

**The Developmental Origins of Health and Disease in Women
from the Michigan Bone Health and Metabolism Study: An
Examination with Longitudinal and Intergenerational Data**

by

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To my husband, Nick, for his sacrifice, patience, and unwavering love and support.

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List of Abbreviations

AIC	Akaike's information criteria
BMI	Body mass index
BW	Birth weight
CI	Confidence interval
cm	Centimeter
dL	Deciliter
g	Gram
GEE	Generalized estimating equations
HDL-c	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
IRB	Institutional Review Board
kg	Kilogram
L	Liter
lbs	Pounds
LDL-c	Low-density lipoprotein cholesterol
m ²	Meters squared
MBHMS	Michigan Bone Health and Metabolism Study
μU	Micro Unit
mg	Milligram
mIU	Milli International Units
mmol	Millimole
oz	Ounce
PAR	Predictive Adaptive Response
TCHS	Tecumseh Community Health Study
U.S.	United States

ABSTRACT

The Developmental Origins of Health and Disease in Women from the Michigan Bone Health and Metabolism Study: An Examination with Longitudinal and Intergenerational Data

by

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Fetal and early life experiences may be associated with development of adult chronic disease and effects may extend across generations. Epidemiologists have adapted these concepts to identify risk factors for chronic disease, but studies with longitudinal or intergenerational data are limited. Using data from a cohort study of Caucasian women, aged 24-50 years in 1992 and followed annually for over 15 years, we evaluated whether low and high birth weight women had different adult body composition, carbohydrate metabolism, or lipid trajectories compared to normal birth weight women. We assessed whether longitudinal risk profiles for diabetes or metabolic clustering differed by birth weight. To better understand intergenerational continuity of risk, we evaluated whether pregnancy characteristics across two generations influenced the birth weight of these women's offspring.

High birth weight women had higher adult body composition measures compared to normal birth weight women; however, slopes did not differ, suggesting the higher body composition measures observed among high birth weight women were constant over time. High birth weight women had steeper rates of change in glucose levels, but no differences were observed in lipid, insulin, or insulin resistance levels or in their trajectories over time compared to normal birth weight women. Body composition, carbohydrate metabolism, and lipid trajectories did not differ between low and normal birth weight women and the risk for developing type-2 diabetes or metabolic clustering did not differ by birth weight groups.

When we examined the intergenerational effects, we found that women with in utero cigarette smoking exposure had offspring who were an average of 136 grams heavier than women without in utero smoking exposure ($p=0.02$). Similarly, women born to older mothers had heavier offspring than women born to younger mothers.

This dissertation expands our understanding of the relationship between birth weight and trajectories in adult body composition, carbohydrate metabolism, and lipids – known risk factors for many chronic diseases - and provides further support of an intergenerational effect on birth weight. Understanding these relationships contributes to knowledge about chronic disease etiology and can motivate research and interventions aimed at improving reproductive and women's health and preventing chronic disease.

CHAPTER 1

Introduction

OVERVIEW

From an evolutionary and biological perspective, the adaptive responses of species to their environment are fundamental to their survival and perpetuation [1]. The “fetal programming” concept stems from this perspective, acknowledging that an insult during a critical period of fetal development has a subsequent impact on an offspring’s survival, growth, and maturation into adulthood [2, 3]. Epidemiologists have expanded this concept through the developmental origins of health and disease paradigm. This paradigm recognizes that the environment extending from conception and through early childhood can affect health later in life [4]. Further, epidemiologists have adapted the developmental origins concept to reflect their perspective of risk factors and the role of risk factor identification in disease, particularly chronic disease prevention.

An underlying assumption of the developmental origins concept is that adverse fetal and infant growth and development are due to adaptations to environmental factors and, when these adaptations are incongruent with the environment and

growth post-birth and into adulthood, they give rise to adverse health later in life [4, 5]. Although the scope of research has expanded to include infancy and childhood experiences, a model for these adaptations is low birth weight, which is frequently used as an integrated proxy of sub-optimal intrauterine environment and a crude measure of deficiencies in fetal oxygenation, accessibility to adequate energy, and nutrient availability. This dissertation research broadened this marker to include high birth weight, which may be a proxy measure of fetal overnutrition.

Based on a rich history in animal husbandry, it was a logical extension that programming effects have generational consequences, such that a pregnancy that encompassed an adverse environment at conception or during fetal development not only affected the offspring from that pregnancy, but also the offspring in later generations. In synthesizing evidence from both epidemiological and animal studies, Drake and Walker have proposed that there is a non-genomic generational effect of fetal programming with respect to low birth weight and cardiovascular disease in human populations [6].

Many epidemiological studies on the developmental origins of health and disease paradigm have described an association between low birth weight and increased risk for a number of chronic diseases, including cardiovascular disease [3, 7-11] and diabetes [3, 12-15]. However, investigations on the relationship between early life experiences and adult health using data collected longitudinally or across multiple generations are limited. Moreover, when data across generations

were available, it often excluded information about selected aspects, such as intrauterine environments, adult health outcomes, or other reasonable measures of personal and community factors that may also influence health status. As a result, studies have often been ecological or cross-sectional in design or utilized linked vital statistics data making it challenging to draw causal conclusions [16]. Finally, as these longitudinal and generational data start to become available, the interdependence and hierarchical structure of the data must be appropriately considered.

The Michigan Bone Health and Metabolism Study (MBHMS) is a prospective cohort study that provided a unique opportunity to examine both elements of the developmental origins of disease concept and subsequent intergenerational effects using population-based data with in-depth measures across two generations of Caucasian families. Participants of the MBHMS were aged 24 to 50 years when their enrollment was completed in 1992, and have completed their 15th evaluation over the past 19 years. Further, birth history data from nearly 1,000 offspring of the MBHMS participants who were born between 1964 and 2006 provided an opportunity to examine birth outcomes across generations.

SPECIFIC AIMS

The purpose of this dissertation was to characterize the effects of the fetal environment, using birth weight as a marker for intrauterine growth, on the longitudinal changes in body composition, carbohydrate metabolism, lipids and

the risk of developing type-2 diabetes or metabolic clustering in adulthood.

Additionally, using pregnancy information across two generations of families, we aimed to investigate the generational determinants of birth weight by evaluating whether a mother's fetal experience was associated with the birth weights of her offspring.

Aim 1. To examine whether body composition (weight, height, body mass index, waist and hip circumference, waist-to-hip ratio, and fat, lean, and skeletal muscle mass) trajectories differ by birth weight category using data from the MBHMS, a population-based sample of middle-class, Caucasian adult women who were aged 24 to 50 years at baseline and who have been followed annually over a 15-year study period.

Aim 2. To determine whether carbohydrate metabolism (glucose, insulin, and insulin resistance) and lipid (total, low-density lipoprotein, and high-density lipoprotein cholesterol, and triglycerides) trajectories and the risk of developing type-2 diabetes or metabolic clustering differ by birth weight category using data from the same study population of MBHMS women.

Aim 3. To evaluate the pregnancy and birth characteristics across two generations of mothers (mother of MBHMS participant and MBHMS participant herself) to investigate the generational determinants of birth weight. Specifically, this aim

assessed whether a mother's own fetal experience was related to the birth weights of her offspring.

PUBLIC HEALTH IMPLICATIONS

Expanding our understanding of the relationship between intrauterine growth and the development of select chronic diseases in adulthood not only contributes to knowledge about human development, but also informs our comprehension of chronic disease etiologies and aids in their prevention [16]. Examining the effect of the intrauterine environment and its long-term health consequences in affected offspring and in the subsequent generations may aid in focusing research, interventions, and public health strategies to improve reproductive health and prevent chronic disease.

BACKGROUND

The developmental origins of disease and health paradigm was adapted by epidemiologists based on biological and evolutionary concepts that the environment during conception and into early life affects subsequent growth and development, including increased risk for disease and adverse health later in life [4, 17, 18]. Early epidemiological approaches to the developmental origins of health concept and its implications on the development of adult diseases involved studies on the association of birth weight with cardiovascular disease. Using death registry data, Barker and Osmond observed that death rates from ischemic heart disease in England and Wales correlated with historical rates of infant

mortality [19]. Barker and Osmond recognized that the geographical distribution of ischemic heart disease among the poor in England and Wales was inconsistent with increasing rates of ischemic heart disease among the affluent living in Western countries and Britain [19, 20]. Indeed, the distribution of heart disease rates reflected post-World War II infant mortality rates, which in Great Britain were frequently used as a proxy of an area's health, development, and quality of life [20]. Simultaneously, Barker observed that other markers of poor social and economic conditions, such as higher smoking frequency and greater dietary fat consumption, were not consistent with the geographic distribution of ischemic heart disease [20]. Based on these observations, Barker hypothesized that the relationship between infant mortality rates and the higher prevalence of ischemic heart disease were due to environmental effects that occurred in utero and during early infancy [3, 4].

Barker's observations of ischemic heart disease and infant mortality rates, as well as similar observations from other investigators, resulted in the consolidation of the "Fetal Origins Hypothesis" which states that poor nutrition in utero causes long-term alterations in a fetus's organization, metabolism, and physiology, subsequently becoming a risk factor for disease in adulthood [3, 18]. The emergence of the Fetal Origins Hypothesis was extended to the developmental origins of health and disease paradigm in order to include not only the intrauterine environment, but that from pre-conception through infancy and early childhood [18]. Epidemiologic investigations of the developmental origins paradigm has

resulted in numerous studies of cardiovascular disease, hypertension, stroke, and diabetes, as well as intermediate markers for these diseases such as blood pressure, glucose intolerance, and total cholesterol. The scope of research has also continued to expand to diseases of cancer, cognition, and the musculoskeletal system.

EXPLANATIONS OF THE DEVELOPMENTAL ORIGINS PARADIGM

The developmental origins of health and disease concept is based on developmental plasticity, which results when one genotype gives rise to multiple phenotypes because of differences in the environment during growth and development [5, 21]. Examples of developmental plasticity occurring in nature are abundant. For instance, the temperature at which alligator eggs incubate dictates the proportion of sex among offspring, the rate of postnatal growth, and skin pigmentation [22]. In humans, an example is in the development of sweat glands. While the number of sweat glands is set at birth, the environment in which the infant is born dictates the number of glands that becomes activated – adults born in cooler climates have a lower number of activated sweat glands than adults born in warmer climates [3, 22]. The developmental origins of health and disease paradigm is an extension of developmental plasticity, in which specific environmental factors result in adaptations during fetal and early life development, and when these adaptations become incongruous with growth and the environment later in life, adverse health and disease occurs [4, 5]. Further, three features of developmental plasticity define the underlying assumptions of

the developmental origins model, specifically: 1.) the types of responses that may manifest is dependent on the characteristics of the environment; 2.) levels of vulnerability differ depending on the timing of the factor that gives rise to a given environment and; 3.) the time span in which environmental factors can impact development is limited [5]. Godfrey has created a conceptual model for the developmental origins of disease, which is provided in Figure 1.1 [23].

