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The Effect of Fetal Programming on Physical Activity Behaviors

Jessica Garay Redmond
Syracuse University

Abstract

Appropriate fetal growth and development largely depends on the health and nutritional status of the mother. Exposure to a stressful intra-uterine environment leads to a series of adjustments, known as fetal programming, which have both short- and long-term implications. Immediately, the growth and development of the fetus is altered, resulting in intra-uterine growth restriction and a small size at birth. Long-term, individuals who experience fetal programming are at higher risk of developing certain chronic diseases.

In the current study, we examined the relationship between size at birth (an indicator of intra-uterine growth restriction and thus, fetal programming) and two main outcomes, physical activity behaviors and muscle strength, in a cohort of healthy young adults. Birth weight was adjusted for gestational age to create a standardized birth weight (SBW). Physical activity behaviors included sedentary behavior and moderate-to-vigorous physical activity, which were both measured using two different accelerometers over a seven-day period. Muscle strength was measured four times: dominant handgrip maximal voluntary contraction (MVC), non-dominant handgrip MVC, left leg MVC, and right leg MVC. Additional measurements included height, weight, body composition, and maximal oxygen consumption (VO_{2max}) as a measure of cardiorespiratory fitness.

A total of 124 participants completed the study. A subset of 75 participants completed the accelerometer measurements and performed a VO_{2max} test. Using data from this subset, no relationship emerged between SBW and time spent in either moderate-vigorous physical activity ($B = 5.642$, $p = 0.088$) or sedentary behavior ($B = -14.571$, $p = 0.422$) among the full cohort of healthy young adults. However, the relationship between SBW on time spent in

MVPA depends on age. Participants aged 18 – 21 (N = 42) years had an increase of 7.02 minutes of MVPA for each unit increase in SBW (p = 0.017). Participants aged 22 – 40 years (N = 33) had a decrease of 10.8 minutes of MVPA for each unit increase in SBW (p = 0.021). Furthermore, there was a non-significant trend toward a sex effect on the relationship between SBW and time spent in SED. Among male participants (N = 15), time spent in SED increased by 26.7 minutes with every 1 unit increase in SBW (p = 0.203). Among female participants (N = 60), time spent in SED decreased by 13.5 minutes for every 1 unit increase in SBW (p = -0.250).

A subset of 100 participants performed the muscle strength testing. Participants born small for gestational age had lower muscle strength in their dominant hand compared to adults born at a normal size for gestational age (B = 1.533 kg/1 SD increase in SBW, p = 0.004). After controlling for sex and lean body mass, SBW explained 8.4% of the variance in dominant handgrip MVC. LBM had a significant indirect effect on the relationship between SBW and dominant handgrip MVC, confirmed by mediation analysis using the Sobel test (p = 0.04), partial posterior p-value (p = 0.025), and hierarchical Bayesian confidence interval (95% CI = 0.063, 1.401). These results suggest that individuals born small not only have muscles that function less well, but also tend to have smaller muscles.

In conclusion, muscle strength is directly related to size at birth among healthy young adults. The effect of FP on later-life physical activity behaviors remains unclear, but may be influenced by age and sex. The results of the current study confirm that permanent physical and physiological effects of FP on skeletal muscle development and performance. More research is needed to determine the role of intra-uterine stress on physical activity behaviors.

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by

Jessica Garay Redmond, MS, RDN, CDN, FAND, CSCS

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M.S. George Washington University, 2010

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Dedication

To all three of my sons – Graham, Duncan, and Jordan. You were each a part of this journey.

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I am grateful for the mentorship of my advisor, Dr. Tom Brutsaert, throughout this process. I appreciate the respect you showed me from day one and the freedom you gave me to establish myself as a scholar. Thank you for navigating me to this point. I would also like to thank the members of my committee – Dr. Tiago Barreira and Dr. Qiu Wang, for their advice and guidance. In particular, I greatly appreciate the efforts of Tiago, the "accelerometer guru". Thank you for sharing your knowledge with me.

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Glossary of Terms

Appropriate for gestational age (AGA) – an individual who is between the 10^{th} – 90^{th} percentiles on the weight-for-age growth chart at birth

Bioelectrical impedance analysis (BIA) – method of measuring body composition to determine body fat percentage and lean body mass

Birth length (BL) – head to foot length of an individual at birth

Birth weight (BW) – weight of an individual at birth

Body mass index (BMI) – ratio of weight to height that is used to classify children and adults as underweight, normal weight, overweight, and obese

Epigenetic changes – methylation of cytosine nucleotide bases on DNA or addition of a methyl or acetyl group on histone proteins, resulting in modified gene expression.

Fetal programming (FP) – theory suggesting that a fetus experiencing intra-uterine stress is subsequently programmed to have increased risk of disease throughout life

Gestational age (GA) – term used to describe the current timepoint of a pregnancy; also used to identify the age at which an individual was born relative to the due date (40 weeks); a typical term pregnancy lasts 37 – 42 weeks gestation

High-density lipoprotein (HDL) cholesterol – a type of lipoprotein found in the body; adequate levels in the bloodstream are needed in order to facilitate the removal of cholesterol from the body; low levels in the bloodstream are considered a risk factor for heart disease

Intra-uterine growth restriction (IUGR) – inadequate fetal growth; can be identified using ultrasound during pregnancy or presumed if an individual is born small for gestational age

Large for gestational age (LGA) – an individual who is above the 90^{th} percentile on the weight-for-age growth chart; also referred to as fetal macrosomia

Lean body mass (LBM) – the amount of an individual's body weight that includes the musculoskeletal systems; this amount does not include body fat mass

Low-density lipoprotein (LDL) cholesterol – a type of lipoprotein found in the body; elevated levels in the bloodstream are associated with an increased risk of atherosclerosis and heart disease

Maximal oxygen consumption (VO_{2max}) – an indicator of cardiorespiratory (aerobic) fitness level; usually measured during a treadmill or cycle test to exhaustion

Maximal voluntary contraction (MVC) – a type of exercise which fully challenges the targeted muscles through an intentional, sustained contraction.

Metabolic equivalent (MET) – a measure representing the oxygen consumed by a person at rest that is used to indicate intensity of activity; one MET represents the oxygen consumed by a person at rest and is approximately 3.5 milliliters of oxygen per kilogram body weight per minute (ml/kg/min).

Ponderal index (PI) – ratio of birth weight to birth length that is similar to body mass index; used to identify small, thin babies who likely experienced intra-uterine growth restriction

Standardized birth weight (SBW) – the variable used in the current study to represent birth weight adjusted for gestational age; more details available in Chapter 3.

Small for gestational age (SGA) – an individual who is below the 10^{th} percentile on the weight-for-age growth chart; may indicate intra-uterine growth restriction

Time spent in sedentary behavior (SED) – during awake hours, any time that an individual spends sitting or lying down

Time spent in moderate or vigorous physical activity (MVPA) – the amount of time an individual is engaged in exercise above 3 metabolic equivalents (METs)

Wake wear time – the amount of time that an individual has worn an accelerometer device while awake

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Chapter 1: Introduction

During pregnancy, stress experienced by the mother, be it physical, psychosocial, or environmental, can create detrimental effects on the offspring. Exposure to war or natural disaster are extreme examples, while a more common source of stress is inadequate maternal dietary intake. Pregnant women need to consume an additional 340 – 450 kilocalories per day during the second and third trimester, with 100 of those kilocalories coming from a protein food source [1]. Several vitamins and minerals also have increased intake needs, including folic acid, iron, and iodine [1]. If maternal dietary intake does not meet the additional requirements, the fetus is likely experiencing intra-uterine stress.

A conceptual framework illustrating the long-term effects of intra-uterine stress is shown in Figure 1. The presence of a stressful intra-uterine environment will cause the developing individual to undergo a series of adjustments, known as "fetal programming" (FP). These adjustments include alterations to the in utero growth and development of tissues and organs such as the liver and pancreas. Overall, this leads to intra-uterine growth restriction (IUGR) and a small size at birth. Factors such as maternal smoking and maternal size also independently influence the risk of IUGR and thus size at birth.

Several mechanisms have been proposed to explain FP adjustments, including placental insufficiency, production of reactive oxygen species, and endoplasmic reticulum stress [2]. However, epigenetic changes that affect expression of genes and transcription of proteins underlie these and other FP adjustments [2, 3]. For example, epigenetic changes in expression of various nuclear receptors may lead to disruptions of primary hormonal pathways (i.e. hypothalamic-pituitary-adrenal axis) and impaired hormone production and release [3, 4].

The sum total of these in utero responses to stress is permanent impairment to an individual's musculoskeletal, cardiovascular, and metabolic health, leading to an increased risk of developing chronic diseases such as obesity, diabetes, heart disease, and osteoporosis at some point during their life [5]. Past research indicates individuals born small are more likely to have higher body fat and lower lean body mass as adolescents or adults compared to peers born at a normal BW [5-16]. Risk factors for metabolic syndrome, including measures of glucose regulation and blood lipids, are altered in individuals who experienced intra-uterine stress. Insulin resistance scores, which reflects elevated glucose and insulin, are higher among adults born at a low BW [17]. Triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol have a tendency to be higher in individuals born at a low birth weight (BW), while high-density lipoprotein (HDL) cholesterol is lower in these individuals, but the strength of these relationships vary from study to study [18, 19]. Heart disease risk, measured in terms of blood pressure or actual diagnosis of coronary artery disease, appears higher amongst individuals who likely experienced intra-uterine stress, although this relationship may demonstrate a "U-shaped" curve, meaning that individuals born both small and large experience higher risk [20, 21]. In addition to heart disease, other chronic diseases may be prevalent in those who experienced intra-uterine stress, including sarcopenia and osteoporosis [22-30]. Lifelong dietary intake patterns (represented by the green box in Figure 1.1) can independently alter adult risk factors for chronic diseases as well as the diseases themselves.

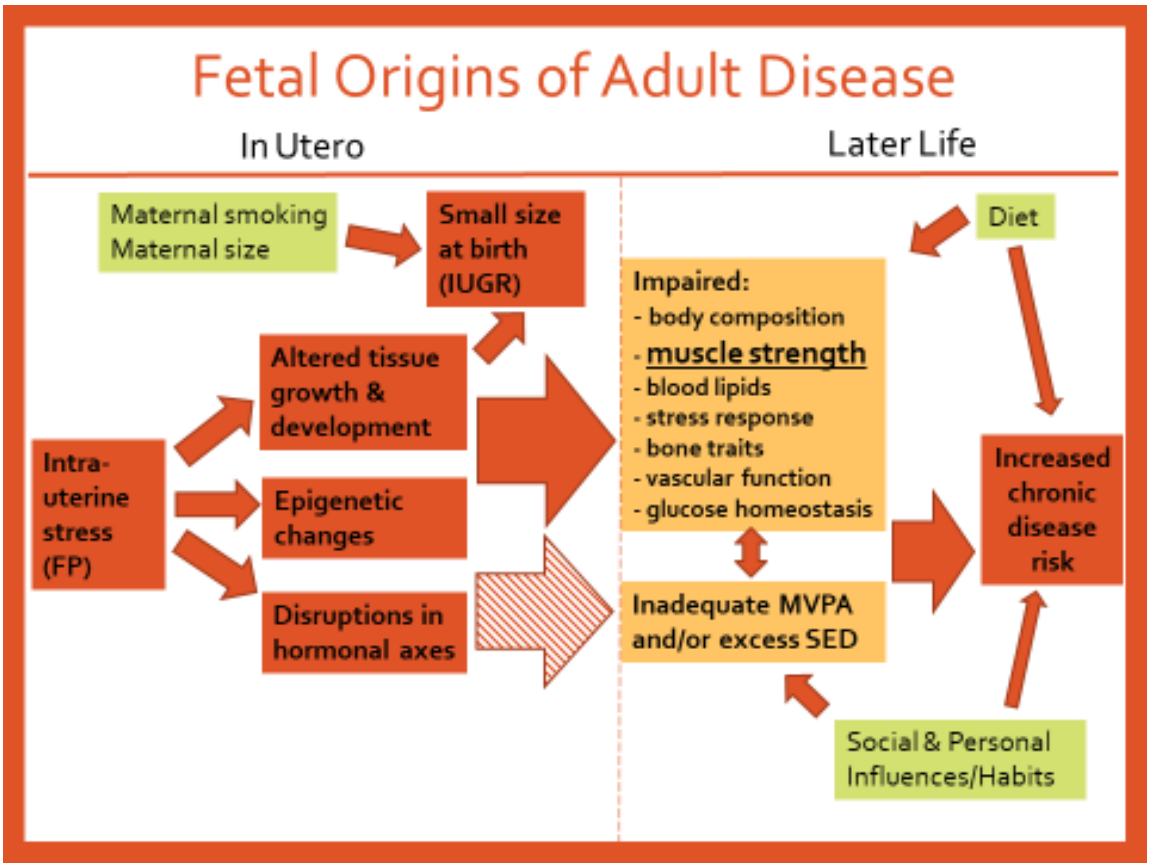

Figure 1.1. Proposed conceptual pathway of the effects of intra-uterine stress.
MVPA = time spent in moderate or vigorous physical activity;
SED = time spent in sedentary behavior

The striped arrow in Figure 1.1 indicates that it is not clear whether or not there is a link between the effects of intra-uterine stress and physical activity behaviors in adulthood. Numerous studies have demonstrated the positive benefits of a physically active lifestyle throughout adulthood, including a lower risk of developing chronic disease compared to less active adults [31-33]. A growing body of research suggests that adequate levels of physical activity may protect those already "programmed". Meeting physical activity recommendations may modify the association between BW and levels of the satiety hormone leptin [34]. Engaging in vigorous physical activity and/or being aerobically fit appears to protect adults who were born

small against the development of metabolic syndrome [35]. Similar studies have found that regular exercise may reduce the risk of developing insulin resistance in both adolescents and adults born small [36, 37]. However, this pattern is not consistently seen in all studies, particularly among adolescents [38]. Emerging research is focused on the negative consequences of accumulating excessive physical inactivity or sedentary behavior, such as increased risk of developing metabolic syndrome [39, 40].

There are also numerous social-cognitive and personal influences on physical activity behaviors in adulthood (represented by the green box in Figure 1), including screen time, perceived barriers, and social support. "Screen time" refers to time spent watching television, using a computer/tablet, and/or playing video games. Television viewing has previously been linked with a low level of physical fitness and an increased risk of being overweight [41]. Perceived barriers to exercise, preferred mode of transportation, and family/friend support are also strong influences on physical activity behaviors [42-46].

There is a bi-directional arrow in Figure 1.1 to reflect that physiological changes may influence an individual's level of physical activity, and vice versa, that participation in physical activity can improve certain biomakers. Among adolescents, engaging in vigorous intensity physical activity is associated with greater lower body muscle strength [47]. Among older adults, expending more energy in physical activity was associated with lower body fat and higher lean body mass in the arms and legs [48]. This selected set of examples demonstrates the interaction between the organ systems of the body and physical activity behaviors.

The goal of this study was to determine whether adults who likely experienced intra-uterine stress spent different amounts of time in sedentary behaviors (SED), such as sitting or lying down (while awake), or in moderate-to-vigorous physical activity (MVPA), compared to

adults who did not experience intra-uterine stress. As shown in Figure 1.1, we hypothesized that the various effects occurring as a result of intra-uterine stress may predispose an individual to engage in less MVPA and accumulate more SED, thus increasing risk of chronic diseases. Animal models confirm that exposure to a nutrient-poor in utero environment leads to less physical activity post-birth, an effect that was stronger among males [49]. Recent analysis of our own survey data revealed that among adults, the odds of self-reporting the "very high" category of physical activity are significantly higher with increasing quartile of BW (adjusted for gestational age, GA) [50]. Among adolescents, it appears that BW does not have a strong association with either physical activity or sedentary time [51]. However, other evidence from adolescents and adults suggests that the true relationship between BW and physical activity may be U-shaped, with the lowest levels of physical activity among those who have the lowest or highest BW [52]. Research investigating the link between size at birth and sedentary behavior is limited, particularly among adults.

Purpose

The purpose of the current study was to objectively measure (using accelerometry) the amount of time spent in MVPA or SED among healthy adults born full-term with varying BW.

A secondary purpose of this study was to measure muscle strength, body composition, and aerobic fitness in this population, and to associate each of these outcome measures with BW.

Specific Aims

Individuals exposed to intra-uterine stress are predisposed to a higher risk of chronic diseases [20, 53-57]. Research has shown that these individuals often have lower muscular strength and higher adiposity compared to individuals who did not experience stress in utero [5, 15, 16, 22-28, 58-60]. Aerobic fitness level may be lower in these individuals, but this finding has not been consistent across studies [61-63]. It is also unclear from the existing literature if intra-uterine stress has any association with physical activity behaviors, including both MVPA and SED.

The main objective of this study was to determine the relationship between birth size (an indicator of IUGR and presumed FP due to intra-uterine stress) and time spent being physically active or sedentary among a cohort of healthy young adults. A secondary objective was to assess the relationship between birth size and muscle strength across this population. The results of this research study contribute to the growing body of evidence investigating the lifelong impact of intra-uterine stress, IUGR, and FP.

As shown in Figure 1.1, physical activity behaviors may be altered in adults who experienced intra-uterine stress. These individuals may have increased levels of SED and/or lower levels of MVPA. Thus, our primary aims in the current study are:

(1) To determine if size at birth is directly associated with time spent in MVPA in adulthood.

(2) To determine if size at birth is directly associated with time spent SED in adulthood.

Based on previous research, it is believed that intra-uterine stress predisposes individuals to have lower muscle strength compared to individuals who were not exposed to this type of stress.

Therefore, the secondary aim of the current study is:

(3) To determine if size at birth is directly associated with muscle strength.

Hypotheses

Related to specific aim #1, we hypothesized the following:

(1) Time spent in SED (as measured by activPAL accelerometer) will be highest among adults born at a low birth weight (BW) controlling for gestational age (GA).
(2) Time spent in MVPA (as measured by ActiGraph accelerometer) will be lowest among adults born at a low birth weight (BW) controlling for gestational age (GA).

Related to specific aim #2, we hypothesized the following:

(3) Birth weight (controlling for gestational age) will be positively associated with grip strength.

Specifically, we predicted that adults born at a low birth weight (BW) controlling for gestational age (GA), would have lower grip strength.

We tested each of these hypotheses after controlling for body size differences and other relevant confounding variables (as appropriate). The specific aims and hypotheses are summarized in the analytic framework shown in Figures 1.2 and 1.3. The main arrow in Figure 1.2 represents specific aims 1 and 2. Other variables shown in the framework represent potential confounding variables. Gestational age (GA) will impact birth weight (BW), which is why in our analysis we have constructed a standardized BW variable that takes GA into account. There are known sex differences in both BW and physical activity behaviors, and therefore sex is included as a potential covariate for both specific aims 1 and 2. Age, body composition (represented by body fat percentage), and aerobic fitness (represented by VO_{2max}) each independently associate with physical activity behaviors, and therefore may influence the overall relationship between

BW and either time spent in MVPA or SED. Lastly, accelerometer wake wear time will impact the amount of time that an individual is recorded achieving MVPA or SED.

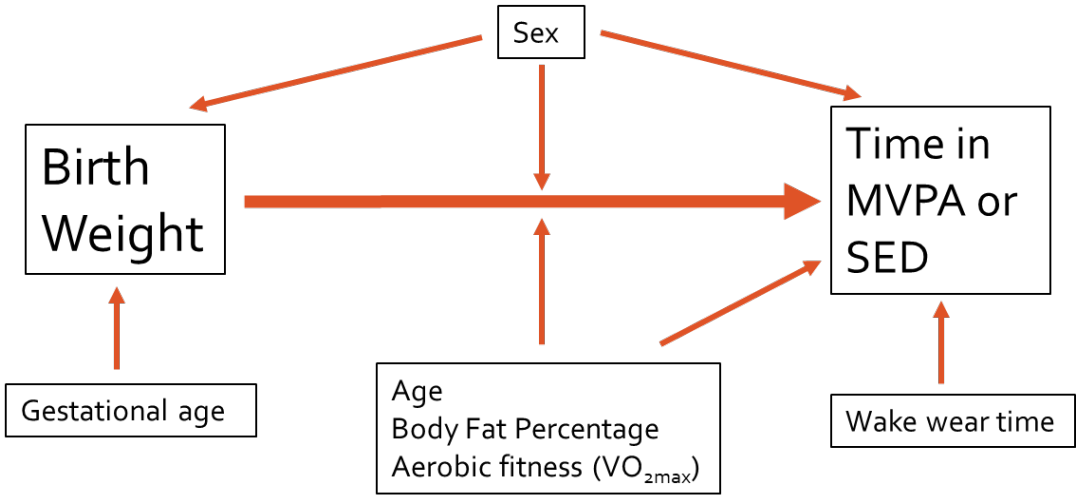

Figure 1.2. Analytic framework for specific aims 1 and 2.

Figure 1.3 displays the analytic framework for specific aim 3. The main arrow shows the overall relationship being tested between size at birth (BW) and adult grip strength. As with Figure 1.2, GA is included since it impacts BW. In our analysis, we did not include GA as a separate covariate since we constructed a standardized BW that takes GA into account. Lean body mass was included in the model to represent body size. Individuals born at a low BW have less lean body mass than peers born at a normal BW, and lean body mass is directly correlated with muscle strength [64]. Therefore, lean body mass is included as a potential mediating variable in the overall relationship tested in specific aim 3. In addition, there are known sex differences in BW, lean body mass, and muscle strength, so it is also included as a possible covariate. More details about the statistical analysis for all specific aims is provided in Chapter 3.

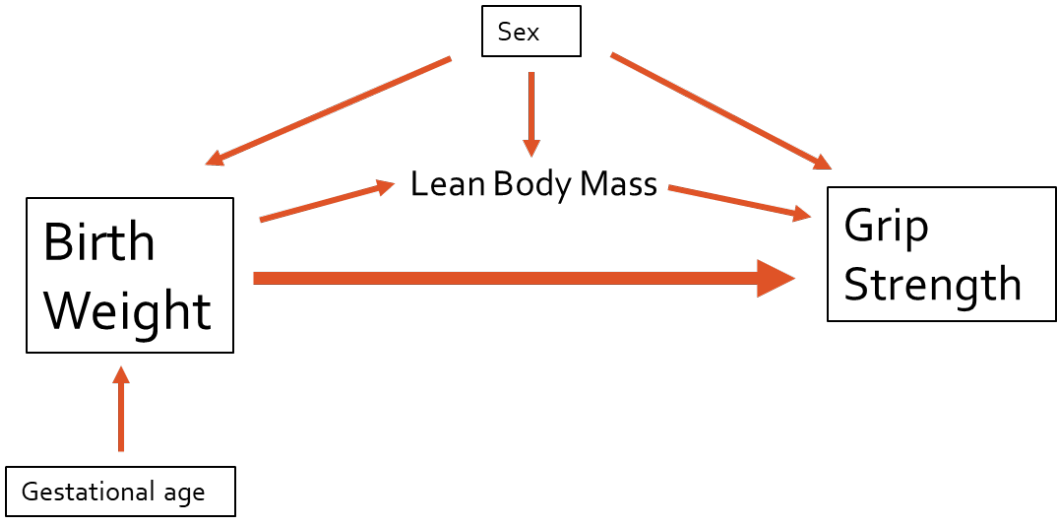

Figure 1.3. Analytic framework for specific aim 3.

Summary of Methodology

In order to test the hypotheses above, we used a cross-sectional design. 124 healthy adults (18-40 years old) participated in our study. Participants were recruited from a pool of individuals who completed an online survey asking for self-reported birth information and current health status. For each individual, the BW and GA provided on the online survey were used to create a standardized BW (SBW) that represents his or her size at birth compared to an expected birth size at that particular GA. From this pool, individuals who met the inclusion criteria (see Chapter 3) for the current study were contacted and asked to participate. Individuals with an SBW indicating possible IUGR were over recruited.

Participants wore two accelerometers (activPAL and ActiGraph) over a seven-day period. The activPAL accelerometer was worn on the thigh, and is generally regarded as the optimal device for measuring time spent in sedentary behavior (SED), as well as breaks in SED.

The ActiGraph accelerometer was worn on the waist, and is generally regarded as the optimal device for measuring moderate-to-vigorous physical activity (MVPA).

In addition to the accelerometer data, the following additional measurements were obtained from each participant: height, weight, body composition (determined by bioelectrical impedance analysis), grip strength, leg strength, and maximal cardiorespiratory fitness (VO_{2max}). Also measured, but not included in the current analysis, were: resting blood pressure, resting heart rate, waist circumference, skin folds, blood lipids, blood glucose, hemoglobin, and dietary habits (using a 24-hour recall and a food frequency questionnaire).

Outline of Dissertation

Chapter 2 provides a thorough review of the existing literature on the topic of intra-uterine stress and includes mention of both human and animal studies. Chapter 3 is a detailed explanation of the methodology used in the current study. The results of the current study are presented in the form of two manuscripts. Chapter 4 reports the results relating to specific aim #3: *Size at birth predicts adult grip strength among individuals born to term.* Chapter 5 includes the results relating to specific aims #1 and #2: *Size at birth does not predict physical activity or sedentary behavior in healthy young adults.* Chapter 6 is a Summary chapter.

