespiratory fitness [CRF], physical activity and number of days monitored) average values were

calculated using all available time points throughout pregnancy: CRF (17 weeks), PA steps/day and days monitored

(17 weeks until delivery).

**Table 2.2.** Adjusted linear regression coefficients assessing the independent association between CRF and birthweight (g).

Predictors	Parameter Estimates		
	$\beta$	SE	p-value
<b>Primary Exposures</b>			
CRF (ml O <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup> )	-8.83	16.77	0.6000
<b>Covariates</b>			
Maternal Age (y)	7.56	12.13	0.5347
Gestational Age (weeks)	144.98	30.14	<0.0001
Gestational weight gain*	10.64	7.30	0.1485
Group Allocation**			
Exercise	60.54	112.38	0.5915

\*Gestational weight gain represents weight gain during 17 weeks and 28 weeks of gestation (corresponding to participant laboratory visits). \*\*Stretching is the referent group.

**Table 2.3.** Adjusted linear regression coefficients assessing the independent association between average PA (steps/day) in pregnancy and birthweight (g).

Predictors	Parameter Estimates		
	$\beta$	SE	p-value
<b>Primary Exposures</b>			
Average PA (steps/day)	0.03	0.03	0.3037
<b>Covariates</b>			
Maternal Age (y)	7.53	12.06	0.5342
Gestational Age (weeks)	144.28	29.97	<0.0001
Gestational weight gain*	10.76	7.24	0.1408
Group Allocation**			
Exercise	-16.06	131.98	0.9304

\*Gestational weight gain represents weight gain during 17 weeks and 28 weeks of gestation (corresponding to participant laboratory visits). Note: No. of PA days represents the number of days the pedometer was worn during pregnancy.

\*\*Stretching is the referent group.

**Table 2.4.** Adjusted linear regression coefficients assessing the joint association between average PA (steps/day) and CRF in pregnancy and birthweight (g).

<b>Parameter Estimates</b>			
<b>Predictors</b>	<b><math>\beta</math></b>	<b>SE</b>	<b>p-value</b>
<b>Primary Exposures</b>			
Average PA (steps/day)	-0.09	0.12	0.4441
CRF (ml O <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup> )	-52.24	41.44	0.2111
Average PA*CRF	0.006	0.006	0.2929
<b>Covariates</b>			
Maternal Age	7.38	12.11	0.5439
Gestational Age	143.64	30.17	<0.0001
Gestational weight gain*	11.28	7.31	0.1268
Group Allocation**			
Exercise	-9.30	132.75	0.9443

\*Gestational weight gain represents weight gain during 17 weeks and 28 weeks of gestation (corresponding to participant laboratory visits). \*\*Stretching is the referent group.

## CHAPTER 3

# ASSOCIATION BETWEEN CHANGE IN MATERNAL PHYSICAL ACTIVITY DURING PREGNANCY AND INFANT SIZE

## **Abstract**

**Purpose:** Significant evidence demonstrates that maternal physical activity (PA) decreases in the prenatal period. Declines in PA are known to produce adverse metabolic effects. The neonatal consequences of these decrements in maternal PA are largely unknown. Previous studies assessing the relationship between maternal PA and infant birthweight failed to account for the natural changes in PA that occur throughout pregnancy. Therefore, the purpose of this study was to describe the relationship between changes in prenatal PA and infant birthweight.

**Methods:** This study employed a prospective design using data from a randomized controlled exercise intervention trial conducted in sedentary, overweight or obese pregnant women with a history of preeclampsia. Women with complete data for infant birthweight, peak oxygen consumption, and daily PA measured via a pedometer (17 weeks to delivery) were included in the analyses. Individual trajectories for prenatal PA were estimated via repeated measures analyses to represent the change in PA from mid-to-late pregnancy. Multiple linear regression models were then performed to determine the association between change in prenatal PA and birthweight. Gestational age, weight gain, maternal age and group allocation were covariates.

**Results:** Eighty-nine pregnant women were included in this study and were, on average, 32 years old, overweight/obese (BMI  $29.97 \pm 7.14$  kg/m<sup>2</sup>) and low-active ( $6,579.91 \pm 2379.17$  steps/day). PA declined from the 4<sup>th</sup> to the 8<sup>th</sup> month of pregnancy ( $-399.73 \pm 371.38$  steps·day<sup>-1</sup>·month<sup>-1</sup>). After adjusting for covariates, multiple linear regression analyses showed that the decline in



prenatal PA ( $\beta = -0.28$  g, 95%CI: -0.70, 0.25 g,  $p=0.35$ ) was not associated with birthweight. In addition, CRF ( $\beta = 0.04$  g, 95%CI: -0.06 g, 0.14 g,  $p=0.697$ ) did not exhibit a moderating effect.

**Conclusions:** The findings of this study demonstrated that maternal PA decreased from mid to late pregnancy. The observed decline was unrelated to infant birthweight. Future investigations employing more rigorous measurements of PA are recommended.

## Introduction

Over the past two decades, increases in mean birthweight and the prevalence of large-for-gestational age neonates have been documented in the U.S. and other developed countries (4, 20). Several adverse health outcomes are associated with higher birthweight, including an increased risk of obesity and related co-morbidities in later life (8). Considerable evidence demonstrates that higher levels of physical activity (PA) during pregnancy are associated with lower infant birthweight (6, 30). This relationship is posited to be a function of the strong metabolic effects of PA (16, 27), whereby an active mother is better able to control the amount of energy supplied to her fetus (1).

Despite the well-established metabolic benefits of PA, recent evidence indicates that over the past 50 years population trends in maternal physical activity have exhibited persistent declines (2). In addition to the population trends, research has demonstrated that maternal physical activity decreases throughout pregnancy (17, 24), with the most precipitous declines observed in the 3<sup>rd</sup> trimester. Declines in PA are known to result in adverse metabolic effects

including impaired control of serum glucose and lipids. Given these trends, decreased maternal PA is a plausible explanation for the rise in the prevalence of larger infants (1, 3).

While reductions in PA during pregnancy are universal across all subgroups of pregnant women, overweight or obese women are the least active group (17, 24). Heavier women have an increased risk of excessive gestational weight gain, thereby potentially exacerbating the decline in maternal PA leading to fetal overgrowth and larger neonates (19, 23, 28). This observation is supported by increased delivery of larger neonates among overweight or obese women (12). Evaluating the association between the decline in maternal PA and neonatal birthweight in this subgroup is important given the increasing prevalence of obesity in women of reproductive age (13).

Currently, no prospective studies have evaluated the relationship between the change in maternal physical activity during pregnancy and neonatal birthweight. Most studies have examined the relationship between average level of maternal physical activity across pregnancy or during specific trimesters and infant size (6). Consequently, these studies failed to account for the naturally occurring changes in physical activity. As such, the associations of the changes in maternal physical activity across the prenatal period and infant birthweight are largely unknown. In addition, no studies have evaluated the potential modifying effect of maternal cardiorespiratory fitness (CRF) on the relationship between change in maternal PA and infant birthweight. CRF is an indicator of habitual physical activity as such, women with higher levels of maternal CRF may protect

against the negative metabolic effects of decreasing levels of PA. Thus, the primary purpose of this study was to describe the relationship between changes in physical activity in mid-to-late pregnancy and infant birthweight, in a sample of overweight or obese pregnant women. A secondary purpose of this study was to evaluate the potential modifying effect of maternal cardiorespiratory fitness on this relationship.

## **Methods**

### *Study Design*

The present study employed a prospective design using data from a five-year randomized exercise comparative trial (RCT). This RCT was designed to assess the effects of a moderate exercise program in the prenatal period on the incidence of preeclampsia its pathological processes (e.g., oxidative stress). The secondary purpose of the study was to assess the effects of exercise on gestational weight gain and birth outcomes (31) .

### *Participant Eligibility & Recruitment*

Pregnant women were recruited from nine prenatal clinics in Michigan. Women were enrolled in this intervention trial if they were 1) less than 14 weeks gestation, 2) history of preeclampsia, 3) had a peak oxygen consumption of  $\leq$  50<sup>th</sup> percentile of women in their respective age-group, 4) had a sedentary lifestyle or had a self-reported physical activity energy expenditure of less than 840 kcals per day. Women were excluded if they had: 1) chronic hypertension or pre-gestational diabetes, 2) medical or physical limitations that inhibit participation in exercise, 3) been advised against the participation in prenatal

exercise by a physician or 4) a low mental acuity and/or language barrier preventing effective communication with research staff.

### *Randomization & Intervention Groups*

Two-hundred and ten pregnant women expressed interest in participating in the RCT, however 41% (n=86) did not meet the eligibility criteria. The remaining eligible pregnant women (n=124) were randomly assigned to an exercise program (n=64) or a stretching program (n=60). The exercise program recommended that the women walk for 40 minutes, five times per week at moderate intensity (55-69% of heart rate reserve). In the stretching program, participants were instructed to mimic the movements of a stretching video of equivalent frequency and duration as the exercise program. With regard to intensity, the participants were instructed to not increase their heart rate more than 10% above resting levels. To monitor compliance to the exercise intensity of each program, the participants wore Polar S810 heart rate monitors and wristwatch devices. More details on the exercise and stretching programs of the RCT can be found elsewhere (32). For the purposes of this study, data were collapsed across the two groups and group allocation was controlled for in the analyses.

### *Outcome Variable: Infant Birthweight*

Infant birthweight, in grams, was the dependent variable in the present study. Birthweight was defined as the weight of the infant at the time of delivery. The data on birthweight was extracted from the mother's medical records.

### *Exposure Variables:*

#### *Change in Physical Activity*

Physical activity was assessed daily using a pedometer (Digiwalker SW200) from weeks 18 gestation until delivery. Each participant was instructed to wear the pedometer, attached via an elastic belt and worn directly above the right hip, during waking hours. Participants were to remove the pedometer prior to sleeping and participation in any water-based activities (e.g. showering, swimming). In addition, participants were asked to keep a daily record of their total daily step counts throughout their prenatal period. Daily steps were collapsed into four-week periods that corresponded to the months of pregnancy: month 4 (18 – 21 weeks), month 5 (22 – 25 weeks), month 6 (26 – 29 weeks), month 7 (30 – 33 weeks), and month 8 (34 – 37 weeks). Nearly 60% of data on daily step counts were missing in 9<sup>th</sup> month of pregnancy (38 – 41 weeks), likely due to delivery, so we excluded this month from the analysis. Prenatal PA was expressed as  $\text{steps} \cdot \text{day}^{-1} \cdot \text{month}^{-1}$ . We did not employ any exclusionary protocols for the PA data. The amount of steps accumulated in pregnancy ranged from 0 to 16,503 steps per day. Change in prenatal physical activity was determined using individual trajectories in PA across the prenatal period (i.e. time) [see Statistical Analysis].

#### *Cardiorespiratory Fitness*

Cardiorespiratory fitness was defined as peak oxygen consumption ( $\dot{V}O_{2\text{peak}}$ ) and expressed relatively as milliliters of oxygen per kilogram per minute ( $\text{ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).  $\dot{V}O_{2\text{peak}}$  was estimated via a submaximal treadmill test at 17

and 28 weeks gestation. The treadmill exercise test followed the Cornell Exercise protocol, a modified version of the Bruce Protocol Treadmill Test. The protocol consisted of each participant walking on a treadmill through eight, two-minute stages with progressive increments speed and grade. Prior to the test, resting levels of heart rate, blood pressure, fatigue, oxygen consumption, carbon dioxide production and minute ventilation were assessed. These same parameters were continuously monitored throughout the exercise test using a portable indirect calorimeter (VO2000, Medical Graphics Corporation, Minneapolis, MN). This device has been previously validated in a sample of sedentary pregnant women (33). Although in the scientific literature CRF is shown to not change significantly, the change in CRF levels between 17 and 28 weeks in this sample were quite variable. As such, for the purposes of this study, CRF at 17 weeks gestation was used to provide an estimate of the average CRF level in early pregnancy.

*Covariate Variables: Maternal and Infant Characteristics*

Several maternal and infant characteristics that may affect birthweight, PA and/or CRF were included as potential covariates. Maternal and infant characteristics included the following: age, gestational weight gain (GWG), gestational age and group allocation. Maternal age (in years) and gestational age (in weeks) were extracted from the participants' medical records. Gestational weight gain in this study was calculated using a non-traditional approach. We used the difference in the weights that were objectively measured at 17 and 28 weeks gestation to express gestational weight gain. GWG was not expressed using the traditional expression, difference in the weight at delivery and pre-

pregnancy weight, because nearly 40% of the data for either of these metrics was missing. However, to compare our non-traditional expression of GWG to a more standard expression, we created an additional GWG variable that represented the difference in weight from 17 weeks gestation to delivery. Because it is assumed that minimal weight is gained in the first trimester (18) and self-reported pre-pregnancy is prone to significant error (26), we found it more appropriate to use the weight at 17 weeks gestation. To create this additional GWG variable, we performed multiple imputation for the 'weight at delivery' and then calculated the GWG variable. After this, we compared the results of the multiple regression analyses (see statistics section) for both expressions of GWG (data not shown). We found that each GWG variable impacted the regression coefficients and standard errors similarly. As a result, we elected to use the weight gained from 17 to 28 weeks gestation to represent GWG.

### *Statistical Analyses*

Group differences in the maternal and infant characteristics between the exercise and stretching programs were determined using Student's t-test and Pearson Chi-square tests. For the main analyses, we performed two multiple linear regression models. In this study, we sought to determine: 1) the effects of change in maternal physical activity in mid-to-late pregnancy on infant birthweight and 2) the modifying effect of CRF on the association between change in PA during pregnancy and infant birthweight. Change in PA in the prenatal period was determined using individual trajectories in PA across time. We performed a random intercept and slope mixed model with repeated measures to estimate

intercepts and slopes of each participant. These estimates were then created as individual variables with the intercept acting as a 'baseline measure of PA' and the slope representing the 'change in PA' across the prenatal period.

For each analysis, infant birthweight was the dependent variable. In the first main analyses, change in maternal PA during pregnancy was the primary independent variable. In the second main analyses, change in maternal PA during pregnancy and CRF were the primary independent variable and modifying variable, respectively. In the latter analyses, we assessed the modifying effect with an interaction term between CRF and change in maternal PA in pregnancy. We first assessed the assumptions of linear regression and no major violations were found. Next, bivariate associations between all the independent variables (primary and secondary) and the outcome variable were performed. Following this, unadjusted multiple linear regression models were performed first, followed by a sequential inclusion of covariates. All analyses were conducted using SAS analytical software version 9.4 (Cary, North Carolina) and the significance level was set at  $\alpha = 0.05$ . The following variables were expressed continuously: change in prenatal PA ( $\text{steps} \cdot \text{day}^{-1} \cdot \text{month}^{-1}$ ), CRF ( $\text{ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), GWG (kg), age (years), gestational age (weeks). Group allocation was treated as a categorical variable with the stretching program treated as the referent group.

### *Missing Data*

For the purposes of this study, only women with complete data on infant birthweight, maternal PA in pregnancy and cardiorespiratory fitness were included in the analyses. As such, only 89 of the 124 eligible pregnant women



were used in the analyses. To assess the possibility of selection bias, we compared the differences in demographics, pregnancy-related and behavioral characteristics of women with and without complete data. We found no significant differences between these groups, thus providing some evidence that excluding these women may not provide biased estimates.

## Results

Table 3.1 presents maternal, prenatal and behavior-related characteristics of this study sample. At 17 weeks of gestation, the average pregnant woman was 32 years old with a BMI classified as overweight/obese (BMI:  $29.97 \pm 7.14$  kg/m<sup>2</sup>). On average, women delivered full-term, normal weight infants (gestational age:  $38.64 \pm 1.88$  weeks; birthweight:  $3477.48 \pm 577.48$ g). The average weight gained in mid-pregnancy (17 to 28 weeks) was approximately 6.5 kilograms. Roughly 14% of infants were born macrosomic, nearly double the prevalence in the United States (~8%) (20). Only 4% of infants delivered were low-birthweight (<2500 g). Women in this sample were considered 'unfit' with an average  $VO_{2peak}$  of  $19.85$  ml O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup> (SD 3.35). In addition, these women accumulated, on average, 6600 steps per day, suggesting participation in a 'low active' lifestyle (Tudor-Locke and Bassett, 2004). In addition, during every month of pregnancy, PA decreased, on average, by nearly 400 steps per day. Specifically, Table 3.2 shows the patterns in maternal PA from mid-to-late pregnancy. As expected, maternal PA declined from month 4 (18 – 22 weeks) to month 9 (38 – 41 weeks), with women accumulating on average  $7227.7 (\pm 2618.5)$  steps·day<sup>-1</sup> and  $5848.5 (\pm 2778.9)$  steps·day<sup>-1</sup>, respectively.

Additionally, this table shows that the number of pregnant women recording their daily PA declined as well, most precipitously in the last month of pregnancy.

The adjusted linear regression coefficients for the association between change in prenatal PA and infant birthweight are presented in Table 3.3. Change in prenatal PA was not significantly associated with infant birthweight ( $\beta = -0.28$  g, 95%CI: -0.70, 0.25 g,  $p=0.35$ ), after adjusting for maternal age, gestational age, weight gain, and group allocation.