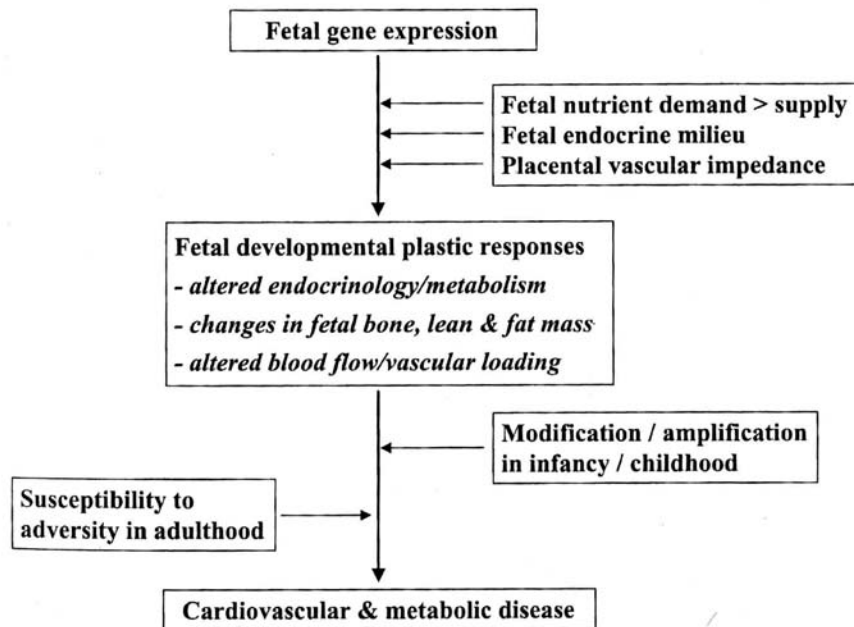


Figure 1.1 A conceptual framework for the developmental-origins hypothesis.
 From Godfrey K. The ‘developmental origins’ hypothesis: epidemiology, in
 Developmental Origins of Health and Disease. Gluckman PD and Hanson MA, eds.
 2006, Cambridge University Press: Cambridge; New York. Reprinted with the
 permission of Cambridge University Press.

Several hypotheses have been proposed to explain the developmental origins of health and disease paradigm. The three most common are: the “Thrifty Genotype” hypothesis, the “Thrifty Phenotype” hypothesis, and “Predictive Adaptive Responses”.

The Thrifty Genotype Hypothesis. The Thrifty Genotype Hypothesis was proposed by Neel in 1962 as an explanation for the increasing prevalence of type-2 diabetes [24]. He suggested that the selection of “thrifty” genes that caused insulin resistance and slow fetal growth was an evolutionary adaptation and survival mechanism in undernourished conditions, but confers a disadvantage in settings of overnourishment [4, 24, 25]. This hypothesis was further adapted to explain the association between smaller birth size and disease risk because insulin is involved in the regulation of fetal growth [5]. However, a strictly genetic explanation dismissed any environmental influences which was inconsistent with findings from experimental animal models or from natural experiments, such as the Dutch Famine [5].

The Thrifty Phenotype Hypothesis. Proposed by Barker and Hales, the Thrifty Phenotype Hypothesis suggests that, under conditions of maternal malnutrition, the fetus learns how to be “thrifty” with its energy needs, resulting in intrauterine growth retardation [26]. Although the learned response is a survival mechanism of the fetus to ensure energy needs are distributed to more important organs during development, it comes at the cost of slower fetal growth and insulin resistance. However, critics of the Thrifty Phenotype Hypothesis argued that extreme maternal undernutrition is necessary to see impaired growth in the fetus, despite evidence of a graded risk of type-2 diabetes associated with birth weight [5]. In other words, the risk of type-2 diabetes appears to be inversely associated

with birth weight, even among those within a normal range of birth weight. Further, this hypothesis does not account for any influences due to genetics.

Predictive Adaptive Responses. A main criticism of both the Thrifty Genotype and Thrifty Phenotype Hypotheses is their unidirectionality, specifically that the risk of disease was only explained for those with fetal growth retardation and under conditions of maternal malnourishment. In addition, these hypotheses focused on fetal development, and did not include the periods of pre-conception, conception, or infancy, which are also still susceptible to developmental plasticity. To address these concerns, Gluckman and Hansen proposed a broader explanation of the developmental origins of disease paradigm with the Predictive Adaptive Response. The Predictive Adaptive Response (PAR) is the hypothesis that gene-environment interactions occurring early in development trigger a physiologic and physical phenotypic change during development, not necessarily for immediate survival, but to provide an advantage for a specific future environment [22]. Using cues and information provided by the mother, the egg, embryo, fetus, and/or infant learns to adapt to a specific environment, which provides a basis for predicting the responses that will be needed to increase its survival and growth later in life. It is theorized that PARs lead to disease when there is a divergence from the environment that was expected to the environment that was actually realized [22, 27].

By acknowledging a phenotypic adaptation in response to a particular environment, the PAR serves as an expansion of the Thrifty Phenotype Hypothesis, while broadening the scope beyond fetal development and maternal undernutrition. Moreover, the PAR represents a type of environmental response assumed with developmental plasticity, except that the effects are not apparent immediately, but rather later in life [5]. A conceptual model developed by Gluckman and Hanson that describe how features of the PAR lead to increased disease risk is provided in Figure 1.2 [5, 17].

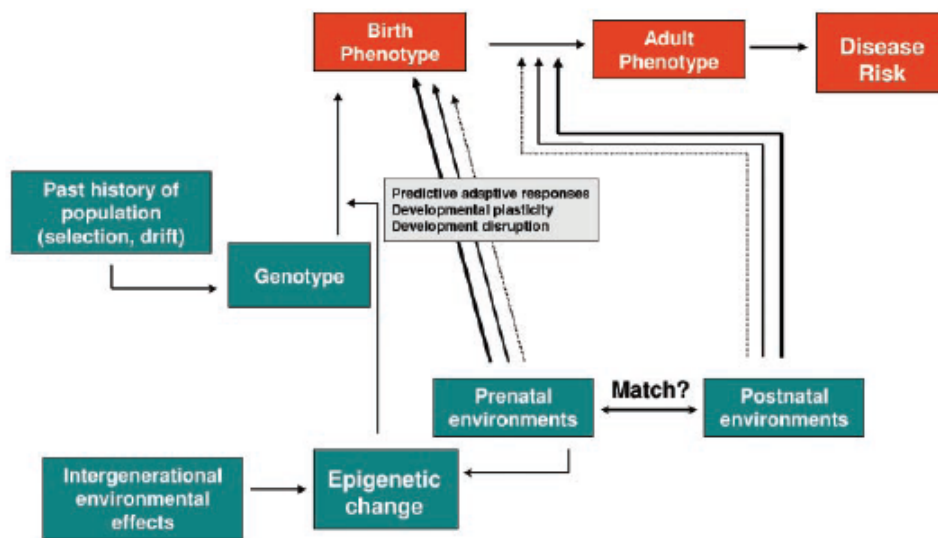


Figure 1.2 A general model of how intergenerational, genetic and environmental, and prenatal and postnatal factors interact to create a pathway to altered disease risk in adulthood.

From Gluckman PD and Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science*, 2004. 305 (5691): 1734. Reprinted with permission from AAAS.

DEVELOPMENTAL INSULTS

Inherent in the developmental origins of health and disease paradigm is the presence of an insult that creates an environment during fetal and early life development that ultimately results in adverse health later in life. One of the most frequently studied insults is maternal nutrition during pregnancy. Indeed, both the thrifty genotype and thrifty phenotype hypotheses explained the association between birth size and diabetes assuming conditions of maternal malnourishment. However, maternal diet is only one of many potential insults. Insults may arise because of maternal characteristics (e.g. physical constraint or age), genes (e.g. polymorphisms), toxicants (e.g. dioxins or nicotine), or social circumstances (e.g. poverty or stress), among many others. Furthermore, more than one insult can occur during growth and development and multiple insults can occur at various times or simultaneously. Insults may reflect deranged oxygen availability or transport, energy availability, nutrient metabolism, impaired temperature control, fluid imbalance, uncontrolled oxidative stress or infection.

A key aspect of the impact of insults is its time of occurrence during development, which can yield different consequences or varying degrees of outcome severity. Specifically, there is a “critical window” with respect to development so that insults that occur during this window are typically more deleterious than insults that occur outside of this window. For example, a male fetus exposed to an antiandrogenic steroid, such as diethylstilbestrol, between the seventh and twelfth week of gestation is more likely to develop a birth defect in

the urethra called hypospadias [28, 29]. Exposure to this compound during the seventh week of gestation results in more severe hypospadias than exposure after the twelfth week when there is markedly less effect on penile development [28, 29].

Typically, insults during the first trimester tend to be more damaging because cell and organ differentiation occur within the first twelve weeks of pregnancy.

However, insults during the second or third trimester can also cause deleterious outcomes. For instance, if growth-restricting insults occur early in pregnancy, infants frequently experience symmetric intrauterine growth retardation at birth because overall development of all cells and organs is slower [30]. However, if the fetus experiences growth-restriction late in pregnancy, nutrients are preferentially distributed to organs that are essential for survival, such as the brain and heart, and the growth of non-vital organs is slowed, causing asymmetric intrauterine growth retardation at birth [30]. Therefore, the insults resulted in negative outcomes but the phenotypic result differed based on the timing of the insult during fetal development.

BIRTH WEIGHT AS A MARKER FOR THE INTRAUTERINE ENVIRONMENT

Numerous studies examining the developmental origins of health and disease concept have attempted to understand how developmental insults alter the environment and give rise to the subsequent risk for chronic disease and adverse

health in adulthood. Direct measurement of the impact of insults during development is ideal, but is often not practical or realistic. Natural experiments, such as fetal and infant growth during wartime famine [31-34], as well as animal models [35-37], where the timing and severity of insults can be manipulated, have provided valuable information about the effects of insults on later disease, but are limited in scope and subject to concerns of generalizability. Since it is difficult to directly measure disruptions, such as anoxia or under-nutrition during development, studies often rely on the use of a proxy measure as a crude representation of the environment during growth [5, 30, 38]. A frequently used birth marker for a sub-optimal intrauterine environment is low birth weight.

The measure of birth weight itself is not believed to cause negative health outcomes in adulthood, but rather is intended to serve as an indicator of the quality of the intrauterine environment that the fetus was exposed to prior to birth [4, 17, 38]. It is acknowledged that fetuses can experience different intrauterine environments but yet have the same weight at birth [3, 4, 38]. Suggesting that low birth weight is not a cause of infant mortality, Wilcox questions the utility of low birth weight as a measure for explaining increases in infant mortality, citing evidence that, in developing nations and higher risk populations where low birth weight is prevalent, there is no increased risk for infant death [39]. These observations, known as the “Low Birth Weight Paradox”, extend to the associations between low birth weight and increased risk for adverse adult health [39, 40]. Thus, birth weight is recognized to be an insensitive measure of fetal

growth and development, and may not necessarily represent one's intrauterine experience. Therefore, the inclusion of birth measures beyond birth weight, such as gestational age, head circumference, length, and ponderal index (a measure of lean mass similar to body mass index) would provide additional information about the quality of intrauterine environment [38, 39]. Further, with the recognition of that developmental plasticity occurs after birth, studies have expanded to include rate of weight gain during infancy and adolescence (i.e. rapid catch-up growth) and feeding patterns and nutrition [7-9, 41-43]. Likewise, a number of maternal factors, including pre-pregnancy body size, age, parity, and smoking, physical activity, or dietary behavior, has also been shown to influence the birth size of the offspring [17, 38]. Therefore, the inclusion of a variety of birth measures and maternal factors are likely to better describe of the quality of the fetal environment than the use of birth weight alone.

INTERGENERATIONAL EFFECTS

Intergenerational influences are described as conditions, exposures, factors, and environments occurring in one generation that affect the growth, development and health of subsequent generations [6, 44]. There is continuing evidence in both animal and human studies that the associations between early life experiences and health later in life extend across multiple generations, suggesting that a developmental insult during a pregnancy may affect not only the offspring of that pregnancy, but offspring in future generations [6, 45-50].

Evidence has shown that the birth weights of offspring are associated with maternal [50-58] and, to a lesser extent, paternal birth weight [50, 51, 53]. Although pregnant women exposed to the Dutch Hunger Winter famine while in their first trimester gave birth to normally sized daughters, their grandchildren were smaller in body size [47-49]. Studies in rats have shown that malnourishment during pregnancy of one generation reduces birth weight in the offspring, and this reduced birth weight persists over multiple generations despite resumption of a non-malnourished diet [45, 46].