Chapter 2: Literature Review

The intra-uterine environment, which provides nourishment to the developing fetus, is dependent on the health and nutritional status of the mother. Thus, if a mother experiences some type of nutritional stress (including but not limited to a nutritional deficiency), the offspring will make a variety of adjustments known as fetal programming (FP). Other sources of maternal stress, such as psychosocial stress, can also cause FP. According to the "fetal origins" hypothesis, the offspring detects the stressful intra-uterine environment and may adjust its metabolism, hormone sensitivity, or levels of hormone production, all of which can disrupt organ development and lead to lifelong health issues [5]. The developing placenta may also be negatively effected, impacting nutrient delivery to key organs such as skeletal muscle throughout the remainder of gestation [65].

In the short-term, FP can compromise the growth and development of the offspring, resulting in intra-uterine growth restriction (IUGR) and measurable differences in birth weight (BW), birth length (BL), and Ponderal Index (PI, gm/cm^3), which is a ratio of BW to BL [66]. Maternal behaviors such as maternal smoking can also lead to IUGR. Specifically, IUGR results in small, thin babies. Individuals born to term (37-42 weeks gestation) who weigh less than 2500 grams are classified as low BW. This is the most common criteria used to identify IUGR; however a PI value less than two is often used when both BW and BL are available. In addition, growth charts can identify individuals who likely experienced IUGR as those who are below the 25^{th} percentile for BW, BL, or head circumference at a given gestational age (GA). Long-term, FP can increase the risk of several chronic diseases.

Fetal Programming Hypotheses

Several hypotheses exist to explain FP. Prior to most epidemiologic research on the topic, the concept of a "thrifty genotype" was proposed by Neel in 1962, stating that in response to a poor nutritional environment, certain genes exhibit "thriftiness" that increase the organism's chances of survival by becoming metabolically efficient – promoting fat storage while conserving energy expenditure [67]. There are several candidate genes proposed, some of which synthesize proteins involved in adipogenesis, oxidative phosphorylation, or insulin signaling [68]. This concept was built upon by early FP researchers, who proposed the "thrifty phenotype" hypothesis. It specified that intra-uterine development is responsible for determining the overall metabolism of the individual, and exposure to a poor nutritional environment in utero would lead the individual to develop a metabolism that efficiently uses energy substrates in the post-natal environment [4, 69]. According to this hypothesis, FP individuals who experience problems with glucose metabolism had improper development of the pancreas (i.e. reduced β-cell number and/or function) in utero [70]. A separate hypothesis, known as "predictive adaptive response", refers to the plasticity demonstrated by a developing fetus in order to selectively adjust phenotypic outcomes to best match the predicted postnatal environment [4, 5]. Similarly, the "developmental origins of adult health and disease" hypothesis proposes that the fetus makes adaptive changes in response to information about the mother's nutritional status, potentially adjusting metabolism, hormone levels or sensitivity, and/or other alterations to the body's programming [5]. Changes to the developing liver may underlie future health problems specifically related to lipid metabolism, creating a higher risk for abnormal lipid levels and insulin resistance in adulthood [71, 72].

A few hypotheses have focused on the etiology of how a particular pathway becomes disturbed. The "fetal insulin" hypothesis suggests that the combined effects of a poor intra-uterine environment, along with an epigenetic alteration in the insulin-mediated growth pathway, predispose the individual to developing insulin resistance [73]. Immediately, this reveals itself in a small, thin baby, as insulin is typically involved in growth during the third trimester of pregnancy, and those who experience IUGR will be programmed to ineffectively respond to insulin. Over the life course, this individual will be at a higher risk of developing insulin resistance and Type 2 diabetes [74, 75].

All of the above hypotheses posit that the fetus is responding to, or preparing for, a nutrient-poor environment, and problems such as increased risk for chronic diseases arise when the individual is subsequently placed in a nutrient-rich postnatal environment. However, individuals exposed to a nutrient-rich prenatal environment may also be at increased risk of disease when also placed in a nutrient-rich postnatal environment, suggesting a general "U-shape" which has previously been seen between BW and disease risk [11, 30]. Relatedly, a "leptin" hypothesis has been proposed, linking leptin production and/or sensitivity to the regulation of energy balance and thus obesity [76]. Evidence from animal models suggests that during early gestation, sub-optimal nutrition leads to leptin deficiency while over nutrition causes leptin resistance to develop in the fetus, capable of causing permanent damage to the arcuate nucleus within the hypothalamus [30]. Interestingly, leptin administered to the fetus in late gestation and/or during lactation appears to partially correct the damage and prevent obesity [76].

Taking a different approach, the "maternal constraint" hypothesis proposes that fetal growth is linked to the physical body size of the mother [5]. Risk factors for maternal constraint

include a woman who is short, pregnant for the first time (or with multiples), or who is very young or very old. The "constraint" may occur due to growth restrictions of the placenta, which could limit distribution of nutrients to the fetus. Another explanation for this phenomenon is that fetal growth (and in particular, organ development) could be effected by imprinted genes for various growth factors [77]. Acknowledging the combined effects of genetics and a poor intra-uterine environment is the "epigenetic" theory: nutritional deprivation in utero leads to modifications in gene expression, thus changing the phenotype of the individual [4, 5]. The modifications may include methylation of the cytosine nucleotide bases on DNA or post-translational modification of the histone proteins on target genes, such as adding a methyl or acetyl group [78]. While the direct correlation between this activity and subsequent health risk is still under investigation, one proposed mechanism is that these modifications may determine gene expression for substances regulating fetal growth and metabolism, such as glucocorticoids [4]. Researchers have recently proposed a "gatekeeper" hypothesis: as a result of a poor intra-uterine environment, only certain genes are directly modified or disturbed, which may have long-term implications [4].

Measurement & Timing Issues

The timing of the intra uterine stress exposure determines the severity of the physiologic effects. Two studies investigating the timing for later effects on coronary heart disease risk disagree about the crucial time for fetal development. Early FP research by David Barker suggested that deprivations during middle to late gestation appear to cause the highest risk of subsequently developing coronary heart disease [55]. More recently, research has suggested that coronary artery disease occurs more frequently among individuals who were exposed to a famine

during early fetal gestation [53]. During the Dutch Hunger Winter, exposure to caloric restriction during the third trimester of pregnancy led to significantly lower BW than women who were unexposed [79]. Exposure during the second trimester also resulted in a lower BW, but not as reduced as the third trimester [79]. There was no effect on BW when the mother experience caloric restriction during the first trimester of pregnancy [79].

Determining what criteria to use complicates the confirmation of whether or not IUGR occurred. Traditionally, birth measures such as BW and birth length (BL) are used. A calculated variable that is often used is the Ponderal Index (PI, gm/cm^3), which is a ratio of BW and BL, similar to the Body Mass Index (BMI) in adults. Low PI may be more useful to identify IUGR than BW alone since it identifies babies born small and thin. However, these measures alone are not a good indicator of fetal growth, as they fail to take into account the influence of gestational age (GA). It is imperative to account for GA, as individuals born pre-term will be of a lower BW due to less time spent in utero. Thus, some past research has identified IUGR by determining if an individual was born "Small for Gestational Age" (SGA), which is typically defined as BW, BL, or PI below the 10^{th} percentile of that particular GA [80]. From this, cut-offs can be made – typically identifying the lower 10^{th} – 25^{th} percentile of PI or BW as indicative of IUGR [81, 82].

Beyond the typical birth markers, placental growth has been used to verify whether IUGR occurred. In a cohort study of over 13000 older adults (approximately 75 years old), a small placental surface area (less than 225 cm^2) was associated with chronic heart failure [83]. This result is interesting considering that chronic heart failure was not associated with BW, BL, GA, or even placental weight [83]. While providing an alternative measure, placental growth is difficult to obtain retrospectively, particularly in older birth cohorts. Liver size may be another indirect indication of IUGR. Ultrasound measurements of liver size were smaller in individuals

with IUGR [84]. However, IUGR-induced changes to liver size will not necessarily lead to noticeable reductions in BW or BL. Instead, abdominal circumference has been used as a marker of the liver size at birth. Limited evidence supports an association between small abdominal circumference at birth and increased levels of blood lipids [72, 85].

Maternal measures, such as pre-pregnancy size, pregnancy weight gain, and the presence of behaviors such as smoking or drinking during pregnancy may moderate IUGR's effects on adult disease risk. Of these, maternal smoking is well-researched, with clear evidence linking smoking during pregnancy to IUGR and low BW [86]. Relatedly, a recent study suggests that maternal exposure to second-hand smoke may also lead to IUGR and low BW [87].

Several studies have also looked at post-natal growth, particularly in the first year of life. If an individual experiences poor fetal growth, he or she may demonstrate rapid catch-up growth in infancy and early childhood, which can lead to a phenomenon known as "early adiposity rebound" [11, 88]. Such a sudden increase in body fat is associated with an increased risk for obesity and Type 2 diabetes later in life [11, 88]. In addition, this rapid change in body composition may alter various hormones associated with normal growth and development, particularly those with roles in lipid metabolism.

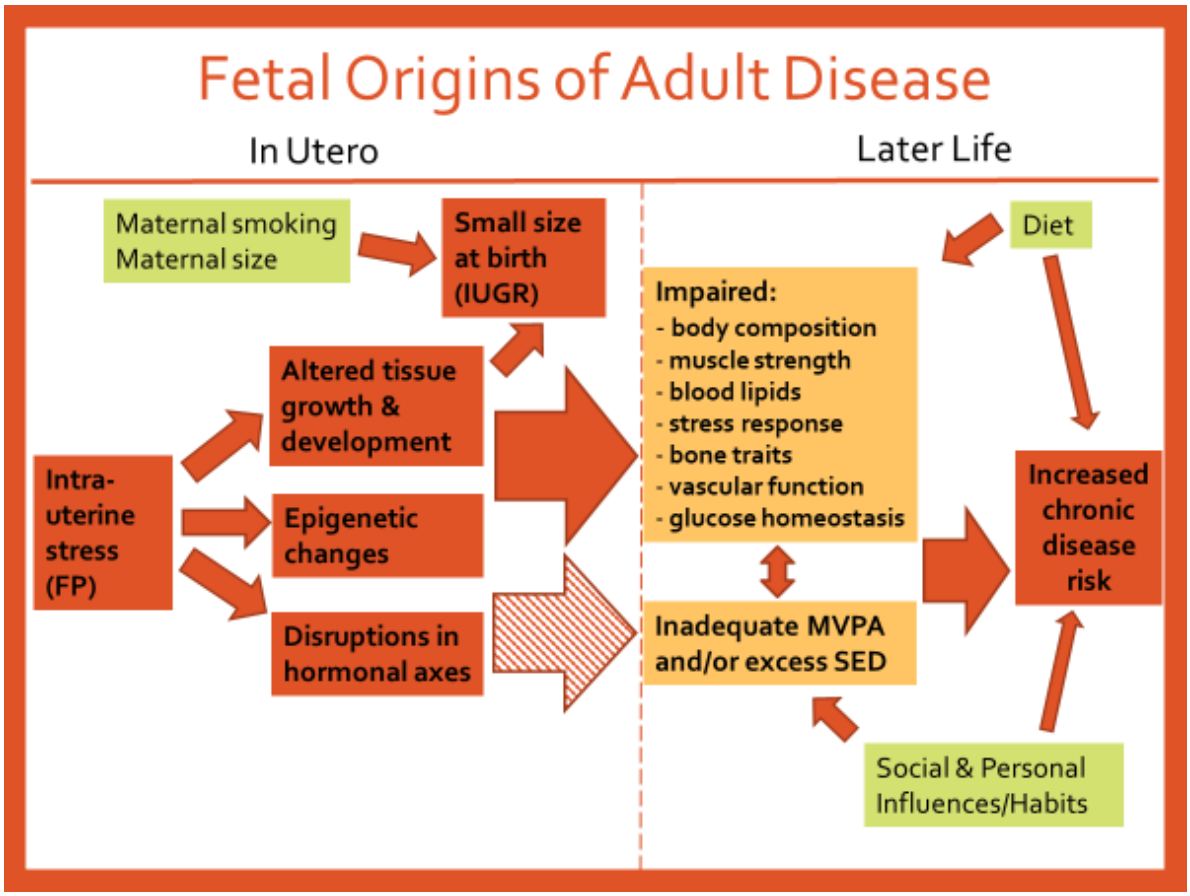

Figure 2.1. Proposed conceptual pathway of the effects of intra-uterine stress.

The conceptual model presented in Figure 2.1 (above) summarizes the various hypotheses previously described. See Chapter 1 for an explanation of this model. The following sections of the literature review will summarize the existing evidence to support later life effects of intra-uterine stress that are described in the model.

Intra-uterine Stress and Disease Risk

Regarding blood lipids, a longitudinal study tracked 344 Dutch individuals born during a famine (who were assumed to have experienced intra-uterine stress). Results revealed that in middle adulthood (average age 58.7 years) females exposed in utero to famine had higher concentrations of total cholesterol, triglycerides (TG), and low-density (LDL) cholesterol as adults compared to an unexposed group, but there was no difference for men [89]. A British cohort study of over 7000 adults aged 44 – 45 found an inverse association in women between BW and total cholesterol and LDL cholesterol [59]. In both sexes, there was an inverse association between BW and TG levels [59]. Other studies have shown that a low BW predicts higher total cholesterol concentrations, specifically in adults who are currently overweight or obese [90, 91]. Results from our own research has shown that individuals classified as low PI (below the 10^{th} percentile) had higher total cholesterol and LDL cholesterol compared to a matched control group [92]. In contrast to these selected results, recent literature reviews have concluded there is no definitive relationship between BW and any of the normally assessed clinical measures of lipid biochemistry [18]. However, these reviews also make clear that more research is needed on the effects of BW on blood lipids among various races or ethnicities [18, 19].

Several studies from a research group in Denmark have compared insulin signaling and glucose metabolism in skeletal muscle. In muscle biopsies of 40 healthy young men, those born at a low BW (below the 10^{th} percentile) had significantly lower levels of protein kinase C, GLUT 4 transporter, and other proteins related to insulin function [93]. The same subjects were then exposed to a hyperinsulinemic euglycemic clamp and had another muscle biopsy taken. This test

revealed that low BW subjects had significantly higher glucose and insulin levels, which led to a higher insulin resistance index [94]. In addition, proteins involved in insulin signaling and activation were effected, specifically higher levels of insulin receptor substrate-1, phosphatidylinositol 3 kinase, and GLUT 4 and lower levels of various protein kinases [95]. Based on this series of studies, the authors concluded that low BW may predispose even healthy young men to a higher risk of insulin resistance.

Recent studies across the life span have investigated the link between BW or PI and predictors of metabolic syndrome or diabetes, namely measures of glucose regulation and blood lipids. Among a cohort of 134 Indian children and adolescents (average age 10 years), low BW subjects (less than 2.5 kg) had significantly higher fasting blood glucose and insulin levels, as well as higher HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) scores, compared to normal BW subjects (2.5-4.5 kg) [75]. Data from over 700 young adults in the Atherosclerosis Risk in Young Adults cohort revealed that a low BW was significantly associated with high triglyceride levels [96]. The same analysis showed that a high BW was related to, but not significantly associated with, low levels of glucose, total cholesterol, and LDL cholesterol and high levels of HDL cholesterol [96]. Taken all together, researchers concluded that low BW individuals had a higher risk of developing metabolic syndrome. Similar results were seen in the Australian Diabetes, Obesity and Lifestyle (AusDiab) study of over 4500 adults. Low BW individuals (less than 2.5 kg) had significantly higher fasting glucose, post-load glucose and hemoglobin A1C levels compared to normal BW individuals (greater than 2.5 kg) [74]. Adjustment for BMI, physical activity (assessed by questionnaire), and other covariates attenuated these relationships in males, but significance remained among females [74]. In a study of over 500 French young adults given an oral glucose tolerance test, subjects born SGA (defined

as BW and/or BL below the 3rd percentile) had significantly higher glucose levels 30 minutes post-test as well as insulin and proinsulin at 30 minutes and 120 minutes post-test [97]. Initial insulin levels were significantly higher for female subjects in the SGA group. No differences were found in blood pressure or blood lipids between the two groups.

When comparing rates of metabolic syndrome among nearly 1000 Chinese adults (aged 41 – 52), those born in the lowest quartile of PI had the highest prevalence, a trend that was significant for males but not for females [98]. One of the earliest epidemiologic studies on this topic was conducted in England among 297 older women. This study found that glucose and insulin were significantly higher in those born under 5.5 pounds, both during a fasted state and 120 minutes after an oral glucose tolerance test [99]. A recent meta-analysis of eleven research studies on this topic confirmed the existence of an inverse relationship between BW and metabolic syndrome [17].

Other epidemiologic research has focused on the association between birth measures and heart disease or hypertension. A large study of over 500 children in Argentina found that systolic blood pressure in childhood (ages 5-9) was weakly and inversely correlated to BW [100]. Children who were currently overweight showed the strongest link between low BW and high blood pressure [100]. Data from the Dutch Famine Birth Cohort analyzed health records for nearly 1000 subjects aged 50-58 years old and discovered that individuals with coronary artery disease tended to be lighter and thinner at birth, but this relationship did not reach significance [53]. Analysis of data from 4630 Finnish men found those born below 2500g had a significantly higher hazard ratio for developing or dying from coronary heart disease [56]. A recent meta-analysis analyzed the association between BW and blood pressure. The authors concluded that systolic blood pressure exhibits a slight “U-shaped” curve, with higher values found in

individuals at either the very low or very high end of the BW spectrum, a relationship that existed to a stronger degree in females than males [20]. Another review article on this topic proposed that hypertension risk may also be related to kidney function, as alterations to this organ have been proposed as part of the fetal response to intra-uterine stress, specifically reducing the number of nephrons [21]. Levels of uric acid, a breakdown product of purine nucleotides and indicator of kidney function, were measured in 78 children (ages 8 – 13). Previous research has shown high levels of uric acid exist in individuals with hypertension [101]. Across the entire study population, uric acid levels significantly inversely correlated with BW [102].

Effect of Maternal Diet: Evidence from Animal Models

Work with animals allows for the manipulation of the maternal diet in a controlled environment to directly observe immediate and long-term impacts of intra-uterine stress. For example, mothers receive either a diet with normal macronutrient distribution or a low-protein (isocaloric) diet during pregnancy. The offspring are then monitored and measured for differences between the two conditions, or further split into groups based on the type of diet they receive post-weaning (i.e. either a normal diet or a high calorie diet). One such study in mice found that the offspring of mothers who received a low-protein diet during pregnancy exhibited growth retardation at birth compared to the offspring of mothers fed a normal diet [103]. The low-protein offspring then demonstrated significantly more catch-up growth during lactation [103]. Rapid post-natal growth (in humans) is associated with an increased risk for obesity and metabolic syndrome later in life [11, 88]. At nine months of age, the low-protein offspring continue to have higher body weight than the control offspring, regardless of the post-natal diet they received [103]. In addition, the low-protein offspring had higher plasma glucose, total

cholesterol, and leptin levels at nine months old, independent of the post-natal diet assignment[103]. The higher total cholesterol and leptin levels may be related to the larger adipocyte size observed in the low-protein offspring. However both measures are also influenced by several other factors, including post-weaning diet assignment, as those in the high calorie diet group had high levels for both measures [103]. A similar study in rats discovered that the offspring of mothers fed a low-calorie diet during pregnancy had significantly higher fasting insulin and leptin levels at nine months of age [104]. The researchers concluded that the unfavorable glucose and insulin values may be due to FP of the pancreas in the low-protein offspring, effecting β-cell production and impairing insulin secretion.

In addition to metabolic disruptions, after nine months the low-calorie offspring exhibited hyperphagia, higher systolic blood pressure, larger retroperitoneal fat pads, and smaller kidney and liver sizes compared to the normal diet offspring [104]. The hyperphagia and blood pressure results were exacerbated if offspring consumed a high-calorie diet post-weaning. The authors concluded that FP of the neuroendocrine control of appetite occurred in the low-calorie offspring [104]. Separately, a recent review of animal research suggested that use of soy isoflavones in the maternal diet may provide cardiovascular protection, specifically through the regulation of nitric oxide synthase and antioxidant enzyme levels, as well as preventing endothelial dysfunction [105].

Effects of Intra-uterine Stress on Physiologic Body Systems

Cardiovascular

The effects of intra-uterine stress also extend beyond chronic disease to specific measurements of blood vessel quality and function. Use of non-invasive techniques such as

brachial artery flow-mediated dilation can be used to assess such changes. Alterations may be present in children or young adults who experienced IUGR, even if they are otherwise classified as healthy [106, 107]. A study of 78 children (ages 8 – 13) found systolic blood pressure significantly higher in the low BW group (less than 2.5 kg) compared to the normal BW group (greater than 3 kg) [102]. Additionally, flow-mediated dilation was significantly lower in the low BW group compared to the normal BW group [102]. Flow-mediated dilation was also significantly associated with BW in a study of 318 young adults (ages 20 – 28) [108]. Among the subjects, those who currently smoke exhibited a lower flow-mediated dilation in each BW category [108]. Forearm blood flow in healthy young men before and after a hyperinsulinemic isoglycemic clamp showed no initial differences, but a significantly higher blood flow in the normal BW group 180 minutes post-clamp [109]. During both control and clamp conditions, the vasodilators adenosine and acetylcholine were infused separately, both causing an increase in forearm blood flow but not significantly differing between the BW groups [109]. Vasodilators were also used to evaluate endothelial function and perfusion in a study of 44 children ages 9 – 13 [107]. Those in the low BW group (2.2kg on average) had significantly lower rates of perfusion after exposure to acetylcholine [107]. Furthermore, there was a significant inverse correlation between BW and carotid stiffness, with low BW subjects born lean having the highest carotid stiffness values [107].

Using different methodology, several recent studies have examined the influence of intra-uterine stress on the circulatory system by measuring retinal arteriole narrowing. A study of over 2000 Australian 12 year olds used retinal images to evaluate vascular changes based on BW status [110]. Results showed that those in the lowest quartile of BW (less than 3 kg) had the narrowest diameter of the retinal arteriole, a significant association that remained after

adjustment for confounding variables [110]. In a study of more than 1300 six year old children, a similar relationship emerged – the smallest arteriolar caliber was seen in the low BW group (less than 2.5 kg) [111]. Using similar methodology, a study of 3800 older US adults (ages 51 – 72) revealed a significant relationship between BW and retinal arteriolar caliber, with those born under 2.5 kg having the lowest values, even after adjusting for BMI, smoking, and blood pressure [112].

Taken together, the results described above suggest that early FP adaptations may inadvertently increase later risk for hypertension and cardiovascular disease. In support of these studies, two recent reviews concluded that endothelial dysfunction and arterial stiffness could occur because of intra-uterine stress [113, 114].

Skeletal

Individuals who experienced intra-uterine stress may have deficiencies in bone geometry, which often appear during adulthood in the form of low bone mineral density (BMD) or low bone mineral content (BMC). Specifically, a longitudinal study of nearly 1000 older adults (ages 60 – 75) found that BW was significantly positively associated with BMC of the lumbar spine and proximal femur [26]. No consistent relationship was observed between BW and BMD in these subjects [26]. A similar study of over 1000 Finnish 31 year-olds found that individuals who experienced growth retardation (a term defined by the researchers as small for GA and low PI) were 2.5 times more likely to have low BMC in the radius as a young adult (31 years old) [27]. However, this study also discovered that underweight status and low calcium intake as an adult were both significant predictors of low BMC. Taken together, the results of this study suggest intra-uterine stress increases the tendency toward impaired bone health but may not be the only factor. Comparable results were found when bone traits were measured in a cohort of 282 adults

(aged 36 years) in the Netherlands, as BW demonstrated a significant association with BMC in multiple locations [25]. However, the relationship lost significance once adult size was accounted for, suggesting a qualitative effect similar to what is seen with skeletal muscle [25]. There was no relationship found between BW and BMD, mirroring a recent review article showing that BW may be linked with BMC but not BMD [24].

There may be an ability to "correct" the FP effects on bone traits through a combination of early life nutrition and physical activity. A study of 312 adults (ages 18 – 24) found that those born small for GA, who did not experience catch-up growth (and now exhibit a short adult stature), had significantly lower BMC and BMD in the lumbar spine and the whole body compared to normal BW controls [29]. These subjects also had lower BMC and BMD compared to similar individuals born SGA who did experience catch-up growth [29].

Neuroendocrine

Undernutrition during the fetal period has a long-term impact on several hormonal cascade systems in the body, including the hypothalamic-pituitary-adrenal (HPA) axis which is responsible for the production of glucocorticoids. Prenatal exposure to excess glucocorticoids such as cortisol is associated with IUGR [115, 116]. The mechanisms underlying this relationship include maternal stress producing excess cortisol, endogenous administration of glucocorticoids, or epigenetic changes that modify the expression of 11β-HSD (11β-hydroxysteroid dehydrogenase) type 1 or type 2 [117]. 11β-HSD controls the amount of maternal glucocortoids able to cross the placental barrier and enter the fetus intact versus becoming converted to cortisone, which is biologically inactive [118, 119]. Methylation of specific sites on the 11β-HSD gene cause decreased expression of 11β-HSD in the placenta, leading to less 11β-HSD present at the placental-fetal barrier and thus more maternal cortisol entering the fetus

[120, 121]. Studies have consistently shown that individuals born at a low BW have higher levels of the hormone cortisol, both in childhood and adulthood [122-125].

