EXTREME BIRTHWEIGHTS AND METABOLIC SYNDROME IN ADULTHOOD

A Thesis
by
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Abstract

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Objective: This study examined the effects of high birthweight (HBW) and low birthweight (LBW) on an individual's risk of developing metabolic syndrome later in life; with consideration of both maternal and individual lifetime behavioral, social, and environmental factors.

Research Methods and Procedures: The Atherosclerosis Risk in Communities (ARIC) dataset was used to identify individuals with metabolic syndrome and individuals who reported either HBW or LBW. Logistic regression analysis was used to evaluate the association between LBW and HBW with metabolic syndrome, while controlling for various social and demographic factors.

Results: A univariate relationship between LBW and future risk of metabolic syndrome was attenuated by pertinent socioeconomic and lifestyle-related risk factors that defined both the

participant and their familial influence, particularly maternal age at the time of birth. A link between HBW and metabolic syndrome was not found.

Conclusions: This work does not support a correlation of birth weight with adult metabolic syndrome. However, the multifaceted risk factors in the development of metabolic syndrome may be attributed to genetic, socioeconomic and lifestyle factors that similarly influence a mother's likelihood of delivering an extreme birthweight infant.

Key Words: Metabolic Syndrome, Low Birthweight, High Birthweight, Fetal Origins of Adult Disease

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Table of Contents

List of Abbreviations

ACOG: American College of Obstetrics and Gynecology

ADA: American Dietetic Association

AGA: Average for Gestational Age

ARIC: Atherosclerosis Risk in Communities

CAD: Coronary Artery Disease

CDC: Centers for Disease Control (U.S.)

CVD: Cardiovascular Disease

FOAD: Fetal Origins of Adult Disease

GDM: Gestational Diabetes Mellitus

GWG: Gestational Weight Gain

HDL: High-density lipoprotein

HBW: High Birth Weight

LBW: Low Birth Weight

LDL: Low-density lipoprotein

LGA: Large for Gestational Age

MetS: Metabolic Syndrome

NHANES: National Health and Nutrition Examination Surveys

PAR: Predictive Adaptive Responses

SES: Socioeconomic Status

SGA: Small for Gestational Age

Foreword

The research manuscript, Chapter 2, will be submitted to *Nutrition*, *The International Journal of Applied and Basic Nutritional* Sciences, a peer-reviewed journal published by Elselvier. The manuscript has been formatted in accordance with the journal's style guide.

Chapter 1: Review of Literature

Part 1: Fetal Programming as a Metabolic Syndrome Risk Factor

The effect of the in-utero environment, gestational age and size have become well accepted factors in the development of an infant's metabolic profile and subsequent chronic disease risk in adulthood.[1] This phenomenon is often referred to as fetal-programming, which refers to the fact that stimuli, when applied during early development, generates permanent changes that persist throughout one's lifespan.[2] Fetal programming may also refer to the linkage between the fetal state and subsequent consequences at later life stages.[3] Birthweight is the most widely used proxy of exposures and insults that occurred in utero as altered fetal growth reflects the degree of maternal and placental support provided to the fetus.[3]

Various hypotheses have been developed regarding the association between extremes in birthweight and increased risk of obesity and metabolic disorders. Among the most common theories linking low birthweight (LBW) to chronic disease are the Barker Hypothesis and the Catch-up Growth Hypothesis.[1,4,5] Although the link between high birthweight (HBW) and chronic disease has been less widely theorized, it has been linked to adult and childhood obesity and insulin resistance.[2] The Critical Period Model and The Accumulation of Risk Model explore the general influence of adverse exposures at various points across the lifespan. Animal models have also been used to study fetal programming phenomena.[6] In sum, these hypotheses and models propose various mechanisms by which genetic, physiological, social, behavioral, and environmental factors can impact fetal

development that may have lifelong physiological implications that can increase risk of developing metabolic syndrome (MetS).[1,4,5]

Importance

In 2010, 9.8% of all U.S. births (excluding births before 24 weeks) were considered preterm, the highest rate among 19 developed countries that were studied. Similarly, approximately 8% of U.S. infants were considered HBW according to the National Vital Statistics Report for U.S. Births in 2015. Overall, 7% of infants had a birth weight >4,000g, 1% had a birth weight greater than 4,500g, and 0.1% had birth weight greater than 5,000g.[7] As chronic disease prevalence continues to rise the relative importance of fetal programming as a possible disease risk factor will become increasingly relevant in the development of public health interventions that either identify individuals at increased risk of metabolic diseases, or work to reduce the occurrence of extreme birthweights altogether. For example, findings of the rapid catchup growth hypothesis imply that regular growth monitoring of LBW infants and parental counseling regarding appropriate growth and feeding in the first months of life may be instrumental in reducing MetS risk later in life.[8]

Birthweight as an Indicator of Metabolic Syndrome Risk

Birthweight is the best available surrogate marker of the quality of the intrauterine environment and is known be representative of the quality of maternal nutritional status during gestation.[2,3] An infant can be classified by birthweight, their size relative to their gestational age, or by gestational age alone (premature, not premature). LBW is considered < 2500 g, very low birth weight is considered < 1500 g, and extremely low birth weight < 1000 g. A neonate born large for gestational age (LGA) is considered larger than it should be relative to the time of the conception. A neonate is considered average for

gestational age (AGA) if born at a "normal" weight relative to the time of conception. A neonate is considered small for gestational age (SGA) if born at a weight smaller than it should be relative to the time of conception [9].

Still, it would be remiss to assume infants born at "normal" birth weights (i.e. not SGA or LGA) did not experience a significant insult that may affect metabolic programming. The insult's timing, type, severity, and duration all may contribute to an infant's development, but may not necessarily be evident in their birthweight.[2] Insults are not limited to malnutrition or maternal dietary patterns, they may also include exposure to inflammation, infection, glucocorticoids, hypoxia, stress, or toxins.[2] For example, although an AGA neonate born to a mother with gestational diabetes mellitus (GDM) appears "normal," the neonate was still subjected to an adverse intrauterine environment and may still be at increased risk of chronic disease in adulthood. Epigenetic factors, such as degree of DNA methylation and gene expression have also been found to influence adult risk of insulin resistance and hypertension, but have no effect on birthweight.[6] In instances where direct measures of nutrient exposure were more verifiable, such as during the Dutch Famine of 1944, fetal birthweight did consistently reflect the undernourishment of mothers.[6] Still, other studies suggest maternal nutritional status, before and during pregnancy, accounts for less than 10% of the variation in fetal weight at birthweight.[6,10] Finally, it should also be acknowledged that most existing literature and models have historically focused on the impact of LBW as a risk factor, despite the need to also consider gestational insults among AGA, large for gestational age (LGA), and premature neonates.[2]

Barker Hypothesis:

The Barker Hypothesis, also known as the Fetal Origins of Adult Disease Hypothesis (FOAD), was first developed in the 1980s.[2] The hypothesis suggests that exposures and events during early fetal development predict a person's future risk of developing adult diseases and conditions such as coronary artery disease, hypertension, obesity, and insulin resistance (MetS).[2] Exposures and events can include stress, both nutritional and non-nutritional, during different critical periods of development, which ultimately result in a state of disease. The theory was originally developed based upon an epidemiological study of European birth registries, but has since been replicated on human cohorts and various animal models.[2] One limitation of the Barker Hypothesis, among other retrospective studies that have been used in the development of related hypotheses, is the failure to account for confounding factors such as maternal infection, infant diet, adult lifestyle factors, and socioeconomic status. Additionally, the quality of data measuring the exposure is limited in many cases.[6]

The thrifty phenotype model has been used to explain Barker's hypothesis. The model largely examines how mismatched environments (intra-uterine vs. extra-uterine environments) result in a series of biological tradeoffs to adapt to the changing environment.[3] It suggests that a single genotype, when influenced by the intrauterine environment, will lead to the production of different phenotypes.[2] A series of predictive adaptive responses (PARs) are made in expectation of the future environment. The period of time in utero and various periods of time thereafter are known as the plastic phases, or the phases in which PARs can be undertaken. The plastic phase varies for different organ systems, but the plastic phase for both the brain and the growth/metabolic pathways extend

well into the postnatal period. During post-plastic phases, PARs cannot be readily undertaken.[3] The greater the degree of mismatch in the post-plastic, extra-uterine environments, the greater the risk of developing disease. More simply, there is an adaptive advantage when the fetal environment reflects the same environment that it will experience in the extra-uterine environment, upon birth. When subjected to nutrient deprivation, the PARs adopted by the fetus do not match the environment of nutrient excess that it will experience later in life, resulting in increased risk of MetS.[2,3]

Fetal programming (via PARs) is regulated by the DNA methylation mechanisms of epigenetics.[3,6,11] Methylation works by altering gene transcription processes by acting on methylation-sensitive binding proteins which impacts gene expression and the cell differentiation processes of organogenesis. The degree of methylation upon various histones is significantly modulated by maternal diet. In fact, some aspects of fetal programming have been linked to alterations in DNA methylation. For example, nutrients such as vitamin B12, folate, and methionine play a distinct role in availability of methyl groups needed for DNA methylation.[11] The impact of a protein-restricted diet without folate supplementation has also been found to induce epigenetic changes upon the glucocorticoid receptor gene that impacts regulation of blood pressure and gluconeogenesis.[12] In sum, maternal diet can produce epigenetic changes in the promotion of genes in offspring that can impact future disease susceptibility.[6,11,12]

Adverse uterine environments, such as nutrient deprivation, during fetal development can alter the projected growth pattern of various organs and systems of the body, leaving the offspring at an increased risk of metabolic disease when exposed to the modern environment of nutrient excess.[3] Reduced fetal growth is a consequence of a natural energy

conservation mechanism in which the fetus reallocates the available nutrients to preserve cardiac function and neural development, but at the expense of a normal growth trajectory. These adaptations subsequently impact the metabolic system's programming. Certain adaptations such as abnormal insulin response and reduced organ vascularity are two examples of possible long-term consequences that increase risk of MetS in adulthood.[2,3] Other studies have found undernutrition in utero to be linked to increases in fetal blood pressure and impaired glucose signaling in adult offspring.[2]