Table 3.4 depicts the adjusted linear regression coefficients for the modifying effect of CRF on the relationship between the change in PA and infant birthweight. The interaction between CRF and change in PA and was not significantly associated with infant birthweight ( $\beta = 0.04$  g, 95%CI: -0.06 g, 0.14 g,  $p=0.697$ ), after adjusting for maternal age, gestational age, weight gain, and group allocation.

## **Discussion**

The primary finding of this study was that, in overweight or obese women, the decrease in maternal physical activity from mid- to late-pregnancy was unrelated to infant birthweight. This study was unique in that it was the first to prospectively follow women from mid- to late-pregnancy and evaluate the association between change in physical activity and infant birthweight. Previous prospective studies assessing this relationship limited their evaluation to the average level of physical activity across pregnancy or during specific trimesters in pregnancy (6, 17). Thus, this study provides a unique examination of the relationship between the decline in PA during pregnancy and infant birthweight.

Moreover, this study was conducted in a sample of overweight or obese pregnant women, an understudied population. Further research is necessary in this group as these women are predisposed to excessive weight gain, low levels of PA and poor metabolic health, all of which are posited to be risk factors for the delivery of larger neonates.

A potential explanation for the null association between the change in maternal PA and infant birthweight is the small magnitude in the change in PA from mid-to late-pregnancy. In this study, a very modest reduction in maternal PA was observed likely consequent to the low active lifestyle led by these women, potentially demonstrating a floor effect. At 17 weeks gestation (i.e. baseline) this sample of women accumulated nearly 6600 steps·day<sup>-1</sup>·month<sup>-1</sup>, which is reflective of low activity. A majority (~3000 – 4000 steps) of these daily step counts were likely the results of everyday activities of daily living [ADLs] (29). The remainder potentially represented leisure time physical activity. Considering the necessity of the engagement in ADLs, PA attributed to ADLs likely did not change significantly during pregnancy. As such, the decrements in PA documented in this study were likely consequent to reductions in leisure-time physical activity (14). On average, the women in this sample decreased their daily steps per month by approximately 400 steps (-399.73 ± 371.38 steps) from the 4<sup>th</sup> month to the 8<sup>th</sup> month of pregnancy. Over a 5-month period, this corresponds roughly to a 2,000-daily step decrement over a 5-month period. This minimal change is consistent with previous studies. For example, Renault et al. (2010) assessed physical activity via pedometers and found an 1,850-step

decrement in steps per day from 13 weeks to 36 – 38 weeks gestation in obese women (24). The small magnitude of the decrement in maternal PA found in this study was likely insufficient to influence fetal energy supply and birthweight, thereby precluding our ability to detect an association.

In support of this interpretation, Clapp et al. (2002) evaluated the effects of various doses of prenatal physical activity in normal weight women on infant size (10). They found that women who decreased their PA delivered heavier, fatter neonates reflected by higher birthweight and greater amounts of adipose tissue compared to women who maintained or increased their PA throughout the prenatal period. The considerable decrement in PA likely altered fetal energy supply, especially in the 3<sup>rd</sup> trimester. This is consequent to the reduction in the maternal skeletal muscle demand for energy, thus increasing energy availability to the fetus (22). The decrement in PA experienced by these women was 200 minutes per week, a markedly greater reduction in the levels of PA relative to the 400-daily step per month decline exhibited in the present study. As such, a larger decrement in prenatal PA may have been necessary to affect infant size.

Another unique aspect of this study was the examination of the moderating effect of maternal cardiorespiratory fitness on the relationship between the change in maternal PA during pregnancy and birthweight. Cardiorespiratory fitness is an indicator of habitual physical activity (7). In addition, given the strong metabolic effects of physical activity (27), we posited that maternal CRF may attenuate the potential adverse effects (i.e. reduced metabolic health) related to reductions in prenatal PA (5) on neonate size. The

findings of the aforementioned study of Clapp et al. (2002) support this hypothesis. The women in that study were previously active and subsequently possessed optimal levels of cardiorespiratory fitness. Despite the increased birthweight and adipose tissue among neonates born to the women who decreased their prenatal PA during the prenatal period, the birthweight and tissue composition of these neonates were still within the normal range (9). This may indicate that higher levels of PA and thus, CRF in the preconception period may have protected the neonate from overgrowth in spite of a decline in maternal PA during pregnancy. In this study, however, we observed that maternal cardiorespiratory fitness does not moderate the relationship between the decline in maternal PA in the prenatal period and infant birthweight.

A possible explanation for the null observation regarding the moderating effects of maternal cardiorespiratory fitness is low variability. Previous studies assessing CRF levels in pregnancy observed low variability among the overweight or obese subpopulation. Davenport et al. (2008), assessed the CRF of overweight and obese pregnant women and found the average CRF, expressed as peak oxygen consumption, of  $21.6 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ( $\pm 3.8 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) (11). The average value and variability (i.e. standard deviation) is lower in comparison to those found in an anthropometrically diverse sample of pregnant women by Mottola et al. (2006). These authors found an average CRF of  $23.7 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and SE of  $5.0 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (21). The lower levels of CRF found in the former study are similar to those found in the present study ( $\text{VO}_{2\text{peak}}$ :  $19.85 \pm 3.35 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). The low variability in CRF found in this study may

be due to the low-active lifestyles led by these women. Habitual PA is a strong predictor of CRF and as such, the low levels of PA found among this sample of women likely resulted in low levels and variability of CRF. In addition, the combination of limited variability in maternal CRF and the small magnitude of the change in PA during pregnancy may have precluded our ability to detect a moderating effect (25).

This study has strengths and limitations. Importantly, this is the first study to examine the association between the changes in maternal physical activity in mid-to-late pregnancy and infant birthweight in a sample of overweight or obese pregnant women. In addition, this study is the first to assess the potential moderating effect of maternal cardiorespiratory fitness on this relationship. An additional strength of this study is the longitudinal measurement of physical activity in the prenatal period. This evaluation allowed us to account for the natural changes in PA from mid-to-late pregnancy and led to a more accurate estimation of its relationship with infant birthweight. Lastly, the use of objective assessments increased the precision of the measurement of physical activity and cardiorespiratory fitness. In addition to these significant strengths, this study has limitations. First, only PA in mid-to-late pregnancy was observed. Thus, any changes occurring prior to 17 weeks of gestation were missed, potentially resulting in a less accurate representation of the changes in PA during pregnancy. Second, the sample size for this study was small (n=90) possibly limiting our ability to detect an association, especially a moderating effect. Third, we did not consider other potential health behaviors that have been documented

to influence infant size, including maternal diet (34). Fourth, while birthweight is the most widely used measure of infant size, it fails to provide information on the tissue composition of the neonate, which is important to future health risks (15).

In conclusion, this study demonstrated that the decline in maternal physical activity during the prenatal period was unrelated to birthweight. In addition, we observed that maternal cardiorespiratory fitness did not moderate the association between the decline in maternal PA during pregnancy and infant birthweight. In spite of these null observations, this study contributes to this rapidly growing area of research in an understudied and important subpopulation. Several recommendations are suggested to address the limitations of this study that will ensure higher quality assessments of these relationships in future investigations. First, the employment of sampling strategies aimed to increase the variability in PA and CRF (i.e. purposive sampling) are encouraged. Second, while pedometers provide an objective assessment of physical activity, they are limited to providing information on PA volume. Consequently, pedometers are unable to capture other important components of PA such as intensity. Intensity of PA may be an important factor to fetal growth given its strong relation to metabolic health. Third, future research should include the assessment of metabolic biomarkers, such as glycemic and lipidemic control, as these parameters are considered the underlying mechanisms to excessive fetal growth and are often ignored in studies. Lastly, more precise measurements of infant anthropometry are needed (i.e. lean and fat mass) as these are important to future health risks of the offspring. In closing, the findings of this study provide no

evidence that the declines in maternal PA during mid-to-late pregnancy are related to infant birthweight and that maternal CRF exerts a moderating effect on this relationship.

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### **Conflict of Interest**

The authors have no conflicts to disclose.



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**Table 3.1.** Sample characteristics of pregnant women, by total and intervention group

	<b>Total</b> (n=90)			<b>Exercise</b> (n=49)			<b>Stretching</b> (n=41)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
<b>Maternal and Infant Characteristics</b>									
<b>Demographics</b>									
Age (y)	90	32.3	4.7	49	32.5	4.4	41	32.1	4.9
Weight (kg)	90	80.4	18.7	49	79.9	19.1	41	81.0	18.4
Height (m)	90	1.6	0.1	49	1.6	0.1	41	1.6	0.1
Body Mass Index (kg/m <sup>2</sup> )	90	30.0	7.1	49	29.7	7.5	41	30.3	6.8
<b>Pregnancy-Related</b>									
Gestational Age (weeks)	90	38.6	1.9	49	38.5	2.0	41	38.8	1.7
Gestational Weight gain*	90	6.5	3.6	49	6.0	2.9	41	7.0	4.2
Birthweight (g)	90	3477.5	577.5	49	3475.5	613.4	41	3479.9	538.6
Macrosomia (%)	90	14.4	-----	49	7.8	-----	41	6.8	-----
<b>Behavioral*</b>									
CRF	90	19.8	3.4	49	20.0	3.1	41	19.7	3.6
Physical Activity	89	6588.7	2416.6	49	7801.4**	2236.4	40	5103.1	1706.0
Change in PA	89	-399.7	371.4	49	-470.6**	374.1	40	-312.9	353.4
No. Days Monitored	89	114.2	32.6	49	114.6	32.6	40	113.6	32.96

Note: \*Gestational weight gain represents weight gain during 17 weeks and 28 weeks of gestation

(corresponding to participant laboratory visits). \*\*denotes significant between-group differences

(p<0.0001). \*PA data on one participant was removed as no data on PA were available, however all

other pertinent data were available. CRF was expressed as  $\text{ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Physical activity was expressed as  $\text{steps} \cdot \text{day}^{-1} \cdot \text{month}^{-1}$

**Table 3.2.** Maternal patterns of average physical activity (steps·day<sup>-1</sup>) from mid-to-late pregnancy, by group

		<b>Total</b>		<b>Exercise</b>		<b>Stretch</b>	
		Mean	SD (range)	Mean	SD (range)	Mean	SD (range)
Gestation*	N						
Month 4	87	7227.7	2618.5 (2426.6-16503.2)	8726.3	2246.8 (4369.2-16503.2)	5465.5	1809.3 (2426.6-9922.4)
Month 5	86	7093.6	2679.5 (1987.8-17526.3)	8333.6	2574.2 (376306-17526.3)	5599.2	1960.9 (1987.8-9867.11)
Month 6	85	6614.4	2551.1 (1705.9-15788.6)	7852.6	2412.9 (4020.7-15788.6)	5082.9	1783.3 (1705.9-8140.1)
Month 7	84	6135.2	2618.1 (186.7-15627.4)	7407.9	2466.9 (3400.7-15627.4)	4666.7	1947.7 (186.7-8260.2)
Month 8	75	5797.2	2521.4 (598.6-14033.9)	6814.8	2408.4 (1915.0-14033.9)	4569.9	2094.5 (598.6-8517.6)
Month 9	37	5848.5	2778.9 (1302.0-14133.5)	6666.4	3121.9 (1858.0-14133.5)	4886.3	1995.3 (1302.00-8315.0)

Note: \*The weeks of gestation that correspond to each month of pregnancy are as follows: Month 4 (18 – 21 weeks), Month 5 (22 – 25 weeks), Month 6 (26 – 29 weeks), Month 7 (30 – 33 weeks), Month 8 (34 – 37 weeks) and Month 9 (38 – 41 weeks)



**Table 3.3.** Adjusted linear regression coefficients assessing the association between change in prenatal PA and infant birthweight, in grams

Predictors	Parameter Estimates		
	$\beta$	SE	p-value
<b>Primary Exposures</b>			
PA Change <sup>†</sup>	-0.227	0.234	0.3462
<b>Covariates</b>			
Baseline PA*	0.017	0.029	0.5512
Maternal Age (y)	5.24	12.00	0.6637
Gestational Age (weeks)	156.17	30.32	<0.0001
Gestational weight gain**	18.31	16.02	0.2565
Group Allocation***			
Exercise	-44.46	135.23	0.7431

Note: †Change in PA is represented by individual trajectories (slopes) of PA

across the prenatal period (See Methods section). \*Baseline PA is represented by

the intercepts of individual trajectories of PA (See Methods section). \*\*Gestational

weight gain represents weight gain during 17 weeks and 28 weeks of gestation

(corresponding to participant laboratory visits). \*\*\* Stretching group is referent.

Physical activity was expressed as steps·day<sup>-1</sup>·month<sup>-1</sup>.

**Table 3.4.** Adjusted linear regression coefficients assessing the modifying effect of CRF on the association between change in prenatal PA and infant birthweight, in grams

Predictors	Parameter Estimates		
	$\beta$	SE	p-value
<b>Primary Exposures</b>			
PA Change	-0.98	1.01	0.3355
CRF	10.08	25.94	0.6987
CRF*PA change	0.040	0.051	0.4333
<b>Covariates</b>			
PA Intercept*	0.023	0.030	0.4473
Maternal Age (y)	5.46	12.12	0.6538
Gestational Age (weeks)	152.29	31.01	<0.0001
Gestational weight gain**	18.22	16.39	0.2695
Group Allocation***			
Exercise	-61.75	137.94	0.6556

Note: Change in PA is represented by individual trajectories (slopes) of PA

across the prenatal period (See Methods section). \*Baseline PA is represented by the intercepts of individual trajectories of PA (See Methods section).

\*\*Gestational weight gain represents weight gain during 17 weeks and 28 weeks of gestation (corresponding to participant laboratory visits). \*\*\* Stretching group is referent. CRF was expressed as ml O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>. Physical activity was expressed as steps·day<sup>-1</sup>·month<sup>-1</sup>.

CHAPTER 4  
OVERALL DISCUSSION

In the United States, nearly 20% of children and adolescents are classified as obese(29). Several adverse cardio-metabolic health outcomes are associated with obesity including type II diabetes and non-alcoholic fatty liver disease(20, 36). Rigorous scientific evidence indicates that participation in sufficient levels of physical activity may reduce the risk of the development of child obesity(23). However, child levels of physical activity cannot explain obesity at birth or infancy. Recent epidemiological evidence indicates that over the past 20 years, the average birthweight of U.S.-born infants has increased(27). In addition, increasing trends in infant macrosomia and large-for-gestational age infants are documented(3, 7, 9). Consequently, heavier neonates have altered growth trajectories(19), predisposing them to obesity. Because child levels of physical activity cannot explain obesity at birth or infancy, this suggests that the development of obesity occurs *in utero*(17, 31). The prenatal period is the most critical period for fetal growth and development and is vulnerable to disturbances. It is well-documented that maternal phenotype (e.g. body mass) and her behaviors can significantly impact fetal growth(4). Thus, it is important to identify maternal factors that may affect fetal growth and subsequently infant size.

Considerable evidence indicates that higher levels of maternal physical activity in the prenatal period protect neonates from overgrowth(35). This relationship is hypothesized to result from improved maternal metabolic health thereby controlling the amount of energy supplied to the fetus, resulting in the development of a healthy-sized neonate(4). This protective effect, however, has only been demonstrated in normal weight women. Little is known about how

maternal physical activity might influence infant size in the overweight or obese population(28, 30, 33). In addition, very few studies have evaluated the association between maternal cardiorespiratory fitness, an indicator of habitual physical activity, and neonatal size. The findings of previous studies are inconsistent with reports of positive, negative and null associations(8, 12, 24). Moreover, to our knowledge, no studies have assessed this relationship in the overweight or obese population. The lack of studies among this subgroup is problematic given the increasing prevalence of obesity in women of reproductive age(18). Moreover, overweight or obese women are the least active in pregnancy(22, 32) and are at an increased risk for excessive gestational weight gain(26), predisposing them to higher rates of delivering macrosomic neonates(16). Therefore, three studies in this dissertation investigated the relationships between maternal body mass, physical activity and cardiorespiratory fitness, prior to and during pregnancy, and infant size.

The purpose of study one was to evaluate the moderating effect of maternal physical activity in the preconception and prenatal periods on the relationship between maternal body mass and infant macrosomia. The purpose of study two was to examine the independent and joint associations between maternal physical activity, cardiorespiratory fitness and infant birthweight, in a sample of overweight or obese pregnant women. The purpose of study three was to describe the relationship between change in maternal PA in the prenatal period and infant birthweight, in a sample of overweight or obese pregnant women. In addition, we examined the potential moderating effect of maternal

cardiorespiratory fitness on the relationship between change in maternal PA and infant birthweight.

In study one, it was observed that maternal body mass was a significant, positive predictor of infant macrosomia. Overweight or obese mothers had increased odds of delivering a macrosomic infant. However, contrary to hypotheses, neither preconceptional nor prenatal PA moderated the association between maternal body mass and infant macrosomia. In study two, it was observed that overweight or obese women led very-low active lifestyles. Maternal PA from mid-to-late pregnancy was unrelated to infant birthweight. Maternal cardiorespiratory fitness was also unrelated to infant birthweight in this group. In addition, maternal cardiorespiratory fitness did not moderate the association between maternal PA and infant birthweight. In study three, it was observed that, in overweight or obese women, maternal PA declined from mid-to-late pregnancy. This decrease in PA was found to be unrelated to infant birthweight.