The neuroendocrine programming that occurs due to FP is also noticeable during times of psychosocial stress. In response to stress, the HPA axis will be activated, as well as the sympathetic-adrenal-medullary (SAM) system [126, 127]. When individuals who experienced FP are exposed to acute stress, their stress response (measured via salivary cortisol and blood pressure) is heightened compared to those who did not experience FP [128-131].

Effect of Intra-uterine Stress on Body Composition

Epidemiologic data shows strong associations between birth measures and body composition for a variety of age groups. A study of 85 children (average age 7.8 years) from the United Kingdom (UK) found body fat percentage inversely associated with BW [6]. This significant relationship persisted even after adjustment for body mass index (BMI, kg/m^2) and physical activity (self-reported on a 3-point scale) [6]. Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) showed that among 6000 children aged 9 – 10, both BW and PI were positively associated with lean body mass in both sexes, even after adjusting for confounding variables [7]. Related findings from a UK study of 78 adolescents (ages 13 – 16) found BW significantly associated with lean body mass, but no relationship between BW and either fat mass or BMI [8]. In a cross-sectional comparison of over 200 Spanish adolescents (ages 13 – 18), BW in females was positively associated with height, weight, bone mass, and fat-free mass [9]. These associations remained even after controlling for GA and physical activity levels (measured via questionnaire) [9]. Looking at data from nearly 400 children and adolescents (average age 11.7 years) in the UK revealed that in both sexes, BW was positively

associated with current height [10]. In males only, BW was positively associated with BMI and fat free mass [10]. It is important to point out that BMI reflects not only fat mass, but also fat-free mass, making it difficult to interpret during periods of growth (puberty) or atrophy (older adulthood). Many epidemiologic studies of children and adolescents have found no association between BW and body fatness, or a slight positive association, which is contrary to the predictions of FP effects. This may be due to the presence of a "U-shaped" relationship, meaning that both low and high BW could predict high body fatness [11].

Large-scale studies of adults have consistently found BW to be a strong predictor of body composition. Results from a cohort of over 1000 Guatamalean adults found BMI at birth was significantly positively associated with adult fat-free mass but not with percent body fat or abdominal circumference [12]. A study of over 1500 young adults from a cohort in India revealed that both BW and PI were positively associated with lean body mass, while BW and BL were each positively associated with height [13]. A study of 32 older males from the UK found that those below the 25th percentile for BW were shorter than those above the 75th percentile for BW [14]. The low BW individuals also demonstrated less fat-free mass, less fat-free soft tissue, and less muscle mass, but a higher body fat percentage, than the high BW group [14]. All of these differences were significant, and remained after adjustment for current weight and height [14]. In addition, several ratios of fat mass, such as nonlimb:limb fat mass and trunk:limb fat mass were significantly higher in the low BW group [14]. A similar study of 143 older adults in the UK found both bone mineral content and lean body mass were significantly positively associated with BW in both sexes [15]. These relationships were independent of various adult lifestyle factors [15].

Effect of Intra-uterine Stress on Skeletal Muscle

Individuals who experienced intra-uterine stress may also have permanent morphological changes to their musculoskeletal system. A longitudinal study of over 600 older adults (average age 69 years) from the UK found that low BW was significantly associated with both forearm and calf muscle cross-sectional area (CSA) [22]. This relationship was attenuated when adjusting for current size, social class, and smoking status, but when analyzing the data among quintiles of BW, the lowest quintile consistently demonstrated a significantly lower muscle CSA in both sexes [22]. A study of 40 young, healthy Danish men found that the low BW individuals had significantly less type IIa muscle fibers in the vastus lateralis muscle and a trend toward larger muscle fibers for all three muscle fiber types, which may predict future risk of insulin resistance [132]. Indeed, two review articles propose that the response of the fetus to IUGR may lead to a reduction in total muscle fibers formed and possibly abnormal hypertrophy of existing muscle fibers along with irregularities in muscle response to insulin and/or use of glucose [133, 134].

These changes to muscle will likely cause reductions in muscle strength. A comparison of 28 females (average age 20.6 years) found that prior to an exercise intervention, the low PI subjects (below the 10^{th} percentile) had lower grip strength than the control group (PI greater than the 10^{th} percentile), a difference that approached significance [135]. There was no difference between the PI groups for maximal voluntary contraction (MVC) of the quadriceps [135]. Measuring grip strength in over 1500 adult women (ages 20 – 40) found a significant relationship between BW and grip strength [60]. Specifically, an increase of 1.1 kg in grip strength could be expected as BW increased by 1 kg [60]. In a longitudinal study of nearly 2000 older adults (average age 61.5 years), a similar relationship emerged, showing that grip strength

increased by 1.8 kg for every 1 kg increase in BW, but this association weakened after accounting for lean mass [136]. Another cohort study of over 2700 adults (53 years old) found that grip strength had a significant association with BW in both males and females [58].

Few studies have investigated exercise performance in, or the effects of exercise training on, individuals exposed to intra-uterine stress. When muscle fatigue was compared among young adult female subjects (using static MVC measurements alternated with dynamic knee extensions), those in the low PI group had a significantly greater reduction in force over time compared to the control group [135]. This suggests a possible difference in quadriceps muscle fiber type distribution, which contributes to higher fatigability in subjects exposed to intra-uterine stress and experienced IUGR. Exercise and muscle performance were also measured in a small group of middle-aged adult women [137]. Subjects underwent 31P magnetic resonance spectroscopy during and after muscular exercise of the flexor digitorum superficialis, a predominantly fast-twitch muscle in the forearm used to move the hand, in order to determine differences in muscle function between PI groups [137]. Subjects in the low PI group fatigued significantly faster than the high PI subjects, and showed a significant fall in phosphocreatine paired with a significant rise in ADP concentration during the exercise [137]. Following the exercise, re-oxygenation of the flexor digitorum superficialis muscle took significantly more time in the low PI group than the high PI subjects [137]. These results suggest that the effects of intra-uterine stress and the resulting FP may cause a decrease or a delay in rates of glycogenolysis and glycolysis during exercise, leading to a depletion of phosphocreatine as that energy system attempts to provide adequate ATP to sustain the muscular activity. More studies are needed to replicate these results in a wider subject population.

Effect of Intra-uterine Stress on Fitness Level

Cardiorespiratory fitness level, an indication of endurance exercise capability, has been measured in a handful of previous FP studies. The ALSPAC study found a positive association between physical work capacity in children and BW, BL, and PI [61]. These researchers noted an increase of 1.12 Watts in physical work capacity for every one SD increase in BW [61]. This effect was consistent between sexes. In a separate study of adolescents, a shuttle-run test was used to predict maximal aerobic fitness (VO_{2max}). Overall, there was no significant association between BW and VO_{2max} [62]. The Young Heart Study was another study of adolescents which used the same shuttle-run test to generate predicted VO_{2max} levels [63]. In this study, BW was significantly associated with fitness levels among 12 year-old subjects, but the relationship disappeared in 15 year-old subjects [63]. After controlling for several covariates (including GA), BW explained approximately 2.4% of the variance in fitness level among 12 year-old males and 1.5% among 12 year-old females [63]. These few studies suggest a trend, but studies in adults are lacking, and future research should employ a consistent measurement of cardiorespiratory fitness such as maximal oxygen uptake (VO_{2max}), which was measured in the current study.

Effect of Intra-uterine Stress on Physical Activity Behaviors

Participation in physical activity has many established benefits, from lowering risk of chronic diseases such as Type 2 diabetes and heart disease to improving muscle strength and bone density [31-33, 39, 138, 139]. Since individuals who were exposed to intra-uterine stress are often at higher risk of developing these chronic diseases, research has investigated the relationship between birth measures and physical activity levels across the lifespan. Our own

survey data from nearly 400 young adults indicates that the odds of self-reporting the "very high" category of physical activity are significantly higher with increasing quartile of BW (adjusted for GA) [50].

At present, the majority of human studies investigating physical activity behaviors (either physically active or sedentary behaviors) [140, 141] use accelerometers, which provide an objective measure of intensity and duration of activity. A large study of adolescents showed no association between BW with levels of accelerometer-measured physical activity [51]. The reason for this lack of association may be due to the possible existence of a U-shaped relationship between BW and physical activity, which is suggested by analysis of a large sample of adolescents and adults [52].

While the true relationship between size at birth and physical activity levels may still be unclear, there are additional benefits seen in people born small who engage in physical activity. Specifically, a recent study of adolescents measured physical activity (via accelerometer) and levels of the hormone leptin, which signals satiety. They found that females who failed to complete 1 hour of MVPA per day had an inverse association between BW and leptin levels [34]. There was no relationship between birth weight and leptin among male adolescents in this study, or in females who completed at least one hour of MVPA per day [34].

A handful of studies have researched the potential benefits of exercise on disease risk among individuals born small. In a group of 462 adult men, risk of metabolic syndrome and hyperinsulinemia were highest among the men who had a low PI [35]. Further analysis revealed that low levels of physical activity and low cardiorespiratory fitness levels exacerbated the relationship between PI and metabolic syndrome risk [35]. For men with a low PI, being physically fit and engaging in regular exercise appears protective against development of

metabolic syndrome. A longitudinal study among a cohort of older adults found a significant interaction between BW and frequency of exercise on rates of type II diabetes and glucose tolerance. Individuals born above 3 kg who exercised three or more days per week (on average in the last 12 months) had low rates of both type diabetes and impaired glucose tolerance [36]. Interestingly, the lowest rates for these measures were found in low BW subjects (less than 3kg) who exercised three or more days per week [36]. Intensity of exercise was also measured, and showed a similar, but non-significant, relationship: low BW individuals who engaged in moderate or strenuous exercise exhibited the lowest prevalence of type II diabetes and the lowest odds ratio for impaired glucose tolerance [36]. A large cross-sectional study of adolescents yielded similar results. Using accelerometry to measure physical activity, physical activity levels appear to modify the risk of developing insulin resistance among the adolescents born at a low BW [37]. Taken together, these results suggest that exercise may be protective for these low BW individuals. It should be pointed out that this pattern is not exclusively seen in previous studies – at least one recent study in children and adolescents found no evidence that physical activity or fitness level attenuate the relationship between size at birth and insulin resistance [38].

Although there are known decrements in muscle as a result of intra-uterine stress, the capacity of individuals to respond to exercise training has not been well researched. A recent study compared the changes in low PI and high PI individuals following a lower-body training program. At baseline, during cycling exercise at 60% and 90% of maximal oxygen uptake (VO_{2max}), the low PI subjects showed significantly higher levels for lactate compared to the high PI group [142]. As a result of the exercise training, the high PI group showed a significantly greater improvement over pre-training values for force production during a fatigue protocol, while the low PI group saw a small but non-significant increase over pre-training values[135].

These results suggest that individuals who were exposed to intra-uterine stress (and experienced IUGR) demonstrate initial differences in exercise and muscle performance. Furthermore, these individuals may not experience the same degree of response to an exercise training program compared to those who did not experience IUGR. Subjects in the low PI group also had improvements in blood lipids as a result of the exercise training, to the extent that differences between the low PI and a matched control group were eliminated [92]. Thus, even if these subjects do not have the same level of response to the exercise training program, they can still improve their overall health and disease risk by engaging in exercise.

A growing body of research has begun to investigate the detrimental effects of a sedentary lifestyle. Dubbed "inactivity physiology", these studies have shown that higher levels of sedentary time lead to less participation in moderate-to-vigorous physical activity, higher levels of body fatness, and higher risk for conditions such as metabolic syndrome [33, 39, 40, 139, 141, 143]. Research looking at birth measures in relationship to sedentary time is limited in human studies, with a study in adolescents yielding no apparent relationship [51]. Data from animal models suggests that IUGR leads to a more sedentary existence, and may coincide with consumption of excess calories [49, 104]. Rats born to mothers consuming a low-calorie diet were significantly less active (and ate significantly more food) compared to similar rats born to mothers consuming a normal calorie diet [49]. This study found a sex effect, with males engaging in significantly less movement compared to females [49]. An interesting aspect of sedentary behavior is the pattern – individuals who break up their sitting time with small amounts activity may be healthier than those who spend long blocks of time in a sedentary behavior [144, 145].

Physical activity behaviors in adulthood may be influenced by FP, but there are several

environmental and social-cognitive influences on physical activity and inactivity as well. Detailed reviews of this body of literature exist elsewhere [43-45, 146]. Specifically, “screen time”, including cell phone use and television viewing, is associated with low levels of fitness and increased sedentary time [41, 43]. This is relevant to research involving college-aged adults, who may be more likely to use such devices. Other influences on physical activity or inactivity behaviors may include perceived barriers to exercise, preferred mode of transportation, family/friend support and exercise behaviors, and self-confidence [42, 43, 45, 46, 146].

Implications for Future Research

Past research in the area of intra-uterine stress has focused on the consequences of FP as well as the possible mechanisms explaining the long-term effects. Studies have consistently shown that experiencing intra-uterine stress, identified by IUGR, is associated with alterations to body composition, including higher body fatness as well as lower muscle strength and quality. Select studies have investigated the relationship between birth measures and physical activity behaviors, with mixed results. Some researchers have concluded that if in fact physical activity and caloric intake patterns are programmed before birth, it might explain the ineffectiveness of many health campaigns targeting adults to change their behaviors. This sentiment remains to be seen.

Most of the FP research on physical activity has occurred in children and adolescents, or has used self-reported measurement of physical activity level. Thus, there is a need to conduct a study to explore the relationship between intra-uterine stress and physical activity behaviors in adults using direct measurement of physical activity with accelerometers.

Chapter 3: Methodology

This cross-sectional study included healthy adults (18 – 40 years old) who were born full-term (37 – 42 weeks gestation).

Participant Recruitment & Screening

Participants were selected from an existing departmental pool of potential research subjects. This pool was created from an online survey sent to members of the Syracuse University campus, including faculty, staff, and students. The survey (see Appendix A) asked about birth information, including birth weight (BW) and maternal smoking during pregnancy, as well as current height, weight, and physical activity level. In most cases, survey respondents obtained birth information from their birth mother. Maternal recall of BW is accurate and reliable, according to past research [147-149]. Respondents were asked to indicate if they were willing to participate in future research studies within the Department of Exercise Science at Syracuse University.

The survey was completed by 1805 respondents. After data cleaning (including the removal of duplicate entries), 1500 respondents remained. Out of this group, 1246 individuals provided BW information. Birth length (BL) was not provided by all participants. Thus, Ponderal Index (PI), which is a ratio of BW and BL, was not used in the data analysis to represent birth size.

Figure 3.1 provides a flowchart of participant recruitment. Invitations to participate in the current study were sent to approximately 40% of the respondents providing BW information. Most of these respondents were chosen at random; however to ensure adequate representation in

the study from individuals who were born small for gestational age (SGA), targeted recruitment occurred. Approximately 50% of the 158 respondents who were identified as SGA (based on self-reported BW and gestational age (GA) information) were contacted.

Prior to enrollment in the study, potential participants were screened regarding the study's inclusion and exclusion criteria:

Inclusion criteria: Ages 18-40 years; Healthy (free of current or previous diagnosis of chronic disease such as heart disease, diabetes, or cancer); Access to birth information, including BW, BL, gestational age (GA), and birth order; Current weight has been maintained for at least the last 3 months.

Exclusion criteria: Premature birth status (defined as less than 37 weeks gestation); Maternal hypertension or diabetes during the subject's gestation; Current Body Mass Index below 18.5 (indicating underweight status) or above 35 (indicating morbid obesity); current pregnancy (or pregnancy within the last year).

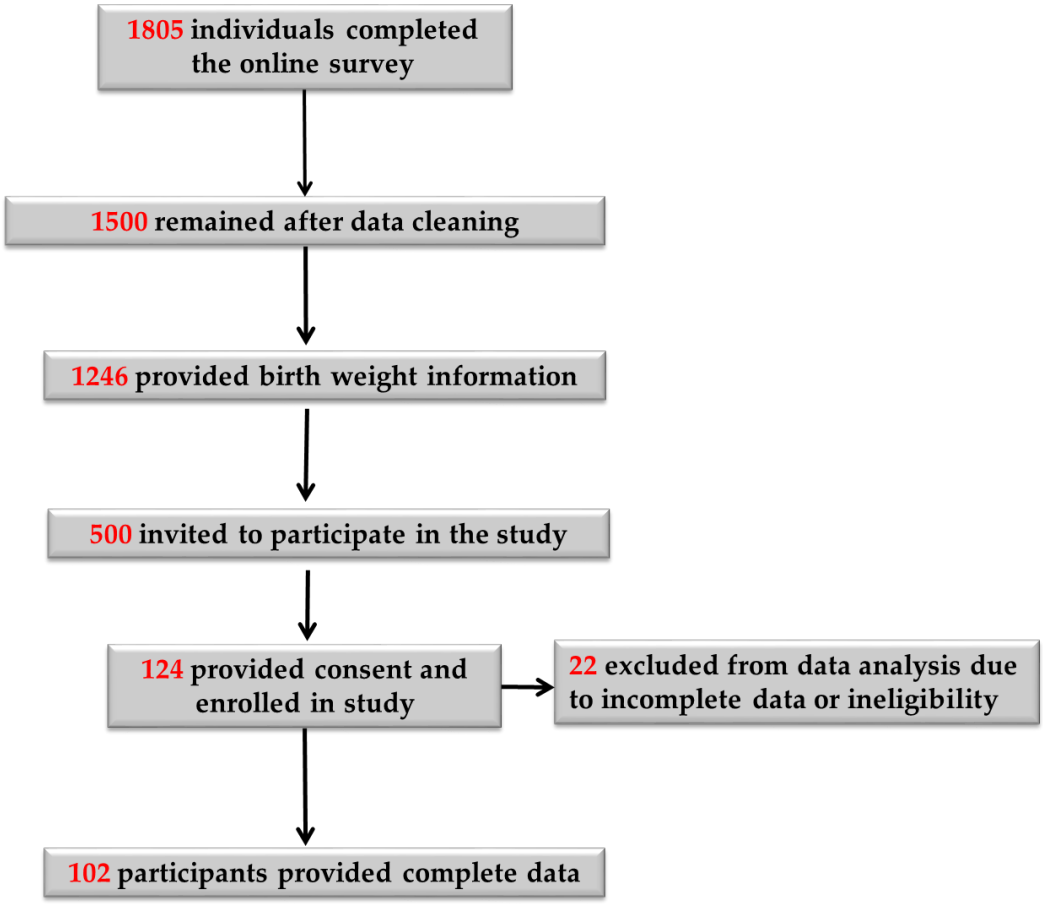

Figure 3.1. Subject recruitment flowchart.

The study population included 124 healthy adults (ages 18-40) who consented and were enrolled in the study. All participants selected for participation in the current study were asked to provide documentation of birth information (BW, BL, and GA). Documentation of birth information was ultimately provided by a subset of the participant pool (N = 62 for BW, N = 22 for GA), and agreement between the self-reported and documented information was good ($R = 0.925$ for BW, $p < 0.001$ and $R = 0.742$ for GA, $p < 0.001$).

Complete data was collected from 102 participants (23.2 ± 5.4 years). The over-recruitment of SGA individuals was successful, as 33% of the study participants (N = 33) were in this category (compared to an expected 25%, N = 25). The 22 participants who were excluded from data analysis either did not complete both study visits (N = 5), did not have adequate accelerometry data (N = 12) and/or were subsequently found to be ineligible based on the inclusion and exclusion criteria (N = 5).

The Syracuse University Institutional Review Board approved this study, and all participants provided written informed consent (see Appendix B).

Protocol Outline

Pre-study visit

Prior to enrollment in the study, an initial meeting was held with each subject to explain the study purpose, participant expectations, and compensation. After verbally agreeing to participate, participants provided written informed consent (see Appendix B).

Study Visit #1

The visit took place in Human Performance Laboratory of the Department of Exercise Science. Upon arrival to the lab, participants completed the Human Performance Lab Health Screening Form (HHQ, see Appendix C) and were briefly interviewed to ensure they met all inclusion criteria. If the participant qualified for the study, the visit continued.

Prior to the visit, participants received e-mail instructions to come in after an overnight fast (or at least 12 hours since their last meal) and to avoid consuming alcohol, soda, juice, or

caffeine (including coffee, tea, soda, or other sources of caffeine) in the 12 hours prior to the start of the visit. Participants were also asked to avoid exercise prior to the measurement.

Height (meters, m) was obtained from a portable stadiometer. Weight (kilograms, kg) was determined using the Tanita SC-240 digital scale (Tanita Corporation, Arlington Heights, IL). The Tanita scale also performed bioelectrical impedance analysis (BIA) to obtain body fat (percent, %) and lean body mass (kilograms, kg). To measure body fat, a single current (90 μA) was transmitted at a high frequency (50 kHz) through the electrodes positioned under the toes. Voltage was then measured using the electrodes positioned under the heels. Body fat was determined by a proprietary Tanita equation, and reported to the nearest 0.1%. Using this information, lean body mass was determined. Bioelectrical impedance analysis (BIA) has previously been validated against dual-energy X-ray absorptiometry as an accurate method to determine body composition [150]. Percent body fat was also measured using the BodPod™ device (Cosmed, Chicago, IL). Circumference measurements were taken of the waist, hips, upper left arm and upper left leg. Skinfold measurements were obtained from the right biceps and triceps. Other measurements taken during visit #1 include a finger-prick blood sample to measure cholesterol, triglycerides, glucose, and hemoglobin. Participants also completed a 24-hour dietary recall.

At the end of the visit, participants were instructed to begin wearing two accelerometers, activPAL (PAL Technologies Ltd, Glasgow, UK) and ActiGraph GT3X+, (ActiGraph LLC, Fort Walton Beach, FL). The activPAL device was placed on the left thigh, approximately centered between the knee and hip, in the middle of the thigh. The ActiGraph device was affixed to an elastic waistband and positioned on the left hip. Participants were instructed to wear both devices for the following seven (7) days, and only to remove the devices when swimming or showering.

A paper log (see Appendix D) was provided for participants to record time periods during which the accelerometers were removed in order to corroborate activities and also indicate periods of non-wear.

Study Visit #2

This visit took place in the Ernie Davis Exercise Science Laboratory after participants completed wearing the accelerometers for a seven-day period. In advance of this visit, participants received e-mail instructions to avoid strenuous physical activity immediately prior to the visit. Upon arrival to the lab, participants rested in a seated position for approximately ten minutes. Following this period of seated rest, participants completed the muscle strength testing.

Muscle strength was measured four times: dominant handgrip MVC, non-dominant handgrip MVC, left leg MVC, and right leg MVC. The handgrip strength measurement was conducted using a Jamar® hand dynamometer (J.A. Preston Corporation, Clifton, NJ). Each participant performed three maximal voluntary contractions (MVC) on each hand, and the highest value from the three trials was used in data analysis. Leg strength was measured using a calibrated MedX Leg Extension machine (MedX Holdings Inc., Ocala, FL). Participants were seated and positioned with the tested leg at a 90º angle. During the test, participants performed an isometric MVC for approximately 5 seconds. On each leg, the highest value from the three trials was used to represent leg strength in the data analysis. Full details about the muscle strength testing are provided in Chapter 4.

Participants completed a VO_{2max} test to measure their cardiorespiratory fitness level. VO_{2max} was measured using open-circuit spirometry (Parvo-medics TrueOne 2400, Sandy, UT). Prior to each test, the gas analyzer and pneumotach were calibrated. Participants were fitted with

a mouthpiece containing a breathing valve to capture expired air, and wore a heart rate monitor across their chest (Polar Electro Inc., Lake Success, NY). During the test, ventilation, expired O_2, and expired CO_2 were measured. Participants began the test walking on a treadmill (Quinton Q4500 treadmill, Cardiac Science Corporation, Bothell, WA or h/p/cosmos Quasar treadmill, Nussdorf, Germany) at 3.5 mph with no incline. After 2 minutes, the speed increased to 5.5 mph with no incline. Every two minutes thereafter the speed increased by 1.0 mph. Once participants reached maximum speed (7.5 mph for women; 8.5 mph for men), the speed remained the same for the remainder of the test, but the incline of the treadmill increased by 2.5% every 2 minutes. Participants were verbally encouraged to continue the test. The test ended when the participant reached volitional fatigue. A participant was considered to have reach his or her VO_{2max} if at least two of the following criteria were met: Respiratory exchange ratio ≥ 1.1, Heart rate ≥ 85% of their age-predicted maximum heart rate (APMHR), and a plateau in VO_2 (defined as a change of no more than 150 ml/min VO_2 with increasing work). These criteria are in line with past research [151-153].

Outcome Measurements: Accelerometer

Accelerometry was used to obtain objective information about physical activity levels as well as sedentary behavior. Two accelerometer devices were worn by participants during the study. The activPAL accelerometer, worn on the thigh, is generally regarded as the optimal device for measuring time spent in sedentary behavior (SED), as well as breaks in SED. The ActiGraph accelerometer, worn on the waist, is generally regarded as the optimal device for

measuring moderate-to-vigorous physical activity (MVPA). Using multiple physical activity monitors is a best practice recommended by leading accelerometry researchers [154].

Acclerometers collected information about the participant's activity continuously over the course of the seven days. Instruction about proper placement of each accelerometer were provided at the end of study visit #1. Full details about the accelerometer methods are found in Chapter 5.