Like SGA infants, infants born prematurely are also believed to be at increased risk of impaired fetal programming due to a mismatch in the fetal environment from the post-natal environment.[3] Prematurity can be classified as: 1) late preterm, born between 34 and 36 completed weeks of pregnancy, 2) moderately preterm, born between 32 and 34 weeks of pregnancy, 3) very preterm, born at less than 32 weeks of pregnancy, or 4) extremely preterm, born at or before 25 weeks of pregnancy.[13] Since premature birth and impaired fetal growth are both considered strategies to cope with an impaired fetal environment, it is difficult to differentiate the impact of prematurity from impaired fetal growth on disease risk.[2,3] In instances of prematurity, the infant is subjected to both altered rates of maturation and altered timing of the transition from the fetal to the post-natal environment, so it remains unclear if and how these factors impact future disease risk.[3] Prematurity has also been found to be a consequence of a mother's poor nutritional status or traumatic exposure at various points in gestation. These findings have been confirmed by findings from the Dutch Winter famine 1944-1945 and earthquake victims.[3,6] Women who experienced famine during the first trimester had an increased incidence of premature delivery. In

another study, women exposed to an earthquake in the first trimester delivered babies more prematurely than mothers exposed to the earthquake later in gestation.[3]

Catch-up Growth Hypothesis:

The catch-up growth hypothesis suggests that LBW does not independently increase risk of developing MetS. Instead, it suggests that infants who specifically experience a period of rapid catch-up growth during the first years of life will be at increased risk of developing MetS.[8] The effect of catch-up growth, however, as an independent risk factor is difficult to quantify given the inevitable biological and sociological consequences of being born SGA.[3] In a systematic review comparing the rapid catch-up growth hypothesis to the Barker hypothesis, 79.6% of risk factors for cardiovascular disease (CVD) and other risk factors were statistically significant for the catch-up growth hypothesis compared to 58.5% of risks factors for the Barker Hypothesis.[8] These findings suggest that rapid catch-up growth is a more common among LBW infants and is a stronger predictor of CVD and related risk factors. However, when comparing the association of LBW and catch-up growth with MetS, both factors correlated with some criteria for MetS later in life and it was not clear which of the two factors played a more dominant role.

Evidence Linking High Birth Weight to Metabolic Syndrome

Like infants born at LBW, SGA or premature, infants born at a HBW or LGA are also at increased risk of metabolic abnormalities. HBW is defined as a birthweight greater than or equal to the 90th percentile and is usually secondary to GDM or idiopathic macrosomia.[2] An obese or diabetic pregnant mother is also likely indicative of an adverse fetal environment and is significantly more likely to deliver a LGA infant, or even a SGA infant.[2,14] GDM is characterized by uncontrolled, elevated blood glucose levels in the

mother that subsequently leads to an excess delivery of glucose and other macronutrients to the fetus.[2] Excessive glucose exposure results in increased fetal production of insulin, the dominant fetal growth hormone, resulting in infants born with increased adiposity, elevated insulin and leptin levels.[2,14] The long-term implications of exposure to GDM in utero may include abnormal hormone regulation, insulin secretion and body composition—known risk factors of MetS.[2]

Evidence exists to suggest that LGA offspring of diabetic mothers were at significantly greater risk of developing MetS in childhood (age 11) compared to AGA offspring of mothers without GDM. The prevalence of two or more MetS criteria was 50% for the LGA/GDM group, compared to a prevalence of 29% among the LGA/control group, 21% among the AGA/GDM, and 18% among the AGA/control group. The prevalence of three or more MetS criteria at age 11 was 15% for the LGA/GDM group, compared with 3.0% to 5.3% for the other groups.[15] Evidence also exists that links maternal obesity to the development of MetS in children, independent of GDM. In a comparison of children born to obese mothers, 84 children were born LGA, while 94 children were born AGA. The children born LGA were 1.81 times more likely to exhibit two or more components of MetS.[14,16] Overall, neonates born LGA or who experience intrauterine exposure to diabetes or maternal obesity are at increased risk of developing MetS. Given the increased obesity prevalence, these findings have implications for perpetuating the cycle of obesity, insulin resistance, and their consequences in subsequent generations.[14]

The widespread prevalence of obesity among women of childbearing age have been acknowledged by both the American College of Obstetrics and Gynecology (ACOG) and the American Dietetic Association (ADA) with 33% of U.S. women classified as obese. Both the

ACOG and ADA recommend pre-conceptional and inter-conceptional counseling about possible short and long-term complications associated with pregnancy while obese be available to all women of childbearing age.[14] Both obesity and excessive weight gain during pregnancy has been linked to gestational diabetes, gestational hypertension, pre-eclampsia, birth defects, Cesarean delivery, macrosomia, perinatal deaths, post-partum anemia, and childhood obesity.[14]

Part 2: Epidemiological Models and Considerations: Linking Birthweight to Adult Disease

The Critical Life Model

The Critical Life Model, or Critical Period Model, closely related to the thrifty phenotype model, suggests that an insult during a specific developmental stage, known as the critical period, may have lifelong health consequences due to alterations in the structure or function of organs, tissues and body systems that may cause disease later in life.[7] The critical period is defined as a specific time frame that can occur in utero, during infancy, childhood or adolescence in which a particular exposure can have adverse or protective effects on development and subsequent disease outcome of an individual. However, exposures that occur outside of the developmental window have no effect. In other words, the model posits that an exposure in a critical period will result in permanent and irreversible damage or disease.[7,8] For example, poor intrauterine development may have an adverse effect on metabolic programming of the infant and lead to type 2 diabetes.[17] An alternate proposed critical period is the first 6 months of life. Weight status at 6 months has been significantly associated with obesity at 5 years of age and in adulthood.[1] In the Barry Caerphilly Growth Study, the predictive value of two critical periods were evaluated. Fetal growth

trajectory was compared to early childhood growth trajectory in the development of hypertension. The study modeled both trajectories and found both critical periods to be determinants of the development of hypertension by age 25.[18] Two critical periods were found to have an influence on adult disease risk, complicating the association between fetal exposures and future disease.

Accumulation of Risk Model

Contrarily, the accumulation of risk model suggests risk factors, separate and independent insults, at each life stage combine to increase disease risk overtime.[17] In additional to an unfavorable fetal environment, insults can include episodes of illness, injuries, environmental exposures, socioeconomic factors and even health damaging behaviors such as smoking. The damage from these insults will accumulate over time and ultimately damage the biological system. The extent of damage is determined by the duration and severity of various insults.[17] This epidemiological transition model, of sorts, suggests initial exposure to early life stress, such a low or high birth weight, in addition to environmental and social variables such as socioeconomic status, geographic location, among accumulate over the life course to influence metabolic patterns into adulthood.[19] The accumulation of risk model also emphasizes the timing of such variables and how they relate to one another and the outcome of interest.[20]

Animal Models

The confounding factors and limitations of epidemiological studies has led to the use of various animal studies that have sought to further explore the biological basis of fetal programming. It should be noted, however, that animal-based models of fetal programming rely on surrogate markers (disease risk factors), rather than occurrences of the diseases

themselves when assessing dietary variables.[6] Interventions investigating the effect of undernutrition range from limiting food take, to restriction of specific micro and macronutrients. Interventions investigating effects of over-nutrition include provision of hyper-caloric, high-fat diets to rats during pregnancy or feeding rats to be obese prior to conception. Interestingly, the metabolic programming effects on offspring of over-nourished mothers are strikingly similar to the effects of undernourished mothers.[6]

To evaluate the impact of a maternal hypocaloric diet on rat offspring, pregnant rats' intake was reduced to 30% usual intake resulting in LBW offspring. In adulthood, the LBW offspring were found to be hypertensive, insulin resistant, more obese and more susceptible to metabolic damage from a hyper-caloric diet.[21] The impact of macro and micronutrient restriction during pregnancy on fetal programming has also been tested on rats. Restricting intake of protein, iron, or calcium during rat pregnancy have all been linked to hypertension.[6] Protein restriction has also been associated with altered feeding behaviors, less physical activity, and increased fat deposition in adulthood.[6] Common to animals subjected to undernutrition in utero, metabolic abnormalities appear to worsen incrementally with age. Similar outcomes among different species such as pigs, sheep, rats, mice and guinea pigs suggests metabolic programming effects that may occur in all mammals.[6]

Maternal overnutrition, particularly the over-consumption of fats (monounsaturated and saturated), has been studied in rats. Offspring of rats fed lard during pregnancy and lactation show evidence of systemic cardiovascular changes such as hypertension, endothelial dysfunction, aortic stiffness, and insulin resistance attributable to impaired insulin secretion from isolated pancreatic islet (beta cells).[6] The types of fat consumed during pregnancy have also been found to affect rat offspring's lipid profile. Pregnant rats who were

fed diets high in saturated fat had offspring with higher LDL cholesterol levels compared to pregnant rats who were fed diets high in polyunsaturated which resulted in offspring with higher HDL cholesterol levels.[6] Increased maternal adiposity in rats prior to conception also lead to offspring at greater risk of obesity in adulthood. Additionally, in both animal and human tissue models, fetal exposure to maternal atherosclerosis has been linked to evidence of plaque formation in utero.[6]

Part 3: Critiquing the Fetal Origins of Adult Disease Hypothesis

Not all studies have found LBW to be associated with increased risk of MetS. For example, in a global meta-analysis, LBW was followed by a decreased long-term risk of overweight while HBW was followed by an increased long-term risk of overweight.[22] The meta-analysis included 21 studies in the analysis after identifying 3,513 possible entries. The pooled odds ratio determined by the mean of a random effects model for LBW and subsequent overweight risk was 0.67 (0.58-0.76), indicating an overall protective effect of LBW on future overweight risk.[22]

Fetal growth is merely a single etiological factor in the development of adult disease from a life course perspective. Consequently, the effect of birthweight is not easily or independently attributable to future health outcomes. Additionally, the epigenetic basis of the thrifty-phenotype hypothesis in itself purposes a life-long interaction between adaptive, genetic changes acquired in utero and the environment throughout life. Consequently, the effects of fetal programming may be dependent on the context of the environment and more proximal adult lifestyle factors and represent only one of many critical periods that should each be considered holistically.[20]