Intergenerational effects have been proposed as an extension of the predictive adaptive response, suggesting that the fetus uses not only information provided by the mother, but also information left by the grandmother for the mother to predict its future environment and prepare itself for optimal growth and survival [6, 59]. The information left by grandmothers may occur either through female germ cells, since oocytogenesis occurs in utero [50, 59] or via shared genetic and environmental factors that persist over multiple generations [50, 60, 61].

PUBLIC HEALTH SIGNIFICANCE

Although the developmental origins of disease and health paradigm is rooted in biology and evolution, these concepts have been adapted by epidemiologists for risk factor identification and to better understand chronic disease etiology and prevention. Many earlier epidemiological studies on the development origins of disease concepts have focused on cardiovascular disease and metabolic disorders,

such as diabetes and metabolic syndrome, but as evidence supporting the developmental origins of these diseases strengthens, the scope of diseases is expanding to include cognitive, musculoskeletal, and neurological diseases as well as cancers and mental illness. Understanding the mechanisms for how insults increase risk for adult chronic disease can inform our understanding of its etiology and its prevention and provide general insight about human development [16, 62].

The inclusion of additional pregnancy and birth information, including growth from infancy to adolescence, social and genetic factors, and longitudinal measures of health in adulthood, will enable researchers to investigate how the external environment interacts with developmental effects during growth to give rise to negative health outcomes as an adult. Studies that collect data across multiple generations can evaluate the influence of intergenerational effects, further investigating the extent of the developmental origins of health and disease impact. The information gathered from these studies can serve as an important guide for the creation of interventions and policies that improve maternal, reproductive, and infant health and chronic disease prevention.

OVERVIEW OF STUDY POPULATION AND DATA COLLECTION

Study Population. The Michigan Bone Health and Metabolism Study (MBHMS) is a longitudinal prospective cohort study that was established to examine changes in women's health prior to and during the menopause transition. In 1988,

recruitment for the MBHMS began among the female offspring of participants of the Tecumseh Community Health Study (TCHS), a population-based cohort study started in 1959 that examined longitudinal health outcomes in Caucasian families from Tecumseh, Michigan. A total of 543 women who were between ages 20 to 40 years were recruited and enrolled into the MBHMS. In 1992, recruitment was extended to a group of women from a Tecumseh community census (Kohl's directory), whose families were not in the TCHS. Upon completion of enrollment in 1992, a total of 664 women aged 24 to 50 years were enrolled into the MBHMS.

Tecumseh, Michigan is largely regarded as a rural community, the majority of whose residents are Caucasian and of middle-class socioeconomic status. All women recruited into MBHMS were residents of Tecumseh at the time of enrollment and many continue to reside there at present. Therefore, the MBHMS study participants represent a racially and socioeconomically homogenous population from a shared community environment. Using demographic data from the MBHMS, this representation was validated with the marital status and education level distributions, which has remained relatively stable over a 15-year time span (Table 1.1). This distribution showed that the majority of MBHMS participants have some college education, a common indicator for middle-class status.

Table 1.1. Distribution of Marital Status and Education Level in 1992 and 2007 among Michigan Bone Health and Metabolism Study Participants¹

	1992	2007
	n (%)	n (%)
MARITAL STATUS		
Married or Widowed	461 (79.4%)	395 (81.1%)
Divorced or Separated	83 (14.3%)	79 (16.2%)
Never Married	37 (6.4%)	13 (2.7%)
EDUCATION LEVEL		
Less than High School	8 (1.4%)	5 (0.8%)
Graduated High School	270 (46.5%)	276 (43.9%)
Some College	303 (52.2%)	348 (55.3%)

¹Totals differ across year and category because of missing data.

Commencing in 1992, excluding two lapses in funding of 13 and 18 months in duration, MBHMS participants have been followed annually and data have been collected in 15 examinations over a 19-year study period. As of March 2008, 561 (84.5%) of the 664 enrolled at the 1992 baseline were still active participants of MBHMS.

While women were pre-menopausal at enrollment into MBHMS, now nearly 20 years into the study, most women are menopausal or transitioning into menopause, thus marking the end of their reproductive capacity. Furthermore, many are at or nearing the age when the intermediate markers as well as the presentation of many chronic diseases are being expressed.

Collection and Management of Birth History Data. During the 1988 examination, when the MBHMS participants were between 20 and 40 years of age, 530 (98%) of the 543 enrolled participants reported their weight at birth. In

order to collect birth weights on the additional women recruited in 1992, as well as to gather additional information on the birth characteristics of all the MBHMS participants, a supplemental telephone-based interview was administered in 2008. A questionnaire was developed to gather data about the participant's birth history, including behaviors and characteristics of her mother while pregnant with the participant (Appendix A). The questionnaire also collected information about the participants' pregnancies and their children's birth characteristics, including their children's birth weights. All participants who were still active in the study in 2008 (n=561) were mailed a letter informing them about the collection of these data, including a copy of the questionnaire that was developed. The questionnaire was pre- and post-tested and the clinic staff was trained on the administration of the questionnaire. The collection of these data was approved by the University of Michigan Institutional Review Board (IRB). The protocol that was sent to and approved by the University of Michigan IRB, including a copy of the letter that was mailed to the participants, is provided in Appendix A.

Collection of these data began in April 2008 and was completed in August 2008. Among those who were still active in the MBHMS in 2008, 82% participated (n=460) in the supplemental telephone-based birth history interview, while 4% (n=22) refused or could not be found and 14% (n=79) could not be reached.

All data collected were entered into a data entry program, which was created using EpiInfo v6. Staff was trained on the use of the data entry software and all questionnaires were double data entered by two independent data entry personnel.

Pedigree Data. Family pedigrees of the MBHMS participants were created during the 1988 and 1992 enrollment. This pedigree information included birth dates of the parents and siblings of the MBHMS participants. With these data, information about birth order, singleton or multiple birth status, and parental ages at time of participant's birth were compiled. The use of these pedigree data supplemented the birth history information collected from the telephone interviews.

MEASUREMENTS

Birth Weights of MBHMS Participants. The birth history data collected from the MBHMS participants in 2008 were intended to serve as a supplement to the birth weight data gathered during the 1988 examination. Since the birth weight data from the 1988 interview were self-reported, efforts were made during the 2008 interview to document birth weight data from either birth certificates or hospital records. However, the information provided on birth certificates is not standardized across the states, so birth weight data were not always available. The majority of participants were born in Michigan during a time period when birth weight was not reported on birth certificates. As a consequence, the sources used to document birth weight information included birth certificates as well as

baby books, hospital records, and memory (either the participant's or a participant's parent).

To determine if there were variations in reporting by source of information, we compared mean birth weights by source of information (Table 1.2). A t-test analysis comparing the mean birth weights by source revealed no statistically significant differences ($p \geq 0.27$).

Table 1.2. Frequency, Mean, and Range of Michigan Bone Health and Metabolism Study Participant Birth Weights, in grams, by Source of Information Reportedly Used in the 2008 Supplemental Interview¹

	n (%)	Mean ± SD	Min	Max
Birth Certificate	61 (16%)	3293 ± 670	1729	5188
Hospital Records / Baby Book	70 (18%)	3373 ± 571	1843	4479
Parent's Memory	166 (44%)	3323 ± 596	1531	5188
Participant's Memory	155 (42%)	3282 ± 636	1361	4990

¹Percents do not sum to 100 because sources were not mutually exclusive.

For 301 women, the birth weights gathered in 2008 could be compared with the birth weights that were self-reported in 1988. Table 1.3 provides the mean difference in birth weights reported in 2008 relative to 1988 by source of information. In general, the differences in mean birth weight between the 1988 and 2008 collection periods were small. However, compared to the 1988 data, birth weights collected from memory had greater variability than birth weights that were documented (Table 1.3). For birth weights collected from the parent's memory, mean birth weight was higher than the 1988 data ($p\text{-diff} < 0.01$), while for birth weights collected from the participant's own memory, the mean birth weight was lower than the 1988 data ($p\text{-diff} < 0.01$). Based on these results, the 2008 birth

weight information was used only if the 1988 birth weight data were missing (n=78).

Table 1.3. Difference in Mean Birth Weight, in grams, of Michigan Bone Health and Metabolism Study Participants Comparing 1988 and 2008 Data Collection by Source of Information Reportedly Used in the 2008 Supplemental Interview¹

	n (%)	Mean ± SD	Min	Max
All Sources Combined	301	-6 ± 234	-1418	1474
Birth Certificate	43 (14%)	-21 ± 251	-652	992
Hospital Records / Baby Book	55 (18%)	-5 ± 137	-468	454
Parent's Memory ²	136 (45%)	39 ± 274	-1418	1474
Participant's Memory ²	127 (42%)	-45 ± 243	-652	1474

¹Percents do not sum to 100 because sources were not mutually exclusive.

²p<0.01 mean difference compared to all other sources.

The birth weight data, which was originally collected in pounds and ounces, was converted to grams and categorized into three levels based on the following clinical cut-points [63]: low birth weight, defined as less than 2500 grams; normal birth weight, defined as 2500 to 4000 grams; and, high birth weight, defined as greater than 4000 grams.

Birth Weights of MBHMS Participant's Offspring. For women who experienced a live birth, the 2008 telephone-based supplemental interviews also collected birth histories, including birth weights, about the MBHMS participants' offspring.

Birth weight, in grams, was a continuous variable and was the outcome of interest for Specific Aim 3.

Body Composition, Carbohydrate Metabolism, and Lipids. Measures of adult body composition were the outcomes of interest for Specific Aim 1 and, along

with risk of type-2 diabetes and metabolic clustering, measures of carbohydrate metabolism and lipids were the outcomes for Specific Aim 2. The body composition, carbohydrate metabolism, and lipid measures were continuous outcomes.

Beginning with the 1992 examination, when the MBHMS participants were between ages 24 and 50 years, and every subsequent year thereafter (excluding two years with lapses in funding), health histories and physical measures were collected and phlebotomy was performed. Specimens were collected fasting and during days 2-7 of the follicular phase of the menstrual cycle. For women who were amenorrheic, specimens were collected on the anniversary of the woman's date of enrollment \pm 15 days.

Adult body composition measures collected during the physical assessment included weight (in kilograms), height, waist, and hip circumference (in centimeters), and fat, lean, and skeletal muscle mass (in kilograms). Balance beam scales and calibrated stadiometers were used to measure weight and height, respectively. Waist and hip circumference were measured using a non-stretching tape measure at the narrowest section of the torso and the widest section of the hip, respectively. Measures of impedance and conductance from bioelectrical impedance analysis were used to collect fat, lean, and skeletal muscle mass [64, 65]. From the 1992 to the 2007 examination, there were a maximum of twelve annual collections of body composition measures.

Beginning in 1993, specimens were assayed for the assessment of carbohydrate metabolism measures, which included glucose and insulin, and the lipid measures of total cholesterol, low- and high-density lipoproteins, and triglycerides. A measure of insulin resistance, the homeostatic model-assessment insulin resistance index (HOMA-IR), was estimated from multiplying fasting insulin ($\mu\text{U/ml}$) by fasting glucose (mmol/L) and dividing the product by 22.5 [66]. Total cholesterol and triglycerides were analyzed using enzymatic methods. High-density lipoproteins were isolated using heparin-2M manganese chloride [67] and low-density lipoprotein levels were calculated using the Friedewald equation [68]. From 1993 to 2007, there were a maximum of eleven annual collections of carbohydrate metabolism measures and a maximum of ten annual collections of lipid measures.