Overall, this dissertation did not support the hypothesis that maternal PA prior to or during pregnancy affects the relationship between maternal body mass and infant macrosomia. In addition, these studies did not find that maternal PA and cardiorespiratory fitness are related to infant birthweight. Previous evidence regarding the modifying effect of maternal PA is extremely limited. Only one study, to our knowledge, has examined this relationship(25) and found that overweight or obese women reporting little to no PA prior to pregnancy were more likely to deliver a macrosomic infant. In study two, our null observations regarding the independent associations of maternal PA and infant birthweight are

consistent with previous studies among overweight or obese women. However, these studies conflict with studies conducted among normal weight women which collectively suggest that maternal PA in pregnancy protects against the delivery of larger infants(35). Study two also provided unique information about the relationship between maternal cardiorespiratory fitness and infant birthweight. No previous studies have assessed this relationship in overweight or obese pregnant women. The null observation of the association between change in maternal PA and infant birthweight, found in study three, conflicts with current literature. Clapp et al. (2002), found that considerable reductions in maternal PA in mid-to-late pregnancy resulted in the delivery of larger, fatter infants compared to mothers maintaining or increasing their PA(12). Despite the null findings observed in this dissertation, these studies contribute to the this rapidly growing area of research, specifically in the overweight or obese subpopulation.

There are several limitations of this dissertation. For study one, maternal body mass and physical activity were evaluated using self-reported methods. It is well-documented that these measures may lead to biased, and less precise estimated associations(5, 34). These methods are prone to misreporting due to social desirability(1), the individual's inability to remember certain behaviors and the length of the recall period(2). The implementation of objective measures of maternal body mass and physical activity behaviors, which are demonstrated to produce more accurate estimates, in future studies are encouraged.

In studies two and three, a small sample size was a significant limitation. The small sample size in this study may have limited our ability to detect and

association via a reduction in statistical power. This limitation however, is common in studies conducted in the pregnant population. Because women become pregnant sporadically, at any given point in time, the number of women in the early stages of pregnancy that are available for study recruitment is small. Thus, recruiting large samples of pregnant women is challenging. Another limitation to these two studies was the assessment of maternal PA. While pedometers are an objective measurement tool, they only capture volume of PA. It is well-documented that other components of PA, including frequency, duration and intensity, are important to several health parameters(21). Thus, objective measurements of PA that are able to measure all components of PA, such as accelerometers, should be used. In addition, we did not consider other potential health behaviors that have been documented to influence infant size, including maternal diet(37). Lastly, a limitation across all studies, is the measurement of infant size. Birthweight is a ubiquitous measure of infant size. However, this metric fails to provide information on the tissue composition of the infant including fat and fat-free mass(11). Determining these parameters is important to future health risks and should be included in future research.

The maternal-child health field is a rapidly growing area of research. While several studies examining the association between maternal PA and infant size have been conducted, much remains to be learned about this relationship, especially in overweight or obese women. Although there is an established inverse relationship between maternal PA and infant size in normal weight women(35), the few studies conducted in overweight or obese women have



reported null associations(28, 30, 33). A lack of a relationship in this subgroup is problematic given that 50% of women of reproductive age are overweight or obese(18). Moreover, these women are predisposed to excessive gestational weight gain(26) and the delivery of larger infants(16). As such, it is imperative that more research is conducted in this understudied subpopulation. Specifically, it would be of public health interest to determine a dose of PA that protects against infant macrosomia. Discovery of such information would be valuable for exercise prescription guidelines for pregnant women.

Much of the evidence evaluating the relationship between maternal PA and infant size is epidemiological. This type of research is important to scientific progress; however, it is only the initial step in describing this relationship. Thus, our knowledge on the mechanisms that underlie this relationship are largely unknown. Further, little research has examined the effects of maternal PA on placental growth and function and its relation to infant size(10, 13). The placenta is a critical organ as it is the conduit through which the mother and fetus communicate and regulates fetal energy supply(6, 14, 15). Thus, evaluating the effects of maternal PA on placental development and function and its relation to fetal growth is important. Further research into these mechanisms will provide a more in-depth understanding of the relationship between maternal PA and infant size.

In summary, the moderating, independent and joint relationships between maternal PA and CRF and infant size were investigated. Across all three studies, maternal PA and CRF were unrelated to infant birthweight or macrosomia.

Similarly, for all three studies, low levels of maternal PA and CRF with restricted variability were a common explanation for the null findings. Despite the null observations, these studies contribute important information on these relationships and serve as an important starting point for this rapidly growing area of research. Given the paucity of studies investigating these relationships, specifically in overweight or obese women, more research is warranted. In closing, these studies did not support the hypotheses that maternal PA or CRF impact infant size.

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CHAPTER 5

PROPOSAL

## Introduction

In the United States, the prevalence of infants born macrosomic or large-for-gestational age is increasing(114). Evidence suggests that neonates with excess adiposity at birth may experience altered growth trajectories possibly attributed to augmented tissue growth during periods of accelerated development(71, 179, 187) (e.g. adiposity rebound, puberty). Consequently, this may predispose neonates to obesity(180) and the associated morbidities in childhood and adolescence.(60, 130)

Maternal size has been identified as a significant predictor of infant size such that larger mothers produce larger offspring(94, 178). Substantial evidence has demonstrated that this relationship is potentially a function of nutrient supply. Nutrient supply has been suggested to be the strongest predictor of fetal growth as any alterations to the availability of nutrients may have dramatic fetal effects such as growth restriction or macrosomia(15, 136). In order to optimize fetal growth, several maternal physiological changes occur, including the onset of peripheral insulin resistance.(76, 81) However, in pregnancies complicated by maternal obesity, these changes have been demonstrated to be exacerbated.(32, 104) In addition, preexisting obesity-related metabolic consequences including central insulin resistance(51) and poor glycemic and lipidemic control(90, 145) may result in the availability of excess nutrients in the intrauterine environment. Given this and the fact that nearly 50% of women of reproductive age in the U.S. are overweight or obese(63), identifying factors that

enable pregnant women to control their metabolic intrauterine environment should be a major public health priority.

Among non-pregnant populations cardiorespiratory fitness and physical activity have been consistently demonstrated to exhibit protective effects on several morbidities and mortality.(24, 25, 168) These effects are likely due to the cardiovascular(49), metabolic(75) and musculoskeletal adaptations(156) that occur with chronic exercise training that may result in improvements such as increased insulin sensitivity and improved glycemic and lipidemic control. Additionally, these effects persist even in the presence of excess adiposity, suggesting that a “healthy” level of cardiorespiratory fitness and participation in an adequate amount of physical activity may mitigate the negative effects of obesity on cardio-metabolic health outcomes.(106, 181) It is reasonable to suggest that this phenomenon may exist during pregnancy, such that a higher level of cardiorespiratory fitness and engagement in a sufficient dose of physical activity at the onset and during the perinatal period may alleviate the adverse consequences of maternal adiposity on infant birthweight via a controlled metabolic intrauterine environment. However, to our knowledge, the impact of cardiorespiratory fitness and/or physical activity on the relationship between maternal adiposity and infant birthweight is largely unknown.

#### *Statement of the Problem*

The major purpose of the proposed study is to determine if participation in physical activity and/or higher levels of cardiorespiratory fitness in the perinatal

period alleviate the adverse effects of maternal overweight and obesity on infant weight status. Specifically, this proposed study will:

1. Determine if maternal physical activity in the preconception and prenatal period moderates the relationship between maternal weight status and infant weight status, in a nationally representative and diverse sample of mothers delivering live-birth infants.
2. Determine if maternal prenatal cardiorespiratory fitness and objectively-measured physical activity independently associate with infant weight status, among a sample of overweight and obese pregnant women.
3. Determine if maternal cardiorespiratory fitness and objectively-measured physical activity jointly associate with infant weight status, among a sample of overweight and obese pregnant women.
4. Determine if change in objectively-measured physical activity is associated with infant weight status, among a sample of overweight and obese pregnant women.
5. Determine if cardiorespiratory fitness influences the relationship between change in maternal objectively-measured physical activity and infant weight status, among a sample of overweight and obese pregnant women.

## *Aims*

The overarching purpose of this dissertation is to evaluate a developing hypothesis that higher levels of maternal physical activity and cardiorespiratory fitness in the preconception and prenatal periods will reduce the negative effects of maternal weight status on infant weight status.

Aim 1: To observe the potential effect of maternal physical activity during the preconception and prenatal periods on the association between maternal weight status and infant weight status, in a representative and diverse sample of women delivering live-birth infants.

*Objective 1A:* To determine if self-reported prenatal physical activity modifies the relationship between maternal pre-pregnancy weight status and infant weight status.

*Objective 1B:* To determine if self-reported pre-pregnancy physical activity alters the moderating effect of prenatal physical activity on the relationship between maternal pre-pregnant weight status and infant weight status.

Aim 2: To observe the potential effect of maternal cardiorespiratory fitness and objectively-measured physical activity during pregnancy on infant birthweight, in a sample of overweight and obese women.

*Objective 2A:* To determine the effect of cardiorespiratory fitness in mid-pregnancy on infant birthweight.

*Objective 2B:* To examine the effect of objectively-measured physical activity in mid-pregnancy on infant birthweight.

*Objective 2C:* To examine the joint effect of cardiorespiratory fitness and objectively-measured physical activity in mid-pregnancy on infant birthweight.

Aim 3: To observe the potential effect of changes in maternal physical activity and cardiorespiratory fitness during pregnancy on infant birthweight, in a sample of overweight and obese women.

*Objective 3A:* To evaluate the effect of change in objectively-measured physical activity from mid- through late pregnancy on infant birthweight.

*Objective 3B:* To determine if cardiorespiratory fitness in mid-pregnancy modifies the association between changes in objectively-measured physical activity from mid- through late pregnancy and infant birthweight.

### *Scope*

Secondary data analyses from one population-based study and one, randomized controlled exercise intervention trial will be performed to address the aims and objectives of this proposed study. (1) The National Maternal and Infant Health Survey sampled resident mothers who had a live birth, fetal death or infant death in the United States in 1988. Mothers aged 15 years and older, delivering live-birth infants, who provided data on anthropometrics (i.e. height and weight) and self-reported physical activity behaviors in the preconception and perinatal periods will be included in the proposed study. In addition, infants of these mothers where data on weight status are provided will also be included in this study. (2) The randomized controlled exercise intervention trial sampled women in early pregnancy (<14 weeks gestation) whom were at risk for

preeclampsia (i.e., sedentary, previous preeclamptic pregnancy) from nine prenatal clinics in one county in the state of Michigan. Pregnant women who had anthropometry and cardiorespiratory fitness measurements and an objective measure of physical activity in the perinatal period will be included in this study. In addition, the infants of these mothers where data on weight status are available will also be included in this proposed study. The study findings from the first study will be generalizable to all U.S. mothers aged 15 years and older, who had live-births in 1988. Generalizations from the second trial will be to all women at high-risk for preeclampsia that are able to participate in physical activity in the perinatal period.

#### *Assumptions*

The proposed study will make the following assumptions:

1. Pre-pregnancy body mass index is a valid and reliable measure of maternal adiposity in the preconception period.
2. The mother is able to accurately recall her pre-pregnancy weight and height after an average period of 17 months postpartum.
3. Self-reported physical activity is a valid and reliable measure of physical activity behavior in the preconception and perinatal periods.
4. The mother is able to accurately recall her physical activity prior to and during pregnancy after an average period of 17 months postpartum.
5. Pedometers are a valid and reliable measure of physical activity, and daily step counts are an accurate measure of daily physical activity behavior.

6. Last menstrual period and ultrasounds are valid and reliable measures to estimate gestational age.
7. Data extracted from the birth certificates and medical records are reported consistently and accurately across all levels (i.e. hospitals, clinics, and states).

### *Limitations*

Pre-pregnancy body mass index will be calculated based on self-reported maternal height and weight which rely on the ability of the individual to recall this information after an extended period of time (~17 months). It has been demonstrated that women over-report their height and underreport their weight, and there may be a systematic bias based on their “actual” level of adiposity, such that larger women may report less accurately.(150) As a result, larger women may be misclassified into lower body mass index categories. Further, self-reported physical activity measures are prone to misreporting (over-reporting or underreporting) due to several reasons (e.g., inability to remember, social desirability)(4, 161), as such women may be inaccurately categorized as active which may nullify the potential moderating effect of physical activity on maternal weight status and infant weight status. One study sampled pregnant women that were at high-risk for preeclampsia and whom completed a run-in period which limits the generalizability of these findings to more compliant pregnant women and may introduce a sampling bias.



### *Relevance of the Proposed Study*

The proposed study will determine if cardiorespiratory fitness and physical activity in the preconception and prenatal periods impact the association between maternal weight status and infant weight status. Consistent evidence has indicated that maternal weight status is positively associated with infant weight status.(98, 193) This relationship is suggested to be a function of nutrient supply, a strong predictor of fetal growth(178). In addition, considerable evidence in non-pregnant populations has demonstrated protective effects of higher levels cardiorespiratory fitness and physical activity on metabolic health outcomes, independent of adiposity.(106) Given the potent metabolic effects of physical activity and exercise,(148) it is of great interest and relevance to determine if higher levels of cardiorespiratory fitness and physical activity in pregnancy mitigate the negative impacts of maternal adiposity on infant weight status. The findings from this study will provide information on whether cardiorespiratory fitness and/or physical activity are potential strategies that enable a mother to protect her fetus from overgrowth.

### **Review of the Literature**

#### *Infant Birthweight*

Birthweight, defined as the weight in grams at the time an infant is delivered, has been identified as an indicator of fetal wellbeing and is considered a strong predictor of infant morbidity and mortality(119, 149). The severity of the health outcomes associated with birthweight is the most marked at the extremes of the birthweight distribution (i.e. growth restriction, macrosomia). Infants

suffering from fetal growth restriction (FGR) or macrosomia are burdened with increased risk of many immediate and long-term health consequences including fetal and neonatal death, obesity, type 2 diabetes mellitus and metabolic syndrome(14, 15, 33, 136). While the suffering of infants born at both birthweight extremes are of significant public health importance, it appears that the birth of larger neonates has become a growing concern, particularly among developing countries.

### *Trends in Infant Birthweight*

Since the 1970s, evidence has suggested upward shifts in the distribution of infant birthweight among several developing countries. Specifically, Skjaerven et al. (2000) reported a 100g-increase in mean birthweight over a 30-year period (1967-1998) in Norway(160). In China, Lu et al. (2011) reported a significant increase in infant birthweight (+73g) from 1994 to 2005(112), with similar increases reported in Queensland, Australia from 1988 to 2005 (+1.9g/year)(103), Sweden from 1992 to 2001 (+35g)(169), Canada from 1981 to 1997 (+35g)(182) and in the United States (1985 to 1998)(9). Conversely, in the United States, some evidence has indicated that mean birthweight declined by approximately 52g from 1990 to 2005(56). This coincides with a recent report by Oken (2013) which suggested that mean birthweight continued to decline (as of 2008) since 1990(128). However, birth data from the most recent National Vital Statistics Report (2013) indicates that from 2006 to 2013 there has been an upward shift in the birthweight distribution for U.S. infants, suggesting that on average infants are being born heavier.(114) Specifically, this report indicates

that the proportion of infants born greater than 3,000g increased from 2006 to 2013 (73.30% to 73.75%, respectively), while the proportion of low birthweight (i.e. 2,500-2,999g) infants has declined over the same 7-year period (18.44% to 18.22%). Despite some inconsistencies in the scientific literature regarding trends in infant birthweight over the past several decades, particularly in the United States, this evidence is suggestive that mean infant birthweight has increased, and that on average, infants are born heavier.

Although some evidence suggests that, on average, infants are born heavier, the mean birthweights reported fall within a “normal” range (i.e. 2500 to 4000g) for a “healthy” infant(81). Given this, it is unclear whether the upward shifts in the birthweight distribution affect the proportion of infants born at the upper extremes (90<sup>th</sup> percentile), representing the largest infants. As such, the use of mean birthweight as a metric to track changes in infant anthropometry, specifically larger infants, may be inadequate. Birthweight is a crude measure of infant anthropometry. Consequently, this metric cannot quantify the tissue composition of an infant. It is generally accepted that a higher birthweight is indicative of greater adiposity and comparable lean body mass compared to infants with a normal birthweight(36). However, it is possible that an infant with an “average or normal” birthweight (2.5 to 3.9 kg), may have significant variations in tissue composition that cannot be detected with the birthweight metric. Sewell et al. (2006) demonstrated this concept when comparing birthweights of infants born to overweight/obese and lean women.(154) These authors reported that mean birthweight did not significantly differ (3436g vs 3284g, respectively)

between these groups of women, however, significant differences in percent body fat (11.6% vs 9.7%, respectively) and fat mass (420g vs 380g, respectively) of infants were found. Infants born to overweight/obese women had higher levels of adiposity compared to their lean counterparts, with no differences in lean body mass. This suggests that birthweight may not be an appropriate measure to evaluate trends in the prevalence of larger infants, specifically those that may be more likely to possess an unfavorable tissue composition. As such, to improve the surveillance of the delivery of larger infants, other metrics may be necessary.