Methodological and theoretical criticisms of the FOAD stem from the broadly defined hypothesis that merely suggests a link between fetal exposures and adult diseases without a verified mechanism by which this occurs.[20,23] Instead numerous instances of correlation have been documented that have too often have failed to test the mechanism by which the two are linked. The unclear mechanism also enables researchers to test an unlimited array of potential nutrition exposures, introducing type I errors or falsely positive findings between exposures and outcomes.[20] Critics of the FOAD hypothesis have also cited a lack of adjustment for confounding factors, particularly SES and adult lifestyle factors such as smoking and physical activity. This issue was particularly of concern in the earliest studies that relied upon birth-records and that lacked sufficient information about social and economic factors.[20]

Statistical errors in interpretation related to modeling and over-adjustment have also been speculated by critics of the hypothesis. For example, a data simulation study that sought to demonstrate how adjustment for current body mass (or other anthropometric measure) may be inappropriate due to its role in the causal pathway between birthweight and adult disease, a phenomenon known as the "reversal paradox".[24] In other words, adult body mass may be a function of birthweight, rather than a confounder.[24] The simulation found adjustment for adult body size to alter conclusions regarding no association, modest associations, and modest positive associations. Creating a series of models that incrementally control for various exposures may enable more accurate interpretation of the role of various confounding exposures.[25] Until adequate randomized controlled trials are developed to test the FOAD hypothesis, the use of correlation and regression analysis to

explore the possible relationship between birth size and adult health outcomes will persist with uncertainties.[24]

Publication bias is another possible limitation that has influenced the availability of studies that do not support the FOAD hypothesis.[20,26] Publication bias occurs when studies with statistically significant or clinically favorable results are more likely to be published than studies with non-significant or unfavorable results.[26] Sources of bias may include time lag bias**,** in which studies with unfavorable or less significant findings are more slowly approved for publishing; language bias in which articles that are not originally written in English are less likely to be translated if they lack significant findings; and selective outcome reporting, in which selected, non-significant study findings are omitted upon publication. Selective emphasis on certain favorable results is another form of bias to consider.[25] These forms of bias may influence the availability of published studies that have found a lack of significant association between birthweight and adult disease risk.[26]

Part 4: Background and Etiology of Metabolic Syndrome and Extreme Birthweights

Metabolic Syndrome Background, Diagnosis

Metabolic syndrome (MetS) is defined as a clustering of risk factors that are associated with increased risk of heart disease, stroke, diabetes, or a combination. In fact, MetS diagnosis has been linked to a 2-fold increase in cardiovascular disease risk and a 3-fold increased risk of developing type 2 diabetes.[27] Risk of death from coronary artery disease (CAD) also increases by 65% among individuals with MetS. The condition is increasingly common among adults worldwide and is diagnosable among an estimated one in four adult patients entering the healthcare setting. MetS is also associated with increased risk of peripheral vascular disease and lipid abnormalities.[28]

A distinct causal pathway has not yet been identified due to the complex pathophysiology of MetS. However, existing evidence suggests higher prevalence among those who are older, sedentary, are overweight or obese, and have developed insulin resistance and increased adiposity. Excess adipose tissue may also play an endocrine function.[29] The increase in visceral body fat associated with MetS results in overproduction of free fatty acids and pro-inflammatory agents that accumulate in the liver and may contribute to the metabolic changes that characterize the syndrome, such as over-production of insulin. Hormonal changes such as in adrenal steroid hormone dehydroepiandrosterone (DHEA), a precursor to both estrogen and testosterone, are another possible factor in the development of MetS. Although men produce more testosterone, reduction in testosterone production can also attribute to increased central obesity and visceral body fat in both men and women. Elevated estrogen levels also have this effect in women.[29]

Various diagnostic criteria for MetS exist depending on the research body. The National Institutes of Health defines MetS by[30]: a **large waistline** (waist measurement of 35 inches or more for women or 40 inches or more for men is a metabolic risk factor, 2) a **high triglyceride level** (triglyceride level of 150 mg/dL or higher or being on medicine to treat high triglycerides is a metabolic risk factor), 3) a **low HDL cholesterol level** (a cholesterol level of less than 50 mg/dL for women and less than 40 mg/dL for men or being on medicine to treat low HDL cholesterol is a metabolic risk factor), 4) **high blood pressure/hypertension** (a blood pressure of 130/85 mmHg or higher (systolic or diastolic) or taking medicine to treat high blood pressure is a metabolic risk factor, and 5) a **high fasting blood sugar** (a fasting blood sugar level of 100 mg/dL or higher or being on medicine to

treat high blood sugar is a metabolic risk factor. This can also include a diagnosis of prediabetes (fasting blood sugar level between 100–125 mg/dL) or diabetes (a fasting blood sugar of 126 mg/dL or higher). Among those with type 2 diabetes, 85% also have MetS which puts them at great risk of developing other chronic diseases than those without MetS.[30] The most common screening factor among the criteria is waist circumference.[28] In fact, one study found MetS to be rare among those with a normal waist circumference.[31] Hypertension, however, is the most frequently occurring diagnosis in primary care.[28]

Low Birth Weight Background, Etiology, Risk Factors

Although a single known cause of low birth weight is unclear, certain risk factors that increase an individual woman's risk of bearing a LBW infant have been identified. LBW is defined as an infant born at 2500 g or less due to preterm delivery, intrauterine fetal growth restriction, or a combination of both. [32] Preterm birth is defined as being born too early (before 37 weeks) resulting in less time for growth and full development. Full gestation is, on average, 280 days, or 40 weeks, from the first day of the woman's last menstrual period. It is during the eighth and ninth month that fetal fat stores begin to develop. Most internal systems are well developed at 37 weeks, but the lungs may still be immature.[33] Fetal growth restriction, contrarily, is a result of inadequate growth and weight gain during a given period of gestation.[34]

LBW risk increases with maternal history of premature births, African-American ethnicity, non-married mothers, maternal age above the age of 25 or being a teen mother, lack of prenatal care, lack of health insurance, substance abuse, and maternal illnesses or infections such as genital or urinary tract infections, preeclampsia, and chronic health conditions such as hypertension.[35] Undernutrition and lack of prenatal weight gain due to

environment or behavioral issues such as an eating disorder is also a possible cause. Premature birth and fetal growth restriction can also be caused by birth defects or heath conditions present at birth. Some evidence suggests that maternal obesity protects against preterm delivery since the risk of having a SGA or pre-term baby decreases as maternal body mass index (BMI) increases.

Contrarily, other evidence has found that obese women are at greater risk of preterm or low birth weight delivery.[14] LBW has been reported in up to 3% of deliveries to obese women.[36] Proposed mechanisms by which obesity increases risk include gestational hypertension and diabetes or an increased obesity-related inflammation that may lead to an early onset of labor.[14] In a population-based cohort study of >226,000 women the prevalence of preterm delivery increased as the severity of obesity increased. The rate of preterm delivery was 8.4% among women with class I obesity, 8.8% with class II obesity, and 10.3% with class III obesity delivered preterm, compared to 7.1% of women who began pregnancy with BMI 25.[37] Although less common, obese women have also been found deliver SGA infants which is believed to be related to impaired placental attachment and poor nutrient profusion to the fetus. Some estimates of SGA delivery among obese women have been estimated between 5.7% and 7.5%.[14] Many of these factors will be reviewed in detail in the *Review of Confounding Factors.*

High Birthweight Background, Etiology, Risk Factors

At birth, 7.5%-8% of infants are macrosomic (weigh more than 4,000 to 4,500 g).[14] Infants born to mothers who were obese prior to pregnancy are more likely to deliver larger for full-term infants than those born to mothers with lower BMIs.[14] In fact, the prevalence of macrosomia among obese women has been reported as high as 20%.[37] LGA infants are

also two-three times more likely among obese women with delivery rates for LGA infants between 16% and 22%, in some studies. The risk of LGA birth is also increased with excessive GWG.[32]

A high fat maternal diet during pregnancy may cause metabolic programming errors in the fetal liver, increased offspring adiposity, and development of features of MetS in adulthood.[6] A study of 24,093 pregnancies in Denmark found that giving birth to HBW infants occurred more frequently among women with high pre-pregnancy weight and height, women who were non-smokers, with parity greater than two, gestational age greater than 42 weeks, and a male infant gender. Women with a low caffeine intake or ten or more years of education were also at statistically significantly higher risk.[38] A Turkish study identified similar risk factors, as well.[39] Compared to control women, a statistically significant correlation between fetal macrosomia and pre-pregnancy BMI, GWG, parity, advanced maternal age, and male fetal sex was found. Maternal BMI and GWG, however, were most strongly associated with macrosomia.[39] A study in Tianjin, China on maternal, pre-pregnancy BMI and GWG also found both higher BMI and excess GWG to be associated with greater risks of pregnancy-induced hypertension, caesarean delivery, and greater infant size at birth.[36]

Immediate complications related to HBW include shoulder dystocia, risk of fetal neural injuries, fetal hypoxia, and maternal hemorrhage.[14] Babies born to obese mothers are also more susceptible to congenital anomalies such spina bifida, heart defects, limb reduction, anorectal atresia, hypospadias, omphalocele, hydrocephaly, and cleft lip and palate.[14] Congenital anomalies occur in about 4.7% of pregnancies among women of ideal weight, compared to in about 5.5% of women who are obese.[37] Increased risk of such

birth defects have been attributed to exposure to excess blood glucose levels related to increased uncontrolled diabetes or the presence of insulin resistance. Another possible cause may be lower intakes of folic acid among obese women, or perhaps lower serum folate levels compared to women at a healthy weight.[14]

Part 5: Review of Confounding Factors Influencing Birthweight

Maternal Socioeconomic Status

Socioeconomic status (SES) is broadly defined as a person's "…lifetime access to knowledge, resources, and opportunities"[40], despite the common use of financial status and educational attainment as indicators. As such, higher SES theoretically reduces a person's exposure to health-threats, while also increasing access to resources should an unanticipated health threat or unplanned pregnancy arise.[40] Consequently, SES is among the most widely studied social determinants of pregnancy outcomes with the magnitude of effect upon infant birthweight estimated to be comparable to the effect of smoking.[41]