Type-2 Diabetes and Metabolic Clustering. Type-2 diabetes and metabolic clustering were dichotomous outcomes for Specific Aim 2 and were assessed at each woman's annual visit. A woman was regarded as having diabetes based on a self-reported physician diagnosis or if she was using anti-diabetic medicines at the time of the annual examination. Metabolic clustering was based on a published definition of cardiometabolic clustering [69]. Women were classified as having metabolic clustering if they had at least two of the following six conditions: 1.) A blood pressure measuring $> 135/85$ mm Hg or use of anti-hypertensive medicines; 2.) A triglyceride level ≥ 150 mg/dL; 3.) A high-density lipoprotein level < 50 mg/dL or use of statins; 4.) A glucose level ≥ 100 mg/dL or use of anti-diabetic

medicines; 5.) A HOMA-IR value > 5.2, which was the 90th percentile cut-off point for the MBHMS sample; and 6.) A C-reactive protein level > 0.74 mg/dL, which was the 90th percentile cut-off point for the MBHMS sample.

Additional Birth Characteristics. With the 2008 supplemental interview, pedigree, and MBHMS annual examination data, additional characteristics about the MBHMS participants own birth as well as her offspring’s births could be used for analysis. Characteristics about the MBHMS participant’s birth included her mother’s age and smoking behavior at the time of her birth, whether they were a singleton or a twin, and their birth order. Characteristics about the MBHMS participants’ offspring births included whether they were from a singleton or multiple birth, birth order, sex, the MBHMS participant’s age and smoking status at time of offspring birth, and amount of weight gained during the pregnancy. A summary of these additional variables is described in Table 1.4.

Table 1.4. Summary of Characteristics Collected about the MBHMS Participant’s Birth and her Offspring’s Births

	Birth Characteristic	Method of Assessment or Estimation
MBHMS Participant	Mother’s age at time of birth	Using pedigree data, subtracted MBHMS participant’s date of birth from mother’s date of birth
	Mother’s smoking behavior at time of birth	Selected from four categories in the 2008 interview: <ul style="list-style-type: none"> • Mother smoked before but not during pregnancy • Mother smoked before and during pregnancy • Mother did not smoke • Does not know

	Singleton birth status-	Based on birth dates from pedigrees and/or selected from two categories in the 2008 interview: <ul style="list-style-type: none"> • Singleton Birth • Multiple Birth
	Birth order	Based on birth dates from pedigrees and/or mother' prior number of live births
Offspring of MBHMS Participant	MBHMS participant's age at offspring's birth	Using 2008 interview data, subtracted offspring date of birth from MBHS participant's date of birth
	MBHMS participant's smoking status at time of birth	Using smoking behavior information from the MBHMS annual examinations, four categories were created: <ul style="list-style-type: none"> • Ex-smoker and quit before pregnancy • Smoker during pregnancy • Never Smoker • Could Not Assess
	Singleton birth status	Based on birth dates from 2008 interviews
	Birth order	Based on birth dates from 2008 interviews
	Sex	Selected from two categories in the 2008 interview: <ul style="list-style-type: none"> • Male • Female
	Amount of weight gained during pregnancy	Open-ended question from the 2008 interview

STATISTICAL ANALYSIS

Composition of Data and Statistical Models for Specific Aims 1 and 2. The MBHMS population is comprised of daughters recruited from families who were in the TCHS. Study participants were evaluated annually and have body composition, carbohydrate metabolism, and lipid measures along with diabetes and metabolic clustering assessments that were collected repeatedly over time.

Therefore, for specific aims 1 and 2, the data were multilevel, comprising the repeated occasions (level 1) nested within the MBHMS participant (level 2), which are nested within families (level 3). The structure of the data for specific aims 1 and 2, which describes the different levels of data are described in Figure 1.3.

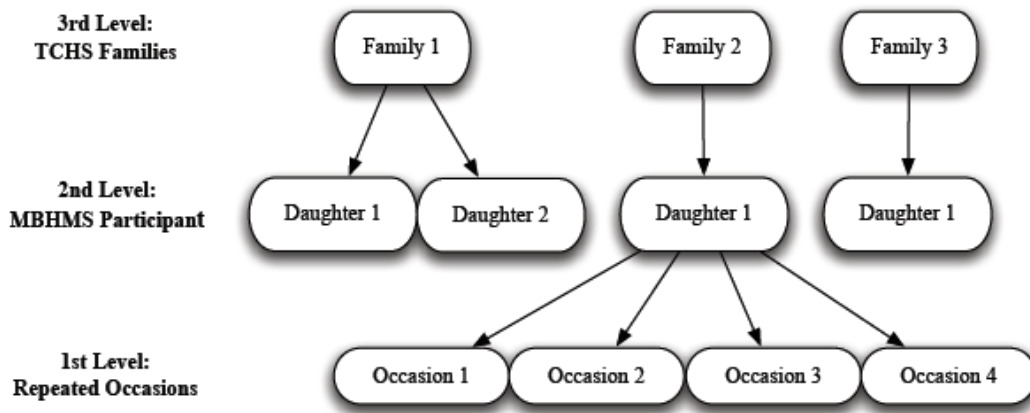


Figure 1.3. The three-level data structure for specific aims 1 and 2

Since the measures of body composition for specific aim 1 and carbohydrate metabolism and lipids for specific aim 2 were continuous, linear mixed effects modeling was used. For linear mixed effects modeling, preliminary analyses included testing the model assumptions and completing steps for model selection to identify the statistical model that would be the best fit for the data. In addition, specific aim 2 examined the risk of developing type-2 diabetes or metabolic clustering, which were dichotomous outcomes; therefore, a marginal model was used.

Diagnostic testing involved determining if each continuous measure had a normal distribution. Since the data were longitudinal, histograms of each body composition, carbohydrate metabolism, and lipid measure at every annual study visit were created and examined to ensure that the distributions were consistent over time. Based on these histograms, weight, body mass index, hip circumference, fat mass, insulin, HOMA-IR, and triglycerides were log-transformed. Following log-transformation, these measures were reexamined to confirm the transformation resulted in a normal distribution.

In preliminary analyses, linear mixed effect models were evaluated to find the statistical model that would best fit the data. Statistical models were evaluated in the following steps: 1.) Comparing the random intercept only to the random intercept and random slope model at the participant-level; 2.) If the random intercept and random slope model was the better model in step 1, identifying the best covariance structure to describe the between-participant random effects; and 3.) Identifying the best covariance structure to describe the residuals (the within-participant variance).

Step 1: Comparison of the Random Intercept Only Model vs. the Random Intercept and Random Slope Model. Since there were no family-level (3rd level) predictors, a random intercept model only was used to specify the between-family variance. At the MBHMS participant-level (2nd level), a random intercept model was compared to a random intercept and random slope model to identify the

model that would best fit the specification of the between-woman, within-family variance. An unstructured covariance structure was employed to avoid any assumptions about the structure of the covariance between the random intercept and random slope. The fixed effects were the same in the random intercept-only model and the random intercept and slope model, which allowed for comparisons using the Akaike's information criteria (AIC) and the log-likelihood ratio test.

For all outcome measures, the AIC was smaller in the random intercept and random slope model compared to the random intercept only model. Consistent with the comparison of the AIC, there were large differences in the negative two log-likelihood values between the two models suggesting statistically significant p-values at two degrees of freedom. The result of these model fitting tests indicated that the model that specified random intercepts and random slopes was a better fitting model for the between-subject variance than the random intercept-only model.

Step 2: Identifying the Best Covariance Structure for the Between-Participant Random Effects. Comparison of the Variance Components and Unstructured covariance patterns revealed that for waist circumference, waist-to-hip ratio, lean mass, skeletal muscle mass, and the carbohydrate metabolism measures, use of the Variance Components covariance pattern was better. However, the Unstructured pattern better described the covariance between the random

intercepts and slopes for weight, height, BMI, hip circumference, fat mass, and the lipid measures.

Step 3: Identifying the Best Covariance Structure for the Within-Participant Variance. To identify the ideal covariance structure around the residuals, the Variance Components, Compound Symmetry, Auto-Regressive (First Order), and Unstructured covariance structures were compared. For all outcome measures, the Unstructured and Compound Symmetry covariance structures would not converge, suggesting models incorporating these covariance patterns were not appropriately fit. Using AIC and the log-likelihood ratio tests, the First-Order Auto-Regressive covariance structure described the best fit around the residuals for all the measures, except for insulin. For insulin, the Variance Components covariance structure provided the best fit.

Establishing the Linear Mixed Effects Models. Based on the findings from the diagnostic testing and the model selection process, the linear mixed effects model used for the body composition, carbohydrate metabolism, and lipid measures is depicted in Equation 1.2. To arrive at this model, we let $Y_{k(i)j}$ be an outcome for the i^{th} participant from the k^{th} family at the j^{th} occasion. Without including any explanatory variables, $Y_{k(i)j}$ was assumed to be from the following model:

$$Y_{ikj} = \alpha + \eta_k + \pi_{0ik} + \pi_{1ik}(\text{Time}_{ikj}) + \varepsilon_{ikj} \quad (1.0)$$

In this model, η_k is the random family effect with a zero mean, π_{0ik} is the participant-specific random intercept, π_{1ik} is the participant-specific random slope of time and ε_{ikj} is the random error. Since we were interested in modeling the effects of birth weight categories on the rates of change of the outcome, we regressed π_{0ik} and π_{1ik} on the birth weight categories in which normal birth weight was the referent, and adjusted for baseline age. This is described with the following models:

$$\begin{aligned}\pi_{0ik} &= \beta_{000} + \beta_{001}(\text{Baseline Age}_{ik}) + \beta_{002}(\text{Low BW}_{ik}) + \beta_{003}(\text{High BW}_{ik}) + b_{0ik} \\ \pi_{1ik} &= \beta_{010} + \beta_{011}(\text{Baseline Age}_{ik}) + \beta_{012}(\text{Low BW}_{ik}) + \beta_{013}(\text{High BW}_{ik}) + b_{1ik}\end{aligned}$$

where $\begin{pmatrix} b_{0ik} \\ b_{1ik} \end{pmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{00} & \sigma_{01} \\ \sigma_{10} & \sigma_{11} \end{bmatrix}\right)$ (1.1)

Substituting the model from (1.1) into the model from (1.0), the full model was:

$$\begin{aligned}Y_{ikj} &= \alpha_1 + \beta_{001}(\text{Baseline Age}_{ik}) + \beta_{002}(\text{Low BW}_{ik}) + \beta_{003}(\text{High BW}_{ik}) + \\ &\beta_{010}(\text{Time}_{ikj}) + \beta_{011}(\text{Baseline Age}_{ik})(\text{Time}_{ikj}) + \beta_{012}(\text{Low BW}_{ik})(\text{Time}_{ikj}) + \\ &\beta_{013}(\text{High BW}_{ik}) + \eta_k + b_{0ik} + b_{1ik} + \varepsilon_{ijk}\end{aligned}$$

where

$$\begin{aligned}\eta_k &\sim N(0, \sigma^2) \\ \begin{pmatrix} b_{0ik} \\ b_{1ik} \end{pmatrix} &\sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{00} & \sigma_{01} \\ \sigma_{10} & \sigma_{11} \end{bmatrix}\right) \\ \begin{pmatrix} \varepsilon_{ik1} \\ \vdots \\ \varepsilon_{ikn} \end{pmatrix} &\sim N\left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix}, \sigma^2 \begin{bmatrix} 1 & \rho & \cdots & \rho^n \\ \rho & 1 & \cdots & \rho^{n-1} \\ \vdots & \vdots & \ddots & \vdots \\ \rho^n & \rho^{n-1} & \cdots & 1 \end{bmatrix}\right)\end{aligned}$$

(1.2)

For Specific Aim 2, an additional linear mixed effect model that included adjustment for adult body mass index was also evaluated. This model was similar to (1.2), except that the model included body mass index as time-varying variable, but excluded body mass index as a random effect.