#### *Trends in Macrosomia and Large-for Gestational Age Infants*

In the scientific literature, there are two metrics frequently used to describe a “large” infant. The first metric is *macrosomia*, which is defined as an infant weighing 4,000 g (> 4.0 kg) or more at delivery, regardless of gestational age. The second metric is large-for-gestational age (LGA), which is defined as an infant born with a birthweight that is at the 90<sup>th</sup> percentile or higher for a specific gestational age, compared to a reference population(127). Because these metrics are specifically used to identify larger infants, it is possible that they may more accurately capture changes in the proportion of infants born at the upper extreme of the birthweight distribution.

Similar to the trends in mean infant birthweight, many developing countries have reported increases in the proportion of infants born macrosomic and large-for-gestational age. Specifically, in China, Shan et al. (2014) documented increases in the prevalence of macrosomic infants from 1996 (6.6%) to 2010 (17.0%)(155). Vranes et al. (2015) reported increases in the proportion of

infants born macrosomic from 1985 (10.2%) to 2009 (13.6%) in Croatia(177). Similarly, in Queensland, Australia, there was an increase in the rate of (+0.8% per year) of macrosomic infants from 1988 to 2005(103). In addition, other countries including North England (1962 to 2000)(19) and Belgium (1991 to 2010)(73) also reported increases in the prevalence of macrosomia, 25% and 18%, respectively. Trends in the proportion of the delivery of large-for gestational age infants are similar in that many developing countries have documented increases in LGA infants. Wen et al. (2003) reported that from 1981 to 1997 there were significant increases in the proportion of term infants (37-40 weeks) born LGA in Canada(182). In addition, Ananth et al. (2002) reported increases in term LGA infants in both Canada from 1985 to 1998.(9) In China, Lu et al. (2011) reported an increase in LGA infants from 1994 to 2000 (13.72% to 18.98%)(112), and remained stable through 2005. Moreover, in Sweden, Surkan et al. (2004) documented a 23% increase in the proportion of LGA infants from 1992 to 2001(169).

Consistent with the conflicting trends in mean birthweight found in the United States, trends in the prevalence of macrosomia and LGA infants in the US follow similar patterns. The trends for both these metrics have been reported to increase, decrease or remain stable over time. For example, Donahue et al. (2010) reported that the prevalence of infants born LGA declined from 1990 to 2005(56). Extending the previous work of Donahue and colleagues, Oken et al. (2013)(128) reported that the proportion of infants born LGA decreased in male and female infants from 1990 (11.1% and 10.5%, respectively) to 2005 (9.4%

and 9.1%, respectively). Ananth et al. (2002) and Zhang et al. (2010) reported stable prevalence estimates for LGA infants from 1985 to 1998 and 1992 to 2003, respectively(9, 195). Interestingly, the former study also reported a 25% reduction in the proportion of infants born macrosomic (2.2% to 1.6%). In addition, Oken et al. (2013) suggested that the prevalence of macrosomia declined nearly 50% from 1990 to 2008(128). Conversely, the most recent data available (2013) from the National Vital Statistics System has documented that the prevalence of macrosomia in the United States is approximately 8.0%(114). While this is lower than the prevalence recorded in 1990 (10.88%) by Oken et al. 2013, it is higher than the prevalence rates reported in 2006 (7.82%) and 2008 (7.62%), which may indicate the emergence of an increasing trend in infant macrosomia. Recent data however, on the trends in the proportion of infants born LGA, do not appear to be present in the current scientific literature.

Overall, the evidence suggests there are increases in the trends of macrosomic and LGA infants; however, as with the mean infant birthweight measure, there are significant limitations to these metrics that may result in the misestimation of the magnitude of these trends and warrant consideration. First, there is a lack of consensus in the scientific literature regarding the birthweight threshold used to define macrosomia. Currently, several thresholds are used (4000 g, 4500 g, or 5000 g) which may affect not only the direction but the magnitude of the trends reported. This was demonstrated in the study conducted by Oken et al. (2013) where macrosomia was defined as a birthweight greater than 5,000 g and the authors reported a 50% reduction in macrosomia from 1990

to 2005. The use of a different threshold, such as 4000 g, would have decreased the magnitude of this reported reduction by 50%, suggesting that macrosomia only declined roughly 25% during this time period. The incongruity regarding the birthweight threshold for macrosomia may be in part due to the outcome associated with a particular threshold. For example, Boulet et al. (2003) investigated adverse outcomes associated with various birthweight thresholds that are often used to define macrosomia (i.e. 4000g, 4500g and 5000g)(27). The authors found that risks of labor complications, birth injuries, and neonatal morbidity increased with each grade of macrosomia, however only infant mortality was associated with infants weighing 5000g or more. The authors suggested that the 4000g-threshold may be best used to predict labor and neonatal complications, however higher thresholds may be more predictive for neonatal morbidity (>4500g) and mortality (>5000g).

In addition to lack of consensus on the definition of macrosomia, the application of a universal threshold for macrosomia across all infants may be inappropriate. It is well-documented that infant birthweight differs by country, race, and infant sex. While determining the prevalence of macrosomia across 23 countries, Koyanagi and colleagues (2013) demonstrated the existence of considerable variability in birthweight among various countries. For example, the average birthweight was lower in Asian (2697-3181g) and Latin (3119-3311g) countries compared to the United States (3455g) and China (3369g)(96). Moreover, it is well-established that male and White infants are born significantly heavier (~200g) than their female and Black infant counterparts.(7) The latter is

supported by a recent study by Ye et al. (2014) that reported a significant increase in risk of adverse perinatal outcomes at different birthweight thresholds for White (>4500g) and Black (>4300g) infants.(189) Given this, it seems that the universal application of the 4000 g or greater threshold may be inappropriate. In addition to the limitations of macrosomia, there are also drawbacks to the use of the large-for-gestational age metric. First, the LGA measure relies on the accuracy of the measurement used to estimate gestational age.(17) The most common method to estimate gestational age is by maternal recall of the first day of her last menstrual period (LMP). The LMP method is subject to considerable error. Kramer et al. (1988) demonstrated that despite a positive predictive value (PPV) of 95% for predicting a term infant, the ability of this method to accurately estimate gestational age significantly decreased for preterm (PPV=0.775) and post-term infants (PPV=.119)(97). This is problematic as the inaccuracy of this method may lead to significant misclassification and misestimation of the prevalence of LGA infants. Second, the classification of an LGA infant is typically determined using an established country-specific reference population; however, many other maternal and fetal factors that have been demonstrated to affect fetal growth are excluded, including maternal weight, parity, race/ethnicity and infant sex.(5, 6, 80) In light of this, the use of customized birthweight percentiles to identify LGA infants have been proposed and studied. For example, Pasupathy et al. (2012) compared the prevalence rates of LGA and macrosomia using customized birthweight percentiles, corrected for gestational age, maternal weight and height, parity, ethnicity and infant sex, to birthweight percentiles of a



standard reference population.(132) This study found that 53% of macrosomic and 25% LGA infants, defined using the standard references population, were misclassified after the adjustment for maternal and fetal characteristics. This suggests that maternal and fetal factors that have been demonstrated to affect fetal growth should be accounted for in the identification of larger infants.

Based on the evidence presented, there appears to be increasing trends in the average birthweight of infants and the proportions of macrosomic and large-for-gestational age infants in many developing countries including the United States. Considering the importance of fetal growth to the health and wellbeing of the infant, the increasing trends in delivery of larger infants, likely characterized by an unfavorable tissue composition (i.e. increased adiposity), should be considered a major public health concern.

#### *Maternal-Fetal and Neonatal Consequences to Macrosomia*

The increasing trends in excessive fetal growth are problematic as macrosomia poses numerous and significant health risks to the mother, fetus and neonate(194). Mothers carrying a macrosomic fetus are at increased risks of complications during labor (e.g. delayed(158)), delivery (e.g. cesarean sections(167)) and the postpartum period (e.g. perineal laceration(8), hemorrhage(163)). Fetuses that are macrosomic may have an elevated risk of mortality, several morbidities (e.g. asphyxia, congenital anomalies)(93), and physical injuries incurred during delivery (e.g. shoulder dystocia(82)). Neonates born macrosomic may be burdened with both immediate (e.g. hypoglycemia, respiratory distress)(93) and long-term (e.g. overweight/obesity(180), altered

growth trajectories(101)) health risks. Given this, the development and delivery of a macrosomic infant is a significant obstetric and public health challenge.

### *Maternal Environment and Nutrient Supply*

While numerous factors have been demonstrated to be related to fetal growth(115) (e.g., maternal age, parity, race/ethnicity), the strongest predictor and likely the underlying mechanism between these factors and fetal growth is nutrient supply to the fetus(74, 178). To ensure that an optimal level of nutrients is available to the fetus, several physiological adaptations occur throughout the gestational period(76, 81). Glucose and amino acids are the primary sources of fuel that are necessary for fetal growth(18). As such, the maternal environment during pregnancy adjusts to prioritize the availability of these substrates.

Marked physiological alterations to maternal metabolism begin and are maximized in the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters of pregnancy, respectively, concurrent with the acceleration of fetal growth. The most critical adaptation to the maternal environment is the development of insulin resistance (IR)(165). This adaptation is transient as it subsides in the postpartum period and is often referred to as the “diabetogenic” state of pregnancy. The onset of IR occurs in the 2<sup>nd</sup> trimester and progressively worsens through the middle of the 3<sup>rd</sup> trimester. The IR predominantly affects the periphery (e.g. skeletal muscle) with reported reductions in insulin sensitivity between 55 to 70%(37). The primary purpose of the development of IR is to reduce maternal uptake and utilization of glucose and amino acids in an effort to spare these substrates for the fetus(131, 164). To

satisfy the metabolic needs of the mother, catabolism of the maternal fat stores deposited in early pregnancy increases dramatically(95).

The presence and severity of IR in pregnancy is most evident in the basal and postprandial periods. In the basal state, consistent evidence indicates that levels of glucose and amino acids are lower compared to non-pregnant women suggesting enhanced fetal uptake of these substrates(66). This phenomenon is often referred to as “accelerated starvation.” Also during this state, maternal levels of free fatty acids are significantly elevated compared to non-pregnant counterparts(95). In addition, insulin levels are also elevated and are higher compared to non-pregnant women. Despite higher levels of insulin, hepatic glucose production is increased (16 to 30%(38)) in the fasting state, likely as an attempt to increase the amount of glucose available to the fetus. Because insulin inhibits the mobilization of glucose, the increased levels of hepatic glucose production may be suggestive of slight central insulin resistance(52).

In the postprandial period, several exaggerated metabolic responses occur. First, the glucose levels increase significantly to a higher peak and are sustained for a prolonged period in pregnant women compared to non-pregnant women, due to the presence of insulin resistance. Second, in order to compensate for the sustained hyperglycemia, the insulin response is augmented by 200 to 250%(31, 34). In an effort to overcome the hyperglycemia found in the postprandial period the significant increase in insulin levels is suggested to help “push” the nutrients (i.e. glucose and amino acids) to the uteroplacental unit for fetal uptake and is referred to as “facilitated anabolism(67).” Failure of the

pancreatic  $\beta$  cells to adequately compensate to the elevated glucose levels often results the diagnosis of gestational diabetes mellitus(28).

Given the importance of nutrient supply to optimal fetal growth and development, the maternal metabolic environment adjusts to ensure adequate availability of nutrients. Disturbances in the maternal environment that may affect nutrient supply may have adverse effects on fetal growth. These disruptions often result in fetal growth restriction or fetal overgrowth, each possessing immediate and long-term effects on the health of the progeny.

#### *Nutrient Supply and Fetal Overgrowth*

In the scientific literature, disruptions in nutrient supply often result in reduced or excessive fetal growth(14, 136). Given the current rise in the delivery of macrosomic and LGA infants occurring in the U.S., disturbances that lead to excess nutrient availability are of particular interest. The most demonstrable example of the effects of excess nutrient supply is found among women with pregnancies complicated by diabetes.

Over a half century ago, while working with women diabetic pregnancies, Jorgen Pedersen formulated the hyperglycemic-hyperinsulinemic model, commonly known as the Pedersen Hypothesis(134, 135). This hypothesis suggests that fetal overgrowth was due to repeated exposure of higher levels of maternal glucose (i.e. hyperglycemia) during pregnancy. In addition, Pedersen speculated that the excessive glucose transferred to the fetus induced fetal hyperinsulinemia. Because maternal insulin cannot cross the placenta(122), it was hypothesized that in response to hyperglycemia, the fetal pancreas secreted

heightened levels of insulin. This is supported by evidence demonstrating enhanced fetal pancreatic growth via increased  $\beta$  cell mass and function (i.e. insulin content and secretion) found among fetuses of diabetic mothers.(142, 192) Augmented levels of insulin are suggested to further stimulate the release of growth-promoting factors (e.g. insulin-like growth factors) subsequently increasing adipocyte deposition in the fetus(65). In support of this, studies have found higher levels of c-peptide, a marker of insulin secretion, and growth factors in macrosomic infants compared to normal weight infants(13).

While diabetic pregnancies (e.g. type I, II and gestational) are associated with the highest risk of delivering a macrosomic infant, only 14% of pregnancies are complicated by diabetes(83). This suggests that diabetic pregnancies are likely not a significant contributor to the increasing trend in the delivery of macrosomic and LGA(58). This may suggest that other maternal factors exhibiting similar perturbations on the intrauterine environment (i.e. hyperglycemia) may be a more plausible explanation. Interestingly, a common co-morbidity of women with diabetic pregnancies is the presence of overweight or obesity. Evidence has indicated that nearly 70% of women with gestational diabetes are overweight or obese(89). Accumulating evidence suggests that maternal pre-pregnancy obesity is a significant, independent risk factor for the delivery of a macrosomic infant(23, 69). In addition, a recent epidemiological surveillance study indicated that nearly half (46%) of women of reproductive age (20 to 39 years) are overweight or obese, with evidence of an increasing trend(63). Given this and evidence supporting maternal body mass as an

independent risk factor for augmented fetal growth, it is plausible that maternal overweight and obesity may be the dominating factor explaining the rise in infant macrosomia.

### *Maternal Obesity and Fetal Growth*

Consistent evidence has demonstrated that maternal size is a significant predictor of fetal size, such that larger mothers produce, on average, larger offspring(74, 178). This relationship is suggested to exist as a function of nutrient supply, whereby larger mothers deliver more nutrients to their fetus compared to their smaller counterparts; potentially due to the augmented amount of maternal energy resources and disruption of the metabolic environment(110, 145).

Evidence suggests that the mechanisms that underlie the relationship between maternal obesity and infant macrosomia are similar to the hyperglycemic-hyperinsulinemic model in the Pedersen hypothesis.(133, 136) Specifically, some studies have indicated that obese mothers may enter the perinatal period with existing metabolic dysfunction (e.g. insulin resistance) which may exacerbate the normal physiological adaptations that occur throughout pregnancy.(90)

Consequently, it is the augmentations of these changes that are suspected to result in increased nutrient availability to the fetus and subsequently enhance fetal growth.

The exacerbations of the pregnancy-induced changes to maternal metabolism are most evident when fetal growth is accelerating. As previously described, the onset of peripheral insulin resistance begins in the second trimester, primarily affecting maternal peripheral glucose uptake. Compared to

non-obese pregnant women, obese pregnant women are suggested to present with pronounced insulin resistance, higher levels of glucose, amino acids, and free fatty acids in the fasting and postprandial periods.(90) Maternal insulin levels are substantially increased (~130%)(34). Despite this, the actual insulin response to a glucose stimulus is reduced compared to non-obese pregnant women (~200-250%)(31), suggesting a potential pancreatic  $\beta$  cell impairment. Further, the suppression of hepatic glucose production via increased insulin levels has been demonstrated to be delayed up to four hours in obese pregnant women which suggests a greater level of central insulin resistance compared to non-obese pregnant women(159). Collectively, these findings indicate that the exaggerated metabolic adaptations in pregnancy found among obese pregnant women may result in a “hypernutrient” intrauterine environment in which the fetus is exposed to prolonged periods of excess nutrient availability. Similar to the Pedersen Hypothesis, the fetal consequences of exposure to excess nutrients in the intrauterine environment include increased adipocyte deposition, altered pancreatic growth and function, and organomegaly(65, 166, 170). In addition, recent evidence has also demonstrated that infants born to obese mothers may have early signs of metabolic syndrome(35).

Considering that nearly half of women of reproductive age are overweight and obese(63), it is plausible that pre-pregnancy overweight and obesity is the dominating force behind the increasing trends in infant birthweight and prevalence of macrosomic infants. Consistent evidence has demonstrated that maternal overweight and obesity exacerbates the normal physiological

adaptations to maternal metabolism occurring throughout gestation potentially resulting in excess nutrient availability to the fetus. The repeated exposure to the maternal metabolic dysfunction in the intrauterine environment may have significant adverse consequences to fetal growth and development, specifically increased adiposity at birth and risk of poor metabolic health outcomes in the future(105).