Construction of Standardized Birth Weight (SBW)

Most previous research focused on FP effects considers all individuals born between 37 – 42 weeks gestation equally, failing to account for the growth that can take place in utero during those five weeks. Figure 3.2 display the percentiles for birth weights across all gestational ages for both males and females based on the U.S. population [155]. The stars illustrate that a neonate weighing approximately 3000 grams at birth would be classified at the 50^{th} percentile if born at 37 weeks but closer to the 20^{th} percentile if born at 42 weeks. Thus, we believe it is more appropriate to evaluate birth size (and identify IUGR) by accounting for an individual's GA.

To better represent size at birth, a standardized birth weight (SBW) variable was constructed using each participant's self-reported BW and GA. All study participants provided their BW in the initial online survey, entering it in pounds and/or ounces. GA was determined using responses from the survey question "How many days BEFORE or AFTER your due date were you actually born?" Assuming the length of typical pregnancy is 40 weeks (280 days), the due date was set to 280 days and each respondent's GA was determined by subtracting or adding the reported number of days from 280. Participants were also asked to provide both the due date and their actual birth date to verify.

There is no universal method to clinically determine GA. The most common approach is self-report of the woman's last (normal) menstrual period (LMP), which can be subject to recall error and/or bias [156]. More recently, ultrasound measurement has been used to confirm a due date. Comparing the due date based on the LMP to the due date generated by ultrasound suggests that the two are most similar for term pregnancies [157, 158]. There are also techniques to determine GA post-birth, although this is believed to be the least accurate option [159]. In the current study, we did not ascertain the method that due date was determined for each participant.

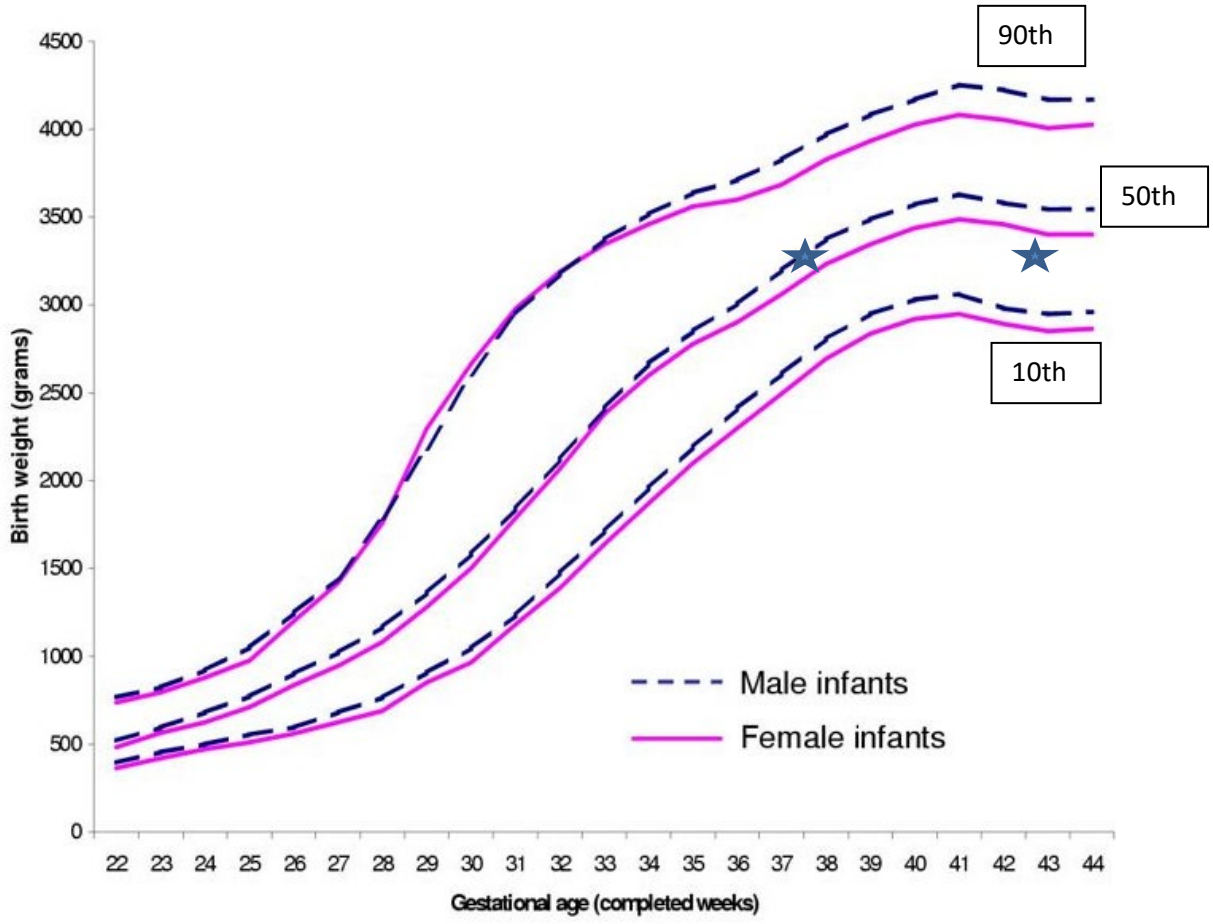

Figure 3.2. 10th, 50th, and 90th percentiles of birth weight by gestational age in male and female infants. Source: [155] Stars represent two infants both weighing approximately 3000 grams born at different GA (37 versus 42 weeks) and thus at different percentiles.

Using the BW and GA information, SBW was determined as follows: Data from a Canadian cohort [160] served as the reference and was used to estimate each subject's predicted BW (based on sex and GA). The GA information was obtained from birth certificates, and the method of determining GA was not universally known, but the researchers stated that early ultrasound was likely used for most participants [160]. Figures 3.3 and 3.4 display the charts and regression equations created from the reference dataset for males and females, respectively. Each participant's GA was entered into the appropriate equation to determine a predicted BW. The difference between each participant's actual and predicted BW was then calculated and converted to a z-score. This value, SBW, indicates whether each individual was born above or below the expected BW, and the magnitude of the difference. Because SBW was used to represent birth size in the data analysis presented, GA was not entered as a separate covariate in the regression models.

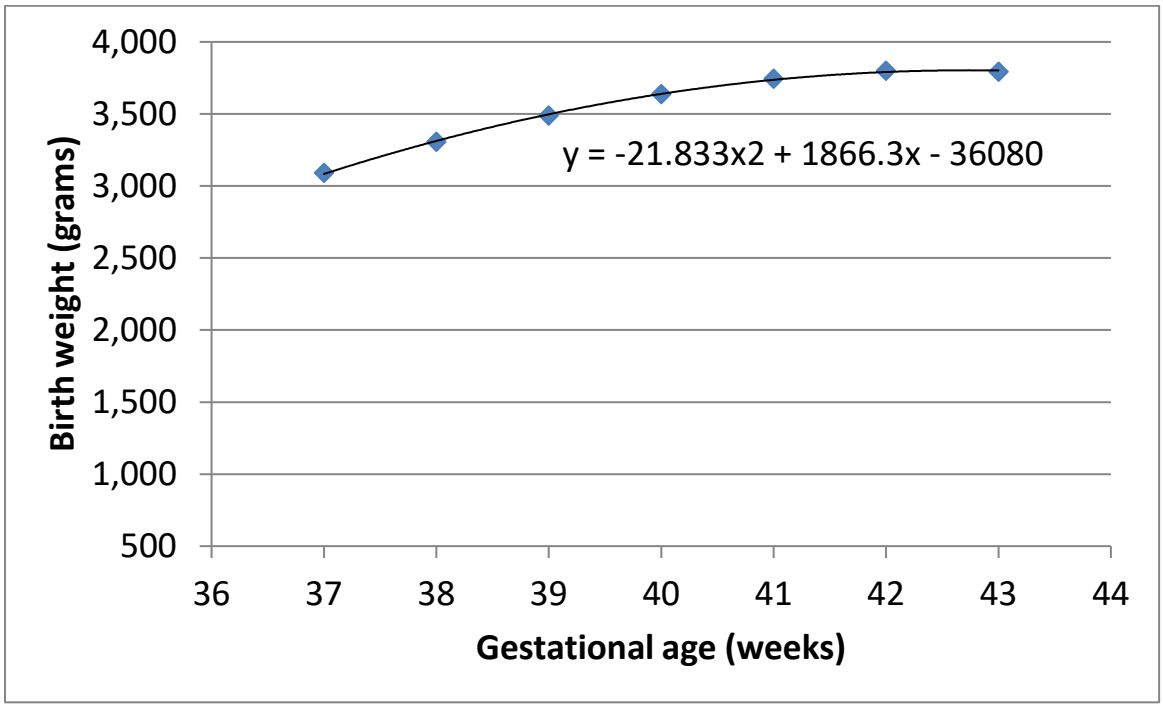

Figure 3.3. Mean birth weight by gestational age in males. Source: [160]

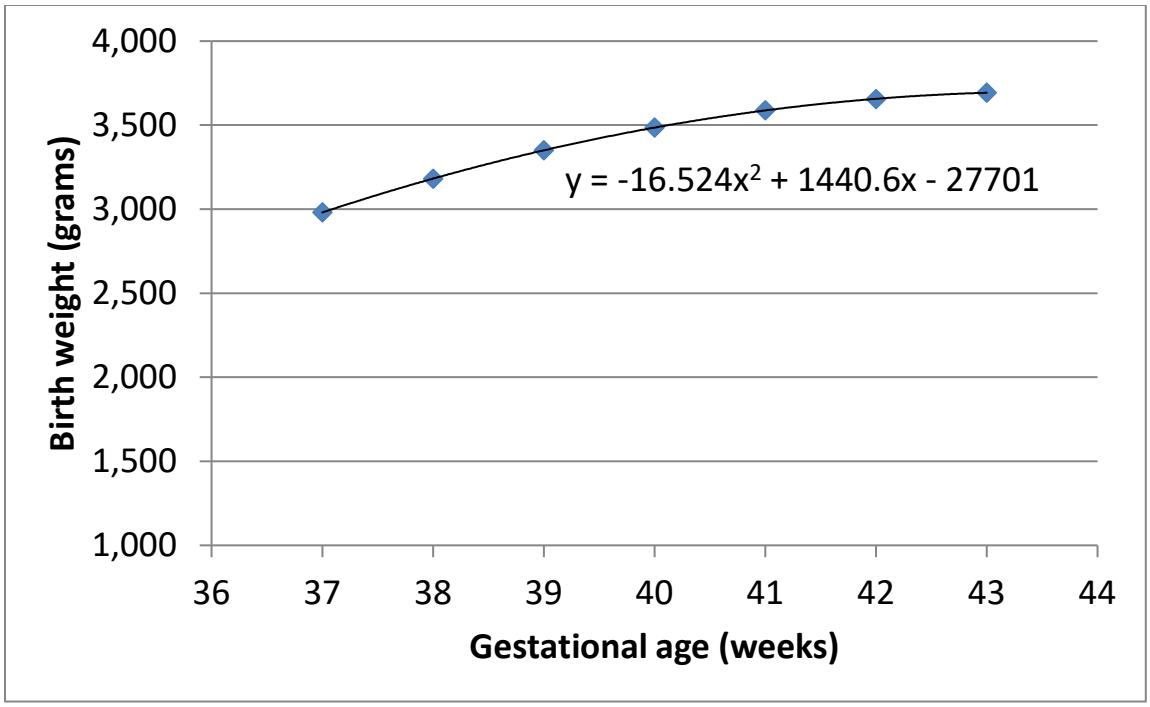

Figure 3.4. Mean birth weight by gestational age in females. Source: [160]

Statistical Analysis Plan

Data analysis was conducted using IBM SPSS Statistics version 23 for Windows (SPSS Inc., Chicago, IL). Significance for all statistical tests was set at $p < 0.05$ for main effects analysis and $p < 0.1$ for post-hoc exploratory interaction effects. All outcome measurements and covariates were evaluated for normal distribution using standard procedures, including visual inspection (histogram), Shapiro-Wilks test of normality, and calculating z-scores of the skewness and kurtosis [161, 162].

Linear regression analysis was used to determine the association between SBW and physical activity behaviors or muscle strength. Several covariates were evaluated for inclusion in both regression models, including sex, age, lean body mass, body fat percentage, maternal smoking and aerobic fitness level (VO_{2max}), while muscle strength and accelerometer wear time

were also considered for the physical activity behaviors. Those with significant associations with the dependent variable were included in the final analytic models for each hypothesis (Table 3.1). Sex was included as a covariate in all models since research has shown that males engage in more accelerometer-measured physical activity than females [140, 163], and have higher muscle strength (due to increased muscle mass), than females [164]. Age was included in hypotheses #1 and 2 because adults engage in less physical activity as they get older [140]. Body fat percentage was included in hypotheses #1 and 2 to account for body composition, as people who engage in more physical activity tend to be leaner, and those who are more sedentary tend to be fatter. Lean body mass was included in hypothesis #3 to account for body size, since a higher lean body mass reflects more muscle cross-sectional area, which is strongly correlated with increase force production and thus higher muscle strength [64]. Aerobic fitness level (VO_{2max}) was included in hypotheses #1 and 2 since there is an inherent association between physical fitness and time spent being physical active or sedentary. Accelerometer wear time, also known as wake wear time, was included in hypotheses #1 and 2 because the amount of time spent wearing an accelerometer device will impact the amount of physical activity and/or sedentary behavior it will capture [165, 166].

Lean body mass (LBM), body fat percentage, and age were centered on the respective mean value and entered as continuous variables. Sex and maternal smoking were both dummy coded and entered as categorical variables.

Below is a sample of the analytic model used to test hypothesis #1:

$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n + e$ where

Y = time spent in sedentary behavior

β_0 = constant (intercept)

X_1 = SBW

$X_2 - X_n$ are covariates (such as sex, age, maternal smoking, lean body mass)

e = error term

Table 3.1. Design of Statistical Analysis

Aim	Hypothesis	Dependent variable	Covariates
1	1	Time spent in SED	Sex, Age, Body fat percentage, Aerobic fitness (VO_{2max}), Accelerometer wear time
1	2	Time spent in MVPA	Sex, Age, Body fat percentage, Aerobic fitness (VO_{2max}), Accelerometer wear time
2	3	Muscle strength	Sex, Lean body mass (proxy for body size)

Chapter 4: *Size at birth predicts adult grip strength among individuals born to term*

Note: This manuscript will be submitted to the journal Medicine and Science in Sports and Exercise.

Abstract

Introduction: A developing fetus exposed to intra-uterine stress is likely to experience intra-uterine growth restriction (IUGR) and undergo fetal programming (FP), resulting in the formation of less muscle mass, likely leading to lower muscle strength throughout life. We assessed the relationship between size at birth and muscle strength, to determine if this relationship was the result of changes to muscle mass or muscle function among those born small for gestational age (SGA).

Methods: One hundred adults (ages 18-40), all singletons born to term (37-42 weeks), participated in the study. Birth weight was adjusted for gestational age (GA) to create a standardized birth weight (SBW). Maximal voluntary contractions (MVC) of dominant handgrip, non-dominant handgrip, and right and left leg extension were measured.

Results: SBW was a significant predictor of dominant handgrip MVC (B = 1.533 kg/1 SD increase in SBW, p = 0.004) after controlling for sex and body size (represented by LBM). SBW explained 8.4% of the variance in dominant handgrip MVC. LBM had a significant indirect effect on the relationship between SBW and dominant handgrip MVC, confirmed by mediation analysis using the Sobel test (p = 0.04), partial posterior p-value (p = 0.025), and hierarchical Bayesian confidence interval (95% CI = 0.063, 1.401). No other muscle strength measures were significantly associated with SBW after controlling for sex and LBM.

Conclusion: The relationship of SBW on muscle strength is partially mediated by muscle mass, since the inclusion of LBM attenuated, but did not remove, the significant association of SBW with dominant handgrip MVC. We conclude that adults born SGA exhibited lower muscle strength in their dominant hand due to a combination of having smaller muscles and having muscles that function less well compared to adults born at a normal size for GA.

Keywords: fetal programming; muscle strength; intra-uterine growth restriction

Abbreviations: BW = birth weight; GA = gestational age; IUGR = intra-uterine growth restriction; FP = fetal programming; SBW = standardized birth weight; MVC = maximal voluntary contraction

Introduction

The intra-uterine environment, which provides nourishment to the developing fetus, is dependent on the health and nutritional status of the mother. If insufficient nutrients are available in this environment, the fetus will experience stress and intra-uterine growth restriction (IUGR) will likely occur. IUGR leads to measurable differences in birth weight (BW), birth length (BL), and/or Ponderal Index (PI, gm/cm^3) [167-169]. In addition, the fetus will likely respond to the intra-uterine stress by making metabolic or hormonal adjustments which can disrupt organ development and lead to lifelong health issues [5]. These adjustments are collectively known as "fetal programming" (FP). Epidemiological data suggests that FP leads to a higher risk of chronic diseases such as heart disease and diabetes [5, 170]. Moreover, FP also effects body composition, leading to higher body fat and lower lean body mass as adolescents or adults compared to healthy peers [5-16].

Past research has consistently revealed a linear relationship between birth size and muscle strength. A recent meta-analysis of 17 studies found muscle strength increased 0.86 kilogram (kg) for every 1 kg increase in birth weight [171]. The lower muscle strength observed among those born small is the result of FP, which causes in utero changes to muscle development. One proposed change is a reduction in the number and/or size of muscle fibers that form in utero due to a lack of available nutrients to support the formation of adequate muscle mass [65, 134, 172]. If there is less muscle mass available, the ability to generate force is likely reduced. Indeed, muscle strength significantly correlates with muscle mass [64]. Regardless of the amount of muscle that forms in utero, the function of these fibers can also be compromised. Improperly developed fibers are unable to contract to their full potential, thus leading to lower force production and overall lower muscle strength throughout life [65, 134, 172]. In order to identify

which type of change occurs – a quantitative reduction in muscle number/size or a detrimental impact on muscle fiber function – both absolute (i.e. total force production) and relative (i.e. force per kilogram body weight) muscle strength is determined. If birth size effects absolute muscle strength but has no effect on relative muscle strength, then a quantitative reduction in muscle number/size is assumed to have occurred. If birth size effects both absolute and relative muscle strength, then we infer both quantitative and qualitative changes due to FP in response to IUGR.

Relative muscle strength can be determined by controlling for muscle cross-sectional area (CSA). Often, adjusting for body size (such as current weight and/or height) is performed instead as a proxy of muscle CSA [22]. Since past research has identified a significant association between BW and fat-free mass, it may be more appropriate to include a measure of body size that represents muscle mass [25, 62]. Large cohort studies have identified fat-free mass (which includes muscle mass) as a possible mediator of the association between BW and muscle strength [62, 136]. In these datasets, controlling for body size using lean (fat-free) body mass reduced or eliminated the association between BW and muscle strength.

When comparing the long-term effects of birth size on muscle strength, most researchers eliminate or adjust for individuals born pre-term (prior to 37 weeks), but treat all individuals born to term (37-42 weeks gestation) as equivalent. In these cases, the World Health Organization definition of low BW, which is a BW less than 2500 grams[1], is often used. However, considerable growth can occur from week 37 to week 42, making it difficult to apply

[1] World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.

the same BW cutpoint to all individuals. It is therefore more meaningful to consider BW relative to gestational age (GA) as the means to identify IUGR. Growth charts (based on representative populations) can identify individuals who are born small for GA (SGA), large for GA (LGA), or appropriate for GA (AGA). SGA individuals are most likely to have been exposed to intra-uterine stress and are therefore at highest risk for FP effects. Several national datasets exist to establish normative BW-for-GA growth charts [155, 160, 173, 174]. Using these datasets, SGA individuals are defined broadly as individuals who fall below the 25th percentile, or more strictly defined by the World Health Organization as individuals who fall below the 10th percentile[1]. For example, a male newborn weighing 3080 grams would be classified at the 50th percentile (indicating AGA) if born at 37 weeks, but if that newborn was born at 42 weeks gestation, he would be classified at the 5th percentile (indicating SGA and possible risk of IUGR) [160]. National datasets can generate growth charts for males and females separately since there are slight sex differences in birth size, with males typically 100-200 grams heavier than females [155]. The current study constructed a standardized variable representing the difference between actual and expected BW, the latter being determined based on sex and GA.

The primary purpose of the current study was to assess the relationship between size at birth and adult muscle strength. Previous studies investigating this association used handgrip maximal voluntary contraction (MVC) testing as a measure of muscle strength. Few studies have measured the relationship between birth size and leg muscle strength [135]. Grip strength is an established indicator of malnutrition, bone mineral density, and mortality risk [175]. Both handgrip and leg muscle strength have been shown to predict mortality risk among older adults [176]. A secondary purpose was to determine if any relationship between size at birth and adult muscle strength was due to reductions in the number of muscle fibers (evidenced by decrements

in absolute muscle strength, or force), reductions in muscle functional capacity (evidenced by relative muscle strength, or force per kilogram fat-free mass), or a combination of both. It was hypothesized that young adults who were born SGA (likely due to IUGR) would demonstrate lower muscle strength compared to individuals who were AGA or LGA as a result of FP-induced changes to muscle size and/or function.

Methods

Participants and Recruitment

The study population included 124 healthy adults (ages 18-40) who had access to birth information. Participants were selected from respondents to an online recruitment survey (N = 1246). A more detailed description of the survey and recruitment procedures is provided in Chapter 3: Methodology. Briefly, the survey asked respondents to self-report birth measures and other birth information (such as parity, maternal health, and maternal smoking), as well as current height, weight, and physical activity level. Potential participants were contacted if they met inclusion criteria (described below). Individuals identified as being born SGA were over-recruited (33% versus an expected 25%) to ensure adequate representation of participants who likely experienced intra-uterine stress in the current study.

To participate in the current study, participants had to meet the following inclusion criteria: a singleton born to term (37-42 weeks gestation); provided birth weight information in the online survey; and maintained their current weight during at least the last 3 months. Participants were ineligible if their mother developed gestational hypertension or diabetes while pregnant. Additionally, participants who were currently underweight (BMI < 18.5), morbidly

obese (BMI >35), pregnant, or recently pregnant (within the last year) were excluded from the study.

Calculation of Standardized Birth Weight (SBW)

A standardized BW (SBW) variable was calculated for each subject based on his or her sex and self-reported birth information. BW and GA were reported by participants in the online survey. A reference dataset from a Canadian cohort [160] was used to estimate each participant's predicted BW based on sex and GA. The difference between each participant's actual and predicted BW was calculated and then converted to a z-score. The resulting value, hereafter referred to as the standardized BW, or SBW, represents BW adjusted for sex and GA. For more details about the calculation of SBW, see Chapter 3: Methodology.

Measurement Procedures

Height, weight, and body fat measurements were taken in the morning. Participants were instructed to avoid exercise prior to the measurement. For complete details about the height, weight, and body fat measurements, see Chapter 3: Methodology.

Muscle strength was measured four times: dominant handgrip maximal voluntary contraction (MVC), non-dominant handgrip MVC, left leg MVC, and right leg MVC. The handgrip strength measurement was conducted using a Jamar® hand dynamometer (J.A. Preston Corporation, Clifton, NJ). Participants self-reported their dominant hand. The order of testing (dominant vs. non-dominant) was randomly assigned. Each participant performed three maximal voluntary contractions (MVC) on each hand, and the highest value from the three trials was used in data analysis. Participants were instructed to stand upright, to hold the dynamometer by their

side, and to squeeze as hard as they could for approximately 3 seconds. These instructions are consistent with NHANES procedures[2].

Leg strength was measured using a calibrated MedX Leg Extension machine (MedX Holdings Inc., Ocala, FL). The MVC test was performed on each leg individually. The leg tested first was randomly assigned. Participants were seated and positioned with the tested leg at a 90º angle. The lower portion of the leg was attached to the immobilized movement arm. During the test, participants held onto handlebars on either side of their body. Participants performed an isometric MVC for approximately five seconds. The force produced by the leg was continuously relayed to a load cell, and the data was recorded using a Power Lab 26T data acquisition system (ADInstruments Inc., Colorado Springs, CO). The MVC test was performed two additional times with a 5-10 second rest in-between trials. The entire procedure was replicated on the opposite leg. On each leg, the highest value from the three trials was used to represent leg strength in the data analysis.

The Syracuse University Institutional Review Board approved this study, and all participants provided written informed consent.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics version 23 for Windows (SPSS Inc., Chicago, IL). All outcome measurements and covariates were evaluated for normal distribution using standard procedures, including visual inspection (histogram), Shapiro-Wilks test of normality, and calculating z-scores of the skewness and kurtosis [161, 162]. Using these

[2] National Health and Nutrition Examination Survey (NHANES) Muscle Strength Procedures Manual. Published April 2011 by the Centers for Disease Control and Prevention.

methods, one subject was identified as a potential outlier for lean body mass and an additional subject was identified as a potential outlier for the leg strength measures. In both cases, the outlier participants had values that were more than two standard deviations above the mean for the respective variable(s). Both participants were removed prior to analysis. Inclusion or exclusion of the outlier participants had no meaningful effect on the study outcomes.

Bivariate correlation testing was performed first to identify associations between SBW and muscle strength. Independent t-tests were used to test sex differences in muscle strength and paired t-tests were used to determine within-subject differences. Linear regression analysis was used to determine the association between SBW and each muscle strength measure. The first analytic model, hereafter referred to as Model 1, assessed the effect of SBW on muscle strength, and included only sex as a covariate. The second analytic model, hereafter referred to as Model 2, included both sex and body size (represented by lean body mass, a proxy measurement of muscle mass) as covariates to determine if body size changed the association of SBW on muscle strength. Lean body mass (LBM) was centered on its mean value, and entered as a continuous variable. Age, height, and maternal smoking were also considered as covariates, but were excluded from the final statistical models because they were not significant. Excluding these potential covariates will reduce bias on coefficient estimates. Mediation analysis was conducted using the Sobel test [177] and confirmed with two additional computational programs – partial posterior methods and hierarchical Bayesian confidence intervals [178]. Significance was set at $p < 0.05$ for all tests.