Establishing the Marginal Models for Diabetes and Metabolic Clustering. In addition to the linear mixed effects models used for the carbohydrate metabolism and lipid measures, generalized estimating equations (GEE) were used to estimate the risk of developing type-2 diabetes or metabolic clustering. While these outcomes were dichotomous, because the covariates and exposures were identical to those used for the linear mixed effects model, the GEE was very similar to the model described in (1.2). The full model is described in Equation 1.3.

$$\log \left\{ \frac{\Pr(Y_{ikj} = 1)}{\Pr(Y_{ikj} = 0)} \right\} = \alpha_1 + \beta_{001}(\text{Baseline Age}_{ik}) + \beta_{002}(\text{Low BW}_{ik}) + \beta_{003}(\text{High BW}_{ik}) + \beta_{010}(\text{Time}_{ikj}) + \beta_{011}(\text{Baseline Age}_{ik})(\text{Time}_{ikj}) + \beta_{012}(\text{Low BW}_{ik})(\text{Time}_{ikj}) + \beta_{013}(\text{High BW}_{ik})(\text{Time}_{ikj}) \quad (1.3)$$

In this model, the outcome is the log odds of developing the diabetes or metabolic clustering, where Y_{ikj} is the dichotomous outcome (Yes/No) for the i^{th} participant from the k^{th} family at the j^{th} occasion. Just as with the linear mixed model described in (1.2), the intercept (α_1) was the population mean and the statistical model included adjustment for participant's age at the baseline examination

(Baseline Age_{ik}). Low and high birth weight (Low BW_{ik} and High BW_{ik}, respectively) were dummy variables, with normal birth weight as the referent. The beta-coefficients for low and high birth weight were the overall risk of developing the disease associated with being either low or high birth weight relative to being normal birth weight. The interactions between the birth weight and time estimated the annual risk of disease over time.

The model in (1.3) was also examined with body mass index as a time-varying covariate.

Data Composition and Statistical Model for Specific Aim 3. The composition of the data for specific aim 3 was also comprised of three levels, but differed from the data used for specific aims 1 and 2 because the outcome of interest was the birth weight of MBHMS participants' offspring. The data were also comprised of three levels – the offspring (level 1) nested within the MBHMS participant (level 2) nested within families (level 3). The structure of the data for specific aim 3 is depicted in Figure 1.4.

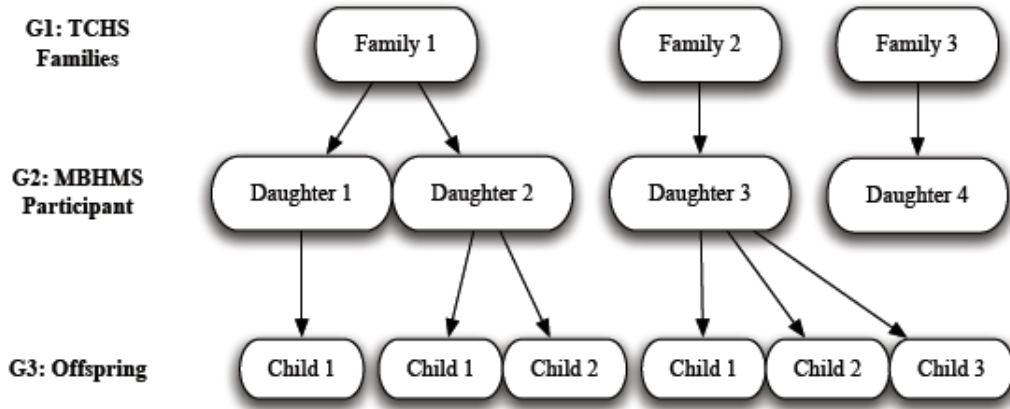


Figure 1.4. The three-level data structure for specific aim 3.

Offspring birth weight was a continuous measure; therefore, linear mixed effect models were used. Despite three levels of data, this mixed effects model was simpler than the one used for specific aims 1 and 2 since only adjustment for maternal and family clustering was necessary. Offspring birth weight was confirmed as having a normal distribution, but additional steps for model selections were not needed. Further, a variety of different birth and pregnancy characteristics were examined as exposures, so the number of covariates in the model varied. A generic full model is given in Equation 1.4.

$$Y_{ikj} = \alpha_1 + \beta_{01j}(X1_{ik}) + \dots + \beta_{0nj}(Xn_{ik}) + \eta_k + b_{0ik} + \varepsilon_{ikj},$$

where

$$\eta_k \sim N(0, \sigma^2) \tag{1.4}$$

$$b_{0ik} \sim N(0, \sigma^2)$$

$$\varepsilon_{ikj} \sim N(0, \sigma^2)$$

In this model, Y_{ikj} is the expected birth weight for the j^{th} offspring of the i^{th} MBHMS participant from the k^{th} family. The intercept (α_1) was the population mean birth weight and the beta-coefficients describe the mean difference in j^{th} offspring birth weight associated with a given birth characteristic(s). The random intercept at the family-level is defined by η_k , the random intercept at the MBHMS participant-level is defined by b_{0ik} , and the random error is described by ε_{ikj} .

SUMMARY AND CHAPTER OVERVIEW

This dissertation expands the existing development origins of health and disease literature by examining not only low birth weight, but also high birth weight, a possible proxy measure for fetal overnutrition, on adult measures of disease and associated risk factors for disease that were collected longitudinally. The availability of birth and pregnancy data across two generations of women permitted the evaluation of an intergenerational influence on the birth weight of offspring from the third generation.

In Chapter 2, the trajectories of adult body composition comparing women who had low and high birth weight to women who had normal birth weight are described. Also comparing across birth weight categories, Chapter 3 examines whether there were different trajectories seen in adult measures of carbohydrate metabolism and lipids as well as whether there were differences in the risk profiles of type-2 diabetes and metabolic clustering. In Chapter 4, birth and pregnancy characteristics from two generations of women were evaluated to

understand their association to birth weight in offspring in a subsequent generation. Finally, a summary of the dissertation's main findings, suggestions for the future direction of developmental origins of health and disease research, and public health and clinical implications are discussed in Chapter 5.

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CHAPTER 2

The Relationship of Birth Weight with Longitudinal Changes in Body Composition in Adult Women

ABSTRACT

Fetal and early life experiences may be associated with chronic disease development. Early studies reported an increased risk of chronic disease, particularly obesity and diabetes, in those with low birth weight. More recent investigations have reported a decreased risk for cardiovascular disease among high birth weight individuals, despite evidence that high birth weight is associated with increased adult weight and lean mass. Since most studies examined adult measures cross-sectionally, the ability to infer causality remains a concern. To address this, we examined the relationship of self-reported birth weight to longitudinal changes in adult body composition using data from 587 women of the Michigan Bone Health and Metabolism Study who were aged 24 to 50 years at baseline.

Low, normal, and high birth weight were defined as <2500 grams, 2500-4000 grams, and >4000 grams, respectively. Linear mixed models were used to

estimate the association between birth weight categories and women's 15-year longitudinal change in adult weight, height, body mass index (BMI), waist and hip circumference, waist-to-hip ratio, and fat, lean and skeletal muscle mass.

Mean birth weight was 3289 ± 580 grams, with 9.2% and 8.9% classified as being low and high birth weight, respectively. Over the 15-year study period, body composition measures increased in all women over time. At baseline, high birth weight women weighed 13% more and had BMI values that were 11% higher than normal birth weight women after adjustment for baseline age. Waist circumference and lean mass were 5.51 cm and 3.91 kg larger, respectively, in high compared to normal birth weight women at baseline. No differences in adult body composition between low and normal birth weight women were observed. Rates of change in the adult body composition measures did not vary between low, normal, and high birth weight women.

In this population of rural mid-western women, those heavier at birth continued that trajectory into adulthood – a longitudinal finding that validates reports from cross-sectional studies. Further research is needed to address whether the higher body composition observed in high birth weight women increases the longitudinal risk for obesity-related chronic diseases over time.

INTRODUCTION

The high prevalence of obesity in the United States is regarded as a major public health problem because of its association with increased risk for chronic diseases, including diabetes, metabolic syndrome, and cardiovascular disease [1, 2],

decreased quality of life [3] and life expectancy [4], and its economic burden [5].

The developmental origins of health and disease theory, an outgrowth of the Barker hypothesis [6], posits that fetal and early life experiences may be associated with the development of select chronic diseases later in life, including adult obesity [7, 8]. Evaluating the contribution of the developmental origins of obesity is important, not only to understand its mechanisms, but for the creation of programs and interventions to prevent obesity and obesity-related diseases.

Although a crude proxy measure, birth weight is frequently used as a marker for the fetal experience, with low birth weight suggestive of a sub-optimal intrauterine environment that includes undernutrition [7, 8]. Previous studies have focused on the relationship of low birth weight with the risk of developing chronic diseases and reported an association between low birth weight and an increased risk for a number of chronic conditions, including obesity, diabetes, cardiovascular disease, metabolic syndrome, osteoporosis, cancer, and dementia [9, 10]. Studies of pregnancy outcomes during famine and starvation have provided further evidence that infants exposed to malnourishment in utero were at greatest risk for obesity later in life [11-14]. Animal models as well as population-based observational studies have confirmed this relationship [15-18].

More recent investigations have expanded the focus of early life exposures to include the full distribution of birth weight, including high birth weight. In contrast to low birth weight, epidemiologic studies of high birth weight have suggested a decreased risk for chronic disease, particularly cardiovascular disease [6, 19, 20], despite evidence that higher weight at birth was associated with higher BMI later in life [21-24]. To better understand this paradox, investigators have examined the relationship of birth weight with body composition measures and consistently reported that high birth weight was associated with higher BMI via higher levels of lean mass [21, 25-27]. In contrast, studies have provided less consistent evidence about the relationship of birth weight to fat mass and fat mass distribution [21, 23, 25-27].

Although the existing literature has examined the relationship of birth weight with health later in life in a wide range of age groups, including early childhood, preadolescence, young adult, adult, and the elderly, the majority of studies have been completed outside the United States, specifically in the United Kingdom and Scandinavia where comprehensive birth data are routinely collected. Most studies examined outcomes cross-sectionally and thus, associations of birth weight with longitudinal outcomes are not well described.

The purpose of this study was to examine the relationship of birth weight with changes in body composition observed over a 15-year study period in a population-based sample of middle-class adult white women. We hypothesized

that body composition trajectories would differ among low and high birth weight women compared to women who were normal weight at birth. Specifically, high birth weight women would have greater weight gain and increases in waist and hip circumference, and have higher levels of BMI and fat and lean mass compared to normal birth weight women over the 15-year study period. We further hypothesized that increased levels in the body composition measures would also be evident in low birth weight women, but not to the extent seen in high birth weight women.

METHODS

Study Population. The study population was from the Michigan Bone Health and Metabolism Study (MBHMS), a prospective cohort study investigating changes in women's health prior to and through the menopause [28]. Recruitment and enrollment began in 1988 and comprised 543 women, aged 20-40 years, who were daughters of the participants in the Tecumseh Community Health Study (TCHS). In 1992, recruitment was extended to age-eligible female residents of Tecumseh, Michigan whose families were not in the TCHS, resulting in the enrollment of an additional 121 women. Upon completion of recruitment, 664 women aged 24-50 years were enrolled into the MBHMS. Since 1992, participants have been evaluated annually over a 15-year study period, excluding two time intervals of 13 and 18 months duration associated with lapses in funding.