### *Maternal Resources Hypothesis*

The substantial body of evidence underlying the Pedersen hypothesis has provided significant insight to the etiology of infant macrosomia, especially in pregnancies complicated by diabetes. More recent evidence however, has indicated that diabetes need not be present in the gestational period for metabolic perturbations to exist in the intrauterine environment.(32) While it suggested that maternal overweight and obesity may play a more significant role in explaining the increasing trends in larger infants(58), a majority of overweight and obese women do not give birth to macrosomic or large-for-gestational age neonates. In fact, a recent meta-analysis evaluating the relationship of maternal obesity on the occurrence of fetal macrosomia found that while the odds of delivering a large-for-gestational age or macrosomic infant (>4000g or >4500g) are increased among obese mothers, only 22.4%, 15.3%, and 3.9% of obese mothers delivered overgrown fetuses, respectively(70). Additionally, 50% of the macrosomic infants in the sample were born to normal weight mothers, and the remaining 50% to overweight and obese mothers. This potentially suggests that other factors may be more influential on fetal growth.



While the evidence to support the adverse influence of maternal weight status on fetal growth is significant, it fails to consider and explain one critical factor that has been demonstrated to have potent effects on human metabolism, that is, physical activity. Until recently, the potential important impact of maternal physical activity on the intrauterine environment and fetal growth has been mostly ignored. The maternal resources hypothesis is a recently developed theory that extends upon the current hypotheses on the influence of the intrauterine environment, with regard to nutrient supply, and fetal growth. The maternal resources hypothesis attempts to explain how maternal phenotype, specifically maternal body composition (i.e. obesity) and behavior (i.e. physical activity) impact the intrauterine environment and subsequently, the development of the fetus(10).

#### *Physical Activity and Nutrient Supply*

During pregnancy, maternal and fetal tissues compete for nutrients. Competition in early pregnancy is low as fetal energy demand is minimal. As pregnancy progresses coincident with accelerated fetal growth, the competition for nutrients increases dramatically. Alterations to the maternal environment in pregnancy (e.g. IR) are orchestrated in a manner to tightly control the competition for nutrients such that adequate levels of nutrients are available to both the mother and fetus. Additionally, maternal behaviors may also change in order to maintain a balanced competition for nutrients such as increases caloric intake (~200-300 kcal per day) and/or reductions in physical activity(91, 92). However, severe changes in these compensatory maternal behaviors,

specifically physical activity, may create an imbalance in the nutrients available to the maternal and fetal tissues thereby adversely affecting fetal growth. For example, higher levels of energy expenditure akin to hard physical labor may result in maternal tissues out-competing the fetus for nutrients and consequently restricting fetal growth. Such an extreme level of physical activity is often found among pregnant women in developing countries(172). Conversely, significant decrements in maternal physical activity may decrease the competition for nutrients between maternal and fetal tissues such that excess nutrients are supplied to the fetus. This extreme is likely what is characteristic of maternal physical activity behavior in the United States. This is evidenced by significant decrements in physical activity with advancing gestation, reports of pregnant women spending nearly 50% of their day in sedentary behaviors and less than 25% of pregnant women achieving the daily 30-minute physical activity recommendation set forth by the American Congress of Obstetricians and Gynecologists (ACOG) and Physical Activity Guidelines for Americans(12, 61, 62).

#### *Impact of Physical Inactivity on Metabolic Control and Fetal Growth*

The maternal resources hypothesis posits that maternal physical inactivity is the primary determinant to the excess nutrient availability in the intrauterine environment as a result of metabolic dysfunction. In support of this hypothesis, it is well established that skeletal muscle tissue accounts for 40% of body mass and nearly 80% of insulin-mediated glucose uptake(16) and as such, is a major determinant of whole-body glucose and lipid homeostasis(2). Consequently, any

disturbances to this function may have adverse metabolic effects to the maternal and fetal environment.

In non-pregnant populations, considerable evidence has demonstrated that physical inactivity is associated with significant reductions glycemic control(21). Specifically, decreased energy expenditure is suggested to induce decrements in peripheral insulin sensitivity, glucose uptake and oxidation via disruption of the insulin signaling pathways(68). Additionally, excess glucose in the muscle is converted to lipids via de novo lipogenesis thereby increasing lipid accumulation in muscle(20). Elevated levels of intramuscular lipids are also proposed to inhibit insulin signaling, therefore may play a role in peripheral IR(138). Collectively, these alterations in the energy flux of the skeletal muscle may induce hyperglycemia.

Decreased levels of physical activity are also suggested to adversely affect lipidemic control(88). Evidence indicates that physical inactivity downregulates lipoprotein lipase (LPL) activity, a key enzyme in the regulation of free fatty acid uptake in skeletal muscle, resulting in elevated blood lipid levels. In addition, free fatty acid oxidation in skeletal muscle is also reduced and available fatty acids are suggested to be diverted to storage, further perpetuating the loss in lipidemic control. Moreover, hyperlipidemia, in addition to hyperglycemia is also hypothesized to increase de novo lipogenesis in the liver and adipose tissue, further elevating blood lipid levels. Consequently, it appears that the presence of hyperglycemia and hyperlipidemia are initiated by physical inactivity and are augmented by each other's presence(26, 87).

While a substantial proportion of the evidence supporting the adverse metabolic effects of physical inactivity has been demonstrated among non-pregnant populations and pregnant animal models, these mechanisms are suggested to occur similarly in pregnant humans. The maternal resources hypothesis hypothesizes that the metabolic consequences of the low levels of physical activity and high levels of sedentary behavior(61, 62) found among pregnant women may augment the existing pregnancy-induced metabolic adaptations (e.g. IR). Specifically, low levels of physical activity may worsen peripheral insulin resistance thereby exacerbating hyperglycemia and hyperlipidemia, especially in the postprandial periods(121) and thus, increasing the maternal-fetal glucose and lipid concentration gradient favoring the diffusion of these nutrients across the placenta and creating a ‘hypernutrient’ environment for the fetus(48, 77).

The fetal consequences to the repeated exposure to a ‘hypernutrient’ environment proposed in the maternal resources hypothesis reflect those found in the Pederson Hypothesis. Excess nutrient availability in the intrauterine environment is suggested to induce fetal hyperinsulinemia via a heightened insulin response of the fetal pancreas(166). As demonstrated, the pancreases of fetuses grown in hyperglycemic environment are shown to have increased mass and function<sup>126</sup>. The fetal hyperinsulinemic environment has been demonstrated to augment the presence of growth factors which may contribute to adipocyte hyperplasia(65, 86) (i.e. more adipocytes). In addition, the maternal resources hypothesis posits that excess nutrient availability has been suggested to

exacerbate fetal adipogenesis via increased number of free fatty acids and glucose transporters, uptake of free fatty acids into fetal adipocytes and triglyceride storage in addition to elevated enzymes that have been suggested to stimulate de novo lipogenesis in fetal adipose tissue(57, 110).

Another unique contribution of the maternal resources hypothesis is the suggestion the excess nutrient availability induced by maternal physical inactivity may also alter fetal skeletal muscle development and function. Skeletal muscle development is nearly complete by the second trimester of pregnancy suggesting that any disruptions in early pregnancy may have a significant and permanent impact on the function of fetal skeletal muscle tissue<sup>129</sup>. Some evidence indicates that maternal metabolic dysfunction has been demonstrated to be associated the reduction in the size of muscle fibers and increased collagen accumulation within fetal skeletal muscle tissue(113). Smaller muscle fibers and accretion of fibrous tissue may impair the ability of muscle to generate force and overall function of skeletal muscle.

The negative effects of physical inactivity on maternal metabolic health posited in the maternal resources hypothesis may be of particular concern for overweight and obese pregnant women. In non-pregnant and pregnant populations, overweight and obese women have been demonstrated to be the least active subgroup(50). Low levels of physical activity in the preconception period may increase the risk of a woman entering pregnancy with existing metabolic dysfunction (e.g., insulin resistance, poor glycemic/lipidemic control)(21, 68). This is problematic given that the development of the fetal

pancreas occurs early in pregnancy(139). As previously described, poor metabolic health may increase nutrient availability and alter the development and function of the growing fetal pancreas, specifically the  $\beta$ -cells. Moreover, evidence has indicated overweight and obese pregnant are at an increased risk of gaining excessive weight during pregnancy(53, 55, 79). In fact, nearly 60% of this subpopulation exceed the weight gain guidelines put forth by the Institute of Medicine(188). Substantial evidence in the scientific literature has demonstrated that excessive gestational weight gain is fairly strongly associated with the delivery of a larger infant. Given the established positive relationship between body weight and energy expenditure(108), it is reasonable to suggest that the augmented levels of weight gained found among overweight and obese pregnant women may be a result of decreased levels of physical activity. That is, the heightened level of energy expenditure of a larger pregnant woman that is required for a given activity may reduce physical activity. Consequently, there are adverse maternal and fetal effects to the decrements in this behavior and weight gain. First, as previously discussed, physical inactivity has negative effects on metabolic health. The associated poor glycemic and lipidemic control affects both the mother and her fetus due to increments in the availability of nutrients. For the mother, the excess nutrients may be partitioned to her fat stores thereby increasing fat deposition and weight gain(29). Unfortunately, this unnecessary gain in weight may perpetuate further reductions in physical activity potentially augmenting metabolic dysfunction and promoting excessive weight gain. For the fetus, the metabolic dysfunction as a direct and indirect consequence of physical

inactivity and weight gain, respectively, may lead to increased placental transfer of nutrients(48, 77) and subsequently enhance fetal growth via altered growth and function of the fetal pancreatic  $\beta$ -cells(166) and consequent adipocyte deposition(86).

Collectively, the maternal resources hypothesis hypothesizes that the disturbances to nutrient supply, the strongest predictor of fetal growth, are a result of reduced levels of physical activity that likely occur in the preconception and perinatal periods. Physical inactivity during gestation is suggested to perturb the metabolic intrauterine environment via considerable decrements in skeletal muscle tissue energy demand and augmentation of the pregnancy-induced insulin resistance resulting in poor glycemic and lipidemic control. Subsequently, excess nutrients are provided to the fetus thereby altering fetal pancreatic  $\beta$  cell mass and function, inducing fetal hyperinsulinemia and promoting hypertrophy and hyperplasia of adipocytes and altered fetal skeletal muscle development. Consequently, the effects of the exposure to metabolic insults in pregnancy potentially result in a metabolically compromised, heavier, fatter neonate with less functional skeletal muscle tissue and a predisposition to adverse cardio-metabolic health outcomes as a child, adolescent and adult (e.g. obesity, type II diabetes).

#### *Physical Activity or Exercise and Fetal Growth*

According to the maternal resources hypothesis, the low levels of physical activity in the perinatal period are suggested to be the primary mechanism for the increasing trends in infant macrosomia and LGA infants. As such, it seems

reasonable to speculate that the participation in adequate levels of physical activity or exercise in pregnancy may improve glycemic and lipidemic control, thereby controlling nutrient supply and protecting against fetal overgrowth. Among pregnant populations, several studies have examined the impact of physical activity or exercise on fetal growth(183). Although physical activity and exercise are related, differences in their influence on health outcomes exist(72, 184). Physical activity is defined as any movement produced by the skeletal muscles that elicit levels of energy expenditure above that equivalent to resting. While exercise falls under the overarching definition of physical activity, exercise is defined as a type of physical activity that is structured, repetitive and goal-oriented with the purpose of improving or maintaining physical fitness(30). Given the differences in these terms, it may be anticipated that the evidence regarding their respective effects on fetal growth may differ and as such, they will be reported separately.

#### *Physical Activity in Pregnancy and Fetal Growth*

Evidence from studies evaluating the impact of physical activity in pregnancy on fetal growth is equivocal. A recent study from Mudd and colleagues (2014) reviewed studies examining the relationship between leisure time physical activity (LTPA) on several maternal and fetal outcomes including fetal growth. The study found that, in general, LTPA was inversely associated with the delivery of a macrosomic or LGA infant and importantly, no increase in risk for the delivery of a small-for-gestational age (SGA) infant(124). These findings are in conflict with another review by Takito et al. (2009), which reviewed



studies assessing the impact of maternal physical activity on neonatal outcomes, inclusive of infant weight status. This study found that women engaging in lower intensity physical activity were associated with increases in infant birthweight whereas participation in vigorous activities was associated with decrements in infant birthweight(173). These associations were only significant in the third trimester of pregnancy, likely due to the increased fetal energy demand.

Interestingly, the association found between vigorous physical activity and infant birthweight varied by activity status of the mother. These authors found that active women reporting participation in vigorous activity in pregnancy was protective against the delivery of a low birthweight infant, however for sedentary women, engaging in vigorous activity in pregnancy increased the risk of a low birthweight infant. The latter finding may be due to the combination of the unaccustomed stress of high intensity activity and the stress from pregnancy-related changes, which may result in a compensatory augmented uptake(175) of nutrients (e.g. glucose) and an abnormal reduction in the nutrients available to the fetus. The former finding is supported by a controlled trial conducted among elite athletes in pregnancy(84). In this study, pregnant athletes were assigned to a moderate or vigorous exercise training regimen. The authors reported increased birthweights among the high intensity group compared to the moderate intensity group.

Studies evaluating the impact of objectively-measured physical activity on fetal growth did not provide any clearer insight on this relationship. Rufriok et al. 2014 performed a secondary data analysis using data from two randomized

controlled trials(151). Physical activity was assessed at 15 weeks and between 32 to 35 weeks of gestation using an Actigraph accelerometer. These authors found that participation in moderate-to-vigorous physical activity or sedentary behavior had no effect on infant birthweight. Similarly, in a prospective cohort study, Morgan and colleagues (2014) found that physical activity was not associated with the delivery of a macrosomic infant(123). Conversely, in a prospective cohort study, Reid et al. (2014) compared the free-living physical activity and sedentary behaviors, via SenseWear Armband, of women predicted to deliver macrosomic infants relative to controls(146). This study reported that women predicted to deliver a macrosomic infant engaged in less physical activity and more sedentary behavior compared to women predicted to deliver non-macrosomic infants.

Based on the findings from these studies, it appears that the impact of physical activity on infant weight status is inconclusive. Several factors may account for the equivocal nature of the evidence of this relationship. First, a majority of studies examining the association between physical activity and fetal growth utilize self-report measures (e.g., questionnaires, interviews) which vary considerably in the questions used to quantify physical activity and the time period for recall of this behavior (e.g. 1 year, 3 months). Moreover, self-reporting methods are notorious for providing inaccurate estimates of physical activity behavior given issues with recall, social desirability etc(4, 161). Further, the timing of the measurements may have also influenced the findings (e.g. early, mid or late pregnancy). While objective measures of physical activity have been

demonstrated to provide more accurate estimates of physical activity, many of the cut-point thresholds used in these studies were derived from studies conducted among non-pregnant populations(111). Considering substantial physiological changes occur in pregnancy including increases in resting energy expenditure(3, 143), it is reasonable to suggest that the intensity threshold between pregnant and non-pregnant populations are dissimilar. Lastly, the ambiguity of this relationship could be due to the variability in the metric used to define infant weight status. Among these studies, various weight status metrics used included infant birthweight, large-for-gestational age (>90<sup>th</sup> percentile), macrosomia (e.g., >4000g, 4500, or >5,000g). Based on the mixed results and limitations of these studies, it appears that the evidence regarding the effect of maternal physical activity in pregnancy on infant weight status is inconclusive.

#### *Exercise in Pregnancy and Fetal Growth*

Given that exercise is structured, repetitive, and progressive in nature(30) it is plausible that exposure to this type of physical activity may exhibit stronger effects on fetal growth. Additionally, compared to the studies assessing free-living physical activity, exercise training studies likely employ more rigorous study designs and methodologies (i.e. randomized controlled trials, supervised) which may provide better insight nature of the relationship between exercise and fetal growth.

Recently, Wiebe et al. (2015) conducted a systematic review of randomized controlled and controlled trials that examined the effects of supervised prenatal exercise on fetal growth(183). The authors of this review

reported that, in general, women participating in supervised exercise programs during the perinatal period had lower odds (31%) of delivering a macrosomic or large-for-gestational age infant. Additionally, reductions in mean infant birthweight were found among infants born to mothers who exercised during pregnancy compared to infants born to non-exercising mothers. Interestingly, this significant finding was restricted to studies conducted among normal weight women (n=26). The three studies implemented among overweight and obese pregnant women found that participation in an exercise program did not elicit any effect on infant birthweight or the delivery of a macrosomic or large-for-gestational age infant. The lack of a significant effect of exercise on infant weight status among overweight and obese pregnant women is similar to the findings of another review assessing the effects of exercise on gestational weight gain. McDonald et al. (2016) examined the effects of exercise interventions on gestational weight gain and found that 75% of interventions that found a statistically significant reduction in weight gain were conducted among normal weight women(117). Considerable evidence has demonstrated a positive relationship between body weight and energy expenditure(11, 108). This suggests that there is increased difficulty with movement among heavier individuals, which may explain why overweight and obese women are the least active in the pregnant population and tend to have the worst compliance to exercise interventions. Lower compliance found among these women likely results in a reduced exercise dose and as such, may be insufficient to impact infant size.