Among women of childbearing age, women of higher SES are more likely to seek out and comply with prenatal care recommendations.[41] This is likely due to better access to higher quality healthcare, better nutrition, a safe environment, less exposure to risky behaviors, and better access to resources during childhood that more likely facilitated a better education, a more rewarding career, and higher SES into adulthood.[40,42] Higher SES is also associated with the development and access to healthy coping skills when faced with daily life-stresses, while lower SES is associated with a higher prevalence of disruptive life events such as family conflict, loss of employment, and reduced access to resources for healthy coping.[42,43]

These trends were evident in a three-generation study that examined a predominantly African American population of mothers and grandmothers of 987 singleton infants, collected over a period of 25 years.[41] Maternal SES during both her own childhood and during pregnancy were independently and significantly associated with infant birthweight, even when controlling for biological factors such as average familial stature, grand-maternal health and maternal health.[41] On average, mothers who were born in households that were poor or near poor had smaller babies than women who were born into adequacy or affluence.[41] Interestingly, small increases in income had larger effects among affluent mothers than among poor mothers. This may suggest that small increases in income among mothers near the poverty line (i.e. moving from welfare to a low-wage job) may not have an effect in improving intergenerational birthweight outcomes. Overall, maternal SES across the life course (during childhood and at the time of pregnancy) is negatively associated with an increased incidence of LBW among women with low SES at the time of pregnancy.[41]

Maternal Educational Attainment

Maternal education, along with maternal SES, is among the best established determinants of birthweight.[41,44–46] Maternal education significantly influences a woman's healthy literacy level, or her ability to seek out, understand and comply with medical advice during pregnancy. In addition, education provides a means of upward economic mobility, which may have transgenerational benefits for her children and grandchildren.[41] Higher education also is known to enhance health behaviors such as improved ability to delay gratification and to set goals such as eating better and exercising regularly.[40]

In a review of U.S. Vital Statistics Natality files from 1970-1999, the role of maternal education on fertility and prenatal care utilization, the likelihood of marrying a higher earner, the adoption of favorable health behaviors, and the likelihood of smoking during pregnancy was examined.[45] Improvements in the country's educational infrastructure in the 1960s-1970s was found to have significantly impacted education among women of child-bearing age over 30 years. Higher levels of education among women during this time period were associated with not only improved infant health, but also increased the likelihood of being married, reduced parity, increased the likelihood of prenatal care utilization, and reduced the likelihood of smoking during pregnancy. Each additional year of education reduced the incidence of LBW by about 10% and reduced the incidence of preterm birth by 6%.

A possible mechanism by which education trans-generationally influences birth outcomes was examined using the National Longitudinal Study of Adolescent to Adult Health (Add Health), a nationally representative U.S. longitudinal study of adolescents (ages 12–18 years) that began in 1994 (n = 90,118). The study found substantial evidence that suggested a link between grand-maternal and grandchild health. Possible mechanisms by which this may occur include early developmental factors during mother's childhood, such as lower maternal educational attainment that is associated with an adverse intrauterine environment, fetal organogenesis, and epigenetic programming. Such programming may then subsequently lead to poorer adult metabolic capacity, adverse pregnancy outcomes, and lower birth weight in the third generation.[46]

A similar study conducted at Johns Hopkins Hospital found comparable results. Among mothers with low education, high grand-maternal education was associated with a 181 g [95% CI 71, 292] increase in infant birthweight, however, among mothers who were

relatively well educated, high grand-maternal education had no effect. These findings suggest that educational achievement can be protective of their own child's birthweight, despite the disadvantage associated with growing up in a household with a poorly educated mother. Still, among women born to well-educated mothers, the resources attained during childhood remain protective over their infants, regardless of that woman's educational attainment.[41]

Maternal Age

When a woman is between the ages of 18 and 35, she is in the prime of her childbearing years and is more likely to conceive a healthy child. Consequently, the incidence of low birthweight and other complications is higher among mothers under the age of 18 or over the age of 35. Advanced maternal age, aged 35 and over at the time of birth, is considered a major risk factor for negative pregnancy and perinatal outcomes in both low- and high-income countries.[47] Similarly, developed and developing countries have consistently reported teen mothers to be at increased risk for pre-term and LBW delivery.[48]

In general, women are now waiting longer to have children. In the U.S, from 2015 to 2016, birth rates decreased among females aged 15–29, increased for those aged 30–49, and remained the same for ages 10–14. The mean age of first birth among women in the U.S. has also increased gradually over time. From 2015 to 2016, mean age of first birth increased from 26.4 to 26.6, a new record high.[7] The importance of identifying risk factors associated with pregnancy at advanced ages will likely continue to grow with these trends and should be considered among women considering postponing a planned pregnancy.[47]

Although, the risks of adverse birth outcomes related to advanced maternal age are well established, it remains unclear whether the association between advanced maternal age

and risk of LBW or preterm delivery can be independently attributed to maternal age or to other confounding factors such as biological, health, and social processes.[47] A Finnish study sought to address this question by first comparing children born to different mothers at different ages, while controlling for observed maternal characteristics. Second, an innovative method that compared birth outcomes between siblings born to the same mother at different ages was used, adjusting for all factors shared by the siblings.[47] The study found advanced maternal age to not be independently associated with an increased risk of LBW or preterm delivery. Instead, unobserved factors such as difficulty conceiving, increased pre-natal care utilization, improved health behaviors mediated the relationship. Although the study's results did not find age to be an independent risk factor, the well-established epidemiological trends still indicate that pregnancy at advanced ages pose an increased risk of giving birth to a LBW or preterm child.[47]

In 2016, the birth rate for U.S teenage women aged 15–19 was 20.3 births per 1,000 women, compared to 22.3 in 2015. Pregnancy among teens 15-19 has continued to decline each year since 1992 among all racial and ethnic groups. Still, U.S. teen birth rate remains higher than in other industrialized countries and teen birth rates continue to vary by race and ethnicity and present a risk factor for delivering SGA or premature infants.[49] Most, but not all, studies have found increased risk of SGA among infants born to teenage mothers, with the youngest groups at the highest risk. Studies that have not reported this association may fail to control for other confounding factors such as adequacy of prenatal care. In a retrospective cohort of U.S. women 25 years and younger, all teenage age groups were at increased risk of pre-term delivery, low birth weight and neonatal mortality compared to non-

teenage groups. Infants born to teenage mothers aged 17 or younger also had a higher risk for low Apgar score at 5 minutes.[48]

Like advanced age, whether age serves as an independent risk factor among teens remains unclear. Adjustment for weight gain did not affect the association, nor did restricting the analysis to white, married mothers with age-appropriate education level, adequate prenatal care, and without smoking or alcohol use during pregnancy. This study suggests, then, that risk of adverse birth outcomes is related to maternal youth, as opposed to socioeconomic factors and prenatal care. These findings refute those of other studies that did not find young maternal age to be an independent risk factor for adverse birth outcomes. These studies attributed risk, instead, to factors such as: black, unmarried, low socioeconomic status and inadequate prenatal care.[50,51]

Maternal Race, Racial Differences in Birthweight

The cause of the disproportionate rate of infant mortality and preterm birth among minority groups has been widely theorized and attributed to factors such as genetic predisposition[52], allostatic load/weathering[53], environment[54], pregnancy behaviors, pre-pregnancy health, a mother's lifetime health status, access to care, lifetime upward economic mobility[55], and unplanned pregnancies, among other factors. LBW, pre-mature, and HBW birth rates differ significantly between different racial groups as evidenced by annual incidence data. In 2016, for example, the rate of preterm birth among black women (14%) was about 50 percent higher than the rate of preterm birth among white women (9%).[56] The preterm birth rate for all racial groups was 11.4%. The rate among blacks was significantly higher at 16.3% compared to 10.2% of non-Hispanic white infants and 11.3% of Hispanic infants. The rate of LBW for singleton births was 6.3% and 8.0% for all

births, including births of multiples. However, the rate for black infants (13.1%) was nearly twice that of white infants (7.0%) and Hispanic infants (7.1%). These disparities persist even when controlling for risk factors such as maternal obesity, smoking, hypertension. Differences in rates of HBW are not well documented, but likely also exist between racial groups.

Maternal Health Behaviors

A women's health status prior to conception is a fundamental factor in achieving a healthy pregnancy outcome as the body adapts to many physiological adjustments.[57] Among these adjustments, a women's metabolic profile takes on an atypical state to ensure an adequate supply of oxygen and nutrients are readily available to the growing fetus. A natural increase in insulin resistance occurs during the later stages of pregnancy to improve substrate availability (i.e. elevated fatty acid and blood glucose levels). During normal gestation a women's lipid profile exhibits elevated blood lipid concentrations. Both total cholesterol and triglyceride levels rise with triglyceride levels reaching two to four times pre-pregnancy levels by the third trimester.[58] In obese women these metabolic changes are significantly compounded and place the mother at greater risk of developing a metabolic disorder, such as gestational diabetes, during the pregnancy.[14]

The epidemiology of obesity from a life course approach suggests that maternal pre-gravid weight has an early and consistent effect on the child's weight status and strongly predicts the likelihood of becoming overweight throughout childhood. Complex transgenerational implications on maternal health should also be considered. For example, GDM is hallmarked by maternal transmission; GDM mothers are more likely to have been born to mothers with T2DM, and GDM offspring are more likely to develop T2DM.[2] *The*

Academy of Nutrition and Dietetics has found that most studies examining the correlation between maternal pre-gravid BMI and childhood weight status have reported adjusted odds-ratios ranging from 2 to 4.[14] Obesity during pregnancy has also been linked to gestational hypertension, pre-eclampsia, birth defects, fetal macrosomia necessitating a Cesarean delivery, perinatal deaths, post-partum anemia, and childhood obesity.[14] In fact, an obese women is more than twice as likely to develop pre-eclampsia than a women of a healthy weight.[14] The prevalence of chronic diseases among women of childbearing age are also rising. Ten percent of women 18-44 years of age have hypertension, with rates rising as women age. Among minority groups, the prevalence of hypertension is also higher with a prevalence of 19% among non-Hispanic black women, 9% among non-Hispanic white women, and 8% among other racial/ethnic categories.[14]