These analyses incorporated data from 587 (88.4%) women for whom birth weights were available and who were from a singleton birth. These 587 women represented siblings from 399 nuclear families with between one and seven daughters. There were 263 families with one daughter in the study, while 100 families had two daughters, 26 families had three, and ten families had between four and seven female siblings in the study.

Birth Characteristics. During the 1988 examination, 530 of the 543 enrolled women self-reported their birth weight. In 2008, the 561 active MBHMS participants were contacted to participate in a supplemental telephone-based interview to further characterize their birth history. These 2008 interviews collected and/or confirmed the birth weight data obtained in 1988, and provided additional birth characteristics, including participant's in utero smoking exposure, mother's date of birth, participant birth order, and whether participant was from a singleton or multiple birth. Among those still active in the MBHMS in 2008, 82% (n=460) participated in the supplemental birth history interview, while 4% (n=22) refused and 14% (n=79) could not be reached.

Self-reported birth weight was converted from pounds and ounces to grams (g) and categorized into groups based on clinical cut-points, including low, defined as less than 2500 g; normal, defined as 2500-4000 g; and high, defined as greater than 4000 g. Since there was little variation in the self-reported birth weight data

gathered in 2008 as compared to 1988, birth weight reported in 2008 was used only if 1988 birth weight data were missing (n=78).

Participant's in utero smoking exposure was classified into three categories: mother smoked before and during pregnancy, mother smoked before but stopped during pregnancy, and mother never smoked. Mother's age at the time of participant's birth was calculated by subtracting the participant's date of birth from their mother's date of birth and was classified into five age groups: 15-19 years old, 20-24 years old, 25-29 years old, 30-34 years old, and 35 years and older. First born status (Yes/No) was derived using participant's birth order.

Body Composition Measures. At each annual MBHMS visit, physical measures of body composition were obtained, including weight (in kilograms), height (in centimeters), waist and hip circumferences (in centimeters), and fat, lean, and skeletal muscle mass (in kilograms). Calibrated stadiometers and balance-beam scales were used to measure height and weight, respectively. Weight divided by the square of the height, in meters, provided the body mass index (BMI) measure. Using non-stretching tape, waist circumference was measured during expiration at the narrowest section of the torso, while hip circumference was collected at the widest section of the hip. Waist-to-hip ratio was calculated by dividing waist by hip circumference. Fat, lean, and skeletal muscle mass were collected using impedance and conductance measures from bioelectrical impedance analysis [29, 30].

Statistical Analysis. Contingency tables and analysis of variance were used to examine frequency distributions and mean differences of the birth characteristics and body composition measures by birth weight categories. Least-square means and chi-square tests evaluated statistical significance across the birth weight categories.

Scatterplots and box plots were created to verify that the random errors around each body composition measure had a mean zero and constant variance suggestive of a multivariate normal distribution. Since data were collected annually, histograms for each body composition measure at each study visit were examined to confirm that the distributions were consistent across the 15-year study period. Non-normally distributed outcomes were log-transformed for analyses, but were back-transformed to their original scale to ease interpretation.

In addition to evaluating the mean baseline body composition measures, linear mixed modeling was used to examine the 15-year trajectories of adult body composition measures. Since the study participants included sisters from the same nuclear family and data were collected longitudinally, the linear mixed models accounted for the within- and between-family variance and the within-subject correlation. The Akaike's information criterion and chi-square tests comparing the log likelihood ratios between reduced and full models identified the ideal covariance structure on the within-subject random effects and around the

residuals. Final models included random intercepts at the family-level and random intercepts and slopes at the subject-level. Birth weight by time interactions in the models were used to determine whether the rates of change in the adult body composition measures varied by birth weight category. All models were adjusted for participant's baseline age, which was centered about the median age of 37 years. Statistical analyses were completed using SAS v9.2 and statistical significance was defined as $\alpha < 0.05$.

RESULTS

In this study population of women born between the years 1942 and 1967, birth weight was normally distributed with a self-reported mean of 3289 ± 580 g and range of 1531 to 5897 g. When categorized using clinical cut-points, the majority (81.9%) of women were normal birth weight with a mean birth weight of 3291 ± 352 g, while 9.2% were low birth weight with a mean birth weight of 2208 ± 259 g and 8.9% were high birth weight with a mean birth weight of 4399 ± 364 g.

Low birth weight women were more likely to be first born (35.3%) compared with normal birth weight women (26.6%), but this difference was not statistically significant ($p=0.19$) (Table 2.1). Women who were low weight at birth were more likely to report in utero smoking exposure than women who were normal or high weight at birth (30.6% vs. 22.3% and 19.1%, respectively); however, these frequencies were also not statistically significant.

The average maternal age at participant's birth was 26.1 ± 6.6 years, 25.8 ± 5.1 years, and 28.8 ± 6.5 years for low, normal, and high birth weight women, respectively. The mean differences in maternal age between normal and high birth weight women were statistically significant ($p < 0.01$). Women classified as low weight at birth were more likely to have been born to a teenaged mother (19.6%), compared to women classified as normal (10.4%) or high weight at birth (10.2%). Normal birth weight women were more likely to have been born to mothers in their twenties (67.7%), while high birth weight women were more likely to have been born to mothers who were at least thirty years of age (44.9%).

The mean baseline body composition values observed in adulthood in low birth weight women did not differ from those of women who were normal weight at birth (Table 2.2). In contrast, high birth weight women had significantly higher mean baseline body composition measures observed in adulthood relative to normal birth weight women, except for height and waist-to-hip ratio. At baseline, low birth weight women weighed 68.6 ± 18.7 kg and normal birth weight women weighed 70.5 ± 15.3 kg ($p = 0.70$); however, high birth weight women weighed 82.2 ± 19.2 kg at baseline, or 16.6% more than normal birth weight women ($p < 0.01$). Similarly, baseline waist circumference for high birth weight women was 6.6 cm higher than normal birth weight women ($p < 0.01$). Mean baseline fat mass in women with high weight at birth was 34.0 ± 15.3 kg, or 28.8% more than the mean baseline fat mass in normal birth weight women ($p < 0.01$).

The fitted linear mixed models indicated that, in general, women experienced an increase in their adult body composition measures over the 15-year study period. However, after adjusting for baseline age, high birth weight women experienced a greater increase in weight, height, BMI, waist and hip circumference, and fat, lean, and skeletal muscle mass compared to normal birth weight (Table 2.3).

At the study baseline, women in the high birth weight group were, on average, 13% ($p < 0.01$) heavier and had BMI and fat mass levels that were, on average, 11% ($p < 0.01$) and 20% ($p < 0.01$) higher, respectively, than women in the normal birth weight group. Similarly, waist circumference and lean mass were an average of 5.51 cm ($p < 0.01$) and 3.91 kg ($p < 0.01$) larger, respectively, in high relative to normal birth weight women at baseline.

Over the 15-year study period, there were no differences in adult body composition or in the trajectories between low and normal birth weight groups of women and only marginal significance in the waist circumference, lean mass, and skeletal muscle mass trajectories of high birth weight women compared to women who were normal weight at birth (Table 2.3).

DISCUSSION

Using clinical cut points for birth weight, this study compared low and high to normal birth weight women to assess whether differences existed in their body composition trajectories as middle-aged adults. In this population-based

longitudinal examination of middle-class Caucasian women from the mid-western United States, women who were heavier at birth continued to be heavier into adulthood. Fitted slopes from mixed effects modeling of the adult body composition measures did not differ across the birth weight categories, suggesting that while women in the high birth weight groups had higher adult body composition measures, their rates of body composition change over time were similar to those of women in the normal birth weight group.

This study is one of the few to examine the relationship between birth weight and longitudinal measures of body composition in adult women using data collected annually over a 15-year time period. The finding that high birth weight women had a greater propensity for higher adult body composition levels corroborates reports from cross-sectional studies that consistently described a positive association between birth weight and weight, BMI, and lean mass later in life. Furthermore, the use of longitudinally-collected data provided additional insight about the trajectories and rates of change in adult body composition in women that have not been previously described. Notably, these data suggest that trajectories are maintained during young adulthood and are not a unique characteristic of middle age, when women are transitioning through menopause.

While we found an association with high birth weight and adult lean mass, fat mass, and waist circumference, no relationship was observed with waist-to-hip ratio, suggesting that the higher levels of adipose tissue in the high birth weight

group of women were not more likely to be centrally distributed. The relationship between birth weight and adult fat mass and waist-to-hip ratio, a frequently used marker for central adiposity, has been less consistently observed in previous studies. A number of studies have reported a positive association between birth weight and fat mass [17, 31, 32], while others describe either no association [27, 33] or an inverse relationship [24]. This has led to the proposal that high birth weight is more strongly associated with the programming of lean mass distribution [21, 25-27].

High birth weight may represent a crude proxy measure for overnutrition during fetal development. Compared to women in the low and normal birth weight groups, a larger proportion of the high birth weight women were born to older (≥ 30 years old) mothers, and this may reflect a unique fetal environment. For example, older maternal age is a risk factor for gestational diabetes [34, 35], and gestational diabetes is associated with larger babies at birth.

Our findings are consistent with previous studies which have investigated the relationship of birth weight with body composition in different age groups, including children [31, 36], teenagers [23, 27], adults [24, 32], and the elderly [33] and all have reported that higher weight at birth or higher ponderal index, a measure of body size used until age two, is associated with higher weight, BMI, and lean mass later in life. These associations persisted in both men and women and regardless of whether body composition data were acquired via dual-energy

X-ray absorptiometry or bioelectrical impedance, or through proxy measures such as skinfold thickness or the calculation of waist-to-hip ratio. The majority of these studies were completed outside of the United States, primarily in countries where birth weight information is routinely collected and archived.

In the Nurses Health Study, high birth weight was positively correlated with higher levels of adult BMI among nurses; however, no other body composition measures were evaluated [22]. Similarly, Leong et al reported a U-shaped relationship between birth weight and BMI in women age 50-79 years living in New Hampshire, Massachusetts, or Wisconsin, suggesting that being either low or high birth weight is associated with higher BMI; however, again, no additional body composition measures were gathered [37]. In contrast, a study of Mexican American and non-Hispanic white women, aged 25 to 64 years, from the San Antonio Heart Study reported no differences in mean BMI or waist-to-hip ratio across birth weight tertiles [38].

A major strength of this study was the ability to analyze effects over a 15 year time frame. Previous research with the ability to assess birth weight and longitudinal changes in adult body composition is limited. In a nine-year study of adults from Amsterdam, Netherlands, who were aged 27 years at baseline and followed over four time points, increasing birth weight in females was associated with decreasing subcutaneous fat mass, truncal fat, and waist circumference over time [18]. However, in this study, those in the highest birth weight tertile were

still within the clinically-accepted range of normal birth weight. Other studies that have collected outcomes longitudinally did not use statistical methods to evaluate birth weight effects over time [32, 39].

This study examined a population-based sample of white women, born between 1942 and 1967, the majority of whom were born and continue to reside in Tecumseh, Michigan, a middle-class community. The homogeneity of the study population permitted analysis with minimal concern for selected confounding factors, such as race, socioeconomic status, and social environment, which are frequently associated with variability in birth weight as well as in adult body composition. Body mass index is considered a crude measure of obesity because of its inability to distinguish whether higher levels are associated with increases in lean or fat mass [26, 40]. Moreover, measures of fat distribution, such as waist-to-hip ratios or skin-fold thickness, are considered unreliable measures of fat mass [26]. Therefore, a strength of this study was the collection of lean, skeletal muscle, and fat mass body composition data as well as fat distribution data.