Conversely, Leet & Flick (2003) conducted a meta-analysis on 30 randomized controlled, controlled trials, and prospective cohort studies evaluating the effects of prenatal exercise on fetal growth(107). Overall, this review found that maternal exercise does not have an appreciable effect on mean infant birthweight. However, among mothers who continued vigorous exercise into the 3<sup>rd</sup> trimester, significant reduction in birthweight (200 to 400g) were found compared to active controls. Interestingly, this reduction in birthweight only applied to women engaging in endurance activity during pregnancy. Participation in non-endurance exercise in the perinatal period did not exhibit any effect on infant birthweight. A recent review evaluated the impact of various types of exercise training (i.e. aerobic, resistance and combined) on maternal and infant health, inclusive of infant weight status. Perales and colleagues (2016) found that for aerobic exercise training studies, reductions in birthweight were found(137). Among resistance exercise training studies, too few studies assessed the effects on infant weight status for the authors to draw any conclusions. Studies exposing pregnant women to both aerobic and resistance training found decreased risk in the delivery of macrosomic infants and reductions in infant birthweight. However, these findings represent only 3 of 21 studies evaluating this relationship, with the remainder reporting no effect on infant weight status.

The conflicting findings regarding the effects of physical activity and exercise on fetal growth may be due to the influence of factors related to the exercise regimen prescribed including, volume and type, timing in pregnancy

(e.g. trimesters), and pre-pregnancy activity of the mother. Clapp and colleagues demonstrated the impact of some of these exercise-related factors in a series of prospective controlled trials implemented in the perinatal period(41, 42, 46). Clapp et al. (2002) examined the effect of exercise volume in pregnancy on fetal growth among a group of active women(42). This study found that pregnant women that maintain or increase their exercise volume  $\geq 50\%$  of preconception levels in mid- to late pregnancy, on average, deliver lighter (3390g vs 3810g) and leaner (8.3% vs 12.1%) infants compared to women who decrease their exercise below this level in similar trimesters. Interestingly, in another study, Clapp & Capeless (1990) compared the effects of two types of endurance exercise (running vs dance aerobics) on birthweight in a sample of active pregnant women(40). Compared to active (pre-pregnancy) controls, women engaging in either types of endurance exercise throughout pregnancy delivered lighter (3381g vs 3691g) and leaner (11.2% vs 16.1%) infants. The birthweights and/or anthropometrics of infants did not differ between the two endurance groups. Conversely, Clapp (2003) speculated that the effect of exercise type on fetal growth may be found when comparing weight-bearing to non-weight bearing exercise(44). Similar controlled studies conducted among active women in pregnancy who were exposed to non-weight bearing exercise (e.g. cycling) found that this type of exercise did not have an effect on birthweight(47). The difference in the effect of these types of exercises on fetal growth may be due to the level of energy expenditure that is associated with each type(102). Consistent evidence has demonstrated that weight-bearing exercise elicits greater levels of energy

expenditure compared to non-weight-bearing exercise. This suggests that the former may reflect a higher intensity of exercise and may explain the reduction in birthweight associated with this type of exercise.

Findings from another study by Clapp et al. (2000) suggest that the effect of exercise on fetal growth may differ based on the activity status of the mother in the preconception period(41). In this study, non-active women were randomized to an exercise condition or control at eight weeks of gestation. Contrary to the findings reported by Clapp et al. (1990, 2002) among active women, the findings from this study demonstrated a positive effect of exercise on birthweight. Previously inactive women that initiated an exercise regimen in pregnancy were found to have heavier infants (3660g vs 3430g) compared to sedentary controls. Body composition (e.g. lean and fat mass) however, was similar between the groups. These findings are in contrast with the meta-analysis of controlled trials conducted by Wiebe et al 2015 and with a large prospective cohort study in Norwegian pregnant women, which found that women reporting an inactive lifestyle in the preconception period delivered lighter infants and were less likely to deliver a macrosomic infant(99). In another study however, Lof et al. (2008) found that pre-pregnancy physical activity was not associated with infant birthweight(109).

Taken together, it appears that the evidence regarding the effects of physical activity and exercise on fetal growth is suggestive of an inverse relationship, such that mothers continuing or initiating exercise in pregnancy may be associated with reduced infant birthweight or decreased risk of delivering a

macrosomic or LGA infant. In addition, it appears that the effect of exercise on fetal growth may vary depending on the exercise-related (e.g. volume) and maternal (e.g. body mass index, activity level) factors. Further, the evidence for this relationship is very limited for overweight and obese women. This is likely due to several factors, which may include small number of exercise trials, low activity levels among this subgroup(50), which likely increases the difficulty of participant recruitment, and this subgroup are often the least compliant(117), which may result in poor adherence to the exercise protocol and potentially diminished effects. The lack of evidence is unfortunate as nearly 50% of women in the preconception period are overweight or obese. Given the considerable evidence demonstrating a positive relationship between maternal adiposity on fetal growth(69, 90), determining whether exercise may be a useful strategy for alleviating the negative effects of maternal weight status on infant weight status should be a public health priority.

### *Cardiorespiratory Fitness in Pregnancy and Fetal Growth*

Cardiorespiratory fitness is defined(171) as the “*ability to engage in physical activities that rely on oxygen consumption as the primary source of energy...and the body’s ability to transport and utilize oxygen.*” Among diverse non-pregnant populations, cardiorespiratory fitness has been demonstrated to be inversely associated with several cardio-metabolic morbidities(118, 168) and mortality(25, 106). Because cardiorespiratory fitness is an attribute of an individual, the mechanisms that underlie its relationship with many cardio-metabolic health outcomes are likely due to the cardiovascular(49),



musculoskeletal(75), and metabolic(156) adaptations that occur as a result of chronic exercise training. As such, higher levels of cardiorespiratory fitness have been demonstrated to be positively associated with metabolic health, characterized by improved glycemic(162) and lipidemic(147) control, insulin sensitivity(120) etc. As indicated in the maternal resources hypothesis, poorer metabolic health in pregnancy as a result of low physical activity, has been suggested to be the primary mechanism that leads to fetal overgrowth. Based on the evidence among non-pregnant populations regarding the relationship between cardiorespiratory fitness and metabolic health, it seems reasonable to speculate that pregnant women possessing a higher level of fitness may 1) demonstrate better metabolic health and 2) deliver infants with reduced birthweights compared to their lower fit counterparts.

### *Cardiorespiratory Fitness in Pregnancy*

Several studies have assessed cardiorespiratory fitness in the perinatal period; however much of this literature has focused on three areas 1) changes in cardiorespiratory fitness with advancing gestation, 2) improvements in cardiorespiratory fitness in response to exposure to exercise training, and 3) responses to exercise, submaximal and maximal fitness testing among active and inactive women.

Although there appears to be inconsistency in the scientific literature regarding the changes in cardiorespiratory fitness with advancing gestation, there is a suggestion that cardiorespiratory fitness is maintained(39, 54, 59, 100, 116, 174). In support of this idea, well-documented maternal physiological adaptations

that occur in pregnancy mimic those achieved by chronic exercise training including increased cardiac output, blood and plasma volume, hematocrit and hemoglobin and decreases in systemic vascular resistance(45, 81). There are two primary purposes to these adaptations. First, these maternal changes ensure that there is adequate blood flow to deliver oxygen and nutrients to the uteroplacental unit and fetus. Second, these alterations also make certain that the mother's normal physiological function is not comprised thereby enabling her to continue usual activities in pregnancy. From an evolutionary perspective, if cardiorespiratory fitness were to decline, this may limit the mother from carrying out necessary tasks (e.g. activities of daily living) potentially reducing metabolic health and imposing adverse effects on the fetus. Additionally, reduced cardiorespiratory fitness may also be disadvantageous during labor and delivery as well as in the early postpartum period, all of which consist of energy demanding tasks (e.g., birth, childcare).

Nonetheless, the ambiguity present in the literature regarding this relationship may be due to several factors. First, the cardiorespiratory fitness testing procedures differ considerably between studies including the mode of exercise (cycle versus treadmill), type of fitness testing (submaximal versus maximal), and equations used to estimate maximal oxygen consumption, which are often validated in non-pregnant populations. Second, significant individual variability exists among these studies which may in part be inherent in nature, but also may be due to the use of small sample sizes. Third, many studies use non-pregnant or postpartum controls to assess changes in cardiorespiratory fitness.

This is problematic as 1) the control subjects used are not the same individual being tested, despite matching on demographic variables, and 2) with respect to postpartum controls, the timeframe in which pregnancy related changes (e.g., cardiac output, blood volume) are normalized is uncertain and varies considerably (e.g. 2 weeks to 52 weeks). Lastly, a considerable majority of the studies assessing cardiorespiratory fitness across pregnancy are conducted among healthy, normal weight pregnant women, which severely limits the generalizability of these findings. In addition, given nearly 50% of women of reproductive age are overweight or obese, there is a large gap in knowledge on how pregnancy influences cardiorespiratory fitness in this population. This is particularly concerning considering the established cardio-metabolic health outcomes that are associated with cardiorespiratory fitness found among non-pregnant populations(106, 168).

Given the cardio-metabolic health outcomes associated with cardiorespiratory fitness, a few studies in the current literature assessed the effects of exercise training in pregnancy on cardiorespiratory fitness. Perales et al. (2016) reviewed the effects of prenatal exercise training on maternal and fetal health and reported that of the four high-quality randomized controlled trials that assessed cardiorespiratory fitness as an outcome, three found significant improvements in aerobic capacity(137). While these results are encouraging, not all exercise training studies that measured fitness were included in this review, and controlled studies have found that exercise did not elicit improvements in cardiorespiratory fitness(78). Although evidence suggests that cardiorespiratory

fitness is maintained in pregnancy, decrements in cardiorespiratory fitness have been documented among control groups in exercise training studies(47, 78, 153, 157). Interestingly, most pregnant women participating in exercise training studies are healthy, potentially active and possess higher levels of fitness. This might suggest that when these women participate as non-exercising controls, they may experience some degree of detraining, which has been demonstrated to reduce aerobic capacity(20), as a result of detraining. Additionally, the maintenance of cardiorespiratory fitness in pregnancy may only apply to those who continue their “usual” activities in the perinatal period.

Perales et al. (2016) concluded that the evidence regarding the positive effect of prenatal exercise training on cardiorespiratory fitness is strong; however, there are enough conflicting findings to suggest more research is needed. For studies reporting null effects, factors that may have attributed to these findings include the prescription of an insufficient exercise dose, poor compliance(117), small sample sizes etc. Another limitation to the evidence regarding this association is the limited number of studies that include overweight and obese pregnant women. It is encouraging however, that the few randomized controlled trials conducted among this population have found significant positive effects(144, 153, 176). In addition, it would be of great interest to evaluate how changes in cardiorespiratory fitness as a result of exercise training influence the infant health.

Another major focus of the scientific literature with regard to cardiorespiratory fitness in pregnancy is its effect on responses to exercise. To

address this question, much of the literature has compared the responses to exercise testing between “fit” and sedentary pregnant women. Pivarnik et al. (1993) demonstrated that, in the third trimester of pregnancy, fit women had a higher cardiovascular respiratory efficiency in response to submaximal exercise, indicated by increased cardiac output, alveolar ventilation, and decreases in the physiological dead space-to-tidal volume ratio relative to sedentary controls(140). In addition, O’Neill et al. (1993), found that a given submaximal workload, trained pregnant women had significantly lower heart rates, and marginally significant increases in oxygen consumption, stroke volume and cardiac output relative to untrained controls(125). Moreover, Wolfe et al. (1994), reported that at peak exercise, aerobically conditioned pregnant women had higher power output, oxygen uptake and heart rate compared to a non-exercising control group(185). Two important concepts can be suggested based on the evidence regarding the relationship between prenatal cardiorespiratory fitness and responses to exercise. First, enhanced responses to exercise as a result of higher levels of cardiorespiratory fitness appear to be maintained throughout pregnancy compared to lower fit pregnant women. With regard to Pivarnik et al. (1993), because the fit women continued to engage in physical activity throughout pregnancy, it is difficult to discern whether the enhanced responses to exercise would have been maintained in pregnancy had these women not participated in exercise. As such, it cannot be concluded that the maintenance of these responses are entirely due to higher levels of cardiorespiratory fitness in pregnancy. However, Clapp et al. (1989) demonstrated that fit women who

continued a moderate-to-high intensity exercise program throughout pregnancy maintained their augmented response to exercise reflected by a similar oxygen consumption at a given submaximal workload across all three trimesters(43). Conversely, the enhanced responses to exercise among fit women whom discontinued their exercise program at the beginning of pregnancy were negatively attenuated, illustrated by increased oxygen consumption at a given submaximal workload throughout pregnancy. These findings potentially suggest that in order to maintain pre-pregnant cardiorespiratory fitness levels in pregnancy, a woman may need to continue to participate in her “usual” activities.

Collectively, from this evidence it seems that cardiorespiratory fitness may be maintained throughout pregnancy, however this may be dependent on the change in activity level of the preconception to prenatal period. In addition, it appears that cardiorespiratory fitness can be improved as a result of prenatal exercise training. Because the exercise programs varied considerably among the exercise training studies, it is difficult to determine a dose that elicits an increase in fitness suggesting more research in this area is needed. Further, it seems that the enhanced responses to exercise as a result of increased fitness (e.g. cardiac output) are maintained in pregnancy; however, this may also be dependent on maternal activity in pregnancy. Lastly, a considerable limitation of this research is the paucity of these studies conducted among overweight and obese pregnant women, a population that may benefit the most from increase aerobic capacity.

#### *Prenatal Cardiorespiratory Fitness and Fetal Growth*

Given the established cardio-metabolic health outcomes associated with higher levels of cardiorespiratory fitness (e.g. improved glycemic/lipidemic control) it seems reasonable to speculate that increased aerobic capacity in the perinatal period may have favorable effects on infant weight status. The underlying mechanisms to support this hypothesis are consistent with those suggested in the maternal resources hypothesis whereby improved glycemic and lipidemic control may control nutrient supply to the infant and restricting growth to within normal ranges.

While several studies have assessed cardiorespiratory fitness in pregnancy, a small number of studies have examined its influence on infant weight status. As such, the evidence for this relationship is limited. Wong et al. (1987) found that infants born to fit pregnant women were, on average, heavier (3733g vs 3680g) compared to lower-fit counterparts(186). Similarly, Errkola (1975) reported that trained pregnant women delivered more infants weighing greater than 3500g compared to lower-fit women suggesting a higher level of fitness was associated with increased birthweight(59). Kardel (1998) evaluated the effect of exercise intensity on maternal and infant outcomes among pregnant elite athletes(84). Pregnant women participating in the higher intensity exercise program resulted in higher levels of cardiorespiratory fitness and the delivery of larger infants (3650g vs 3590g) compared to women in the moderate intensity exercise program. Conversely, Clapp et al (2002) demonstrated that fit pregnant women continuing their exercise program into late pregnancy had lighter (3390g vs 3810g) and leaner (8.3% vs 12.1%) infants compared to less fit women whom

decreased their exercise in mid-pregnancy(42). Both Pomerance et al. (1973), Price et al. (2005) and Bisson (2013) found that cardiorespiratory fitness had no association with infant birthweight(22, 141, 144).

Based on the current scientific literature it appears that the evidence regarding the effect of maternal cardiorespiratory fitness on infant weight status is equivocal and very limited. Several limitations may explain the present ambiguity. First, there was considerable variability in the fitness testing protocols such as the mode (cycle vs treadmill), equations used to estimate maximal oxygen consumption and thresholds used to determine “fit” versus “unfit.” Second, although evidence indicates that cardiorespiratory fitness is maintained during pregnancy, the timing of the fitness assessments (i.e. 1<sup>st</sup> – 3<sup>rd</sup> trimester) between studies was highly variable, potentially attenuating the magnitude of its association with infant weight status. Third, various metrics of infant weight status were used across the studies including birthweight, macrosomia and percent body fat each of which provide different information on infant anthropometry. Fourthly, most of these studies utilized small samples potentially increasing the difficulty of detecting a difference in infant weight status. Lastly, nearly all of the studies were conducted among normal weight samples suggesting that the evidence of this relationship among overweight and obese pregnant women is severely limited.

#### *The Moderating Role of Prenatal Physical Activity and Cardiorespiratory Fitness*

Given the well-documented potent effects of both physical activity and cardiorespiratory on cardio-metabolic health, it seems reasonable to suggest that



active and/or fit pregnant women may demonstrate improved metabolic control enabling better control of nutrient supply to the fetus thereby protecting the fetus from potential overgrowth. Considerable evidence has indicated that high levels of maternal adiposity are positively associated with the delivery of larger infants(69). In addition, increased adiposity has also been demonstrated to be associated with decreased metabolic health. Assuming this, it may be hypothesized that physical activity and/or cardiorespiratory fitness may moderate the association between maternal adiposity and infant weight status. That is, physical activity and/or a higher level of cardiorespiratory fitness in the preconception-prenatal period may alleviate the negative effects of maternal adiposity on birthweight such that the fetus may be protected from overgrowth.