As the prevalence of obesity grows in the U.S.[59] the number infants born to obese women also grows. These complications are exacerbated by excess weight gain during pregnancy and other post-natal factors that may confound this finding.[14] Breastfeeding is believed to have a protective effect against obesity[1], yet some evidence suggests a lower rate of breastfeeding among obese mothers.[14] Familial role modeling and early development of eating behaviors may also influence this finding.[1] The long-term implications of maternal obesity on her child's risk of developing obesity and MetS suggests a cyclic pattern that may be perpetuating the obesity epidemic.[14]

Post-natal Factors, Breastfeeding

The first postal-natal exposures are another factor that have been shown to influence metabolic programming. The first weeks of life makeup a critical period of metabolic development due to the malleability of the human metabolism as all previous nutrition was

received passively in utero via the umbilical cord. An infant's growth velocity in its first 6 months of life has been strongly associated with childhood obesity and adolescent obesity, which are known to increase significantly obesity risk into adulthood. Systemic reviews indicate that rapid growth in the first two years of life are associated with an OR of later obesity ranging from 1.4-5.7.[1] Additionally, mothers with an increased risk of macrosomic delivery are also more likely to have an infant with rapid post-natal growth; a "double-hit" to the infant's metabolic profile.[1]

The postnatal environment, however, may offer an optimal period for nutritional intervention to optimize metabolic health among premature and SGA infants. Breast-feeding exclusivity and its role in early weight gain and its biological impact in metabolic programming is among the most widely studied post-natal factors. Breastfeeding has been widely accepted as a preferred alternative to infant formula, in part because of its protective effect against obesity later in life.

A variety of mechanisms have been evaluated in determining how breastmilk may influence obesity risk.[1] An emphasis on infant body composition and adiposity in the first months, particularly first 6 months, and the effect of later obesity risk are supported by findings in the weight gain patterns of breast-fed infants compared to formula fed infants. Infants fed human milk gain weight more slowly beginning at 3 months, while gaining length at the same rate as infants who are formula fed.[1] The composition of breast milk also dynamically changes during stages of lactation to meet the needs of the growing infant. In general, breast milk contains a matrix made up of 87% water, 3.8% fat, 1.0% protein, and 7% lactose. The fat and lactose, respectively, provide 50% and 40% of the total energy of the milk.[60] Formula, however, is often higher in protein, which has been linked to rapid post-

partum catch-up growth that may increase chronic disease risk.[1] Hunger cues and other eating behaviors may also be more naturally developed among breastfed infants.[1,60]

Obese mother's milk, mothers with diabetes, and overall maternal diet are all factors that strongly influence milk composition and the nutrition the infant receives. Overweight women may produce milk higher in glucose, insulin, and fat than lean mothers. Hormone levels such as adiponectin and leptin also vary with maternal BMI. Regardless of maternal BMI, breastfeeding remains protective in promoting optimal growth velocity and in preventing later obesity compared to formula feeding.[1]

Maternal Alcohol and Tobacco Use

Women are consistently advised to abstain from all alcohol consumption during pregnancy.[58] According to data from the 2006-2010 Behavioral Risk Factor Surveillance System (BRFSS), among pregnant women, the estimated highest prevalence estimates of reported alcohol use during pregnancy were among women ages 35-44 (14.3%), white women (8.3%), college graduates (10%), and women who are employed (9.6%). Still, research on alcohol use during pregnancy is limited by alcohol consumption among women who do not know they are pregnant.[58] The use of self-reported data and lack of biological markers also limits the quality of existing epidemiological studies. Alternate evidence also suggests that different levels of alcohol consumption have differing effects on subtypes of preterm birth.[57]

Cigarette smoking is among the most prevalent and preventable causes of adverse pregnancy outcomes.[57,61] Mothers who are former smokers are not at increased risk of adverse pregnancy outcomes. Smoking during pregnancy has been linked to placental abruption, reduced birth weight, and increased infant mortality.[57] The magnitude of effect

that smoking has on pregnancy, like alcohol, remains unclear and the correlation between smoking to preterm birth is surprisingly modest in many studies.[57] A more recent study in Japan found maternal smoking to be related to LBW, short birth length and small head circumference. The point in time in which a women smokes during pregnancy also variably affects birth outcomes.[57]

Gender Differences in Birthweight

A universal difference in birthweight between male and female infants has been noted and linked to differences in the future prevalence of insulin resistance between genders. Gender-specific genes have been found to make a female fetus more insulin resistant resulting in not only lower birthweight, but also increased risk of diabetes in adulthood as evidenced by the higher prevalence of type II diabetes among young, female populations.[62] Higher concentrations of the insulin and insulin precursors have also been consistently found in the cord plasma of female infants, despite birth at lower birthweight, which suggests females are intrinsically more insulin resistant than males. On average, females were born 111g lighter than males, yet have a 13.3% higher cord plasma insulin concentration. The effect was even larger (18.1%) when infants of each gender were pair-matched by birthweight.[63] The same gender differences were also found in instances of diabetic gestation suggesting gender-specific modulation of insulin is maintained even in adverse environments.[62]

Part 6: Review of Confounding Factors Influencing Metabolic Syndrome

Educational Attainment and Socioeconomic Status

The literature has consistently found that educational attainment is a strong predictor of life expectancy and reduced chronic disease risk, including metabolic syndrome. For

instance, at age 25, U.S. adults without a high school diploma can expect to die 9 years sooner than college graduates according to a study conducted by the Agency for Healthcare Research and Quality (AHRQ).[64] In the United States, the range of educational attainment has continued to grow, resulting in a larger gap in health status in high vs. low educated individuals. These gaps are particularly evident among low SES and minority groups. Individuals of lower SES have less access to education, are more likely come from families of low educational attainment and to have low educational status themselves. Such factors make these individuals more likely to experience disease that may lead to loss of physical and cognitive function.[40,65]

Low educational attainment tends to be multi-generational (i.e. run in families). It has been found that a mother's educational attainment is strongly associated with improved health outcomes. Educational attainment is also strongly influenced by personality, family dynamics, the surrounding community, and societal policies at large which interact with one another to dictate what constraints or opportunities an individual may have access to.[64]

There is strong evidence promoting improved educational attainment as a means of preventing and/or improving health disparities at all levels of the ecological framework. Education serves as a "filtering mechanism" that influences a person's choice of partner, employment, social circle and life experiences—all of which influence health behaviors. Consequently, it is unclear what elements associated with educational attainment are most influential in improving health.[64,65]

At the individual level, education enhances personal control and improves ability to think critically and solve problems, thereby enhancing a person's ability and confidence to control events and life outcomes. Personal control is also linked to self-monitoring and

improved health behaviors such as improved coping skills.[64] The higher cognitive ability gained from education enables individuals to understand their own medical care needs and improves their navigation of the healthcare system. Higher education is not only known to increase financial stability, but is also associated with access to social networks that can provide emotional support and health-benefits such as insurance. Financial stability also translates to more resources to purchase nutritious foods and free-time for recreational physical activity.[40,64,65] Perhaps most importantly, better access to resources and financial stability enables a person to live and raise a family in a community that not only supports a healthy lifestyle, but also provides their children with a quality education of their own.[64]

Age

MetS is characterized by concurrent abnormalities in glucose levels and lipid profile.[29] Its onset is associated with age-related changes such as age-accelerated biological conditions, age-dependent adaptive factors, growth hormone resistance, low triiodothyronine syndrome[29,66], mental and physical changes.[29] Physical changes such as loss of lean body mass and changes in body composition also occur as visceral fat and intramuscular fat increase. Based on National Health and Nutrition Examination Surveys (NHANES) data from 2003–2006, it was estimated that males and females 40–59 years of age are about three times as likely as those 20–39 to have MetS. Males 60 years of age and over were more than four times as likely, and females 60 years of age and over were more than six times as likely as the youngest age group to meet the criteria. It is estimated that 50% of adults 60 and older meet diagnostic criteria for MetS.[67]

With additional genetic and environmental factors, aging exponentially increases risk of developing MetS.[29] Based on NHANES data collected between the years 1999 and 2006, the prevalence of MetS increased with age among 41,474 participants, 18 and older without a history of cardiovascular disease (CVD). The prevalence was 6.6% among young adults (age 18-29) and 34.6% among older adults (age 70 and older).[68] NHANES data also indicted that young adults tended to have lower levels of high-density lipoprotein cholesterol, less glucose intolerance, and less hypertension. Similar trends have been observed among the Australian population in which the observed prevalence of MetS also increased with age. Low levels of high-density lipoprotein (HDL) cholesterol and high triglyceride levels, however, did not increase with age. Elevated blood glucose levels increased four to six times with age, while hypertension increased threefold.[31] Both studies found younger individuals to exhibit different diagnostic components of MetS compared to older groups which may have important implications in the clinical management among individuals of different ages.[31,68]

Race

MetS affects 50 million American adults,[28] or about 34% of the adult population, yet the prevalence of MetS is known to be disproportionately higher among some racial and ethnic minority groups. Variation by race, however, is different for males and females.[60][67] Sufficient screening criteria for accurate detection and diagnosis may also be lacking among minority groups.[28] This may be, in part, due to differences in body type (i.e. MetS may exist at smaller waist circumferences among other groups). For example, MetS is known to be under-diagnosed by as much as 50% among Hispanics, compared to whites.[28]

After adjusting for age, MetS varied by race, ethnicity, sex and the risk factor examined. White and Hispanic males had a higher prevalence of hypertriglyceridemia and low HDL cholesterol compared to black males. White males, however had a higher prevalence of abdominal obesity than black males. Finally, hypertension was most prevalent among black males. There were no significant associations between hyperglycemia and race and ethnicity for males.[67]