A potential limitation of this study was that birth weight data were self-reported, although a number of studies have described the validity of self-reported birth data [41, 42]. A recent study by Tehranifar et al found good level of agreement and sensitivity in self-reported birth weight when compared to medical records [43]. Although the MBHMS women interviewed in 2008 were asked to refer to birth documents to validate their birth weight, many continued to rely on their

memory or the memories of their family members; however, the information gathered in 2008 was designed to supplement birth weight data already collected in 1988. Since both periods of data collection relied primarily on recall, it is likely that the 1988 data was less prone to recall bias because it occurred 20 years earlier and during the participants' childbearing years, when women may be more likely to think about their own birth weights in consideration of their own children's births. It has also been suggested that self-reported low birth weight is less sensitive to measurement error than normal or high birth weight [43], so our finding of no association may also be due to the attenuation of effects due to measurement error.

This study reported no differences in body composition between low and normal birth weight women, in contrast to a number of studies describing an association with low birth weight and obesity [11, 17, 18]. However, many of those studies were based on prenatal exposure to famine and malnutrition, unlikely occurrences in our middle-class study population.

Studies have speculated that low birth weight may be more closely related to the programming of fat mass distribution later in life. However, it is unclear whether the mechanism for adult fat mass distribution is due to low birth weight representing a proxy for a specific fetal insult and/or whether an interaction with rapid catch-up growth after birth is implicated. Our findings suggested that low birth weight was not directly associated with adipose distribution; however,

limited information on birth characteristics in our data prohibited the examination of other possible mechanisms.

In conclusion, these data support previous findings that high birth weight was related to higher levels of adult body composition, including higher levels of lean mass. Although cross-sectional studies have suggested that the association with lean mass may explain the decreased risk of certain chronic diseases in high birth weight populations, it is not known whether this decreased risk in chronic diseases will continue to be seen longitudinally. Our finding that high birth weight was not associated with centrally distributed fat mass despite a positive association with fat mass suggests the need to examine whether high birth weight women have a decreased risk for chronic diseases in which central adiposity is a risk factor, such as metabolic syndrome and type-2 diabetes.

Table 2.1. Birth Characteristics of Women from the Michigan Bone Health and Metabolism Study by Birth Weight Category, n=587^a

	BIRTH WEIGHT CATEGORY		
	Low (<2500 g)	Normal (2500 - 4000 g)	High (>4000 g)
N (%)	54 (9.2%)	481 (81.9%)	52 (8.9%)
BIRTH CHARACTERISTIC			
<i>Birth Order</i>			
First Born	18 (35.3%)	116 (26.6%)	13 (26.0%)
Not First Born	33 (64.7%)	320 (73.4%)	37 (74.0%)
<i>Mother's Age^b</i>			
15 - 19 years	10 (19.6%)	45 (10.4%)	5 (10.2%)
20 - 24 years	18 (35.3%)	176 (40.7%)	11 (22.5%)
25 - 29 years	8 (15.7%)	117 (27.0%)	11 (22.5%)
30 - 34 years	8 (15.7%)	66 (15.2%)	12 (24.5%)
35 and older	7 (13.7%)	29 (6.7%)	10 (20.4%)
<i>Mother's Smoking History</i>			
Smoked before but not during pregnancy	1 (2.8%)	24 (7.6%)	1 (2.4%)
Smoked before and during pregnancy	11 (30.6%)	71 (22.3%)	8 (19.1%)
Did not smoke	24 (66.7%)	223 (70.1%)	33 (78.6%)
^a Values do not sum to totals because of missing data.			
^b p<0.01 High vs. Normal			

Table 2.2. Mean Body Composition at Baseline (1992) by Birth Weight Category in Women from the Michigan Bone Health and Metabolism Study, n=587

	BIRTH WEIGHT CATEGORY		
	Low (<2500 g)	Normal (2500 - 4000 g)	High (>4000 g)
Birth weight (g)	2208.1 ± 259.2	3290.6 ± 352.1	4398.5 ± 363.5
Age (years)	37.7 ± 4.5	36.8 ± 4.9	36.0 ± 6.0
BODY COMPOSITION			
Weight (kg)	68.6 ± 18.7	70.5 ± 15.3	82.2 ± 19.2 ^a
Height (cm)	161.9 ± 6.6	163.6 ± 5.8	165.4 ± 5.8
BMI (kg/m ²)	26.1 ± 6.6	26.3 ± 5.6	30.0 ± 6.7 ^a
Waist Circumference (cm)	78.9 ± 15.3	79.1 ± 12.6	85.7 ± 15.1 ^a
Hip Circumference (cm)	103.3 ± 15.7	103.3 ± 12.1	111.6 ± 13.3 ^a
Waist-to-Hip Ratio	0.76 ± 0.06	0.76 ± 0.06	0.76 ± 0.06
Fat Mass (kg)	25.6 ± 13.7	26.4 ± 11.6	34.0 ± 15.3 ^a
Skeletal Muscle Mass (kg)	19.9 ± 2.7	20.3 ± 2.5	21.9 ± 2.6 ^a
Lean Mass (kg)	42.8 ± 6.7	44.0 ± 6.4	48.2 ± 6.4 ^a
^a p<0.01 compared to Normal			

Table 2.3. Fifteen-Year Longitudinal Relationship of Birth Weight with Adult Body Composition in Women of the Michigan Bone Health and Metabolism Study, aged 24 to 50 years at Baseline (1992), n=587^a

	Low Birth Weight (<2500 g)						High Birth Weight (>4000 g)					
	Main Effect			Slope			Main Effect			Slope		
BODY COMPOSITION	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Log Weight (kg)	-0.03	0.03	0.37	0.001	0.001	0.41	0.13	0.03	<0.01	0.001	0.001	0.26
Height (cm)	-1.15	0.82	0.16	-0.001	0.010	0.96	1.83	0.82	0.03	0.0003	0.010	0.97
Log BMI (kg/m ²)	-0.01	0.03	0.73	0.001	0.001	0.42	0.10	0.03	<0.01	0.001	0.001	0.27
Waist Circumference (cm)	-0.45	1.92	0.81	0.091	0.104	0.38	5.51	1.92	<0.01	0.182	0.100	0.07
Log Hip Circumference (cm)	-0.005	0.02	0.77	0.0004	0.001	0.67	0.06	0.02	<0.01	0.001	0.001	0.15
Waist-to-Hip Ratio	-0.003	0.01	0.75	0.001	0.001	0.34	0.01	0.01	0.49	0.0001	0.001	0.89
Log Fat Mass (kg)	-0.04	0.06	0.46	0.002	0.003	0.54	0.19	0.06	<0.01	0.002	0.003	0.44
Lean Mass (kg)	-0.97	0.96	0.31	0.035	0.040	0.38	3.91	0.96	<0.01	0.065	0.039	0.09
Skeletal Muscle Mass (kg)	-0.29	0.37	0.43	0.010	0.015	0.52	1.52	0.37	<0.01	0.023	0.015	0.11

^aAdjusted for Participant's Age at Baseline.

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CHAPTER 3

The Relationship of Birth Weight with Longitudinal Changes in Carbohydrate Metabolism, Lipids, and Risk of Diabetes or Metabolic Clustering in Adult Women

ABSTRACT

Increased incidence of diabetes and cardiovascular disease, and its associated cardiometabolic risk factors, are commonly reported among those with lower birth weights, but the relationship of high birth weight with subsequent chronic disease risk is less understood. Data examining the effect of birth weight on trajectories of cardiometabolic risk factors over time are limited. We described the relationship of birth weight groups with longitudinal changes in carbohydrate metabolism and lipid measures and the risk of developing type-2 diabetes or metabolic clustering – a condition similar to metabolic syndrome - in 587 women of the Michigan Bone Health and Metabolism Study who were between ages 24-50 years at baseline.

Low, normal, and high birth weight were defined as <2500 grams, 2500-4000 grams, and >4000 grams, respectively. Linear mixed modeling was used to estimate the association between birth weight categories and women's 15-year longitudinal change in levels of glucose, insulin, insulin resistance, triglycerides, and total, low-, and high-density lipoprotein cholesterol.

Generalized estimating equations were used to evaluate the baseline and annual risk of developing type-2 diabetes or metabolic clustering.

Glucose levels increased at a rate of 0.63 mg/dL per year among high compared to normal birth weight women ($p < 0.01$). Trajectories of insulin, insulin resistance, and lipids did not differ by birth weight group. Relative to normal birth weight, the risk at baseline of diabetes in low and high birth weight women was 0.36 and 1.54, respectively; the comparable risks for metabolic clustering were 1.31 and 1.60, respectively. Risks were similar after adjustment for participant's baseline age and adult body mass index and were not statistically significant ($p > 0.05$) across the birth weight groups.

This study contributes to our understanding of how birth weight is associated with adult glucose trajectories, providing additional insight about the possible role of fetal growth and development in glucose metabolism and regulation in women. Additional studies with longitudinal data are needed to determine whether these findings can be replicated in other populations.

INTRODUCTION

Support for the developmental origins of disease and health theory [1-3] comes from studies that have related low birth weight with an increased risk for type-2 diabetes [3-8], coronary heart disease [3, 9-13], and metabolic syndrome [14-17] in adulthood. In a meta-analysis of 30 studies, birth weight was inversely associated with the risk of type-2 diabetes among middle-aged and older populations, even after adjustment for potential confounding factors such as age, sex, body mass index, and socioeconomic status [18]. Likewise, an increased risk of coronary heart disease and metabolic syndrome has been reported among adults who were low weight at birth, with the risk further exacerbated by rapid catch up growth during infancy and childhood [9, 10, 13, 14, 16, 19].

While evidence for the association between low birth weight and risk for chronic disease is frequently reported, less attention has been paid to the relationship of high birth weight to chronic disease risk. Studies have described a decreased risk for cardiovascular disease in adults who were high weight at birth [20-22], despite the evidence that study participants had a greater likelihood for obesity later in life [20, 23, 24]. The reports describing the relationship between high birth weight and risk for type-2 diabetes or metabolic syndrome, however, are few in number and the findings are inconsistent. In primarily Caucasian men and women from the Health Professionals Follow-up Study and the Nurses' Health Study, respectively, those in the high birth weight groups had the lowest risk for diabetes [25, 26]. A study in Iceland, where high birth weight is common, high birth weight was protective for having diabetes in adulthood [27]. However, in studies among the North American Indian populations, a U-shaped relationship has been

reported between birth weight and adult diabetes prevalence [28, 29]. Most studies have also reported a decreased risk for metabolic syndrome among those in the highest birth weight category [14-16].

In a review of carbohydrate metabolism measures in 48 studies, most investigations showed that low birth weight was associated with higher levels of fasting glucose and insulin resistance, but acknowledged that a few studies found no or positive associations [30]. In a meta-analysis of 58 studies, total cholesterol was inversely associated with birth weight – levels were 1.39 mg/dL higher per kilogram decrease in birth weight [31]. This negative relationship has been consistently reported in other reviews and cross-sectional examinations with investigators concluding that the magnitude of the decrease in cholesterol measures associated with low birth weight does not have considerable public health impact [31-33]. Notably, few studies have described the relationship between birth weight category and change in these intermediate metabolic markers over time.

Much of the reported work has been undertaken in British and Scandinavian wartime cohorts and combined data from men and women, despite evidence that cardiovascular risk factors vary by sex [34-36]. In a study of women of reproductive age from the San Antonio Heart Study, higher levels of mean glucose and insulin were observed among Mexican Americans with lower birth weight, but not among Non-Hispanic Whites [37]. However, no differences were reported in lipid levels by ethnicity [37]. In a study of African American women from Philadelphia, birth weight was not associated with

measures of insulin and risk of diabetes [38]. Data on the associations of birth weight with risk factors for diabetes and cardiovascular disease in middle-aged U.S. women are lacking.