Currently, to our knowledge, only two studies exist in the scientific literature that have assessed physical activity as a potential moderator on the relationship between maternal adiposity and infant weight status. Fleten et al. (2010) evaluated the direct and indirect associations between exercise in pregnancy on infant birthweight and maternal adiposity in a large Norwegian birth cohort(64). These authors found that exercise (at 17 and 30 weeks gestation) when accounting for maternal body mass index, resulted in a minor impact on infant birthweight. Interestingly, these authors did not explore the impact of the change in exercise from early to late pregnancy and the potential influence on birthweight. In addition, the authors did not describe in any amount of detail the potential moderating effect of exercise in pregnancy on the relationship between maternal adiposity and infant birthweight. In another study, Krogsgaard et al.

(2013) assessed the moderating effect of pre-pregnancy physical activity on the relationship between maternal adiposity and infant weight status in a Norwegian cohort(99). These authors found that for overweight and obese women, those women who reported no or low level of physical activity in the preconception period were more likely to give birth to a heavier neonate and had increased odds of delivering a macrosomic infant compared to women who reported participating in physical activity in the pre-pregnancy period. According to these authors, concluded participation in pre-pregnancy physical activity may attenuate the association between maternal adiposity and infant weight status.

In the present scientific literature, no studies exist which assess the potential moderating effect of cardiorespiratory fitness on the association between maternal adiposity and infant weight status. However, assumptions based on evidence in non-pregnant populations may be drawn to support this relationship. Considerable evidence among non-pregnant populations has demonstrated that higher levels of cardiorespiratory fitness are inversely associated with several cardio-metabolic health outcomes independent of adiposity(106). This may suggest that higher fitness may alleviate the adverse effects of adiposity on metabolic health. Thus, among pregnant women it is hypothesized that a higher level of cardiorespiratory in pregnancy may attenuate the association between maternal adiposity and infant weight status. However, to our knowledge this has not yet been assessed in the literature.

## *Summary*

Given the high prevalence of overweight and obesity in the pregnant population and the robust association between maternal weight status and infant weight status, a strategy that enables a woman to control her metabolic intrauterine environment should be a public health priority. Considering the potent effects of physical activity and cardiorespiratory fitness on metabolic health, it seems reasonable to suggest that these factors influence fetal growth in the perinatal period. However, the evidence regarding the potential moderating effect of physical activity and/or fitness on the relationship between maternal adiposity and infant weight status is largely unknown.

## **Study One**

### *Purpose*

The aim of this study is to determine if maternal physical activity in the preconception and perinatal periods modify the association between maternal weight status and infant weight status among a nationally representative and diverse sample of women delivering live-birth infants. We will address the purpose of this study with two objectives. In the first objective (*Objective 1A*), we will determine if prenatal physical activity modifies the association between maternal weight status and infant weight status. In the second objective (*Objective 1B*), we will determine if pre-pregnancy physical activity alters the moderating effect of prenatal physical activity on the relationship between maternal weight status and infant weight status.

## **Methods**

### *Study Design & Sampling*

The National Maternal Infant Health Survey (NMIHS), conducted by the National Center for Health Statistics in 1988, employed a follow-back survey study design. Existing data from this study will be used to address the aim of this study. The NMIHS sampled women who had a live birth, fetal death or infant death in 1988. In order to make inferences on the nationally representative sample, the NMIHS used a complex survey design that drew stratified samples from live births, fetal and infant deaths in the U.S. (except Montana and South Dakota), identified via registered birth and death certificates. For the purposes of this study, only women delivering live-birth infants will be included. Within live-birth sampling frame, two sampling strata were formed based on the child's race (Black or other than Black) and infant birthweight (<1500g, 1500-2499g, ≥2500g). Within each of the sampling stratum, birth certificates were sorted by maternal marital status and age prior to sampling. In this study, Black infants and very low-birthweight (<1500g) and moderately low-birthweight infants were oversampled. Further details on the sampling procedures are provided elsewhere(152).

### *Study Population & Data Collection*

A total of 13,417 live-birth infants were sampled. Mothers of these infants were mailed a 35-page questionnaire which inquired about prenatal care, maternal health habits, delivery of the infant, hospitalizations pre- and post-delivery, previous and subsequent pregnancies, maternal and paternal sociodemographic characteristics and the infant's health. The recall period,

defined as the time between the delivery of the infant and the receipt of the maternal questionnaire, was on average 17 months (6 to 32 months). Of the 13,417 mothers who delivered a live-birth infant, 9,953 mothers responded to the questionnaire (74.2%). The characteristics of mothers differed among those whom responded and did not respond to the questionnaire. The questionnaire was more likely to be completed by mothers who were between 20 to 39 years, White, married, had fewer than four children, received early prenatal care, more education, and resided in the Midwest region of the U.S. Additionally, mothers of low birthweight infants (<2500g) were also less likely to respond. *Because there are maternal and fetal physiologic differences between single and multiple (e.g., twins) pregnancies, our analyses will be further restricted to women with singleton pregnancies who delivered a live-birth infant (n=9089).*

*Outcome Variable: Infant Birthweight*

Infant weight status will act as the primary outcome variable of interest and be expressed as a continuous and categorical variable. As a continuous outcome, infant weight status will be expressed as infant birthweight, defined as the weight in grams at the time of delivery. As a categorical outcome, we will use established cut-points in the scientific literature to identify large-for-gestational-age infants ( $\geq 90^{\text{th}}$  percentile), average-for-gestational age (11<sup>th</sup> to 89<sup>th</sup> percentile) and small-for-gestational age ( $\leq 10^{\text{th}}$  percentile)(6). Data on infant birthweight and gestational age were extracted from the infant birth certificate.

*Exposure Variable: Maternal Pre-Pregnancy Body Mass Index*

Maternal pre-pregnancy body mass index (BMI) will act as the primary independent variable. BMI will be calculated using the standard equation:  $BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$ . Maternal height was self-reported on the mother's questionnaire in feet and inches as follows: *"How tall are you as of now?"* Because height does not change during pregnancy, her height at the time the questionnaire was administered will serve as "maternal pre-pregnancy height." Pre-pregnancy weight was self-reported on the mother's questionnaire in pounds as follows *"What was your weight just before becoming pregnant..."* For ease of interpretation, maternal pre-pregnancy BMI will be categorized into three groups using widely accepted cut-points(1) as follows: underweight ( $\leq 18.49 \text{ kg/m}^2$ ), normal ( $18.50 - 24.99 \text{ kg/m}^2$ ), overweight ( $25.00 - 29.99 \text{ kg/m}^2$ ) and obese ( $\geq 30.00 \text{ kg/m}^2$ ).

#### *Moderating Variables: Maternal Physical Activity*

Maternal physical activity in the preconception and perinatal periods will act as moderating variables. Pre-pregnancy physical activity was self-reported on the mother's questionnaire by the following question: *"Did you exercise or play sports at least three times a week before you got pregnant?...include brisk walking for ½ hour or more, jogging, aerobics swimming etc."* The response was recorded as "yes" or "no." Prenatal physical activity will be self-reported on the mother's questionnaire by the following question: *"Did you exercise or play sports at least three times a week after you got pregnant?...include brisk walking for ½ hour or more, jogging, aerobics swimming etc."* The response was recorded as "yes" or "no." Additionally, in order to quantify a dose of prenatal

physical activity, we will use the following question: “*How many months of this pregnancy did you exercise or play sports at least 3 times per week?*” The response format was 0 to 10 months. While we acknowledge that these questions specifically refer to ‘*exercise*’ in the preconception and prenatal periods, we surmise that the information provided with regard to this behavior is more reflective of ‘*physical activity*.’ As such, we will use the term ‘*physical activity*’ when referring to this behavior.

### *Maternal Covariates*

#### *Demographics*

Maternal demographic characteristics that may be considered potential covariates include age and race/ethnicity. These data were self-reported and extracted from the birth certificate and mother’s questionnaire, respectively. Maternal age was reported in number of years. Race was reported in the following groups: White, Black, Asian or Pacific Islander or Other. For ethnicity, mothers indicated whether they were from Spanish or Hispanic origin or ancestry. Responses were recorded as “yes” or “no.” Racial and ethnic groups will be collapsed into the following categories: Non-Hispanic White, Non-Hispanic Black, Hispanic and Other.

#### *Pregnancy-Related Covariates*

Maternal pregnancy-related characteristics that may be considered potential covariates include net gestational weight gain and parity. Net gestational weight gain will be calculated using three variables: pre-pregnancy weight, weight just prior to delivery and infant birthweight. Weight gain variables

were self-reported in pounds and were retrieved from the mother's questionnaire. Infant birthweight was extracted from the birth certificate. Gestational weight gain will be calculated by first subtracting pre-pregnancy weight from weight just prior to delivery to determine gestational weight gain.

### *Maternal Behaviors*

Maternal behaviors that may be considered potential covariates include smoking status and alcohol use. These data were self-reported and extracted from the mother's questionnaire. Smoking status and alcohol use were determined by whether or not the mother smoked and/or drank in the last 12 months before delivery. Responses were recorded separately, in a "yes" or "no" format.

### *Infant Covariates*

Infant characteristics that may be considered potential covariates include sex and gestational age. Data on infant sex and gestational age were extracted from the birth certificate. Sex of the infant was recorded as male or female. Gestational age was reported in weeks. The method used to calculate gestational age likely varied but may have included last menstrual period or physician's estimate (e.g. ultrasound or Dubowitz/Ballard).

### **Statistical Analyses**

To determine if pre-pregnancy and prenatal physical activity influence the relationship between maternal weight status and infant weight status, multiple linear and multinomial logistic regression analyses will be performed. The only difference between these two analyses is the expression of the outcome variable



(infant weight status). In the multiple linear regression analyses, infant weight status will be expressed continuously as birthweight in grams. In the multinomial logistic regression analyses, infant weight status will be expressed as a categorical variable with three levels: large-for-gestational age (LGA), average-for-gestational age (AGA) and small-for-gestational age (SGA). AGA will act as the referent group. For both analyses, the expressions of the primary independent, moderating and covariate variables and the model building steps will be identical.

### *Study Variables*

For all the analyses the following variables will be expressed categorically: maternal body mass index (*four levels: underweight, normal weight [referent], overweight, and obese*), pre-pregnancy and prenatal physical activity (*two levels: yes and no [referent]*), maternal race/ethnicity (*four levels: Non-Hispanic White [referent], Non-Hispanic Black, Hispanic, and Other*), smoking and alcohol status (*two levels: yes and no [referent]*), and infant sex (*two levels: male [referent] and female*). The following variables will be expressed continuously: *physical activity dose (number of months)*, maternal age (*years*), net gestational weight gain (*pounds*), and gestational age (*weeks*).

### *Model Building*

All statistical models will be built in the following stages. (1) Bivariate associations will be assessed between all the predictor variables (i.e. independent, moderating and covariates) and both expressions of the outcome variable. (2) The crude association between maternal body mass index and

infant weight status will be examined with a bivariate association and assumptions of the statistical methods will be assessed (e.g. linearity, normality).

(3) To assess the main effect of *prenatal* physical activity, this variable will be entered into the model with the maternal body mass index. (4) To determine the unadjusted moderating effect of prenatal physical activity, an interaction term between maternal body mass index and prenatal physical activity will be entered. (5) Maternal and infant covariates will then be individually added to the model.

To determine if *pre-pregnancy* physical activity alters the impact of *prenatal* physical activity on the association between maternal body mass index and infant weight status, steps 3 through 5 will be repeated to build a new model inclusive of this variable. That is, *pre-pregnancy* physical activity will first be added the unadjusted model (from step 3) as a main effect. Then, the interaction between *prenatal physical activity* and maternal BMI will be added (see step 4). To address the moderating effect of *pre-pregnancy* physical activity a three-way interaction term will be generated. However, before this, two additional two-way interactions must also be entered into to the unadjusted model, 1) maternal BMI and *pre-pregnancy* physical activity, and 2) *pre-pregnancy* and *prenatal* physical activity. The two-way interactions will be entered individually, followed by a three-way interaction between *pre-pregnancy* physical activity, maternal BMI and *prenatal* physical activity. Lastly, maternal and infant covariates will be added separately.

In addition, the NMIHS employed a complex survey design in order to collect a nationally, representative sample of registered births (and deaths) of infants born

to mothers in the U.S. in 1988. Weights were generated to account for this study design and allow for inferences to be made on the population level. As such, weights will be used in all statistical analyses. All statistical analyses will be performed in SAS, using PROC SURVEYREG and SURVEYLOGISTIC (version 9.4). An alpha level of 0.05 will be used to denote statistical significance for all analyses. For multiple linear regression analyses, mean regression coefficients ( $\beta$ ) and their respective 95% confidence intervals will be estimated. For multinomial logistic regression analyses, odds ratios and the corresponding 95% confidence intervals will be calculated.

## **Study 2**

### *Purpose*

The aim of this study is to determine the effect of maternal cardiorespiratory fitness and objectively-measured physical activity on infant weight status in a sample of overweight and obese pregnant women. We will address this study with three objectives. In the first objective (*Objective 2A*), we will evaluate the independent association between cardiorespiratory fitness in mid-pregnancy on infant weight status. In the second objective (*Objective 2B*), we will examine the independent association between objectively-measured physical activity in the perinatal period and infant weight status. In the third objective (*Objective 2C*), we will assess the joint association of maternal cardiorespiratory fitness and objectively-measured physical activity in the perinatal period and infant weight status.

## **Methods**

### *Study Design*

To address the aim of this study, data from a randomized comparative trial (RCT) conducted between November 2001 and July 2006 will be used(190).

Briefly, the primary purpose of the RCT was to examine the effects of moderate intensity exercise during pregnancy on the incidence of preeclampsia and the pathophysiological progress of preeclampsia (e.g. oxidative stress). Secondary outcomes of the exercise trial included maternal weight gain and birth outcomes.

### *Participant Eligibility & Recruitment*

Pregnant women were recruited from nine prenatal clinics under two medical care systems in Michigan. From 14 to 17 weeks of gestation, a run-in period was conducted with weekly lab visits that consisted of a medical record review, cardiorespiratory fitness test, survey administration and a thorough explanation of the exercise trial.

In order to be eligible for the exercise trial pregnant women were: 1) less than 14 weeks gestation, 2) diagnosed with preeclampsia in a previous pregnancy, 3) had a peak oxygen consumption  $\leq$  50<sup>th</sup> percentile of women in their respective age-group, 4) participated in a sedentary lifestyle or had a self-reported energy expenditure of < 840 kcals per day. Pregnant were excluded from the exercise trial if they: 1) were diagnosed with chronic hypertension or pre-gestational diabetes, 2) had medical or physical limitations that prevented them from participating in exercise, 3) were instructed not to exercise during pregnancy by a physician or 4) were unable to communicate with research staff

due to low mental acuity or unable to speak English. A total of 210 women agreed to participate in the study and 41% (n=86) of these women were excluded during the run-in period.

#### *Randomization and Intervention Groups*

After the four-week run-in period (18 weeks of gestation), 124 participants were randomly allocated to the intervention group (n= 64) or comparative group (n=60) using a random numbers table. The intervention group consisted of a walking exercise program. Participants in this group were instructed to walk for 40 minutes, five times per week at a moderate intensity (55-69% maximum heart rate). In the comparative group, participants engaged in a stretching program of equivalent frequency and duration of the exercising group, however were instructed to not exceed a 10% increase in resting heart rate. Stretching sessions consisted of the women following stretching movements delivered via a videotape. All participants wore Polar S810 heart rate monitors to validate their adherence to the exercise or stretching programs. In addition, women wore wristwatch devices to enable them to track their heart rates during exercise or stretching sessions to monitor their target heart rates. Target heart rates were calculated using the Karvonen formula<sup>(85)</sup> for the desired exercise intensities.

#### *Outcome Variable: Infant Weight Status*

Infant weight status will act as the primary outcome variable of interest and be expressed as a continuous and categorical variable. As a continuous outcome, infant weight status will be expressed as infant birthweight, defined as the weight in grams at the time of delivery. As a categorical outcome, we will use

established cut-points in the scientific literature to identify large-for-gestational-age infants ( $\geq 90^{\text{th}}$  percentile), average-for-gestational age ( $11^{\text{th}}$  to  $89^{\text{th}}$  percentile) and small-for-gestational age ( $\leq 10^{\text{th}}$  percentile)(7). Data on infant birthweight and gestational age were extracted from medical records.