White females had the lowest prevalence of abdominal obesity and hyperglycemia compared to black and Hispanic females. Hispanic females also had a higher prevalence of low HDL cholesterol than the other two groups. As with males, black females had the highest prevalence of hypertension among the groups, however, they had the lowest prevalence of hypertriglyceridemia. Overall, black males were about one-half as likely as Hispanic white males to meet the criteria for MetS. Conversely, black and Hispanic females were about 1.5 times as likely as white females to meet the MetS diagnostic criteria.[67]

The interaction between SES and ethnicity may also impact MetS prevalence between groups. According to the 2009 U.S. Census Bureau, blacks and Hispanics experience poverty levels two to three times higher than those of whites.[40,43] Still, health disparities between race are not solely dependent on SES. A 2010 study found that even when controlling for SES, racial disparities in health often remain.[69] Additionally, disease and disability are influenced variably by SES depending on the racial and ethnic group of interest.[40,69] For instance, the relationships between income and education are the same for all ethnic groups, while the strongest socioeconomic effects are seen among white's health outcomes.[40] Despite differences in how race and ethnicity and SES influence health disparities, both ultimately affect the resources a person may have access to when faced with

sickness and the likelihood of developing a lifestyle-related chronic illness.[43] The complex dynamic between the two is well illustrated by the "Hispanic paradox," which describes the better than expected health experienced by low SES Hispanics when compared to other low SES group.[69]

Sex

Key differences in the presentation and prevalence of MetS have been noted between men and women in some studies[27], but not in others.[70] Possible differences in risk factor clustering by sex may be related to the prevalence of glucose intolerance, body fat distribution, adipocyte size and function, hormonal regulation of body weight and adiposity, and the influence of estrogen decline.[27] In a comparative study of age and sex matched subjects, 29% of women and 23% of men met the criteria for MetS diagnosis. Among women, elevated BMI, low HDL cholesterol, increased waist circumference and hyperglycemia were significantly associated with MetS, while among men hypertension and elevated triglycerides were most significant.[27] NHANES data collected from 1999-2010, however, found no significant gender disparities in MetS prevalence, despite a rate that was four times higher among women in previous years. Women, however, consistently had a greater prevalence of abdominal obesity than men.[70]

Smoking and Drinking

Smoking has long been associated with adverse health outcomes based on evidence that tobacco exposure can increase blood pressure, waist circumference, triglycerides, and reduce HDL cholesterol. Active smokers are also more likely to be insulin resistant.[71] Despite such evidence, some epidemiological studies still find smoking to be protective in the development of MetS. The inconsistent findings may be attributable to differing

definitions of MetS and variability in individual baseline information between studies. To address the inconsistent findings, a meta-analysis of prospective studies was conducted to evaluate how smoking influences the onset of MetS. Active smokers were found to have a 26% greater risk of MetS compared to nonsmokers. Overall, active smoking is significantly associated with development of MetS, while smoking cessation significantly reduced risk.[72]

The association between alcohol consumption and MetS is complicated by varying frequency, type, and if consumed with or without a meal. Findings also differ between studies. Among 4510 white participant in The National Heart, Lung, and Blood Institute Family Heart Study, alcohol consumption was associated with a lower prevalence of MetS, regardless of which type of alcohol was consumed, which differed from the findings of a Brazilian study.[73,74]

An analysis of the Brazilian Longitudinal Study of Adult Health found light consumption (less than 4 drinks per week) of alcoholic beverages with meals to be inversely associated with the MetS (≤4 drinks/week: OR = 0.85, 95%CI 0.74–0.97; 4 to 7 drinks/week: OR = 0.75, 95%CI 0.61–0.92), compared to individuals who did not drink alcoholic beverages at all. Greater consumption of alcohol consumed outside of meals was significantly associated with increased risk of MetS (7 to 14 drinks/week: OR = 1.32, 95% CI 1.11–1.57; ≥14 drinks/week: OR = 1.60, 95% CI 1.29–1.98). Wine, which is more often consumed with meals, was more significantly associated with lower MetS prevalence. Contrarily, drinking predominantly beer, which occurred most often outside of meals, was more significantly associated with increased MetS prevalence.[74]

Part 7: Summary of Literature Findings

The association between birthweight and MetS remains inconclusive due to the reliance on epidemiological studies and lack of randomized controlled trials among humans when examining FOAD and metabolic programming.[24] Still, existing literature suggests a relationship between the two, but has so far failed to explain the mechanism or causal pathway by which birthweight impacts future disease risk. Extreme birthweight and MetS are mutually influenced by various social determinants, such as educational attainment, socioeconomic status, race, gender, among others. Common factors between the two suggest not only a confounded association between the two, but also the need to identify moderating factors that reciprocally contribute to the causal pathway. Although a moderator variable does not necessarily explain the relationship between a dependent and independent variable, a significant moderator variable can result in an amplified or reduced effect between the independent and dependent variables.

The relevance of identifying a causal pathway (mediating factors) or moderating factors across the life course can be instrumental in addressing chronic disease risk among high risk populations, such as those born at extreme birthweights and at lower SES.[46] Perhaps most importantly, public health strategies designed to manipulate the biology of fetal growth are less easily designed and implemented than those that aim to influence postnatal growth and nutrition. Instead identifying the most significant postnatal influences on adult health would offer a greater likelihood that practical public health interventions could be devised and investigated in this emerging field.[24]

Chapter 2- Research Manuscript

EXTREME BIRTHWEIGHTS AND METABOLIC SYNDROME IN ADULTHOOD

A Thesis
by
EMILY CURLIN
May 2018

Abstract

Objective: This study examined the effects of high birthweight (HBW) and low birthweight (LBW) on an individual's risk of developing metabolic syndrome later in life; with consideration of both maternal and individual lifetime behavioral, social, and environmental factors.

Research Methods and Procedures: The Atherosclerosis Risk in Communities (ARIC) dataset was used to identify individuals with metabolic syndrome and individuals who reported either HBW or LBW. Logistic regression analysis was used to evaluate the association between LBW and HBW with metabolic syndrome, while controlling for various social and demographic factors.

Results: A univariate relationship between LBW and future risk of metabolic syndrome was attenuated by pertinent socioeconomic and lifestyle-related risk factors that defined both the participant and their familial influence, particularly maternal age at the time of birth. A link between HBW and metabolic syndrome was not found.

Conclusions: This work does not support a correlation of birth weight with adult metabolic syndrome. However, the multifaceted risk factors in the development of metabolic syndrome may be attributed to genetic, socioeconomic and lifestyle factors that similarly influence a mother's likelihood of delivering an extreme birthweight infant.

Key Words: Metabolic Syndrome, Low Birthweight, High Birthweight, Fetal Origins of Adult Disease

Background

Risk for developing metabolic abnormalities (that later manifest as metabolic syndrome (MetS)) may begin in utero and be first evidenced by an infant's weight at birth, long before developing any symptoms. The relevance of these risks is of growing importance with the high occurrence of extreme birthweights and premature births in the United States (U.S). Among all U.S. births in 2010, 9.8% (excluding births before 24 weeks) were considered preterm, the highest rate among 19 developed countries that were studied.[75] The Centers for Disease Control reports about 9% of births to be of low birthweight (LBW) or very low birthweight and an estimated 35% of Americans to have MetS; with both conditions occurring at disproportionately higher rates among minority and underserved populations.[40] Similarly, nearly 8% of U.S. infants were considered high birth weight (HBW) according to the National Vital Statistics Report for U.S. Births in 2015.[7]

Various hypotheses and models propose possible mechanisms by which genetic, physiological, social, behavioral, and environmental factors can impact fetal development that may have lifelong physiological implications that increase risk of developing MetS. Still, the magnitude by which social and environmental factors concurrently impact such physiological factors should be carefully considered in light of both abnormal birthweight and chronic disease.[1,5,17]

A HBW may indicate the mother's excess gestational weight gain, development of gestational diabetes (GDM), pre-pregnancy obesity, circulating triglyceride concentrations, or degree of inflammation during pregnancy.[14,58] An obese or diabetic pregnant mother is also likely indicative of an adverse fetal environment and is significantly more likely to

deliver a large for gestational age (LGA) infant, or even a small for gestational age (SGA) infant.[2,14] Excessive glucose exposure, secondary to GDM, results in increased fetal production of insulin, the dominant fetal growth hormone, resulting in infants born with increased adiposity, elevated insulin and leptin levels.[2,14] The long-term implications of exposure to GDM in utero may include abnormal hormone regulation, insulin secretion and body composition—known risk factors of MetS.[2]

LBW may result from inadequate caloric intake, poor pregnancy nutrition, alcohol, drug or cigarette use, intrauterine growth restriction (such as when birthing multiples), inadequate prenatal care, pregnancy complications, or in babies born to teen mothers.[14,58] LBW risk increases with maternal history of premature births, African-American ethnicity, non-married mothers, maternal age above the age of 25 or being a teen mother, lack of prenatal care, lack of health insurance, substance abuse, and maternal illnesses or infections such as genital or urinary tract infections, preeclampsia, and chronic health conditions such as hypertension.[35] Undernutrition and lack of prenatal weight gain due to environment or behavioral issues such as an eating disorder are also possible causes. Like SGA infants, infants born prematurely are also believed to be at increased risk of chronic disease in adulthood since premature birth and impaired fetal growth are both considered strategies to cope with an impaired fetal environment. As a result, it is difficult to differentiate the impact of prematurity from impaired fetal growth on disease risk.[2,3]

Many of the same factors that influence a mother's likelihood of delivering a high or low birthweight infant are also known to influence the development of MetS. MetS is linked to parent's and child's educational attainment, socioeconomic status (SES), and lifetime health behaviors.[40] LBW and HBW infants are more likely to be born to younger mothers

or obese mothers, respectively, and into environments of lower educational attainment, SES, and unfavorable health behavior role modeling.[58] The interrelated factors that influence birthweight, familial upbringing, and the development of MetS make differentiating causal factors a complex matter.[17]

Various hypotheses have been developed regarding the association between extremes in birthweight and increased risk of obesity and metabolic disorders. Among the most common theories linking LBW to chronic disease are the Barker Hypothesis and the Catch-up Growth Hypothesis[1,4,5]. Although the link between HBW and chronic disease has been less widely theorized, it has also been linked to adult and childhood obesity and insulin resistance.[2] The Critical Period Model and The Accumulation of Risk Model explore the general influence of adverse exposures at various points across the lifespan.[17,20] Animal models have also been used to study fetal programming phenomena in an effort to overcome the limitations of epidemiological studies.[6]