Results

Complete data was collected from 102 of the 124 participants initially enrolled. Twenty-two participants were excluded from data analysis because they either did not complete all research activities and/or were subsequently found to be ineligible based on the inclusion and exclusion criteria listed above. Two participants with complete data were identified as outliers and were removed prior to analysis (see Methods for detailed explanation). A profile of the 100 remaining participants included in the data analysis (77 females, 23 males) is provided in Table 4.1. In general, participants were young and healthy.

Table 4.1. Descriptive characteristics of study participants.

	Full sample (N = 100)	**Females (N = 77)**	**Males (N = 23)**
Age (years)	23 ± 5 (18 – 40)	23 ± 6 (18 – 40)	23 ± 4 (18 – 36)
Ethnicity (% Caucasian)	74	80	61
Current BMI	23.6 ± 3.4 (18.5 – 35.0)	23.5 ± 3.6 (18.5 – 35.0)	24.0 ± 3.0 (20.0 – 34.9)
Current % Body Fat	25.4 ± 8.4 (11.0 – 47.5)	28.0 ± 7.6 (14.3 – 47.5)	16.7 ± 4.1^ (11.0 – 31.8)
Current LBM (kg)	49.1 ± 8.2 (39.4 – 77.0)	45.2 ± 3.2 (39.4 – 53.4)	62.3 ± 5.9^ (53.2 – 77.0)

Values are mean ± standard deviation (range), or percent frequency.
BMI = Body Mass Index; LBM = Lean Body Mass
^Significantly different between males and females, $p < 0.001$

Table 4.2 displays birth characteristics for the full sample (N = 100), as well as male and female participants separately. Based on unadjusted BW, 2% of our participant pool was below the 2500 gram threshold commonly used to identify low BW. However, 32% of the participant pool was considered SGA, defined as below the 25th percentile on the BW-for-GA growth chart.

Table 4.2 shows the values for BW, GA, BW adjusted for GA (Difference in BW), and the z-score of this adjusted BW (SBW).

Table 4.2. Birth characteristics

	Full sample (N = 100)	**Females (N = 77)**	**Males (N = 23)**
Birth weight (grams)	3438 ± 513 (2324 – 4763)	3460 ± 486 (2353 – 4763)	3361 ± 601 (2324 – 4621)
Gestational age (weeks)	40.0 ± 1.1 (37.0 – 42.1)	40.1 ± 1.1 (37.9 – 42.1)	39.7 ± 1.1 (37.0 – 42.0)
Difference in BW: Actual BW – Predicted* BW (grams)	-44.6 ± 490.8 (-1127.1 – 1147.7)	0.1 ± 474.5 (-965.8 – 1147.7)	-194.1 ± 525.1 (-1127.1 – 837.1)
SBW^	0.002 ± 1.002 (-2.209 – 2.437)	0.093 ± 0.969 (-1.879 – 2.437)	-0.303 ± 1.072 (-2.209 – 1.803)

*Based on sex and gestational age, developed from Kramer et al 2003.
^SBW (standardized BW) is the z-score of Difference in BW. For more details, see Methods.
Values are mean ± standard deviation (range).

Table 4.3 shows the results of the muscle strength tests. Dominant handgrip MVC was significantly higher than non-dominant grip MVC in the full sample ($p < 0.001$) and in both sexes ($p<0.001$ for females; $p = 0.004$ for males). Left leg MVC was significantly higher than right leg MVC in the full sample ($p = 0.004$), apparently driven by the large difference among male ($p = 0.022$), but not female ($p = 0.083$), participants. Across all muscle strength measures, male participants had significantly higher muscle strength than female participants ($p < 0.001$ for all MVC tests).

Table 4.3. Results of muscle strength testing

Muscle strength (kg)	Full sample (N = 100)	Females (N = 77)	Males (N = 23)
Dominant handgrip MVC	37.6 ± 10.2^	33.2 ± 5.6^	52.3 ± 7.8^*
Non-dominant handgrip MVC	35.2 ± 9.9	31.0 ± 5.6	49.2 ± 8.0*
Left Leg MVC	88.0 ± 36.5[#]	75.1 ± 25.7	131.4 ± 33.9[#]*
Right Leg MVC	82.9 ± 32.4	71.9 ± 24.0	119.8 ± 29.6*

Values are mean ± standard deviation. MVC = maximal voluntary contraction
*Significant difference between males and females, $p < 0.001$
^Significant difference between dominant and non-dominant, $p < 0.001$ (full sample), $p < 0.001$ (females), $p = 0.004$ (males)
[#]Significant difference between left leg and right leg, $p = 0.004$ (full sample) and $p = 0.022$ (males)

All muscle strength measures were significantly correlated with each other in the full sample (Table 4.4). Among male participants, dominant handgrip MVC was significantly correlated with non-dominant handgrip MVC ($R = 0.839$, $p<0.001$) and left leg MVC was significantly correlated with right leg MVC ($R = 0.756$, $p<0.001$). Neither handgrip MVC measure was significantly correlated with either leg strength measure in male participants. Among female participants, dominant handgrip MVC was significantly correlated with non-dominant handgrip MVC ($R = 0.860$, $p<0.001$) and with both leg strength measures ($R = 0.529$, $p < 0.001$ for left leg MVC; $R = 0.485$, $p<0.001$ for right leg MVC). In addition, non-dominant handgrip MVC in female participants was significantly correlated to both leg strength measures ($R = 0.508$, $p<0.001$ for left leg MVC; $R = 0.449$, $p<0.001$ for right leg MVC). Similar to the male participants, left leg MVC was significantly correlated with right leg MVC ($R = 0.799$, $p<0.001$) among female participants.

In the full sample, SBW was not significantly correlated with grip strength or leg strength (Table 4.4). However, among female participants, there was a significant correlation between SBW and both dominant handgrip MVC (R = 0.380, p = 0.001) and non-dominant handgrip MVC (R = 0.298, p = 0.008) (data not shown). This pattern was not observed in male participants (R = 0.309, p = 0.151 for dominant handgrip MVC; R = 0.231, p = 0.288 for non-dominant handgrip MVC) (data not shown). SBW was not significantly correlated with leg strength in males (R = 0.122, p = 0.579 for left leg MVC; R = -0.019, p = 0.931 for right leg MVC) nor females (R = 0.158, p = 0.171 for left leg MVC; R = 0.141, p = 0.220 for right leg MVC).

Table 4.4. Correlation matrix for muscle strength testing measurements with SBW.

	SBW	**Dominant handgrip MVC**	**Non-dominant handgrip MVC**	**Left Leg MVC**
Dominant handgrip MVC				
R	0.080			
p-value	0.430			
Non-dominant handgrip MVC				
R	0.038	0.944		
p-value	0.704	<0.001		
Left Leg MVC				
R	0.000	0.741	0.717	
p-value	0.999	<0.001	<0.001	
Right Leg MVC				
R	-0.031	0.702	0.673	0.872
p-value	0.758	<0.001	<0.001	<0.001

Tables 4.5 and 4.6 present results from the linear regression analysis of SBW on selected covariates and muscle strength. Model 1 (Table 4.5) controlled for sex (full sample analysis), and

Model 2 (Table 4.6) controlled for sex as well as body size by including lean body mass (LBM). In both models, SBW was a significant predictor of dominant handgrip MVC. In Model 1, 12.7% of the variance (represented by the partial η^2 variable in Table 5) in dominant handgrip MVC was explained by SBW. As SBW increased by one SD, dominant handgrip MVC increased by 2.219 kg ($p < 0.001$). In Model 2, SBW explained 8.4% of the variance in dominant handgrip MVC. As SBW increased by one SD, dominant handgrip increased by 1.533 kg ($p = 0.004$). Thus, the relationship of SBW on muscle strength is mediated by muscle mass, since the inclusion of LBM attenuated the association of SBW with dominant handgrip MVC, reducing the partial η^2 from 12.7% (Model 1) to 8.4% (Model 2). A significant indirect effect of LBM on the relationship between SBW and dominant handgrip was found using the Sobel test ($p = 0.04$), partial posterior p-value ($p = 0.025$), and hierarchical Bayesian confidence interval (95% CI = 0.063, 1.401), indicating partial mediation.

A similar pattern existed for non-dominant handgrip MVC. In Model 1, both SBW and sex are significant predictors, collectively explaining 71.6% of the variance in non-dominant handgrip MVC. However, introducing LBM in Model 2 causes the effect of SBW on non-dominant handgrip MVC to near, but not reach, significance. Regarding leg strength, neither right nor left leg MVC was significantly affected by SBW. This pattern was consistent in both Model 1 and Model 2.

Table 4.5. Association of SBW and sex on muscle strength measures (Model 1).

Muscle Strength Measure	**SBW**			**Sex**		
	B (95% CI)	p-value	Partial η^2	B (95% CI)	p-value	Partial η^2
Dominant handgrip MVC	2.219 (1.046, 3.391)	<.001	.127	19.974 (17.196, 22.753)	<.001	.677
Non-dominant handgrip MVC	1.713 (0.507, 2.919)	.006	.076	18.905 (16.047, 21.763)	<.001	.640
Right leg MVC	2.444 (-2.677, 7.565)	.346	.009	48.912 (36.775, 61.049)	<.001	.397
Left leg MVC	4.096 (-1.473, 9.665)	.148	.021	57.948 (44.750, 71.146)	<.001	.439

N = 100

Overall R^2 for Dominant handgrip MVC = 0.679

Overall R^2 for Non-dominant handgrip MVC = 0.640

Overall R^2 for Right leg MVC = 0.398

Overall R^2 for Left leg MVC = 0.439

Partial η^2 indicates how much of the variance in the outcome variable is explained by each independent variable.

Table 4.6. Association of SBW, sex, and lean body mass on muscle strength measures (Model 2).

Muscle Strength Measure	**SBW**			**Sex**			**LBM**		
	B (95% CI)	p-value	Partial η^2	B (95% CI)	p-value	Partial η^2	B (95% CI)	p-value	Partial η^2
Dominant handgrip MVC	1.533 (0.508, 2.558)	.004	.084	6.201 (1.134, 11.269)	.017	.058	0.791 (0.534, 1.049)	<.001	.280
Non-dominant handgrip MVC	1.026 (-0.0.39, 2.091)	.059	.037	5.112 (-.153, 10.376)	.057	.037	0.792 (0.525, 1.060)	<.001	.265
Right leg MVC	0.592 (-4.393, 5.578)	.814	.001	11.740 (-12.909, 36.389)	.347	.009	2.136 (0.884, 3.387)	.001	.107
Left leg MVC	1.716 (-3.575, 7.008)	.521	.004	10.183 (-15.978, 36.345)	.442	.006	2.744 (1.416, 4.073)	<.001	.149

N = 100

Overall R^2 for Dominant handgrip MVC = 0.769

Overall R^2 for Non-dominant handgrip MVC = 0.736

Overall R^2 for Right leg MVC = 0.462

Overall R^2 for Left leg MVC = 0.523

Partial η^2 indicates how much of the variance in the outcome variable is explained by each independent variable.

Results of the regression analysis are shown for each sex in Table 4.7. As with the full sample, there was a significant effect of SBW on dominant handgrip MVC among female participants, both before and after controlling for body size. In Model 2, SBW explained 10.6% of the variance in dominant handgrip MVC. Non-dominant handgrip MVC was significantly associated with SBW in female participants in Model 1, but after controlling for body size this association became marginally non-significant ($p = 0.052$). Neither of the leg strength measures were significantly associated with SBW among female participants. There was no significant effect of SBW on any muscle strength measure among male participants.

Table 4.7. Association of SBW on muscle strength measures by sex.

Muscle Strength Measure		**Females (N = 77)**			**Males (N = 23)**		
		B (95% CI)	p-value	Partial η^2	B (95% CI)	p-value	Partial η^2
Dominant handgrip MVC	Model 1	2.212 (0.971, 3.452)	.001	.144	2.239 (-0.883, 5.360)	.151	.096
	Model 2	1.673 (0.549, 2.797)	.004	.106	1.117 (-1.496, 3.730)	.383	.038
Non-dominant handgrip MVC	Model 1	1.712 (0.451, 2.972)	.008	.089	1.717 (-1.561, 4.994)	.288	.053
	Model 2	1.065 (-0.010, 2.140)	.052	.050	0.817 (-2.257, 3.890)	.586	.015
Right leg MVC	Model 1	3.498 (-2.142, 9.138)	.220	.020	-0.530 (-13.040, 11.980)	.931	.000
	Model 2	1.873 (-3.637, 7.383)	.500	.006	-3.310 (-15.606, 8.986)	.581	.016
Left leg MVC	Model 1	4.179 (-1.846, 10.203)	.171	.025	3.861 (-10.368, 18.090)	.579	.015
	Model 2	2.071 (-3.660, 7.802)	.474	.007	0.461 (-13.337, 14.260)	.945	.000

Partial η^2 indicates how much of the variance in the outcome variable is explained by each independent variable.

Discussion

The results of this study suggest that birth size (a proxy indicator of IUGR and thus, intra-uterine stress) effects adult muscle strength. The presumed mechanism for this relationship is two-fold: intra-uterine stress simultaneously decreases the amount of muscle fibers and causes a reduced function of existing muscle fibers. In a statistical model controlling only for sex, SBW explained 12.7% of the variance in dominant handgrip MVC. After controlling for sex and body size (represented by LBM), SBW remained a significant predictor of dominant handgrip MVC, explaining 8.4% of the variance. In this model, dominant handgrip MVC increased by 1.533 kg for every one SD increase in birth size (adjusted for gestational age). By introducing body size as a covariate, the effect of SBW on muscle strength was reduced but remained significant. This suggests that intra-uterine stress not only leads to less muscle fibers, but muscle fibers that have reduced function as well. Non-dominant handgrip MVC also had a significant association with SBW ($p = 0.06$), but introducing a body size control caused the effect to become non-significant ($p = 0.059$). No relationship was found between SBW and leg MVC, but leg MVC values were positively and significantly associated with handgrip MVC, similar to past findings [58]. Similarly, a previous study of older adults found a strong association between birth size and muscle size in the forearm (muscles involved in generating handgrip MVC), but a weaker association between birth size and muscle size in the leg [22]. However, these associations became non-significant after adjusting for adult height and/or weight (except for forearm muscle size in males, which remained significant after adjustment), suggesting that IUGR leads to reduction of muscle mass only [22].

It is well established that individuals who were exposed to intra-uterine stress and experienced IUGR have unfavorable body composition as children and adults, manifested as

increased body fatness [5-16] and less muscle mass [25, 62]. Since being born small creates an individual with less musculature [22], it leads to lower muscle strength, an effect seen across the lifespan [58, 60, 135, 136, 171]. A recent study demonstrated that childhood grip strength was significantly associated with birth size, but this effect disappeared after controlling for childhood body size, leading the researchers to conclude that in utero muscle development was a key determinant of later life muscle strength [179]. Studies also suggest that individuals who were exposed to intra-uterine stress may have a low muscle-to-fat ratio in adulthood, due to the combined quantitative effects of FP on skeletal muscle and adiposity [14, 65, 136]. This ratio may help identify individuals with "sarcopenic obesity", which in turn may predict chronic disease risk [65, 180]. Body composition was measured in this study; however, muscle-to-fat ratio was not significantly related to birth size (results not shown).

There is also previous evidence that exposure to intra-uterine stress leads to functional decrements in muscle. A meta-analysis of the association between birth weight and grip strength found that for every 1 kg increase in birth weight, grip strength increased by 2.06 kg; controlling for adult size removed some, but not all, of this association [181]. A more recent meta-analysis confirms this pattern: after adjusting for adult body size (in this case, height), muscle strength increased by 0.86 kg for every 1 kg increase in birth weight [171]. These analyses suggest that FP leads to both a reduction in muscle mass and a decreased muscle performance, since the adjustment for body size (and thus muscle size) did not completely remove the association between birth size and muscle strength. In a recent study, females born small had significantly lower grip strength (and fatigue resistance of the leg) compared to females born at a normal size even after controlling for fat-free mass [135]. In the current study, the relationship between SBW and grip strength was strongest among female participants.

There are several possible mechanisms to explain the effects on muscle strength caused by exposure to intra-uterine stress. One consequence is suboptimal myogenesis, leading to reductions in subsequent muscle mass. Primary and secondary muscle fibers develop during the first and second trimester, and tertiary muscle fibers complete development by the beginning of the third trimester [133, 182, 183]. If the maternal diet is inadequate in total calories during the first and/or second trimester of gestation, then the total number of muscle fibers formed may be permanently reduced in the offspring, depending on the fiber type and the specific muscle [184, 185]. Skeletal muscle fiber type, as well as the fiber size, are impacted if maternal caloric restriction occurs throughout pregnancy, extending into the third trimester [182]. In particular, poor maternal intake during the second trimester may cause fewer fast-twitch fibers to develop [186]. It appears that inadequate protein intake during the second trimester is the prime nutrient responsible for impaired myogenesis, reducing the number and size of skeletal muscle fibers that develop, and even decreasing the size of the neuromuscular junction, in rats [187, 188]. During the second and third trimesters, placental insufficiency may cause reductions in nutrient delivery and availability to fetal tissue [65]. When the placenta experiences reductions in blood flow, it will divert blood to the brain in lieu of blood to skeletal muscle [65]. The fetal muscle fibers will then experience less hypertrophy and develop fewer myonuclei during the third trimester [133]. Separately, animal models have shown that in utero exposure to hypoxia may also cause IUGR due to changes in blood flow towards the brain and heart at the expense of peripheral tissue such as skeletal muscle [189, 190].

An emerging consequence of intra-uterine stress is the effect it has on telomere length and possible accelerated aging of tissues, including muscle. Telomere length is a known marker of biological age and recent research has suggested it can indicate IUGR status or growth during

infancy. Specifically, neonates born LGA were found to have longer telomeres and higher lean mass in infancy [191]. The directionality of the relationship is not clear – are individuals with shorter telomeres more susceptible to the effects of intra-uterine stress, or does the presence of the intra-uterine stress cause shorter telomeres? Individuals who were exposed to intra-uterine stress and experienced IUGR likely have shorter telomeres, which may influence in-utero myogenesis and/or subsequent sarcopenia in adulthood, thus contributing to both potential mechanisms effecting adult muscle strength. Indeed, research has shown a significant and direct correlation between telomere length and grip strength in older adults [192]; however this relationship may be influenced by the level of inflammatory markers such as interleukins [193]. Given that exercise participation appears to maintain telomere length [194], specifically in skeletal muscle cells [195], it may be of utmost importance for individuals born small to engage in regular exercise throughout their life. Furthermore, shortened telomeres are also associated with a higher risk of Type 2 diabetes, poor diet, and possibly obesity [194], all of which are more likely among people who experienced IUGR [5, 11, 54, 55, 57, 88].

A challenge facing FP research is obtaining accurate birth information from adult participants. In the current study, participants were asked to self-report birth weight, birth length, and gestational age. Past research has shown maternal recall of birth information is very accurate [147, 148]. However, other prospective FP studies rely on hospital records, which provides information that is more accurate. An additional limitation of the current study was the use of lean body mass as a proxy measurement of muscle mass. Future studies may wish to measure muscle cross-sectional area for the muscles involved in the strength tests performed.

From a public health standpoint, the relationship between birth size and muscle strength has several implications for health and exercise professionals. For those working with pregnant

women, education about, and monitoring of, appropriate weight gain may help prevent IUGR. Dietary recommendations to consume additional calories and protein during the second and third trimesters should be promoted to pregnant women. When working with individuals who were previously identified as SGA, assessment of muscle strength and promotion of strength-training exercises may be beneficial. More research is needed to determine the extent to which lifelong physical activity, and specifically resistance training, can offset this programmed effect. If individuals who were exposed to intra-uterine stress have muscle fibers that are of lower quality, they may reach a maximum muscle strength that cannot be overcome with resistance training. If an insufficient number of muscle fibers was generated in utero, then resistance training could lead to hypertrophy of these existing muscle fibers, improving muscle strength. Individuals who were exposed to intra-uterine stress may be capable of skeletal muscle hypertrophy beyond that of an individual who did not.

Based on the results of the current study, adults born small for gestational age exhibited lower muscle strength in their dominant hand, suggesting a combination of having smaller muscles and having muscles that function less well compared to adults born at a normal size for gestational age. Individuals who exposed to intra-uterine stress and experience IUGR (as evidenced by being born SGA) may be permanently programmed to have less muscle mass, and therefore lower muscle strength, compared with individuals without intra-uterine stress exposure. These individuals may also have muscle fibers that developed improperly, resulting in inadequate force generation during muscle contraction. Future studies are needed to confirm if either (or both) of these effects are seen across other muscle groups in the body. In addition, intervention studies should be developed to determine the role of resistance training to increase strength in this population.

Chapter 5: *Size at birth does not predict physical activity or sedentary behavior in healthy young adults*

Note: This manuscript will be submitted to the International Journal of Behavioral Nutrition and Physical Activity

Abstract

Introduction: Exposure to stress in utero can effect fetal growth and development, potentially leading to intra-uterine growth restriction (IUGR) as well as fetal programming (FP). The presence of IUGR may increase an individual's risk of low birth weight while FP is believed to increase chronic disease risk. Physical activity is known to lower chronic disease risk, while time spent in sedentary behvior has been identified as increasing chronic disease risk. The purpose of the current study was to determine the relationship between size at birth and engagement in either moderate-to-vigorous physical activity (MVPA) or time spent in sedentary behavior (SED).

Methods: 124 healthy young adults wore two accelerometer devices (ActiGraph and activPAL) for at least seven days. MVPA was obtained from the ActiGraph (AG) device, and SED was determined using the activPAL (AP). Self-reported birth weight (BW) was adjusted for gestational age (GA), creating a standardized birth weight (SBW). Linear regression analysis was used to determine the association between SBW and time spent in either MVPA or SED.

Results: Participants (N = 75) who wore both accelerometers for a minimum of four days (mean 6.2±0.8, range 4-7 days) and who successfully completed a VO_{2max} test were included in the analysis. Overall, participants accumulated an average of 56±24 min/day of MVPA and 614±96 min/day of SED. After adjustment for covariates (varied by model), no significant main effect

was detected between time spent in MVPA and SBW (B = 5.642, p = 0.088). However, there was a significant interaction between SBW and age in the model. For participants aged 18 – 21 (N = 42) years, MVPA increased by 7.02 minutes for each unit increase in SBW, a significant effect (p = 0.017). For participants aged 22 – 40 years (N = 33), MVPA significantly decreased by 10.8 minutes for each unit increase in SBW (p = 0.021). No significant main effect was observed between time spent SED and SBW (B = -14.571, p = 0.422), although there was a significant interaction between SBW and sex in the model. In male participants (N = 15), time spent in SED increased by 26.7 minutes with every 1 unit increase in SBW (p = 0.203). In female participants (N = 60), time spent in SED decreased by 13.5 minutes for every 1 unit increase in SBW (p = -0.250).

Conclusion: Among healthy young adults, the effect of exposure to in utero stress (which can lead to small size at birth) on engagement in physical activity or sedentary behavior depends on age and sex.

Keywords: fetal programming; intra-uterine growth restriction; physical activity; sedentary behavior

Abbreviations: BW = birth weight; GA = gestational age; IUGR = intra-uterine growth restriction; FP = fetal programming; SBW = standardized birth weight; MVPA = moderate-vigorous physical activity; SED = sedentary behavior

Introduction

Intra-uterine stress, due to environmental factors such as poor maternal diet and/or maternal smoking, can lead to intra-uterine growth restriction (IUGR). This in utero experience also causes changes to fetal development in terms of body structure and physiology. Fetal programming (FP) is the term used to describe these changes, and many are believed to have lifelong impacts.

Previous epidemiological studies have established that small size at birth, a common marker of IUGR and strong indication of FP, increases an individual's risk of developing chronic conditions such as diabetes and cardiovascular disease [5, 55, 196]. Evidence also suggests that low birth weight (BW) is associated with higher body fat percentage and lower lean body mass in childhood, adolescence, and adulthood [7, 9, 12, 14]. Having less lean body mass is one possible explanation for the lower muscle strength observed among individuals who have experienced IUGR and were likely exposed to intra-uterine stress [135, 171, 179]. What remains unresolved is if FP influences lifelong behaviors such as physical activity participation or accumulation of sedentary behavior.