### *Exposure Variables: Cardiorespiratory Fitness and Physical Activity*

#### Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF) will act as a primary exposure variable and be expressed as a continuous variable. CRF was defined as peak oxygen consumption ( $\dot{V}O_{2\text{peak}}$ ) which was estimated via a submaximal treadmill test. CRF was assessed twice, at 17 and 28 weeks of gestation. The exercise testing followed the Cornell Exercise Protocol(129). This protocol consisted of walking on a treadmill through eight, two-minute stages with progressive increments in speed and grade. Prior to the initiation and throughout the exercise test, heart rate, blood pressure, fatigue, oxygen consumption, carbon dioxide production and minute ventilation were continuously monitored. The metabolic and respiratory markers were assessed using a portable indirect calorimeter (VO2000, Medical Graphics Corporation, Minneapolis, MN), which has been previously validated in a sample of sedentary pregnant women(191). Heart rate was measured using a Polar S810 heart rate monitor (Warminster, PA) and blood pressure was assessed using a standard sphygmomanometer. Fatigue was measured using the Borg's Scale of Rating of Perceived Exertion(126). The exercise test was terminated if one of the following criteria is achieved: 1) an RPE of 13 to 14, 2) the participant's heart rate fell between values that

correspond to their 85% target heart rate and 85% age-predicted max heart rate, 3) participant request to terminate, or 4) diastolic blood pressure increases more than 10 mmHg.  $\dot{V}O_{2peak}$  was determined by the highest amount of oxygen consumed during the exercise test.  $\dot{V}O_{2peak}$  was expressed relative to participants' body weight as milliliters of oxygen per kilogram per minute ( $mL O_2 \cdot kg^{-1} \cdot min^{-1}$ ).

### Physical Activity

Physical activity will be the primary exposure variable and be expressed as a continuous variable. Daily physical activity was measured using a pedometer (Digiwalker SW200) worn on the participants' waist. The participants were instructed to wear the pedometer during waking hours and to remove them during sleep and any water-based activities (e.g., showering, swimming). Additionally, the participants were asked to keep a log of their total daily step counts. The pedometers were distributed to the participants at 18 weeks of gestation and were retrieved at the end of pregnancy (prior to delivery). For the purposes of this study, total daily steps counts will be averaged across all the available days for each participant to provide an estimate of average daily physical activity.

### *Covariate Variables: Maternal and Infant Characteristics*

Maternal and infant characteristics that may be considered potential covariates include: maternal body mass index (BMI), maternal age, gestational weight gain (GWG), gestational age and group allocation. Maternal BMI will be calculated using the standard equation:  $BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$ . Due to the considerable

missing data for the self-reporting of pre-pregnancy weight (39%), both maternal height and weight at 17 weeks of gestation will be used to calculate BMI. Height and weight were objectively measured during a research lab visit using a standard stadiometer and balance beam scale, respectively. Maternal age and gestational age were extracted from the participants' medical records. Because the exposure of this intervention trial was exercise, which may influence some of the primary independent variables and the outcome variable, we will control for group allocation.

In the scientific literature, GWG is often calculated using self-reported pre-pregnancy weight and weight recorded just prior to delivery. Although both of these variables are available, a significant proportion of these data are missing, 39% and 38%, respectively. As such, GWG will be calculated using three alternative weight variables: weight measured at 17 and 28 weeks gestation and infant birthweight as follows  $[(\text{weight}_{28\text{weeks}} - \text{weight}_{17\text{weeks}}) + \text{birthweight}]$ . In the 3<sup>rd</sup> trimester of pregnancy, fetal growth continues to accelerate and a large proportion of the weight gained is attributable to the weight of the fetus. Because the weight gained during weeks 17 and 28 only capture the beginning of third trimester (weeks 26 to 40), we will add infant birthweight (in pounds) to the weight gained between weeks 17 and 28 as a surrogate measure for maternal gestational weight gain. We recognize that weight may be gained in the first trimester, however only minimal amounts have been documented and consequently we may underestimate GWG.



To determine whether our calculation would be an appropriate representation of maternal weight gain, we compared it to another GWG method which utilized the limited data available on weight just prior to delivery [(weight<sub>delivery</sub> – weight<sub>17 weeks</sub>)]. We calculated the difference between these two measures as follows: ((weight<sub>28weeks</sub> – weight<sub>17weeks</sub> + birthweight) – (weight<sub>delivery</sub> – weight<sub>17 weeks</sub>)). We then computed the average of these differences, in pounds. The average difference between these measures was -2.62 lbs. That is, our measure of GWG, underestimated weight gain, on average, by 2.62 lbs. Based on what appears to be a minimal difference between these two measures, we will use the alternative measure of GWG in order to maximize all available data.

### ***Statistical Analysis***

To determine the effect of maternal cardiorespiratory fitness and prenatal physical activity on infant weight status, multiple linear and multinomial logistic regression analyses will be performed. The only difference between these two analyses is the expression of the outcome variable (infant weight status). In the multiple linear regression analyses, infant weight status will be expressed continuously as birthweight in grams. In the multinomial logistic regression analyses, infant weight status will be expressed as a categorical variable with three levels: large-for-gestational age (LGA), average-for-gestational age (AGA) and small-for-gestational age (SGA). AGA will act as the referent group. For both analyses, the expressions of the primary independent and covariate variables and the model building steps will be identical.

### *Study Variables*

For all the analyses the following variables will be expressed continuously: cardiorespiratory fitness (*ml O<sub>2</sub>/kg/min*), prenatal physical activity (*steps per week*), maternal body mass index (*kg/m<sup>2</sup>*), maternal age (*years*), gestational weight gain (*pounds*), and gestational age (*weeks*). Group allocation (*two levels: intervention and control*) will be expressed as a categorical variable.

### *Model Building*

All statistical models will be built in the following stages. (1) Bivariate associations will be assessed between all the predictor variables (i.e. independent and covariates) and the both expressions of the outcome variable. (2) To assess the independent effects of the primary independent variables (i.e. cardiorespiratory fitness and physical activity) on infant weight status, will be assessed with a bivariate analysis in separate models. (3) Maternal and infant covariates will then be individually added to each model.

To determine the joint effect of cardiorespiratory fitness and physical activity, we will create an interaction term between cardiorespiratory fitness and physical activity. Prior to examining the interaction between cardiorespiratory fitness and physical activity, we will include cardiorespiratory fitness as a main effect in the unadjusted model (from step 2). After this, we enter the interaction. Maternal and infant covariates will then be added individually to each model. This analysis will be carried out separately with both expressions of infant weight status. Given that participants in this sample have a cardiorespiratory fitness level  $\leq 50^{\text{th}}$  percentile of their respective age-group, we will retain

cardiorespiratory fitness as a continuous variable to avoid further reducing the variability in this variable. If the interaction term is significant, we will then assess the effect of physical activity on infant weight status on varying levels of cardiorespiratory fitness by generating estimate statements. Because there are no established standards for cardiorespiratory fitness in pregnant women, we will select fitness levels for the estimate statements that correspond to values at the 25<sup>th</sup>, 50<sup>th</sup> and 75<sup>th</sup> percentiles. We will use these values and compare the differences in the slopes for the effect of physical activity on infant weight status between the selected cardiorespiratory fitness levels. For all analyses statistical significance will be determined at an alpha level of 0.05. For multiple linear regression analyses, mean regression coefficients ( $\beta$ ) and their respective 95% confidence intervals will be estimated. For multinomial logistic regression analyses, odds ratios and the corresponding 95% confidence intervals will be calculated.

### **Study 3**

#### *Purpose*

The aim of this study is to determine the effect of change in prenatal physical activity and cardiorespiratory fitness on infant weight status in a sample of overweight and obese pregnant women. We will address this study with two objectives. In the first objective (*Objective 3A*), we will evaluate the association between the change in prenatal physical activity and infant weight status. In the second objective (*Objective 3B*), we will examine the potential moderating effect

of cardiorespiratory fitness on the association between prenatal physical activity and infant weight status.

## **Methods**

### *Study Design*

To address the aim of this study, the same data from the randomized comparative trial (RCT) in Study Two will be used. Briefly, the primary purpose of the RCT was to examine the effects of moderate intensity exercise during pregnancy on the incidence of preeclampsia (PE) and the pathophysiological progress of preeclampsia (e.g. oxidative stress). Secondary outcomes of the exercise trial included maternal weight gain and birth outcomes(190).

### *Participant Eligibility & Recruitment*

Pregnant women were recruited from nine prenatal clinics under two medical care systems in Michigan. From 14 to 17 weeks of gestation, a run-in period was conducted with weekly lab visits that consisted of a medical record review, cardiorespiratory fitness test, survey administration and a thorough explanation of the exercise trial.

In order to be eligible for the exercise trial pregnant women were: 1) less than 14 weeks gestation, 2) diagnosed with PE in a previous pregnancy, 3) had a peak oxygen consumption  $\leq$  50<sup>th</sup> percentile of women in their respective age-group, 4) participated in a sedentary lifestyle or had a self-reported energy expenditure of < 840 kcals per day. Participant exclusion criteria are detailed in Study Two. A total of 210 women agreed to participate in the study and 41% of these women were excluded during the run-in period.

### *Randomization and Intervention Groups*

After the four-week run-in period (18 weeks of gestation), 124 participants were randomly allocated to the exercise intervention group (n= 64) or comparative [stretching] group (n=60) using a random numbers table. Further details on the exercise and comparative groups are provided in Study Two.

### *Outcome Variable: Infant Weight Status*

Infant weight status will act as the primary outcome variable of interest and be expressed as a continuous and categorical variable. As a continuous outcome, infant weight status will be expressed as infant birthweight, defined as the weight in grams at the time of delivery. As a categorical outcome, we will use established cut-points in the scientific literature to identify large-for-gestational-age infants ( $\geq 90^{\text{th}}$  percentile), average-for-gestational age ( $11^{\text{th}}$  to  $89^{\text{th}}$  percentile) and small-for-gestational age ( $\leq 10^{\text{th}}$  percentile)(7). Data on infant birthweight and gestational age were extracted from medical records.

### *Exposure Variable: Physical Activity*

Physical activity will also act as a primary exposure variable and be expressed as continuously. Daily physical activity was measured objectively using a pedometer (Digiwalker SW200) worn on the participants' waist. The participants were instructed to wear the pedometer during waking hours and were to be removed during sleep and any water-based activities (e.g., showering, swimming). Additionally, the participants were asked to keep a log of their total daily step counts. The pedometers were distributed to the participants at 18 weeks of gestation and were retrieved at the end of pregnancy (prior to delivery).

For the purposes of this study, an average change score in physical activity will be calculated (for details see Statistical Analysis section).

*Moderating Variable: Cardiorespiratory Fitness*

Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF) will act as a moderating variable and be expressed as a continuous variable. CRF was defined as peak oxygen consumption ( $\dot{V}O_{2peak}$ ) which was estimated via a submaximal treadmill test. CRF was assessed twice, at 17 and 28 weeks of gestation.  $\dot{V}O_{2peak}$  was expressed relative to participants' body weight as milliliters of oxygen per kilogram per minute ( $\text{mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Given that CRF has been demonstrated to remain constant throughout pregnancy, we will average the CRF values at 17 and 28 weeks gestation to represent the 'average prenatal CRF level.' For further methodological details on the CRF testing, please refer to the Methods section in Study Two.

*Covariate Variables: Maternal and Infant Characteristics*

Maternal and infant characteristics that may be considered potential covariates include: maternal body mass index (BMI), maternal age, gestational weight gain (GWG), gestational age, group allocation and baseline physical activity. Maternal BMI will be calculated using the standard equation:  $\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$ . Due to the considerable missing data for the self-reporting of pre-pregnancy weight (39%), both maternal height and weight at 17 weeks of gestation will be used to calculate BMI. Height and weight were objectively measured during a research lab visit using a standard stadiometer and balance

beam scale, respectively. Maternal age and gestational age were extracted from the participants' medical records. Because the exposure of this intervention trial was exercise, which may influence some of the primary independent variables and the outcome variable, we will control for group allocation.

In the scientific literature, GWG is often calculated using self-reported pre-pregnancy weight and weight recorded just prior to delivery. Although both of these variables are available, a significant proportion of these data are missing, 39% and 38%, respectively. As such, GWG will be calculated using three alternative weight variables: weight measured at 17 and 28 weeks gestation and infant birthweight as follows  $(((\text{weight}_{28\text{weeks}} - \text{weight}_{17\text{weeks}}) + \text{birthweight}))$ . For further details on the calculation of this variable, please see the Methods section in Study Two.

### ***Statistical Analysis***

To determine the effect of maternal cardiorespiratory fitness and change in prenatal physical activity on infant weight status, multiple linear and multinomial logistic regression analyses will be performed. The only difference between these two analyses is the expression of the outcome variable (infant weight status). In the multiple linear regression analyses, infant weight status will be expressed continuously as birthweight in grams. In the multinomial logistic regression analyses, infant weight status will be expressed as a categorical variable with three levels: large-for-gestational age (LGA), average-for-gestational age (AGA) and small-for-gestational age (SGA). AGA will act as the

referent group. For both analyses, the expressions of the primary independent and covariate variables and the model building steps will be identical.

### *Change in Prenatal Physical Activity*

To best represent the change in the observed patterns of physical activity behavior, we will calculate a change score that maximizes the available data. Prenatal physical activity was measured daily via pedometry from week 18 of gestation until delivery, and is expressed as step counts. We will calculate the change in step counts through a series of stages. First, we will collapse daily step counts into average weekly steps counts for each individual. Second, we will then calculate a baseline level of physical activity by averaging weekly step counts for the first four weeks of measurement (i.e. 18 to 22 weeks). Using a four-week measurement period may provide some advantages including accounting for changes in behavior due to reaction to the device and providing a more accurate representation of physical activity behavior. Also, during this four-week period, gestational weight gain has not yet accelerated, which may influence levels of physical activity and thus, minimal changes in physical activity patterns will likely have occurred. Third, we will create five, four-week periods (22 to 26 weeks, 26 to 30 weeks, 30 to 34 weeks, 34 to 38 weeks, and 38 to 42 weeks) and for each we will compute the average weekly step counts. Fourth, we will then determine the average change (or difference) in step counts between each of these five periods and baseline physical activity levels. Based on previous scientific literature, we will assume that the change in physical activity may differ between trimesters, with the largest declines occurring in the third trimester. As such, we



will initially create two “physical activity change variables,” one for the second trimester (weeks 22 to 26) and another for the third trimester (weeks 26 to 42). In addition, it is possible that within the third trimester, the changes in the average weekly steps across the remaining four periods may differ considerably. As a result, we will examine the four periods of the third trimester to determine if large differences in the changes in average weekly step counts are present. A 10% difference between the monthly periods will be considered a “large” difference. If no large differences are present, then all four periods will be collapsed and an average weekly step count for the entire third trimester will be calculated. In the case where large differences exist, then an additional physical activity change variable in the third trimester may be created.

### *Study Variables*

For all the analyses the following variables will be expressed continuously: changes in prenatal physical activity in the second trimester and third trimester (*steps per week*), baseline physical activity (*steps per week*), cardiorespiratory fitness (*ml O<sub>2</sub>/kg/min*), maternal body mass index (*kg/m<sup>2</sup>*), maternal age (*years*), gestational weight gain (*pounds*), and gestational age (*weeks*). Group allocation (*two levels: intervention and control*) will be expressed as a categorical variable.

### *Model Building*

All statistical models will be built in the following stages and performed separately with each expression of infant weight status. (1) Bivariate associations will be assessed between all the predictor variables (i.e. independent, moderator and covariates). (2) Because there will be more than one variable that represents

change in physical activity (i.e. 2<sup>nd</sup> and 3<sup>rd</sup> trimesters), each variable will be entered individually into the model, beginning with the change in the 2<sup>nd</sup> trimester. This will assess the unadjusted effects of changes in prenatal physical activity on infant weight status. (3) Maternal and infant covariates will then be individually added to each model.

Next, to determine the moderating effect of cardiorespiratory fitness on the relationship between changes in prenatal physical activity on infant weight status, we will create an interaction term between cardiorespiratory fitness and each change in physical activity variable. Prior to examining the interaction, we will thoroughly assess the relationships between these variables in the subsequent stages. (1) We will first examine the unadjusted main effects of cardiorespiratory fitness and change in physical activity in the *2<sup>nd</sup> trimester* on infant weight status. (2) We will assess the unadjusted main effects of cardiorespiratory fitness and change in physical activity in the *3<sup>rd</sup> trimester* on infant weight status. (3) We will then examine the unadjusted main effects of cardiorespiratory fitness and the changes in physical activity in the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters, added sequentially. (4) Using the model from step 3, we will enter an interaction term between cardiorespiratory fitness and change in physical activity in the *2<sup>nd</sup> trimester*. (5) Using the model from step 4, we will add another interaction term between cardiorespiratory fitness and change in physical activity in the *3<sup>rd</sup> trimester*. (6) Maternal and infant covariates will then be added individually to each model. Given that participants in this sample have a cardiorespiratory fitness level  $\leq 50^{\text{th}}$  percentile of their respective age-group, we will retain cardiorespiratory fitness as

a continuous variable to avoid further reducing the variability in this variable. If the interaction term is significant, we will then assess the effect of physical activity on infant weight status on varying levels of cardiorespiratory fitness by generating estimate statements. Because there are no established standards for cardiorespiratory fitness in pregnant women, we will select fitness levels for the estimate statements that correspond to values at the 25<sup>th</sup>, 50<sup>th</sup> and 75<sup>th</sup> percentiles. We will use these values and compare the differences in the slopes for the effect of changes in physical activity in the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters on infant weight status between the selected cardiorespiratory fitness levels. For all analyses, statistical significance will be determined at an alpha level of 0.05. For multiple linear regression analyses, mean regression coefficients ( $\beta$ ) and their respective 95% confidence intervals will be estimated. For multinomial logistic regression analyses, odds ratios and the corresponding 95% confidence intervals will be calculated.

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