The Barker Hypothesis, also known as the Fetal Origins of Adult Disease Hypothesis (FOAD), was first developed in the 1980s.[2] The hypothesis suggests that exposures and events during early fetal development predict a person's future risk of developing adult diseases and conditions such as coronary artery disease, hypertension, obesity, and insulin resistance (MetS).[2] The thrifty phenotype model has been used to explain Barker's hypothesis. The model largely examines how mismatched environments (intra-uterine vs. extra-uterine environments) result in a series of biological tradeoffs to adapt to the changing environment.[3] There is an adaptive advantage when the fetal environment reflects the same environment that it will experience in the extra-uterine environment, upon birth. When subjected to nutrient deprivation, the adaptive responses adopted by the fetus do not match

the environment of nutrient excess that it will experience later in life, resulting in increased risk of MetS.[2,3]

The Catch-Up Growth Hypothesis suggests that LBW does not independently increase risk of developing MetS. Instead, it suggests that infants who specifically experience a period of rapid catch-up growth during the first years of life will be at increased risk of developing MetS.[8] The effect of catch-up growth, however, as an independent risk factor is difficult to quantify given the inevitable biological and sociological consequences of being born SGA.[3] When comparing the association of LBW and catch-up growth with MetS, both factors correlate with some criteria for MetS later in life and it remains unclear which of the two factors play a more dominant role.[8]

The Critical Life Model, suggests that an insult during a specific developmental stage, known as the critical period, may have lifelong health consequences due to alterations in the structure or function of organs, tissues and body systems that may cause disease later in life.[7] A critical period is defined as a specific time frame that can occur in utero, during infancy, childhood, or adolescence, in which a particular exposure can have adverse or protective effects on development and subsequent disease outcome of an individual.[7,8] For example, weight status at 6 months has been significantly associated with obesity at 5 years of age and in adulthood.[1]

The Accumulation of Risk Model is an alternate epidemiological framework that suggests risk factors, separate and independent insults, at each life stage combine to increase disease risk overtime.[17] In addition to an unfavorable fetal environment, insults can include episodes of illness, injuries, environmental exposures, socioeconomic factors and health damaging behaviors such as smoking. The damage from these insults accumulate over

time and ultimately damage the biological system.[17] This epidemiological transition model, of sorts, suggests initial exposure to early life stress, such as low or high birth weight, in addition to environmental and social variables such as SES, geographic location, among others, accumulate over the life course to influence metabolic patterns into adulthood.[19]

Among related studies and theoretical frameworks, not all conclusions are consistent.[8,22] For example, in a meta-analysis that included 643,902 persons from 66 studies and 26 countries, LBW was associated with a reduced risk of long-term overweight, while HBW was associated with an increased risk.[22] These results refute the previously discussed hypotheses related to LBW. Fetal growth is merely a single etiological factor in the development of adult disease from a life course perspective. Consequently, the effect of birthweight is not easily or independently attributable to future health outcomes. Additionally, the epigenetic basis of the thrifty-phenotype hypothesis in itself purposes a life-long interaction between adaptive, genetic changes acquired in utero and the environment throughout life. Therefore, the effects of fetal programming may be dependent on the context of the environment and more proximal adult lifestyle factors and represents only one of many critical periods that should each be considered wholistically.[20]

Methodological and theoretical criticisms of the FOAD stem from the broadly defined hypothesis that merely suggests a link between fetal exposures and adult diseases without a verified mechanism by which this occurs.[20,23] Instead numerous instances of correlation have been documented that have too often have failed to test the mechanism by which the two are linked.[20] Critics of the FOAD hypothesis have also cited a lack of adjustment for confounding factors, particularly SES and adult lifestyle factors such as smoking and physical activity. Statistical errors in interpretation related to modeling and

over-adjustment have also been speculated.[25] Until adequate randomized controlled trials are developed to test the FOAD hypothesis, the use of correlation and regression analysis to explore the possible relation between birth size and adult health outcomes will persist with uncertainties.[24]

Publication bias is another possible limitation that influences the availability of studies that did not support the FOAD hypothesis.[20,26] Publication bias occurs when studies with statistically significant or clinically favorable results are more likely to be published than studies with non-significant or unfavorable results.[26] Selective emphasis on certain favorable results is another form of bias to consider.[25] These biases could consequently influence the availability of published studies that found a lack significant association between birthweight and adult disease risk.[26]

FOAD investigations continue to become more widespread and generally support the role of adverse fetal environments and exposures on long-term chronic disease due to increased adiposity, vascular dysfunction, impaired glucose homeostasis, elevated blood pressure, and increased risk for renal and CVD risk in adulthood.[76] However, the mechanism by which birthweight influences metabolic programming remains inconclusive.[5] Verifying an association through careful statistical interpretation and then validating the mechanism of the relationship is vital in identifying how fetal origins of disease can have lifelong implications related to increased risk of developing chronic diseases or MetS. This study sought to explore the magnitude of the relationship between birthweight and MetS in adulthood and to identify possible mediators, moderators, and confounders that can inform the future development of interventions to address the current chronic disease epidemic.

Methods

The Atherosclerosis Risk in Communities (ARIC) Study began in 1987 in four field centers: Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN. Each cohort consisted of approximately 4,000 randomly selected and recruited individuals ages 45-64. Each of the 15,792 participants underwent an initial comprehensive examination in 1987-1989 that enabled researchers to gather baseline medical, social, and demographic data. The participants were then re-examined every three years thereafter: 1990-92, 1993-95, 1996-98. During the study's fourth exam with 11,656 participants, socioeconomic data, including participant's reported birthweight, were collected that informed this study's research question.[77]

The independent variables were derived using participant's responses to two sets of questions related to their birthweight. Participants who reported a low birthweight on a categorical scale from low to high were then combined with participants who reported a numerical birthweight value less than 5.5 lbs. These individuals were defined as LBW. The same method was used in identifying participants who reported a high birthweight or a reported numerical birthweight value greater than 8.8 lbs. These individuals were defined as HBW.

The dependent variable was defined by the presence of MetS, or not, among participants. The variable was derived by first identifying participants who met the diagnostic criteria for each of the five MetS factors using the criteria defined by the National Institutes of Health.[30] The diagnostic criteria included: 1) large waistline (waist measurement of 35 inches or more for women or 40 inches or more for men), 2) a high triglyceride level (triglyceride level of 150 mg/dL or higher or being on medicine to treat

high triglycerides, 3) a low HDL cholesterol level (a cholesterol level of less than 50 mg/dL for women or less than 40 mg/dL for men or being on medicine to treat low HDL cholesterol, 4) high blood pressure/hypertension (a blood pressure of 130/85 mmHg or higher, systolic or diastolic, or taking medicine to treat high blood pressure, and 5) a high fasting blood sugar (a fasting blood sugar level of 100 mg/dL or higher or being on medicine to treat high blood sugar. This last criteria can also include a diagnosis of prediabetes (fasting blood sugar level between 100–125 mg/dL) or diabetes (a fasting blood sugar of 126 mg/dL or higher). Each of the MetS criteria was coded dichotomously (0, 1) for each participant. The total number of MetS diagnostic criteria a given participant met equaled their MetS severity score, scaled 0-5. Those with 3 or more factors were considered to have MetS.[30]

Alternate covariates were included in the analysis to control for environmental, social, and behavioral differences among the participants. Demographic factors controlled for included age, race, and sex. Social and familial factors included age of mother at participant's birth, parents' years of education, participant's years of education, participant's age, participant's household income, participant's Medicaid enrollment status, drinking status, smoking status, and level of physical activity. SPSS version 24 (IBM Company, Chicago, IL) software was used to calculate the descriptive statistics of the ARIC population and to conduct binomial logistic regression modeling that was used to analyze the derived independent and dependent variables, and relevant covariates.

Results

The study population was made up of 45% males and 55% females with an average age of 62.8 years of age at the time of ARIC study's fourth examination. A summary of the study population's defining characteristics is shown below in *Table 1*.

Table 1. Study population characteristics, male versus female.

Participant Characteristics	Male	Female
Sex	45%	55%
Age	63.3 (52-75)	62.3 (53-75)
Black	18%	25%
Medicaid Enrollment	9.0%	5.5%
Average Household Size	2.3 ± .89	2.2 ± 1.01
Mother High School Graduate	77.3%	76.9%
Participant College Educated	29%	26%
Current Drinker	58%	43%
Current Smoker	16%	14%
Metabolic Syndrome Risk Factors		
Average BMI (kg/m^2)	28.4 ± 4.5	29.1 ± 6.3
Metabolic Syndrome Average Score (0-5)	2.7 ± 1.41	2.7 ± 1.42
Metabolic Syndrome Prevalence	55.8%	56.2%
Metabolic Syndrome Diagnostic Criteria		
Elevated Waist Circumference	52%	78%
Elevated Blood Pressure	63%	63%
Low HDL	49.8%	42.5%
Elevated Triglycerides	42.5%	40.0%
Elevated Blood Glucose/Diabetes Diagnosis	62%	47%
Birthweight Risk Factors		
Average Birthweight (lbs.)	8.1 ± 1.8	7.2 ± 1.7
Cohort Classified LBW	2.0%	5.0%
Cohort Classified HBW	9.0%	5.0%

Upon examining the association between extreme birthweight and MetS, neither HBW nor LBW were significant predictors of MetS, in univariate (shown in *Table 2*) or multivariate analysis, when controlling for demographic and social factors (shown in *Tables 3-6)*. Sex, age, mother's age at birth, participant's years of education, physical activity level,

and current drinking/smoking behaviors, however, were significantly associated with MetS based on binomial logistic regression modeling. Females were .78 times as likely as males to have MetS ($p < 0.001$). Mother's age at birth, but not mother's educational attainment, was significantly associated with MetS. With each additional year of age, a woman's risk of delivering a HBW or LBW infant decreased by 1.9% ($p < 0.001$). In all models; a univariate model, a model controlling for demographic factors only, and the full model previously discussed, LBW and HBW were not significant predictors of MetS.