Engagement in moderate-to-vigorous intensity physical activity (MVPA), which includes any form of activity that causes a noticeable increase in heart rate and equates to an energy expenditure of 3 metabolic equivalents (METs) or more[3], is a known protective factor against heart disease [197]. Conversely, time spent sedentary (SED), which refers to awake time in a seated or lying down position that produces energy expenditure of 1.5 METs or less, increases

[3] http://www.who.int/dietphysicalactivity/physical_activity_intensity/en/

risk of metabolic syndrome and overall mortality [40, 198, 199]. Current recommendations focus on attaining physical activity more so than avoiding sedentary behavior. The Institute of Medicine's recent recommendations aimed at preventing childhood obesity suggest that toddlers and preschools spend at least 15 min/h engaging in some form of physical activity and avoid sitting for more than 30 min in a row [200]. The Physical Activity Guidelines, released in 2008 by the U.S. Department of Health and Human Services' Office of Disease Prevention and Health Promotion, do not specifically address sedentary time for either children or adults, but encourage adults to avoid physical inactivity. Canadian Sedentary Behavior Guidelines state that young children (0-4 years) should avoid sitting for more than 1 h consecutively and limit screen time (none is recommended for children under 2) [201]. Guidelines for older children and adolescents recommend no more than 2 h/d of screen time and to minimize prolonged sitting [201]. According to the Physical Activity Guidelines, children and adolescents need to engage in at least 1 h/day of physical activity (aerobic, muscle-strengthening, or bone-strengthening) [202]. Adults need to obtain either 150 min of moderate intensity exercise or 75 min of vigorous intensity exercise each week [202].

Given the negative effects of FP on body composition, muscle strength, and overall disease risk compared to the positive effects of participation in physical activity (and the negative consequences of time spent in SED), researchers are now investigating if there is a relationship between birth size (representing likely IUGR and FP) and engagement in MVPA or SED. Identifying such a relationship would imply that FP effects extend beyond physiological changes to also influence behaviors. There is some evidence from animal research that this is the case. Research in rats has demonstrated that undernutrition in utero causes offspring to engage in less physical activity and accumulate more time sedentary than animals exposed to a sufficient

nutritional environment in utero [49, 203]. Rats who were undernourished in utero (but adequately fed post-birth) accrued less voluntary movement at 35 days of age compared to rats provided with a normal in utero environment (and similar post-birth diet) [49]. When pregnant rats were given a low-protein diet to create in utero nutritional stress, female offspring engaged in less locomotor activity at 13 months of age, as well as male offspring exposed to the low-protein diet early in gestation [203]. Results from human studies interrogating the relationship between birth size and engagement in MVPA or SED, however, are mixed. Most past studies have relied on questionnaires or some form of self-report to determine amount of time spent in physical activity or sedentary behaviors. Among adolescents and adults, several studies report that those born small engaged in less physical activity [204, 205]. Other studies have found no association between birth size and physical activity in both children and adults [206, 207], particularly after controlling for covariates such as current lean body mass [208]. However, a recent meta-analysis of 13 cohort studies in adolescents and adults concluded that a U-shape relationship exists between BW and leisure-time physical activity (LTPA) [52]. Both individuals born small (less than 2.76 kg) and individuals born large (greater than 4.75 kg) have a lower probability of engaging in LTPA compared with individuals born at a normal size [52]. Interestingly, when adjusting for GA, the odds are further reduced among both extremes of BW, suggesting that under- or over-nutrition in utero may be related to subsequent LTPA behavior in adulthood [52].

Participation in MVPA may have additional benefits on individuals exposed to intra-uterine stress. Engagement in MVPA attenuated the relationship seen between high BW and high BMI in adolescent females [209]. Among adults born small, physical activity participation was associated with reduced occurrence of diabetes and lowered risk of metabolic syndrome [35, 36].

While most past research has focused on physical activity levels, a large birth cohort study found that BW was inversely associated with time in SED, but only in women [210].

The majority of past studies have measured MVPA or SED using questionnaires, which are subject to recall bias, overestimation of physical activity, and underestimation of sedentary behavior [211, 212]. Recently, studies have begun to use accelerometers to objectively measure both time spent in physical activity (across intensity levels) as well as time in SED. Most of these studies have concluded there is no association between birth size and physical activity [38, 51, 213-216]. A single study found a positive association between BW and time spent in SED, but this relationship appeared to be driven by individuals at the high and low extremes of birth weight [217]. In addition, the association was partially mediated by waist circumference [217]. Individuals who are born small are more likely to have high body fat as adults [9, 218]. It is therefore possible that this relationship creates a selection bias in which lean individuals choose to engage in physical activity more so than obese individuals do. Currently, due to inconsistent methodology and conflicting results from past research, the role of birth size on later-life physical activity or sedentary behavior remains unresolved.

Of the studies mentioned above, the majority tested for an association of BW or Ponderal Index (birth weight / birth length^3) on physical activity without taking into account gestational age [35, 36, 38, 205-209, 214, 216, 217]. The remaining studies did adjust or control for GA [51, 52, 204, 210, 213, 215]. It is important to consider BW relative to GA as the means to identify IUGR and presumed FP since engagement in leisure-time physical activity is lower among individuals born preterm [219, 220]. Several national datasets exist to establish normative BW-for-GA growth charts [155, 160, 173, 174]. Using these datasets, small for GA (SGA) individuals are clinically defined as individuals who fall below the 25th percentile, or more

strictly defined by the World Health Organization as individuals who fall below the 10th percentile[1]. In addition, since there are sex differences in birth size, with males typically 100-200 grams heavier than females [155], national datasets generate growth charts for males and females separately. The current study only included participants born between 37-42 weeks gestation, and constructed a standardized variable representing the difference between actual BW (self-reported) and expected BW (based on sex and GA, derived from a national dataset [160]). This allows for evaluating the association of BW on MVPA or SED independently of the confounding influence of GA.

The purpose of the current study was to determine the association between size at birth (an indicator of IUGR and presumed FP) and engagement in MVPA or time spent in SED. We hypothesized that participants born small for GA would achieve less MVPA and more SED time than those born at an appropriate size for GA.

Methods

The Syracuse University Institutional Review Board approved this study, and all participants provided written informed consent.

Participants and Recruitment

The study population included 124 healthy adults (ages 18-40) who had access to birth information. Participants were selected from respondents to an online recruitment survey (N = 1246). A more detailed description of the survey and recruitment procedures is provided in Chapter 3: Methodology. Briefly, the survey asked respondents to self-report birth measures and other birth information (such as parity, maternal health, and maternal smoking), as well as

current height, weight, and physical activity level. Potential participants were contacted if they met inclusion criteria (described below). Individuals identified as being born SGA were over-recruited (33% versus an expected 25%) to ensure adequate representation of participants who likely experienced IUGR in the current study.

To participate in the current study, volunteers had to meet the following inclusion criteria: a singleton born to term (37-42 weeks gestation); provided birth weight information in the online survey; and maintained their current weight during at least the last three months. Participants were ineligible if their mother developed gestational hypertension or diabetes while pregnant. Additionally, participants who were currently underweight (BMI < 18.5), morbidly obese (BMI >35), pregnant, or recently pregnant (within the last year) were excluded from the study.

Calculation of Standardized Birth Weight (SBW)

A standardized BW (SBW) variable was calculated for each participant based on his or her sex and self-reported birth information. See Chapter 3 for full details about the construction of this variable. The SBW is useful because it allows analysis of the BW association with MVPA or SED, adjusting for GA and sex effects on BW.

Measurement Procedures: Accelerometry

Participants wore two different accelerometer devices to objectively measure and quantify MVPA and SED. Participants were instructed to wear an activPAL (AP, PAL

Technologies Ltd, Glasgow, UK) and ActiGraph GT3X+, (AG, ActiGraph LLC, Fort Walton Beach, FL) for a seven day period, including while asleep, only removing the devices when coming into direct contact with water (i.e. bathing or swimming). The AP device was placed in the middle of the left thigh, approximately centered between the knee and hip. This device was placed directly on the skin and adhseive was used to keep it in place. The AG device was attached to an elastic waistband and positioned on the left hip.

AP is a uni-axial monitor containing an inclinometer to determine body (limb) position. The sampling rate was 20Hz, and the device data was downloaded in 15-second epochs using the activPAL3™ software (version 7.2.32). The AG device is a triaxial accelerometer, generating activity counts for each axis and a vector magnitude representing the combination of all 3 axes. In the current study the data was collected at a frequency of 80 Hz. Data from the AG device was downloaded from the ActiLife software (version 6.13, ActiGraph LLC); the default filter was used for activity data and the low-frequency extension filter was used for sleep data (part of a separate analysis). For data analysis, accelerometer data was converted to counts and summed over a 60-s epoch. Additional data provided for each epoch included step counts and body position (by angle estimation from acceleration).

A previously validated algorithm was applied to the AG accelerometer data to separate sleep wear time from awake wear time [221, 222]. Data from sleep wear time was not used in the analysis of activity patterns described below. Periods of non-wear were identified using the AG accelerometer data and defined as consecutive blocks of at least 60 minutes of zero activity counts, including up to 2 consecutive minutes of activity counts less than 100. These criteria are in line with the NHANES definitions of non-wear [140]. Data from the AP device were also inspected for non-wear time, and days containing a discrepancy of 7000 total steps/d or more

between the two devices were discarded from analysis. Accelerometer data was inspected prior to data analysis in order to determine whether the subject complied with instructions regarding wearing the acclerometer. A complete day of acclerometer use was defined as at least 10 hours of wear time while awake, which is consistent with the minimum set by the U.S. National Health and Nutrition Examination Survey (NHANES) [140]. A minimum of 4 days (including at least 1 weekend day) of wear data was necessary in order for participants to be included in data analysis. This criteria is in line with past research suggesting at least 3-5 days of accelerometer data [154, 223].

After initial inspection and processing, accelerometer data from awake wear time was analyzed to determine how much time participants spent in SED and MVPA. Time spent in SED was identified from the AP device using the proprietary classification of "sitting/lying" from the AP software. The AG device defines sedentary behavior as less than 100 counts per m, which is based on previously established cut-points [224, 225], and used extensively in research on sedentary behavior [141, 144, 145, 226, 227]. Time spent in MVPA was identified from the AG device and defined as greater than 2020 counts per m, approximately 3 metabolic equivalents (METs) [140].

Measurement Procedures: Other

Height, weight, and body fat measurements were taken in the morning. Participants were instructed to avoid exercise prior to the measurement. Weight (kilograms, kg) was measured using the Tanita SC-240 digital scale (Tanita corporation, Arlington Heights, IL). This scale also uses bioelectrical impedance analysis to determine body fat (percent, %). Participants completed

a VO_{2max} test to measure their aerobic fitness level. VO_{2max} was measured using open-circuit spirometry (Parvo-medics TrueOne 2400, Sandy, UT). Complete details of these measurements are available in Chapter 3.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics version 23 for Windows (SPSS Inc., Chicago, IL). All outcome measurements and covariates were evaluated for normal distribution using standard procedures, including visual inspection (histogram), Shapiro-Wilks test of normality, and calculating z-scores of the skewness and kurtosis [161, 162].

Bivariate correlation testing was performed first to identify associations between SBW and either time spent in MVPA or SED. Independent t-tests were used to test sex differences, and paired t-tests were used to determine within-subject differences, in time spent in MVPA and time spent in SED. Data were visually inspected for any evidence of a U-shape association between time spent in MVPA and SBW or time spent in SED and SBW. No U-shape was detected in the full sample or by sex for either of the above relationships.

Linear regression analysis was then used to determine the association between SBW and either time spent in MVPA or SED. Several covariates were considered for inclusion in the regression models, including: sex, age, lean body mass, body fat percentage, aerobic fitness level, (accelerometer) wake wear time (the amount of time the accelerometer was worn while the participant was awake), and maternal smoking. Sex and maternal smoking were both dummy coded and entered as categorical variables. LBM, body fat percentage, and age were centered on the respective mean value and entered as continuous variables. Interactions were tested between

SBW and all covariates as well as between covariates, pairwise. The final model for MVPA included sex, age, body fat percentage, aerobic fitness level (VO_{2max}), (accelerometer) wear time, and the interaction term for SBW with age. The final model for SED included sex, age, body fat percentage, aerobic fitness level (VO_{2max}), (accelerometer) wear time, and the interaction term for SBW with sex. Significance was set at $p \leq 0.05$ for main effects and $p \leq 0.1$ for interaction effects.

Results

Complete data was collected from 75 of the 124 participants initially enrolled. Twenty-two participants were excluded from data analysis because they either did not complete both study visits (N = 5), did not have adequate accelerometry data (N = 12) and/or were subsequently found to be ineligible based on the inclusion and exclusion criteria (N = 5). An additional twenty-seven participants were excluded from data analysis because they did not meet the criteria for a true VO_{2max} test. Descriptive characteristics of the 75 participants included in the data analysis (60 females, 15 males) is provided in Table 5.1.

Table 5.1. Descriptive characteristics of study participants.

Variable	Full sample (N = 75)	Females (N = 60)	Males (N = 15)
Age (years)	23 ± 5 (18 – 40)	23 ± 5 (18 – 40)	24 ± 5 (18 – 36)
Ethnicity (% Caucasian)	76	77	73
Current BMI	23.5 ± 3.1 (18.7 – 33.5)	23.6 ± 3.4 (18.7 – 33.5)	23.5 ± 1.83 (20.0 – 26.0)
Current % Body Fat	25.8 ± 8.4 (11.0 – 47.5)	28.2 ± 7.7 (14.3 – 47.5)	16.3 ± 2.8^ (11.0 – 20.2)
Current LBM (kg)	48.4 ± 7.6 (39.4 – 68.2)	45.1 ± 2.9 (39.4 – 53.0)	61.8 ± 5.1^ (53.2 – 68.2)
Maternal Smoking during pregnancy[#] (% yes)	4/73 (5.5%)	2/59 (3.4%)	2/14 (14%)

Values are mean ± standard deviation (range), or percent frequency.
BMI = Body Mass Index; LBM = Lean Body Mass
^Significantly different between males and females, $p < 0.001$
[#] N for maternal smoking = 73 (2 participants – 1 female, 1 male – did not provide this information)

Table 5.2 displays birth characteristics in the full sample, as well as male and female participants separately. Based solely on unadjusted BW, only 1 out of 75 participants was below the 2500 gram threshold commonly used to identify IUGR. However, 22 out of 75 participants (29%) were considered SGA, defined as below the 25th percentile on the BW-for-GA growth chart. Table 5.2 shows the values for BW, GA, BW adjusted for GA (Difference in BW), and the z-score of this adjusted BW (SBW).

Table 5.2. Birth characteristics

	Full sample (N = 75)	**Females (N = 60)**	**Males (N = 15)**
Birth weight (grams)	3484 ± 505 (2353 – 4763)	3487 ± 483 (2353 – 4763)	3474 ± 603 (2580 – 4621)
Gestational age (weeks)	40.0 ± 1.1 (37.9 – 42.1)	40.0 ± 1.1 (37.8 – 42.1)	39.9 ± 1.0 (38.0 – 42.0)
Difference in BW: Actual BW – Predicted* BW (grams)	7.7 ± 479.1 (-948.7 – 1147.7)	37.2 ± 461.3 (-948.7 – 1147.7)	-110.0 ± 545.7 (-886.8 – 837.1)
SBW^	0.11 ± 0.98 (-1.84 – 2.44)	0.17 ± 0.94 (-1.84 – 2.44)	-0.13 ± 1.11 (-1.72 – 1.80)

*Based on sex and gestational age, developed from Kramer et al 2003.
^SBW (standardized BW) is the z-score of Difference in BW. For more details, see Methods.
Values are mean ± standard deviation (range).

Participants wore both accelerometers for an average of 6.2 ± 0.80 days (range 4-7 days). Within each day, participants wore the devices for an average of 929 ± 88 min (range 685-1180 minutes). Table 5.3 displays the descriptive statistics for the accelerometry measures. There were no differences between females and males.

Table 5.3. Results of accelerometer measurement

	Full sample (N = 75)	**Females (N = 60)**	**Males (N = 15)**
Time spent in MVPA, ActiGraph (minutes)	56 ± 24 (15 – 117)	54 ± 23 (15 – 117)	65 ± 27 (16 – 94)
Steps/day, ActiGraph	9675 ± 3357 (4222 – 18606)	9530 ± 3428 (4222 – 18606)	10253 ± 3096 (4827 – 14610)
Time spent in SED, activPAL (minutes)	614 ± 96 (299 – 781)	607 ± 96 (299 – 781)	641 ± 92 (483 – 773)

Values are mean ± standard deviation (range).

Table 5.4 shows the results of correlation testing between SBW and the accelerometer measures. Measures of birth size were not significantly correlated with time spent in MVPA or SED. As expected, MVPA is significantly positively correlated with steps/day. Both MVPA and steps/day were significantly inversely correlated with time spent in SED.

Table 5.4. Correlation matrix for activity measurements with SBW.

	SBW	**Time spent in MVPA**	**Steps/day**
Time spent in MVPA			
R	0.061		
p-value	0.602		
Steps/day			
R	0.100	0.888	
p-value	0.395	**<0.001**	
Time spent in SED			
R	0.004	-0.337	-0.414
p-value	0.975	**0.003**	**<0.001**

Results of the linear regression analysis testing the relationship of SBW with time spent in MVPA or SED are shown in Tables 5.5 and 5.6. Both models also include sex, age, body fat percentage, VO_{2max} (ml/kg/min), and accelerometer wake wear time as covariates. The model for MVPA also includes an interaction term for SBW*age while the model for SED also includes an interaction term for SBW*sex. No significant association was detected between either time spent in MVPA or SED and SBW. Table 5.5 shows that aerobic fitness (i.e. VO_{2max}) was the strongest significant predictor of MVPA, explaining approximately 30% of the variance. For every unit increase in VO_{2max}, participants engaged in 1.547 more minutes of MVPA. Age was also a significant predictor of MVPA, explaining approximately 9% of the variance. For every year older than 18 years of age, participants engaged in 1.142 less minutes of MVPA. The interaction

term between SBW and age was also significant, explaining 8.3% of the variation in the model (p = 0.017).

Table 5.5. Association of SBW and select covariates on time spent in MVPA.

Time spent in MVPA	B (95% CI)	p-value	Partial η^2
SBW	5.642 (-0.855, 12.139)	.088	.043
Sex	3.825 (-10.611, 18.261)	.599	.004
Age	-1.142 (-2.021, -0.264)	**.012**	.091
Body fat percentage	0.620 (-0.125, 1.364)	.101	.040
VO_{2Max} (ml/kg/min)	1.547 (0.975, 2.119)	**≤.001**	.303
Wake Wear Time	-0.006 (-0.061, 0.048)	.814	.001
SBW*age	-1.011 (-1.832, -0.190)	**.017**	.083

N = 75
Overall R^2 = 0.414
Partial η^2 indicates how much of the variance in the outcome variable is explained by each independent variable.

To better understand the meaning of the significant interaction between SBW and age on time spent in MVPA, exploratory analysis was conducted. Age was dichotomized into "young" (18 – 21 years old, N = 42) and "old" (22 – 40 years old, N = 33) groups. Subsequent regression analysis by group (Table 5.6 and 5.7) revealed that the relationship between SBW and MVPA is significant, but the direction of the relationship varies between "young" and "old" participants. Among the "young" group, time spent in MVPA increased by 7.02 minutes for each unit increase in SBW. In these participants, SBW explained 15.3% of the variation in MVPA (p = 0.017). Among the "older" group, time spent in MVPA decreased by 10.8 minutes for each unit increase in SBW. This represented 18.7% of the variation in MVPA (p = 0.021). For both of these exploratory analyses, VO_{2max} remained a significant predictor of time spent in MVPA. In

the "young" group, body fat percentage emerged as an additional significant predictor, explaining 13.6% of the variation in MVPA (p = 0.024). For every percent increase in body fat, MVPA increased by 1.04 minutes.

Table 5.6. Association of SBW and select covariates on time spent in MVPA among "young" participants aged 18 – 21.

Time spent in MVPA	B (95% CI)	p-value	Partial η^2
SBW	7.019 (1.360, 12.679)	**.017**	.153
Sex	-2.963 (-22.668, 16.742)	.762	.003
Age	-2.453 (-7.944, -3.038)	.371	.023
Body fat percentage	1.040 (0.142, 1.938)	**.024**	.136
VO_{2Max} (ml/kg/min)	1.631 (0.786, 2.447)	**≤.001**	.305
Wake Wear Time	-0.046 (-0.114, 0.022)	.176	.052

N = 42
Overall R^2 = 0.486
Partial η^2 indicates how much of the variance in the outcome variable is explained by each independent variable.

Table 5.7. Association of SBW and select covariates on time spent in MVPA among "old" participants aged 22 – 40.

Time spent in MVPA	B (95% CI)	p-value	Partial η^2
SBW	-10.771 (-19.814, 1.727)	**.021**	.187
Sex	-2.802 (-25.243, 19.640)	.799	.003
Age	-0.653 (-2.115, 0.809)	.367	.031
Body fat percentage	0.117 (-1.248, 1.482)	.861	.001
VO_{2Max} (ml/kg/min)	1.723 (0.763, 2.683)	**.001**	.344
Wake Wear Time	0.030 (-0.058, 0.117)	.493	.018

N = 33
Overall R^2 = 0.532
Partial η^2 indicates how much of the variance in the outcome variable is explained by each independent variable.

Table 5.8 shows that accelerometer wake wear time was largely associated with time spent in SED, explaining 27% of the variance. As accelerometer wake wear time increased, time spent in SED also increased, an expected relationship. In addition, VO_{2max} was a significant predictor of time spent in SED, explaining 9.2% of the variance. As VO_{2max} increased, time spent in SED decreased by 2.96 minutes. This result aligns with the positive relationship between VO_{2max} and time spent in MVPA among the participants. In addition, the term representing the interaction of SBW with sex was significant, explaining 6.6% of the variance in the model.

Table 5.8. Association of SBW and select covariates on time spent in SED.

Time spent in SED	**B (95% CI)**	**p-value**	**Partial η^2**
SBW	-14.571 (-36.962, 7.821)	.422	.010
Sex	56.432 (-1.627, 114.490)	.057	.053
Age	-2.340 (-5.865, 1.185)	.190	.026
Body fat percentage	0.639 (-2.336, 3.613)	.670	.003
VO_{2Max} (ml/kg/min)	-2.962 (-5.236, -0.688)	**.011**	.092
Wake Wear Time	0.546 (0.327, 0.765)	**≤.001**	.269
SBW*Sex	46.880 (4.048, 89.711)	**.032**	.066

N = 75
Overall $R^2 = 0.386$
Partial η^2 indicates how much of the variance in the outcome variable is explained by each independent variable.

Exploratory analysis was conducted to further understand the significance of the interaction between SBW and sex on time spent in SED. Repeating the regression analysis by sex did not reveal any significant associations between SBW and time spent in MVPA or SED (Table 5.9). However, the pattern of the relationship between SBW and time spent in SED differed by sex. In male participants (N = 15), time spent in SED increased by 26.7 minutes with every 1 unit increase in SBW. In female participants (N = 60), time spent in SED decreased by

13.5 minutes for every 1 unit increase in SBW. Both of these relationships were non-significant. Among females (N = 60), age and VO_{2max} were significantly associated with time spent in MVPA. In both sexes, wake wear time continued to be the most significant variable related to time spent in SED, although VO_{2max} was a significant predictor among females.

Table 5.9. Association of SBW and select covariates by sex.

		Females (N = 60)			**Males (N = 15)**		
		B (95% CI)	p-value	Partial η^2	B (95% CI)	p-value	Partial η^2
Time spent in MVPA	SBW	5.426 (-1.787, 12.639)	.137	.041	9.102 (-11.235, 29.439)	.332	.118
	Age	-1.311 (-2.260, -0.362)	**.008**	.127	0.548 (-2.836, 3.932)	.719	.017
	VO_{2Max} (ml/kg/min)	1.590 (0.918, 2.263)	**≤.001**	.298	1.500 (-0.026, 3.025)	.053	.391
	SBW * age	-0.690 (-1.666, 0.287)	.162	.036	-2.296 (-4.717, 0.125)	.060	.374
Time spent in SED	SBW	-13.459 (-36.683, 9.765)	.250	.024	26.729 (-17.346, 70.805)	.203	.173
	Wake Wear Time	0.522 (0.281, 0.763)	**≤.001**	.258	0.805 (0.061, 1.548)	**.037**	.400
	VO_{2Max} (ml/kg/min)	-3.467 (-6.239, -0.696)	**.015**	.104	-1.530 (-6.517, 3.456)	.505	.051

MVPA: Overall R^2 = 0.390 (females); 0.583 (males)
SED: Overall R^2 = 0.352 (females); 0.540 (males)
Partial η^2 indicates how much of the variance in the outcome variable is explained by each independent variable.

Discussion

In the current study featuring a cohort of healthy young adults, the effect of birth size on time spent in MVPA or time spent in SED depends on the age and sex of the participants. A significant positive relationship between SBW and MVPA was observed among 18 – 21 year old participants while a significant inverse relationship between SBW and MVPA was observed among 22 – 40 year old participants. Regarding the relationship between SBW and time spent in SED, there was a (non-significant) positive relationship in males and an inverse relationship in females. Previous accelerometry-based studies found no relationship when evaluating the association of BW (controlling for GA) with MVPA or SED [51, 213, 215]. Other accelerometry-based studies that looked at BW without adjusting for GA also found no association with physical activity [38, 214, 216]. All of these previous accelerometer-based studies were conducted in children; the current study is believed to be the first to objectively measure MVPA and SED (using two different devices) among young adults who likely experienced FP.