Table 2. Univariate association between extreme birth weight and metabolic syndrome in adulthood

Predictor Variables	P	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Low birthweight	0.090	1.206	0.971	1.498
High birthweight	0.182	0.902	0.775	1.050

Table 3. Association between low birth weight and metabolic syndrome, controlling for demographic factors.

Predictor Variables	P	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Low birthweight	0.041	1.256	1.009	1.562
Black Race	<0.001	1.294	1.176	1.425
Female Sex	0.599	1.021	0.945	1.103
Age (per year)	<0.001	1.034	1.027	1.041

Table 4: Association between high birth weight and metabolic syndrome, controlling for demographic factors.

Predictor Variables	P	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
High birthweight	0.356	0.931	0.799	1.084
Black Race	<0.001	1.286	1.168	1.416
Female Sex	.528	1.025	0.949	1.108
Age (per year)	<0.001	1.034	1.027	1.041

Table 5. Full Model for association between low birth weight and metabolic syndrome

Predictor Variable	P	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Low Birthweight	0.774	1.049	0.756	1.457
Female Sex	<0.001	.775	0.687	0.875
Black Race	0.916	1.010	0.846	1.204
Age (per year)	0.011	1.016	1.004	1.028
Mother Age At Birth	<0.001	0.981	0.971	0.992
Mother's Education	0.512	0.989	0.956	1.023
Father's Education	0.718	0.995	0.967	1.023
Medicaid Enrolled	0.764	1.043	0.792	1.373
Household Income	0.059	0.960	0.920	1.002
Education (per year)	<.001	0.968	0.952	0.983
Activity Level	<.001	0.817	0.757	0.881
Current Smoker	0.005	0.793	0.674	0.933
Current Drinker	<.001	0.749	0.661	0.849

Table 6. Full Model, association between high birth weight and metabolic syndrome

Predictor Variable	P	Odds Ratio	95% C.I for Odds Ratio	
			Lower	Upper
High Birthweight	0.896	0.985	0.790	1.230
Female Sex	<.001	0.776	0.687	0.876
Black Race	0.925	1.008	0.846	1.203
Age (per year)	0.011	1.016	1.004	1.028
Mother’s Age At Birth	<.001	0.981	0.971	0.991
Mother's education	0.516	0.989	0.956	1.023
Father's Education	0.713	0.995	0.967	1.023
Medicaid Enrolled	0.762	1.043	0.793	1.373
Household Income	0.060	0.960	0.920	1.002
Education (per year)	<.001	0.968	0.952	0.983
Activity Level	<.001	0.817	0.757	0.881
Current Smoker	0.005	0.794	0.675	0.934
Current Drinker	<.001	0.749	0.661	0.849

In an exploratory logistic regression analysis of possible predictors of HBW and LBW, only participant sex was a significant predictor of HBW; and only female sex, Black

race, and mother's age at birth were significant predictors of LBW. With each year of age, a mother's risk of delivering a LBW infant decreased by 4.2%. Female sex was associated with a significant increase (OR: 3.2, $p < 0.001$) in risk of LBW, but was associated with a reduced risk of HBW (OR: .558, $p < 0.001$). Although race was significant in this analysis, a lack of birthweight data among black participants likely confounds this finding. Although maternal education was not a significant predictor of birthweight, maternal age was a significant predictor of LBW. An inverse relationship between mother's age at birth and the occurrence of LBW was found; a finding that is consistent with the literature. The findings of the analysis are shown below in *Table 7* and *Table 8*.

Table 7. Individual and maternal factors associated with low birth weight

Predictor Variable	P	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Black Race	0.002	0.364	0.190	0.696
Female Sex	<.001	2.881	1.916	4.333
Number of Brothers	0.781	0.983	0.870	1.111
Number of Sisters	0.981	1.001	0.888	1.130
Mother's Education	0.331	1.053	0.949	1.168
Father's Education	0.531	0.970	0.883	1.066
Mother's Age at Birth	0.011	0.955	0.922	0.989
Mother's History of DM	0.911	1.030	0.617	1.717

Table 8. Model of individual and maternal factors associated with high birth weight

Predictor Variable	P	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper

Black Race	0.107	0.755	0.536	1.062
Female Sex	<.001	0.524	0.416	0.661
Number of Brothers	0.846	1.007	0.935	1.085
Number of Sisters	0.617	1.019	0.946	1.098
Mother's Education	0.435	1.028	0.960	1.100
Father's Education	0.639	0.986	0.928	1.047
Mother's Age at Birth	0.551	0.994	0.973	1.015
Mother's History of DM	0.402	1.147	0.832	1.581

Discussion

Although no significant association between extreme birthweights and MetS was identified in the study, analysis of literature and significance of covariates suggest certain demographic and socioeconomic factors may confound the hypothesized relationship. Alternatively, this study may indicate a lack of association between birthweight and MetS. These findings may also suggest that the mechanism by which fetal programming contributes to increased MetS risk is not always evident by birthweight. Overall, the findings of this study were not consistent with the literature and did not support the Barker Hypothesis, the thrifty phenotype model, the critical life models or the findings of previous animal studies.

The study cohort consisted of an above average number of individuals with MetS and a below average number of individuals born at extreme birthweights compared to the American population. The prevalence of MetS was significantly higher (56%) than prevalence rates reported in the literature (35%),[40] which can likely be attributed to the advanced age of the study population.[31] Metabolic syndrome was similar among females (56.2%) than males (55.8%) in this population, but elevated waist circumference was also significantly more common among females (78%) compared to males (52%), consistent with existing literature.[70] HBW rates among males (9%) were comparable to prevalence rates

reported in the literature (8%).[60] All other extreme birthweights occurred less frequently among this population than others cited in the literature.[7]

This study was limited in scope by the availability of data on maternal factors during pregnancy and on early stages of post-natal life. It cannot be assumed that infants born at "normal" birthweights (i.e. not SGA or LGA) were not subjected to a significant insult that may affect metabolic programming and their future disease risk. An insult's timing, type, severity, and duration all may contribute to an infant's development, but may not necessarily be evident in their birthweight.[2] Insults can include exposure to malnutrition or maternal dietary patterns, in addition to inflammation, infection, glucocorticoids, hypoxia, stress, or toxins.[2] For example, although an AGA neonate born to a mother with GDM appears "normal," the neonate was still subjected to an adverse intrauterine environment and may still be at increased risk of chronic disease in adulthood. Epigenetic factors, such as degree of DNA methylation and gene expression have also been found to influence adult risk of insulin resistance and hypertension, but have no effect on birthweight.[6] In instances where direct measures of nutrient exposure were more verifiable, such as during the Dutch Famine of 1944, birthweight did consistently reflect the undernourishment of mothers.[6] Still, other studies suggest maternal nutritional status, before and during pregnancy, accounts for less than 10% of the variation in fetal weight at birthweight.[6,10] Finally, it should also be acknowledged that most existing literature and models have historically focused on the impact of LBW as a risk factor, despite the need to also consider gestational insults among AGA, LGA, and premature neonates.[2]

Still, this study's outcome does not necessarily refute the Accumulation of Risk Model or catch-up growth hypothesis due to the study's inability to account for all critical

periods, particularly during the post-natal period or among infants who experienced an insult that was not evidenced by an extreme birthweight. Limitations in existing studies may also explain the difference in findings. For instance, the original Barker Hypothesis failed to account for confounding factors such as maternal infection, infant diet, adult lifestyle factors, and socioeconomic status. Additionally, the quality of data measuring the exposure is limited in many cases.[6] Publication bias and statistical errors in interpretation have also been speculated by critics of the hypothesis.[20,25,26]

Many common risk factors such as SES, race, gender, educational attainment, among others mutually influence extreme birthweight and MetS. Common factors between the two suggest not only a confounded association between the two, but also the need to identify moderating factors that reciprocally contribute to the causal pathway. Although a moderator variable does not necessarily explain the relationship between a dependent and independent variable, a significant moderator variable can result in an amplified or reduced effect between the independent and dependent variables.

The relevance of identifying a causal pathway (mediating factors) or moderating factors across the life course can be instrumental in addressing chronic disease risk among high risk populations, such as those born at extreme birthweights and at lower SES.[46] Perhaps most importantly, public health strategies designed to manipulate the biology of fetal growth are less easily designed and implemented than those that aim to influence postnatal growth and nutrition. Instead, identifying the most significant postnatal influences on adult health would offer a greater likelihood that practical public health interventions could be developed and explored in this emerging field.[24]

A key limitation of this study is the use of birthweight as the only indicator of adverse fetal environment or insults in utero. An infant born at a "normal" birthweight may still have experienced significant insults in utero that increase risk of MetS in adulthood. Additionally, the timing, type, and severity of various exposures may contribute to an infant's development, but may not necessarily be evident in their birthweight.[2] If nothing else, these findings may suggest that the mechanism by which fetal programming contributes to increased MetS risk is not always evident by infant birthweight.

Other limitations include the ARIC dataset's lack of birthweight data among black participants, who are known to experience disproportionately higher rates of both premature and LBW births.[78] The ARIC dataset also lacked information regarding maternal behaviors prior to pregnancy, during pregnancy, and post-natal factors (i.e. breast feeding and the rate of post-natal growth) that have been found to significantly influence birthweight and fetal programming.[1] Finally, birthweight was reported many years later, which may have resulted in errors, under-reporting or misreporting of participant's birthweights.

Conclusions

This analysis did not support the hypothesis that extreme birthweight influences an individual's risk of developing MetS later in life. Certain factors showed more statistical significance in the predictive models for MetS than others; such as participant's years of education, activity level, current drinking, and smoking status; and mother's age at which she gave birth. The interaction between various familial and behavioral factors, in addition to complex and uncertain causal pathways, likely contribute to the study's lack of significant results. Alternatively, the lack of significant results could suggest that, contrary to existing literature, no association between birthweight and MetS exists. Additional research is needed

to rule out birthweight as a significant risk factor and to isolate the most significant and modifiable factors that may mediate the association between birthweight and MetS.

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Vita

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