Two studies have identified an unexpected association between BW and time spent in MVPA or SED. A recent study of children and adolescents (ages 6 – 18) found a significant positive association between BW and accelerometer-measured sedentary time, with an increase of 4 minutes of SED for every 1 kg increase in BW, suggesting that those born small achieve the least amount of SED [217]. However, controlling for waist circumference attenuated the BW effect on sedentary time by 32% [217]. Using path analysis, another accelerometer study in children (ages 8 – 10) determined that BW had a significant indirect effect on both time spent in MVPA or SED, but this was mediated through the direct effect of BMI on both outcomes [228]. For both BW and BMI, as each of these increased, MVPA decreased and SED increased, again

suggesting that individuals with a smaller BW accrue more MVPA and less SED than those born at a large BW [228]. The results of these two studies are in contrast to the expected effects of intra-uterine stress on later life physical activity behaviors, reaffirming the need for additional research in this area. It should also be noted that children have required (albeit declining) opportunities to engage in physical activity compared to adults, making these previous studies an imperfect comparison to our results.

Engaging in physical activity and/or limiting physical inactivity appears to be important and beneficial for individuals who were exposed to intra-uterine stress and experienced FP. Indeed, among female adolescents, those who self-reported higher levels of MVPA had a lessened relationship between their BW and current BMI [209]. Among children who accumulate low levels of MVPA or high levels of sedentary behavior (measured via accelerometer), BW was significantly associated with obesity and body fat [229]. Although not directly related to body composition, older adults who self-reported engaging in physical activity at least 3 days per week had a lower risk of developing Type 2 diabetes than those who were less physically active [88].

Behaviors, whether they are physically active or sedentary in nature, are largely influenced by post-natal and environmental factors. Social factors such as family or peer support, and personal habits such as screen time each separately impact the amount of time spent in MVPA or SED [43, 45, 146, 230]. Participants in the current study appear to differ from typical young adults in terms of their accumulation of time spent in MVPA or SED. On average, participants achieved 56 minutes of MVPA per day during the study, an amount much higher than previously measured in adults participating in the National Health and Nutrition Examination Survey (NHANES), which observed 6.7 minutes of accelerometer-measured

MVPA [231]. However, participants also achieved an average of 611 minutes of sedentary behavior – an amount higher than a study of U.S. NHANES participants which showed an average of 506 ± 87 minutes spent sedentary [141]. Therefore, our results may not be generalizable to the general population. Participants in the current study did exhibit expected patterns with regard to participation in MVPA. Our analysis revealed that time spent in MVPA increased with increasing aerobic fitness (i.e. VO_{2max}). In addition, MVPA levels decreased with increasing age, an effect seen in NHANES data [140].

A limitation of the current research is the small sample size compared to previous birth cohort studies that included several thousand participants [38, 215, 217, 228, 229]. However, this study benefitted from using the most acceptable current methods for measuring physical activity and sedentary behavior. In many previous studies, no association was seen between BW and MVPA [51]. A benefit of a large sample size is the ability to detect a U-shaped relationship between birth size and MVPA, as a separate meta-analysis identified [52]. We visually inspected our data and found no evidence of a U-shaped relationship. Lastly, a large sample size provides adequate statistical power to include covariates that may influence birth size and subsequent FP effects, such as maternal smoking [86, 232], birth order, and maternal size. In our study, only 4 out of 73 of participants reported their mothers smoked during pregnancy. As a result, we elected not to include maternal smoking as a potential covariate in our regression models. Separately, a recent study of the association between BW and self-reported leisure-time physical activity in adults included birth order in as a covariate but it was not significant [205]. In the current study, birth order did not have a significant association with either MVPA or SED and was thus not considered for inclusion in the final regression models for either outcome variable. Lastly, a study in children found that total activity counts (measured by accelerometer) and total energy

expenditure were significantly associated with maternal weight but not with BW [214]. This suggests maternal size is a potential confounder of any relationship between size at birth and physical activity behaviors, but we did not obtain maternal height or weight information from participants in the current study.

In conclusion, among healthy young adults, the effect of birth weight (controlling for GA) on time spent in MVPA is dependent on age, and the effect of birth weight (controlling for GA) on time spent in SED depends on sex. To our knowledge, this study is the first to use two accelerometers, one to measure MVPA and another to measure SED (due to the superior accuracy of each device for the different measures) among adults who likely experienced FP. This study adds to the growing literature base suggesting that although FP effects an individual's physiology, the effect it has on adult behaviors may be influenced by age and/or sex. Future studies should continue to investigate the interactive role of early life factors (including size at birth and maternal behaviors), adult physiological markers (such as aerobic fitness, body composition and muscle strength), and objectively-measured physical activity or sedentary behavior. By comparing large cohorts across these variables, future studies will have adequate power to identify potential interactions of age or sex on the relationship of size at birth with physical activity behaviors.

Chapter 6: Summary

In the current study, we found a significant association between BW (controlled for GA) and dominant handgrip strength among a cohort of healthy young adults. This relationship persisted despite the partial mediation of lean body mass, which is a strong predictor of muscle strength. Our conclusion was that dominant handgrip strength was impacted by the dual consequences of FP – a reduced muscle mass and a reduced muscle function. We did not find any association between birth size and leg strength, although leg strength was highly and significantly correlated with grip strength in our participants.

Among participants in our study, BW (controlled for GA) did not have a significant main effect on accelerometer-derived measurement of physical activity or inactivity. However, the direction of the effect between SBW and MVPA varies by age status and the relationship between SBW and time spent in SED varies by sex. Our study stands out among other accelerometer-based FP studies as the first to measure activity using two different accelerometer devices simultaneously, and also to perform this measurement in adults. As other researchers have suggested, there are many social and environmental factors that appear to strongly influence decisions to engage in physical activity or sedentary behavior, such as support from family and friends and having opportunities within the built environment to engage in physical activity [42, 233, 234]. The majority of our study population consisted of individuals on a large, urban university campus. Although we did not directly measure access to gyms, parks, or other facilities for physical activity, our data suggest that the current study participants were, overall, more physically active than the general U.S. population. The same factors could also explain time spent in sedentary behavior.

The results of the current study suggest that being born small, which we assume indicates IUGR occurring as a result of intra-uterine stress and subsequent FP, impacts muscle strength due to an effect on both muscle size and muscle function. This conclusion was reached because there was a significant association of birth size on muscle strength both before and after adjustment for lean body mass (a proxy measure of muscle mass). These results suggest that the presence of intra-uterine stress can lead to decreased muscle fiber formation and/or inadequate muscle fiber development in utero.

In contrast to the strong relationship seen between birth size and muscle strength, size at birth appears to have a relationship with adult physical activity behaviors that is effected by the interactions of age (with MVPA) and sex (with time spent in SED). These findings need to be replicated in a larger sample of healthy adults in order to confirm the relationship. At the moment, we believe that the consequences of intra-uterine stress appear to be strongest for physiological development of body tissues, including both adipose and muscle. Engagement in physical activity or sedentary behaviors may also be effected by intra-uterine stress, but are likely influenced to a greater extent by social or environmental factors such as peer influence, availability of gyms, etc.

One of the strengths of the current study was the method of controlling for GA. Unfortunately, many studies looking at the role of BW fail to account for GA, which we consider a methodological problem since growth can vary quite widely among "term" infants (born between 37-42 weeks gestation). Furthermore, knowing that preterm birth is associated with problems independently of IUGR and FP, failing to account for GA may lead to inappropriate conclusions. Studies can avoid this by eliminating individuals born preterm or including gestational age as a covariate. Our approach was to do both – we excluded participants who were

born prior to 37 weeks gestation, and we also constructed a variable that illustrated each participants deviation from expected BW based on their GA. This novel strategy eliminated the need to include GA as an additional covariate in our regression model, which we believed strengthened the overall model and conclusions based on the results.

Future Directions

Given the results of the current study, future research should evaluate the effectiveness of strength training to help improve muscle strength among those born small. A study from our research group provided an 8-week exercise training program to young adult females born small compared to peers born at an appropriate size. The results demonstrated improvement among the female participants born small, but they were unable to fully catch-up to the comparison group [135]. It is unclear how long the improvement will last after exercise training ceases. Since the current study did not see a relationship between birth size and lower body muscle strength, future studies should investigate separately the role of upper and lower body strength training. In addition, given the potential impact of FP on bone measures (described in Chapter 2), a future intervention study should incorporate impact-based strength training, such as boxing, to determine the effect on both muscle strength and bone health.

Another extension from the current study is to compare birth size (and presumed FP) among collegiate athletes versus non-athletes. The phenomenon of a "selection effect" is often used to describe how or why certain individuals progress to the collegiate or professional levels. Future studies could help shed light on whether this "selection effect" actually begins before birth. To date, there have not been any published studies looking directly at birth size, although several papers have found an effect of date of birth, birth order, place of birth/early life, and

overall family size on athletic success, particular in male ice hockey [235, 236]. Combining this idea with the strength training intervention described above, a future study could determine the role of birth size on differences in training adaptations among athletes on the same sports team.

Future longitudinal studies may also wish to consider the impact of maternal behaviors, such as exercise during pregnancy, on offspring body composition and engagement in physical activity. A recent study suggests that women who are physically active during their pregnancy are more likely to have children who are physically active, but this needs to be replicated in studies using a more objective measurement of physical activity [237]. By measuring women during pregnancy, it is also possible to directly observe or assess various maternal behaviors or potential sources of stress, such as smoking habits or drug use, exposure to environmental pollution, psychosocial stress, maternal diet, and maternal physical activity level.

Although the current study did not include any measures of DNA methylation or telomere length, advancements in technology make this type of information more accessible to researchers and the public alike. Several studies have discovered prenatal diet and physical activity are potential sources of epigenetic changes such as methylation patterns at specific regions of DNA [2, 238, 239]. In addition, telomere length appears to be determined to some extent in utero, and a shortened telomere length is linked with FP while longer telomere length is associated with higher lean body mass [191, 240]. Taken together, future FP research should consider measuring DNA methylation of genes involved in skeletal muscle development, metabolism and hormone production as well as measuring telomere length [182, 240]. A longitudinal approach with repeated measures of these variables is ideal in order to determine the effect of post-natal influences.

Conclusion

In conclusion, exposure to intra-uterine stress can cause both short- and long-term effects on the offspring. Short-term effects include intra-uterine growth restriction, which immediately manifests itself as a small, thin baby. Long-term effects are wide-ranging, but ultimately occur because of the fetal programming experienced by individuals in response to in utero stress. The current study confirms that those born small have lower muscle strength because of fetal programming. The effect of exposure to intra-uterine stress on engagement in physical activity or sedentary behaviors remains unclear, but may be influenced by sex and/or age.

Appendix

A: Recruitment Survey

B: Informed Consent (IRB approved)

C: Health History Questionnaire

D: Accelerometer Log

E: Reference List

F: Curriculum Vitae for Jessica Redmond

A: Recruitment Survey (via Survey Monkey)

Thank you very much for your interest! Because we are collecting information to support scientific research, we are required to administer an "informed consent".
Please read the following page carefully before deciding whether to give your consent.

1. ELECTRONIC INFORMED CONSENT
SYRACUSE UNIVERSITY SCHOOL OF EDUCATION
Exercise Science
Project Title: Determining your eligibility for participation in future Exercise Science studies of Fetal Programming.

Dr. Tom Brutsaert of Syracuse University, Syracuse, New York, USA, is collecting information to determine participant eligibility for research to be conducted by the Dept. of Exercise Science. He conducts ongoing studies that are focused on how intrauterine growth affects later life physical performance. To determine your eligibility we need some basic information regarding your birth characteristics. If this information is on hand, the survey will take approximately 10 minutes to complete. However, you may not know the answers to some questions. You should skip these, but plan on returning to the website to complete your survey once that information has been obtained.

THE INFORMATION THAT YOU PROVIDE IN THIS SURVEY WILL BE USED TO
DETERMINE YOUR ELIGIBILITY FOR FUTURE RESEARCH ONLY.

You will not receive compensation for providing this information, but you could be selected to participate in a future research project that will provide compensation. If you are selected, we will contact you with details. Willingness to provide information on this survey does not imply willingness to serve as a future research participant. That is, if you are contacted based on eligibility, we will provide you with detailed information on the study so that you can once again make an informed decision with regards to participation.
The information that you provide here will be held as confidential, and we will take precautions to protect confidentiality. In this regard, the SurveyMonkey account is accessible by password only, and data will be stored on password protected computers in locked offices in the Department of Exercise Science, Syracuse University.
Your participation is voluntary, you may withdraw from the Survey at any time and you do not need to answer any question that you don't want to. If you complete the survey, you may also request to have your information removed from our data base by emailing Dr. Brutsaert at tdbrutsa@syr.edu

Risks and Discomforts: There is the risk that confidentiality will be breached, but as described we will take steps to minimize that risk as much as possible.
Benefits: There are no direct benefits to you from participation in this survey, but there are potential benefits to others as we seek to understand how early life experience impacts adult chronic disease risk.

If you have any questions, concerns, complaints about this survey, you may contact Dr. Tom Brutsaert at tdbrutsa@syr.edu, tel: 13154439696 (USA)
If you have any questions about your rights as a research participant, you have questions, concerns, or complaints that you wish to address to someone other than the investigator, if you cannot reach the investigator, contact the Syracuse University Institutional Review Board at 13154433013 (USA).

PLEASE PRINT A COPY OF THIS INFORMED CONSENT FOR YOUR RECORDS.

☐All of my questions have been answered, I am over the age of 18 and I wish to complete the survey in order to have my name put into consideration for a future study
☐I do not wish to complete the survey and would like to exit this survey

Other
1. Please provide your contact information.
Name:
City/Town:
State:
ZIP:
Email Address:

2. What is your current status at Syracuse University/SUNY ESF?
Note: We welcome your responses to this survey even if you are not affiliated with Syracuse University or SUNY ESF.
☐Freshman
☐Sophomore
☐Junior
☐Senior
☐Masters student
☐PhD student
☐Other (please specify)

3. If you are a Syracuse University/ESF student, what is your expected date of graduation?
☐May 2015
☐May 2016
☐May 2017
☐May 2018
☐Other (please specify)

4. Are you generally available in the summer to participate in research studies i.e., do you stay in the Syracuse area during the summer?
☐Yes ☐No

5. What is your age in years?

6. What is your gender?
☐Male ☐Female

7. Please select from the following ethic/race categories, or choose "I do not wish to provide this information". If more than one category applies to you, please select both.
Note: Hispanic origin is asked about in a separate question.
☐Black
☐White
☐Native American or Alaska Native
☐Asian or Pacific Islander
☐I do not wish to provide this information
☐Other (please specify)

8. Are you of Hispanic, Latino, or Spanish origin?
☐No
☐Yes
☐I do not wish to provide this information

9. What is your height in feet and inches? (Remove shoes before measuring.)
☐Feet
☐Inches

10. What is your current weight in pounds?

11. Do you currently smoke cigarettes on a daily basis?
☐Yes, I do
☐No, I do not

1. Compared with other Syracuse University students, how do you rate yourself with respect to your physical activity level? Physical activities include but are not limited to things like walking to school, going to the gym (working out), running, cycling, intramural sports, yardwork, lifting, and so forth (please circle one):

☐Much lower than average physical activity i.e., I am basically sedentary.
☐Lower than average physical activity
☐Average physical activity level
☐Higher than average physical activity level
☐Much higher than average physical activity level.

2. Please indicate if you were a member of any of the following activities in high school or college:

	High School	College	Other (please specify)
Varsity sports team			
Junior varsity sports team			
Sports club			
Intramural sports			
Marching band			

3. Have you ever participated in a Physical Education (PED) or Dance (DTS) course through the iMove program at Syracuse University?

☐Yes
☐No

The next series of questions ask about the physical activity you have done in the last 7 days. In these questions, "moderate" physical activity refers to something that makes you breathe somewhat harder than normal, while "vigorous" physical activity refers to anything that makes you breathe much harder than normal.

4. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling? If none, please enter "0"
Days per week:

5. How much time did you usually spend doing vigorous physical activities on one of those days?
Example: If I spent 1 1/2 hours in vigorous activity, I would enter 1 hour + 30 minutes. Alternatively, you could also enter 0 hours + 90 minutes.
If you did not perform any vigorous physical activity, please enter "0".
Hours per day:
Minutes per day:

6. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or playing doubles tennis? Note: Do not include walking.
If you did not perform any moderate physical activities, please enter "0".
Days per week:

7. How much time did you usually spend doing moderate physical activities on one of those days?
Example: If I spent 2 1/2 hours in moderate activity, I would enter 2 hour + 30 minutes.
Alternatively, you could also enter 0 hours + 150 minutes.
If you did not perform any moderate physical activity, please enter "0".
Hours per day:
Minutes per day:

8. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?
This includes walking at work, at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.
If you did not perform any walking, please enter "0".
Days per week:

9. How much time did you usually spend walking on one of those days?
Example: If I spent 1 1/2 hours walking, I would enter 1 hour + 30 minutes. Alternatively, you could also enter 0 hours + 90 minutes.
If you did not perform any walking, please enter "0".
Hours per day:
Minutes per day:

10. During the last 7 days, how much time did you spend sitting on a week day? Include time spent at work, at home, while doing course work and during leisure time. This may include time sitting at a desk, visiting friends, reading, or sitting or lying down to watch TV.
Example: If I spent 6 1/2 hours sitting, I would enter 6 hours + 30 minutes. Alternatively,
you could also enter 0 hours + 390 minutes.
Hours per day:
Minutes per day:

In order to gauge your suitability for our research program, it is essential that we have birth weight, birth length, and some sense of how much before or after your due date you were born. If you need to call mom, and then revisit the website to enter the remaining information, please do so, using the link provided in your email.

1. Please enter your approximate birth weight in pounds plus ounces. For example, 7 pounds, 3 ounces will be entered as 7 in the first row and 3 in the second row. Note: You may need to ask your mother to look this information up for you. It may be recorded in a family scrap book (birth announcement, newspaper clipping, hospital records).
Birth weight in pounds
Plus ounces

2. Please enter your approximate birth length in inches eg., 21 inches. Note: You may need to ask you mother to look this information up for you. It may be recorded in a family scrap book (birth announcement, newspaper clipping, hospital records).
Birth length in inches

3. To the best of your knowledge, were you born "to term"? This means that you were born following a pregnancy of normal length. The World Health Organization defines normal length of pregnancy as 37-42 weeks.

☐Yes
☐No
☐I don’t know

4. Please tell us about when you were born compared to your expected date of birth (i.e. your "due date). Note: If you do not know this information, you may answer the following question instead.

I was supposed to be born on (Month) (Day)
I was actually born on (Month) (Day)

5. If you do not know the information needed for the above question, you may answer this question instead: Do you know how many days BEFORE or AFTER your due date you were born?
Note:Please enter your value in DAYS in the appropriate box. Enter a number into ONLY ONE of the boxes below. If you were born on your due date, enter a zero into either box.
Days BEFORE due date:
Days AFTER due date:

1. How old was your mom when she gave birth to you?
Age (in years)

2. What is your birth order in your family?
☐I am an only child
☐I am the oldest
☐I am the middle (of 3 or more)
☐I am the youngest
☐Other (please specify)

3. Are you a twin or triplet?
☐Yes
☐No

4. To the best of your knowledge, did your mom develop gestational diabetes while she was pregnant with you?
☐Yes
☐No
☐I don't know

5. To the best of your knowledge, did your mom develop gestational hypertension (high blood pressure) or preeclampsia while she was pregnant with you?
☐Yes hypertension
☐Yes preeclampsia

☐Yes both
☐No
☐I don't know

6. To the best of your knowledge, did your mom smoke cigarettes while she was pregnant with you?
☐Yes
☐No
☐I don't know

7. What is the highest level of education that your mom completed?
☐Less than high school diploma
☐High school diploma or GED
☐Some college
☐College degree (BS, BA, etc.)
☐Some graduate school
☐Graduate degree (MA, MS, PhD, MD, etc.)
☐Other (please specify)

If there is anything else that you would like to communicate to Dr. Brutsaert, please use this box to do so....

Thank you for your time. This completes the survey. For those of you who opted not to take the survey, you will not hear back from us. For those of you who provided information, many thanks. If you are eligible for a future study, we will contact you with further details.

B: Informed Consent

Syracuse University
Department of Exercise Science
201 Women's Building
820 Comstock Avenue
Syracuse, NY 13210
(315) 443-2114

Project Title: Effect of Fetal Programming on Physical Activity Behaviors
Principal Investigator: Tom D. Brutsaert, PhD.
Telephone: (315) 443-2114
E-mail: tdbrutsa@syr.edu

Background/Purpose:

Researchers in the Department of Exercise Science at Syracuse University are interested in studying the effects of fetal programming on participation in various types of physical activity.

You are being asked to participate in this research study because you have previously given your consent to be contacted when considered eligible for future studies conducted by the Department of Exercise Science at Syracuse University on the topic of Fetal Programming.

Fetal programming refers to the lack of proper nutrition during fetal growth and development, and is believed to have lasting impacts on health status. Right now, scientists do not fully understand if fetal programming is linked to later-life physical activity or physical inactivity. The purpose of this study is to measure physical activity levels in a cross-section of healthy adults across the birth weight spectrum.

Please note:

Your participation in this study is voluntary. Please read this form in its entirety, and feel free to ask questions about the study, before you make a decision about whether or not to participate in the study.

If you decide to participate in this study, you will be asked to sign this consent form. Your signature indicates your agreement to participate in this study. However, at any time you may withdraw from participating in the study. If you are a student, your participation in, or withdrawal from, this study will not affect your grade in courses in any way.
A copy of the consent form can be provided to you if you wish.

Study Procedures: Measurements

If you choose to participate in this study, your time involvement will include 2 visits to the Department of Exercise Science at Syracuse University. Each visit will take approximately 1 hour to complete. All measurements will be performed by individuals who are trained/certified in that technique. Measurements will only be done the minimum number of times necessary to obtain a valid reading. You have the right to stop measurements at any time.

Visit #1:

For this visit (which will last approximately 1 hour), we will ask that you come in to the lab after an overnight fast (at least 12 hours since your last meal). We will also ask that you refrain from exercising or consuming alcohol or caffeine (including coffee, tea, soda, or other sources of caffeine) on the day that you will come into the lab.

During the visit, you will be asked to fill out and sign this consent form. In addition, you will be asked a few questions by the researchers, and you will complete the Human Performance Lab Health Screening Form, which asks about your medical history. You have the right to refuse responding to any questions you are not comfortable answering; however, we may not be able to include you in the study without complete medical history information. Following this initial interview, the research staff will determine if you are eligible to participate as a subject in this study. If you are eligible, the visit will continue.

Researchers will measure your weight (using an electronic scale), height and waist circumference (both using a tape measure), and sagittal abdominal height (using a ruler). Your body fat percentage will be measured using the BodPod™. You will need to wear a bathing suit or other tight fitting clothing for this test. You will be asked to enter a small chamber that contains a window where you can see the researcher at all times. Once inside, you will sit inside the chamber. The door will be closed for 1-2 minutes at a time. During this time the device will measure the air being displaced by your body. There is little to no risk involved with this procedure.

In addition, during this visit you will have a finger-prick blood sample taken by trained research staff. The finger-prick is similar to techniques used by diabetic patients to monitor blood glucose. Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, c-reactive protein, hematocrit, and hemoglobin levels will be measured. Alcohol prep pads will be used to clean your finger prior to the finger prick. A band-aid will be used to cover the area upon completion. Researchers will be wearing appropriate sterile gloves (non-latex in case of allergy) at all times. You will be asked to provide a urine sample (in a nearby restroom), which will be tested for compounds indicating kidney and liver function. You will also be asked to complete a 24-hour dietary recall using a National Cancer Institute website, which will take approximately 15 minutes to complete.

At the end of this visit, you will be provided with 2 devices known as accelerometers. These will measure your physical activity levels. You will receive instructions regarding proper placement of each device. You will be instructed to wear both devices for a period of seven days during both your awake and sleeping hours. During the seven day period that you wear the accelerometers, you will be asked to complete an Activity Monitor Daily Log.

At the end of this visit you will be provided with several questionnaires to fill out on your own, including:
- The International Physical Activity Questionnaire (IPAQ) long, self-administered version, which will be used to assess habitual physical activity levels.
- The Minnesota Leisure-Time Physical Activity Questionnaire, which will be used to assess habitual physical activity levels.
- The KIHD 12-month Leisure Time Physical Activity History, which will be used to assess habitual physical activity levels.
- The Fred Hutchison Cancer Research Center Food Frequency Questionnaire (FFQ), which will be used to assess habitual dietary patterns.
- The Pittsburgh sleep quality index, which will be used to assess sleeping patterns.
- State-Trait Anxiety Inventory, a 40-item questionnaire, which will be used to assess levels of stress.

Completion of all of the surveys listed above will take approximately 1 hour.

Visit #2:

You will be instructed to come to the Ernie Davis Exercise Science Laboratory for a visit lasting approximately 1 hour. This visit will be scheduled to occur after you have completed wearing the accelerometers for a seven day period. You will return both accelerometers, and all questionnaires, at this visit. Prior to this visit we will provide instructions to you about how to prepare for this visit. Specifically, we will ask that you avoid strenuous physical activity on the day that you will come into the lab. You will also be instructed to bring or wear athletic clothes and shoes.

When you first arrive, you will be instructed to sit down for 10 minutes of quiet rest. During this time, subjects will have their blood pressure measured using an automated device. You will also be instructed to wear a chest-strap heart rate monitor, which will record your heart rate.

You will perform two tests to determine your muscle strength. One of these tests will require you to squeeze a device (known as a handgrip dynamometer) as hard as you can for less than 5 seconds. This will measure your grip strength. The second test will require you to press both legs into a padded bar as hard as you can for less than 5 seconds. This will measure your leg strength.

Your maximal aerobic fitness level will be measured by performing a VO_{2max} test. This test will require you to walk and run on a treadmill until you reach exhaustion (typically less than 10 minutes). You will begin walking at 3.5 miles per hour. Every 2 minutes the speed will be increased, causing the subjects to eventually run. Once subjects reach the maximum speed for their sex (7.5 mph for women; 8.5 mph for men), the speed will remain the same for the remainder of the test, but the incline of the treadmill will increase every 2 minutes. This test typically lasts less than 10 minutes.

During the test you will wear a heart rate monitor and a face mask (covering your mouth and nose). The face mask provides air to you but collects all of your exhaled air. Researchers will be closely monitoring you during this test to provide support as needed. You may feel uncomfortable while wearing the mask. You can stop the test at any time.

Potential Risks:

Overall, the risks associated with participating in this study are less than minimal. Communicating with the researchers throughout all study visits will reduce the risks. If at any point you are uncomfortable, or feel pain, please tell the researchers immediately.

The specific risks from the study visits are as follows:

1. On the Human Performance Lab Health Screening Form (HHQ), it is possible for participants to answer "No" to question 21 indicating that their health care provider does not know the participant is regularly experiencing a possible sign/symptom of disease. If the participant answers "No" to this question, we will instruct participants to contact their primary care physician or the university health center immediately to discuss this symptom. Furthermore, the participant will be excluded from the study.

2. On the HHQ, it is possible for participants to answer "Yes" to question 22 indicating that they are indeed currently experiencing a sign/symptom of disease such as chest pain or shortness of breath. If the participant responds "Yes" to this question, we will contact emergency medical services immediately. While waiting for EMS to arrive, the participant will be placed in the supine position on a cushioned medical table with pillow, with the legs slightly elevated and allowed to rest comfortably.

3. Body composition will be determined using the BodPod™, which requires you to wear a bathing suit or other tight-fitting clothing, and to sit in a small enclosed space for a period of 1-2 minutes. We will also measure body composition using skinfold calipers, which involve pinching a small amount of skin in order to detect levels of subcutaneous fat. You may feel slight discomfort during the 2-3 seconds of each “pinch”.

4. Muscle strength will be measured using a handheld dynamometer and a leg dynamometer. The handheld device may feel uncomfortable while being held tightly in the hand. You can choose to end the test at any time. There is a small risk of muscle strain and soreness associated with strength testing. However, you will be carefully instructed and supervised for the muscle strength testing by the examiners, who are experienced in performing these tests.

5. Blood pressure will be measured using a conventional automated device (similar to those found in Walmart, Walgreens, Rite Aid etc). The compression associated with cuff inflation may be uncomfortable but is very brief (< 1 min). In the event that high blood pressure is detected (defined by the American Heart Association as systolic pressure > 140 mmHg and/or diastolic pressure > 90 mmHg), we will wait 5-10 minutes and conduct an additional measure. If participants are nervous, this may give a high value (“white coat” effect). If the additional reading is also elevated, participants will be excluded from the study and will be instructed to contact their primary care physician. In the rare event that blood pressure readings warrant immediate medical attention (i.e. hypertensive crisis = resting systolic pressures >180 mmHg according to AHA), we will contact emergency medical services immediately.

6. There may be discomfort associated with the actual finger stick during the blood sample. We will only perform the finger stick 2-3 times, and we will use different fingers each time to reduce discomfort. We will apply ice to the area if you desire. There is a small risk of infection associated with obtaining blood from a finger prick from analysis of blood lipids. Great care will be taken to minimize this risk by ensuring that the equipment used is clean and sterile. All personnel associated with this study have undergone all necessary Syracuse University bio-hazard safety training.

   A finger lancet will be used to obtain a tiny droplet of blood from the index finger and discarded in an appropriate and clearly labeled bio-hazard receptacle. A different lancet is used not only for each participant, but for each test. An alcohol wipe will be used to clean off the skin. A band-aid will be used to cover the sample site immediately after completion. Study personnel will be wearing safety gloves at all time. These safeguards are in accordance with suggestions by the CDC for "Infection Prevention during Blood Glucose Monitoring".

   If a participant has high cholesterol (defined as total cholesterol >240 mg/dl) they will be informed to contact their primary care physician. In our experience when working with young, apparently healthy adults between the age of 18-35, this is rare.

7. The VO2max test involves performing aerobic exercise until exhaustion. Specifically, you will begin walking at 3.5 miles per hour. Every 2 minutes the speed will be increased, causing the subjects to eventually run. Once subjects reach the maximum speed for their sex (7.5 mph for women; 8.5 mph for men), the speed will remain the same for the remainder of the test, but the incline of the treadmill will increase every 2 minutes. This test typically lasts less than 10 minutes.

   This can be an uncomfortable experience for those unfamiliar with such exercise. The test itself is difficult, and may cause subjects to feel dizzy or light-headed. In rare instances, fainting or loss of consciousness may occur. In addition, the equipment involved (a face mask covering the mouth and nose to collect expired gas) may make subjects uncomfortable. In some cases, people may feel anxious or scared about not having enough air as they near exhaustion. There is a risk that you may trip or fall during the test, but you will be constantly monitored by researchers to prevent this from happening. Although unlikely, if an adverse event occurs, a researcher trained in CPR will respond. There will always be a researcher trained in CPR present during the VO2max testing. In addition, the Ernie Davis Fitness Center, located just down the hall from the Ernie Davis Exercise Science Laboratory, houses an AED (automated external defibrillator). You will be monitored throughout the test, including your heart rate and your rating of perceived exertion, to ensure your safety. Other physical cues such as skin color and coordination will also be monitored. The test will be stopped immediately if we feel that you are at risk of an adverse event. Alternatively, you can stop the test at any time by giving the researchers a previously agreed upon signal (i.e. placing your hands on the handrail of the treadmill). You will be verbally encouraged as you approach exhaustion, and will be provided with towels and water as soon as the test ends. Following the test, you will have the option to walk slowly for a few minutes in order to cool down.

8. There is a small risk of your confidentiality being breached as you will be providing us with your health information. However, the researchers will attempt to minimize this risk. Specifically, each subject will be assigned a number. The key linking subject name to number will be kept in a password protected file on a password-protected computer, and only available to the researchers. All documents containing subject information will only use the subject's number, not the subject's name. These documents will be stored in a locked drawer in our lab (which is locked when not in use). The researchers are not immune from legal subpoena about illegal activities. Although it is very unlikely, if law enforcement officials asked to see your data, researchers would have to provide it to them.

Blood and urine samples will be immediately analyzed and the results transferred to a data sheet containing the subject's assigned ID number. The samples will be properly discarded after analysis, in accordance with Syracuse University bio-hazards policy.

Benefits:

Your participation in this study may or may not benefit you. You will receive information and education about your general health, including body fat measurement, blood lipids, hematocrit and plasma volume calculations and hemoglobin measures. Information regarding habitual physical activity, assessment of your dietary intake, aerobic fitness level, and muscle strength will be made available to you. As a result of the blood pressure assessment, we may learn that you have high blood pressure, in which case we will advise you to seek medical intervention. If your measures are indicative of a crisis situation, we would obtain transport to Upstate / Crouse or the hospital of your choice. This information may be a considered a secondary benefit from blood pressure screening. As a result of the blood lipid test, we may learn that you have high cholesterol in which case we would advise you to contact their primary care physician. This information may be considered a secondary benefit from the blood lipid testing. The information learned from this study may be useful for future research.

Voluntary Participation:

Your participation in this study is entirely voluntary and you may refuse to participate or discontinue participation at any time without penalty or loss of benefits to which you would normally be entitled. Your decision about whether or not to participate in the study will not affect your relationship with Syracuse University.

Costs/Payments:

There are no costs to you or your insurance carrier for participating in this study. All subjects will be entered into a raffle for the chance to win a $50 Amazon gift card. A total of two gift cards will be given away.

All subjects, regardless of whether or not they complete the study in its entirety, will be entered into the raffle. Subjects who complete the study in its entirety will have an additional raffle entry. Overall odds of winning the gift card are approximately 1 in 125.

Questions:
If you have any questions about the research, or in the event of a research related injury, please contact Tom Brutsaert, Ph.D. at (315) 443-2114, or Jessica Redmond at (315) 877-5744. If you have any questions about your rights as a research subject, or if you sustain a research-related injury, or if you have questions, concerns, or complaints that you wish to address to someone other than the investigators (or if the investigators cannot be reached), please contact the Syracuse University Institutional Review Board Office at (315) 443-3013.

In Case Of Injury:
In the event of illness or physical injury resulting from taking part in this research study, medical treatment will not be compensated for. You will be responsible for any costs not paid by your insurance company. No other compensation is offered by Syracuse University. Syracuse University have no plans to give you money if you are injured. You have not waived any of your legal rights by signing this form.

Resources:
Syracuse University students, employees, and faculty may contact Syracuse University Health Services (315-443-9005), Syracuse University Academic Services (315-443-2506), Syracuse University Counseling Services (315-443-4715) or their health care provider. Participants that are not affiliated with Syracuse University will be referred to their health care provider.

For More Information:
If you experience a research-related injury, or have any questions, concerns, or complaints about this study, please feel free to contact Dr. Tom Brutsaert at any time. You can reach Dr. Brutsaert at tdbrutsa@syr.edu or (315) 443-2114. If you cannot reach Dr. Brutsaert or if you would like to speak to someone else about this study, you can call the Syracuse University Institutional Review Board (IRB) at (315) 443-3013.

CONSENT TO PARTICIPATE IN RESEARCH & AUTHORIZATION TO USE AND SHARE PERSONAL HEALTH INFORMATION:
I hereby give my consent to participate in this research study and agree that my personal health information can be collected, used and shared by the researchers and staff for the research study described in this form. I will receive a signed copy of this consent form if I desire. By signing this consent form, I acknowledge that I am 18 years of age or older.

_____
Name of subject

_____ _____
Signature of subject Date

_____ _____
Signature of Person Obtaining Consent/Authorization Date

_____
Name of Person Obtaining Consent/Authorization

C: Health History Questionnaire

Study ID:_____

Human Performance Lab Health Screening Form

Date_____

Age _____ Gender _____

Please answer the following questions as honestly as you can. Your patterns of responses will determine whether you may participate in the study.

Known Diseases (Medical Conditions)

1. List the medications and dietary supplements you take on a regular basis. (Include prescription and non-prescription, aspirin, vitamins/minerals, nutrition supplements [Ensure, Boost, etc.])

   _____

   _____

2. Has your health care provider ever told you have diabetes? No Yes
   If yes, please indicate (circle) whether it is:
   Insulin dependent diabetes mellitus: IDDM
   Non-insulin dependent diabetes mellitus: NIDDM
3. Do you have acute or terminal illness (if so, please explain below)? No Yes

   _____

4. Have you ever had a stroke, heart attack or heart trouble? No Yes
5. Has your health care provider ever told you that you have a heart murmur? No Yes
6. Have you had a head injury in the past 3 months? No Yes
7. Do you have asthma /take asthma medication? No Yes
8. Has your health care provider ever told you that you have kidney or liver disease? No Yes
9. Has your health care provider ever told you that you have chronic pulmonary or respiratory disease? No Yes
10. Has your health care provider ever told you that you have peripheral artery disease? No Yes
11. Has your health care provider ever told you that you have high blood pressure? No Yes

12. Has your health care provider ever told you that you have high cholesterol? No Yes

13. Do you smoke cigarettes on a daily basis? No Yes

14. Have you lost or gained weight in the previous 6 months? No Yes
    If yes, how much weight? _____

15. Has a first degree relative (e.g. father, mother, sister, brother, or child) suffered from a heart attack or diagnosed cardiovascular disease? No Yes

Relative	Age	Did they pass away?

16. Do you often have pains in your heart, chest, neck, jaw, arms or other areas especially during exercise? No Yes

17. Do you regularly get pains in you calves or lower legs during exercise which are not due to soreness or stiffness? No Yes

18. Do you experience swelling or accumulation of fluid in or around your ankles? No Yes

19. Do you often feel faint or have spells of severe dizziness during exercise? No Yes

20. Do you often get the feeling that your heart is beating faster, racing, or skipping beats, either at rest or during exercise? No Yes

21. If you answered YES to question(s) 17-21, does your health care provider know that you have this/these symptom(s)? No Yes

22. If you answered YES to question(s) 16-20, are you currently experiencing this/these symptom(s) RIGHT NOW? No Yes

23. With which hand do you write? Left Right

24. What is the highest grade/level of schooling/education completed?

8th Grade Some HS HS some college college graduate school

25. What is your marital status?

single in a steady relationship living with partner

married for first time remarried separated divorced

widowed

Menstrual Status (answer these questions only if you are a female)

At what age did you have your first menstrual period? _____

What was the date of your last menstrual period?_____

Have you ever been amenorrheic (only 1-2 periods in a year)? _____ If yes, for how long? _____

If your last menstrual cycle was greater than 28 days ago and/or you have a history of amenorrhea are you currently under the care of a health care provider? _____

Do you use oral contraceptives or hormone replacement therapy? _____
Which kind? _____ What dose?_____ If yes, for how long? _____
Do you take the withdrawal/Placebo pills?_____
Do you use Depo-Provera for birth control? _____
If yes, for how long have you used this method?_____

Have you ever experienced menstrual irregularity?_____ Please describe (i.e. number of skipped menses, or prolonged menses): _____ How long did this occur?-
_____

Do you currently experience a menstrual cycle? _____
If yes, how many periods in a year do you have? _____ and how many days between periods? _____
If no, how many years ago did you have a regular menstrual cycle (10-12 a year)?_____

D: Accelerometer Log

Activity Monitor Daily Log

Day 1:_____

What time did you: Wake up? _____ Go to sleep? _____

Please indicate any time you did not wear the accelerometers (i.e. showering, swimming, etc.):

*(example: 8:05-8:25 am – shower)*_____

Day 2:_____

What time did you: Wake up? _____ Go to sleep? _____

Non-wear time: _____

Day 3:_____

What time did you: Wake up? _____ Go to sleep? _____

Non-wear time: _____

Day 4:_____

What time did you: Wake up? _____ Go to sleep? _____

Non-wear time: _____

Day 5:_____

What time did you: Wake up? _____ Go to sleep? _____

Non-wear time: _____

Day 6:_____

What time did you: Wake up? _____ Go to sleep? _____

Non-wear time: _____

Day 7:_____

What time did you: Wake up? _____ Go to sleep? _____

Non-wear time: _____

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F: Curriculum Vitae

Jessica Garay Redmond
560 White Hall, Syracuse University
Syracuse, NY 13244
(315) 443 – 3479
jgredmon@syr.edu

PROFESSIONAL EXPERIENCE

Aug 2018 - present	Syracuse University *Assistant Professor,* Dept. of Public Health, Food Studies and Nutrition
2016 - 2018	Utica College *Assistant Professor* of Biology: Physiology & Nutrition

EDUCATION

Dec 2018 (expected)	Syracuse University Ph.D. in Science Education, area of specialization: Exercise Science Dissertation: Effect of Fetal Programming on Physical Activity Behaviors
2010	George Washington University M.S. in Exercise Science, area of focus: Nutrition & Eating Behaviors
2005	Yavapai County Health Department (Prescott, AZ) ACEND-approved Dietetic Internship
2004	Cornell University B.S. in Nutritional Sciences with honors; B.S. in Human Development

PUBLICATIONS

Goodman EM, **Redmond J**, Elia D, Harris SR, Augustine MB, Hand RK. (2018). Assessing clinical judgment and critical thinking skills in a group of experienced integrative and functional nutrition Registered Dietitian Nutritionists. *Journal of the Academy of Nutrition and Dietetics*. https://doi.org/10.1016/j.jand.2018.03.026

Goodman EM, **Redmond J**, Elia D, Harris SR, Augustine MB, Hand RK. (2018). Practice roles and characteristics of integrative and functional nutrition Registered Dietitian Nutritionists. *Journal of the Academy of Nutrition and Dietetics*. https://doi.org/10.1016/j.jand.2018.03.027

Barreira TV, **Redmond JG**, Brutsaert TD, Schuna Jr. JM, Mire EF, Katmarzyk PT, Tudor-Locke C. (2018). Can an automated sleep detection algorithm for waist worn accelerometry replace sleep logs? *Applied Physiology, Nutrition, and Metabolism,* https://doi.org/10.1139/apnm-2017-0860

Babcock MC, Lefferts WK, Hughes WE, Fitzgerald KL, Leyer BK, **Redmond JG**, Heffernan KS. (2015). Acute effect of high-intensity cycling exercise on carotid artery hemodynamic pulsatility. *European Journal of Applied Physiology*, 115:1037-1045.

Bidwell AJ, Fairchild T, **Redmond J**, Wang L, Keslacy S, Kanaley JA. (2014). Physical activity offsets the negative effects of a high fructose diet. *Medicine & Science in Sports & Exercise*, 46(11):2091-2098.

Spartano NL, Augustine JA, Lefferts WK, Hughes WE, **Redmond JG**, Martin ED, Kuvin JT, Gump BB, Heffernan KS. (2014). Arterial stiffness as a non-invasive tissue biomarker of cardiac target organ damage. *Current Biomarker Findings*, 4: 23-34.

Redmond JG, Gage TB, Kiyamu M, Brutsaert TD. (2013). The effect of intra-uterine growth restriction on blood lipids and response to exercise training. *American Journal of Human Biology*, 25(6): 844-6.

Miller WC, **Redmond JG**, Vaux-Bjerke AT. (2013). Activity patterns and perceptions about active transport to school. *American Journal of Health Behavior*, 37(2): 190-198.

Garay J. (2011). Peru. In Edelstein, S (Ed.) Food, Cuisine, and Cultural Competency for Culinary, Hospitality, and Nutrition Professionals. Sudbury, MA: Jones and Bartlett.

Levitsky DA, **Garay J**, Nausbaum M, Neighbors L, DellaValle DM. (2006). Monitoring weight daily blocks the freshman weight gain: a model for combating the epidemic of obesity. *International Journal of Obesity*, 30:1003-1010.

CONFERENCE PRESENTATIONS

Redmond JG. Public Policy 101. **Presentation** at the New York State Academy of Nutrition & Dietetics Annual Meeting, May 2018.

Goodman E, **Redmond J**, Skipper A, Augustine MB, Elia D, Harris S, Hand R. *Critical thinking skills and applications among integrative dietitians*. **Poster** presented at Academy of Integrative Health & Medicine, October 2017.

Arboleda C, **Redmond JG**, Barreira T. *MVPA, Peak 1, and Peak 30 min cadence relationship with cardiovascular health* **Thematic poster** presented at the American College of Sports Medicine Annual Meeting, June 2017.

Redmond JG. *Let's move! Using exercise to engage non-majors in A&P.* **Workshop** presented at the Human Anatomy and Physiology Society Annual Conference, May 2017.

Barreira T.V., **Redmond J**, Schuna Jr J, Brutsaert T, Tudor-Locke C. *Can time spent at 0 steps/min be used as a proxy of sedentary behavior or sedentary time?* **Poster** presented at the 6th International Congress on Physical Activity and Public Health, November 2016.

Redmond JG. *Exercise is medicine: What RDNs need to know*. **Presentation** at the New York State Academy of Nutrition and Dietetics Annual Meeting, May 2016.

Redmond JG. *Fetal programming: Is your weight what your mom ate?* **Presentation** at the Weight Management Dietetic Practice Group Annual Symposium, April 2016.

Redmond JG. *You are what your mom ate: Fetal programming 101.* **Presentation** at the New York State Academy of Nutrition & Dietetics Annual Meeting, May 2015.

Redmond JG, Babcock MC, Leyer BK, Fitzgerald KL, Lefferts WK, Hughes WE, Heffernan KS. *Effect of body composition on anaerobic power in Division 1 women's ice hockey players*. **Poster presented** at the American College of Sports Medicine Annual Meeting, May 2014.

Fitzgerald KL, Babcock MC, Hughes WE, Lefferts WK, Leyer BK, **Redmond JG**, Heffernan KS. *Aortic wave reflections are associated with anaerobic power production in young adults.* **Poster** presented at the American College of Sports Medicine Annual Meeting, May 2014.

Babcock MC, Leyer BK, Fitzgerald KL, Lefferts WK, Hughes WE, **Redmond JG**, Heffernan KS. *No sex differences in carotid artery stiffness and blood flow pulsatility following high-intensity exercise.* **Poster presented** at the American College of Sports Medicine Annual Meeting, May 2014.

Redmond J, Wang Q, Brutsaert T. *Effects of intra-uterine growth restriction on self-reported physical activity level in adults.* **Oral presentation** at the International Society for Behavioral Nutrition and Physical Activity Annual Meeting, May 2014.

Garay JL, Miller WC. *Physical activity of elementary school children in the Safe Routes to School program*. **Poster presented** at the International Society for Behavioral Nutrition and Physical Activity Annual Meeting, June 2009.

OTHER PRESENTATIONS

Redmond JG. *Pole pole: Making it to the roof of Africa.* **Presentation** to occur for the GeoTalk Seminar Series, Utica College, December 2017.

Redmond JG. *Lifelong effects of fetal programming*. **Presentation** for the Asa Gray Biological Society Seminar Series, Utica College, September 2017.

Redmond JG. *Mythbusters: The facts about food allergies and intolerances.* **Presentation** at the Greece School District Nurse Training, June 2017. Sponsored by the American Dairy Association North East.

Redmond JG. *The learning connection: Enhancing academic success through healthy school environments.* **Presentation** at the Rochester School District Nurse Training, May 2017. Sponsored by the American Dairy Association North East.

Redmond JG. *Sports nutrition*. **Presentation** to the NYSPHSAA Field Hockey Championship Banquet, November 2015. Sponsored by the American Dairy Association.

Redmond JG. *Kids are drinking what?!* **Presentation** to the Central New York Dietetic Association, October 2015. Sponsored by the American Dairy Association.

GRANTS & AWARDS

2017	Utica College Campus Administrator, Get FRUVED *($3000)*
2016	Fellow, Academy of Nutrition and Dietetics
2016	Emerging Dietetic Leader, NYS Academy of Nutrition & Dietetics
2011, 2015	Student Research Grant, School of Education, Syracuse University *($1000)*
2009, 2012	University Fellowship, Syracuse University *(tuition)*

PREVIOUS TEACHING EXPERIENCE

2010 – 2016	*Adjunct Instructor/Teaching Assistant*, Syracuse University
2010 – 2016	*Adjunct Instructor*, Onondaga Community College
2008 – 2009	*Adjunct Instructor*, George Washington University

NON-ACADEMIC WORK EXPERIENCE

2009 – present	*Owner,* Major League Wellness
2014 – present	*Consultant,* American Dairy Association North East
2015 – 2018	*Consultant,* Kelly's Choice, Wellness Corp. Solutions, Balancing Life Issues
2011 – 2012	*Nutrition Coach (& RPM instructor)*, Trillium Fitness
2007 – 2008	*Oncology Nutrition Specialist*, Washington Cancer Institute
2005 – 2007	*Nutrition Resource Manager*, Food Bank of Central NY

PROFESSIONAL CERTIFICATIONS & CREDENTIALS

ServSafe™ Instructor and Proctor, National Restaurant Association
Registered Dietitian (*Certified in Adult Weight Mgmt.),* Committee on Dietetic Registration
Certified Strength & Conditioning Specialist, National Strength & Conditioning Association

PROFESSIONAL ASSOCIATION ACTIVITIES

2018 – present	*Research Chair,* Dietitians in Integrative and Functional Medicine DPG
2017 – present	*Public Policy Coordinator,* NYS Academy of Nutrition & Dietetics
2017 – 2018	*State Ambassador,* Dietitians in Integrative and Functional Medicine DPG
2017 – 2018	*Nominating Cmte.,* Dietitians in Integrative and Functional Medicine DPG
2015 – 2017	*Secretary,* Dietitians in Integrative and Functional Medicine DPG
2014 – 2015	*Social media manager,* New York State Academy of Nutrition & Dietetics
2012 – 2016	*Public relations/Membership chair*, Central New York Dietetic Association
2010 – 2012	*Secretary*, Nutrition Education for the Public DPG
2010 – 2011	*Newsletter section editor,* Weight Management DPG
2009 – 2011	*Professional development co-chair,* Central New York Dietetic Association
2006 – 2012	*Reviewer,* Journal of Nutrition Education and Behavior

SERVICE ACTIVITIES

2018 – present	*External Reviewer*, Utica College Institutional Review Board
2017 – 2018	*Member,* Utica College Institutional Review Board
2016 – present	*Analyst,* Evidence Analysis Library, Academy of Nutrition & Dietetics
2016 – 2018	*Member,* DIFM DPG-Academy of Nutrition & Dietetics Working Group
2016	*Member,* Faculty/staff search committees (4), Utica College

2015 – present	*Member,* Sports Nutrition Advisory Panel, American Dairy Association
2005 – present	*Chair/ volunteer,* Cornell Alumni Admissions Ambassador Network of CNY
2013 – present	*Nutrition Expert,* Greatist.com
2012, 2015	*Invited speaker,* W.H.E.E.L. Club, Pre-Health Society, Syracuse University
2012 – 2013	*Student member*, Promotion and tenure committee, Syracuse University
2012, 2013	*Invited speaker,* Women's Soccer, Women's Ice Hockey, Syracuse Univ.
2010 – 2011	*Student member*, Faculty search committee, Syracuse University