The purpose of this study was to describe the relationship of low and high birth weight classification to the risk of developing type-2 diabetes and metabolic clustering – a condition similar to metabolic syndrome characterized by excess body fat and cardiometabolic dysfunction - in a population-based sample of middle-class, Caucasian women born post-World War II (1947 -1967) who were followed annually over a 15-year time period. We also examined the association of birth weight groups with longitudinal changes over 15 years in carbohydrate metabolism and lipid measures, acknowledged risk factors for type-2 diabetes and cardiovascular disease. We hypothesized that the lipid trajectories and the risk of developing metabolic clustering would be similar across the birth weight groups, but that women in the low birth weight group would have higher levels of glucose and insulin resistance and carbohydrate metabolism trajectories suggestive of glucose intolerance compared to women in the normal birth weight group. We further hypothesized that women in the low birth weight group would have an elevated risk for type-2 diabetes over time.

METHODS

Study Population. Participants were from the Michigan Bone Health and Metabolism Study (MBHMS), a longitudinal cohort study examining changes in women's health prior to and through the menopause [39]. In 1988, a total of 543 women, aged 20-40 years and

who were offspring of participants from the Tecumseh Community Health Study (TCHS), were recruited and enrolled into MHBMS. In 1992, a supplemental recruitment included an additional 121 age-eligible women who were residents of Tecumseh, Michigan but whose families were not TCHS participants. Since 1992, participants have been evaluated annually over a 15-year time period, excluding two time periods with lapses in funding of 13 and 18 months duration. This report includes data from 587 (88.4%) women from a singleton birth for whom birth weight information was available. The collection of these data was approved by the University of Michigan Institutional Review Board.

Birth Characteristics. At the 1988 examination, 97.6% of the MBHMS participants self-reported weight at birth. In 2008, women were asked to participate in a supplemental telephone-based interview to further describe their birth history. Among the 561 women available for interview in 2008, 82% provided supplemental data. As there was little variation between the self-reported birth weight data collected in 2008 compared to the 1988 data, birth weights collected in 2008 were used for the 78 women for whom there was no 1988 birth weight data. Based on clinically established cut-points, birth weight in grams (g), was categorized into three groups: low (<2500 g), normal (2500-4000 g), and high (>4000 g).

Carbohydrate Metabolism and Lipid Measures. Annual visits included the collection of health histories and physical assessment and the performance of phlebotomy. Specimens were collected fasting and in days 2-7 of the follicular phase of the menstrual cycle. For

amenorrheic women, specimens were collected on the anniversary of the woman's enrollment \pm 15 days. Biological samples were aliquoted and stored at -80 degrees Centigrade without thaw until assay.

Lipids were assayed beginning in the second year (1993) of the study and included low-density and high-density lipoprotein cholesterol (LDL-c and HDL-c, respectively), total cholesterol, and triglycerides. Lipids were assessed from EDTA-treated plasma using an Eastman Kodak analyzer (model E700; Eastman Kodak Company, Rochester, NY, USA). Total cholesterol and triglycerides were analyzed by enzymatic methods and HDL-c was isolated using heparin-2M manganese chloride [40]. LDL-c was calculated using the Friedewald equation [41].

Specimens were assayed for glucose and insulin beginning in 1993. Glucose levels were determined using a hexokinase-coupled reaction on a Hitachi 747-200 (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA) and insulin levels were assayed with an RIA (DPC Coat-a-count, Los Angeles, CA, USA). The homeostatic model-assessment insulin resistance (HOMA-IR) index was calculated as fasting insulin (μ U/ml) multiplied by fasting glucose (mmol/L) divided by 22.5 [42].

Calibrated stadiometers and balance-beam scales were used to measure height and weight, respectively. Weight, in kilograms, divided by the square of the height, in meters, provided the body mass index (BMI) measure.

Women were characterized as having diabetes based on a self-reported physician diagnosis or use of anti-diabetic medications at the time of the assessment. Using a published definition of cardiometabolic clustering [43], women were classified as having metabolic clustering if they had at least two of the following six conditions: 1) a blood pressure measure greater than 135/85 mm Hg or use of anti-hypertensive medication; 2) a triglyceride level greater than or equal to 150 mg/dL; 3) a HDL-c level less than 50 mg/dL or use of statins; 4) a glucose level greater than or equal to 100 mg/dL or use of anti-diabetic medications; 5) a HOMA-IR value greater than 5.2, the sample's cut-off value for the 90th percentile; and 6) a C-reactive protein level greater than 0.74 mg/dL, the sample's 90th percentile cut-off value.

Statistical Analysis. Histograms for each outcome at every study visit were examined to ensure that the distributions were similar over the 15-year time period. Outcomes that were not normally distributed were log-transformed for analyses, but were back-transformed to their original scale for ease of interpretation. Unadjusted mean and standard deviations of the carbohydrate metabolism and lipid measures by birth weight categories were estimated and tested for statistical significance using analysis of variance and least squared means.

Since the study participants included sisters from the same nuclear family and data were longitudinal, linear mixed models were used to examine the effect of birth weight on the change in carbohydrate metabolism and lipids over time, accounting for within- and between-family variance and within-subject correlation. Birth weight was a categorical

variable and statistical models included dummy variables for low and high birth weight, with normal birth weight as the referent group. All models included family-level random intercepts and subject-level random intercepts and slopes. The Akaike's information criterion identified the best fitting covariance structure for the random effects and the residuals.

Statistical models also included birth weight by time interactions to determine whether the fitted slopes of the metabolic measures varied over time by birth weight category. Models were adjusted for participant's baseline age and current BMI at time of annual assessment.

Generalized estimating equations (GEE) were used to estimate the baseline and annual risk of developing type-2 diabetes and metabolic clustering across the birth weight categories, accounting for the within- and between-family variance and the within-subject correlation. The annual risk was estimated by including birth weight by time interaction terms in the models. GEE models were adjusted for participant's age at baseline and adult BMI. Statistical significance was defined at $\alpha=0.05$ and analyses were completed using SAS v9.2.

RESULTS

Self-reported birth weight was normally distributed with a mean of 3289 ± 580 g and range of 1531 to 5897 g. Birth weights were classified as normal (mean=3291 g) in

81.9% of participants, low (mean=2208 g) in 9.2% of women and high (mean=4399 g) in 8.9% of women.

Cross-Sectional Analysis of Metabolic Measures. Glucose levels at the study baseline did not differ among low and high birth weight groups compared to the normal birth weight group. In contrast, the baseline mean insulin and HOMA-IR levels in the high birth weight group were significantly higher compared the normal birth weight group (Table 3.1). Mean baseline insulin level in the low birth weight group was 14.0 ± 6.8 mIU/L and 14.3 ± 10.1 mIU/L in normal birth weight group (p-diff=0.98); as compared with 18.4 ± 19.0 mIU/L in high birth weight group - a value 28.7% higher than the normal birth weight group (p-diff=0.05).

While there were no differences in mean baseline triglyceride and HDL-c levels across birth weight categories, women in the low birth weight group had higher baseline mean total cholesterol and LDL-c levels compared to the normal birth weight group (Table 3.1). At baseline, the mean total cholesterol for the low birth weight group was 224.0 ± 48.7 mg/dL compared to a mean of 204.2 ± 44.3 mg/dL for the normal birth weight group (p-diff=0.01). Mean baseline total cholesterol in the normal birth weight women was comparable to the values observed in the high birth weight group [195.5 ± 36.5 mg/dL (p-diff=0.40)]. The baseline mean LDL-c level was 13% higher in the low birth weight group compared to the normal birth weight group (147.0 mg/dL vs. 130.6 mg/dL, p-diff=0.03), but was 4% lower in the high birth weight group compared to the normal birth weight group (125.3 mg/dL vs. 130.6 mg/dL, p-diff=0.66).

Longitudinal Analysis of Metabolic Measures. Fitted slopes from the linear mixed models of the glucose trajectory was steeper for the high birth weight group compared to the normal birth weight group ($p < 0.01$) (Figure 3.1A). In the model that only included participant's baseline age, glucose was an average of 2.02 mg/dL higher at baseline and increased at a rate of 0.63 mg/dL per year in the high birth weight group relative to the normal birth weight group. While the inclusion of adult BMI attenuated the differences in the slopes of the glucose trajectories between high and normal birth weight women, they remained statistically significant ($p < 0.01$) (Figure 3.1B). No statistically significant differences in the glucose trajectories were observed between the low and normal birth weight groups.

While there were differences in glucose levels and trajectories according to birth weight classification, we observed no differences in the insulin or HOMA-IR trajectories over time across the birth weight groups before or after adjustment for baseline age or adult BMI (Table 3.2).

The low birth weight group had, on average, higher total, LDL-c, and HDL-c cholesterol measures at baseline, which declined over time (Table 3.2). In comparison, the high birth weight group of women had, on average, lower total, LDL-c, and HDL-c cholesterol measures at baseline that increased over time (Table 3.2). However, these patterns were not statistically significant in the models that adjusted for baseline age. In the models that adjusted for adult BMI, the increases observed in total and LDL-c cholesterol levels

among the low compared to normal birth weight group and the decreases seen in total and LDL-c cholesterol levels among the high compared to normal birth weight group were strengthened (Table 3.2).

Risk of Developing Diabetes and Metabolic Disease. When we estimated the baseline disease risk and the subsequent risk of developing type-2 diabetes and metabolic clustering, we found that low birth weight group had 0.36 (CI: 0.05-2.81) the odds of having diabetes at baseline compared to normal birth weight group and which increased by 7% (CI: -4%-20%) annually. In contrast, the high birth weight group had 1.54 (CI: 0.35-6.83) the odds of having diabetes at baseline relative to normal birth weight group and these odds decreased by 1% (CI: -10%-9%) annually. These patterns remained after adjustment for baseline age and adult BMI (Table 3.3). Low and high birth weight groups had a 1.31 (CI: 0.41-4.21) and 1.60 (CI: 0.24-10.46) baseline odds, respectively, of having metabolic clustering compared to normal birth weight women, but these estimates were also not statistically significant (Table 3.3). These patterns remained after adjusting for baseline age, but inclusion of adult BMI in the models resulted in an increased risk of metabolic clustering to 1.61 (CI: 0.40-6.53) among women in the low birth weight group and decreased the risk of metabolic clustering to 0.66 (CI: 0.19-2.31) among women in the high birth weight group.

DISCUSSION

This study examined the relationship between birth weight and longitudinal measures of carbohydrate metabolism, lipids and the risk of developing type-2 diabetes or metabolic

clustering in a population-based sample of middle-class Caucasian women born between 1947 and 1967. Over the 15-year study period, high birth weight women experienced a steeper rate of change in their glucose levels compared to the rate of change among normal birth weight women. Glucose trajectories were not different between low and normal birth weight women and insulin and insulin resistance trajectories were similar across the birth weight groups. Although mean baseline total cholesterol and LDL-c was higher in the low relative to normal birth weight group, these differences were weaker in the longitudinal analysis. Further, the longitudinal analysis showed that lipid trajectories over time as well as the baseline and annual risk of developing type-2 diabetes or metabolic clustering did not vary across the birth weight groups.

This is one of the first studies to evaluate the relationship between birth weight and longitudinal changes in carbohydrate metabolism, lipids, and the risk of type-2 diabetes or metabolic clustering in U.S. adult women born in the post-war baby boom era. Although we observed no association between birth weight classification and insulin, insulin resistance, lipids, and risk of diabetes or metabolic clustering over time, our finding that high birth weight women had steeper increases in their glucose measures over time compared to normal birth weight women represents new information not previously described in the existing literature.

In a review of 48 published reports that examined the relationship of birth weight to adult glucose measures, most studies reported that lower weight at birth was associated with higher levels of adult glucose [30]. However, these investigations did not examine the

glucose trajectories. Our observation that women with higher weight at birth experienced a steeper rise in adult glucose measures that may indicate that high birth weight is a risk factor for the increasing prevalence of diabetes or the earlier presentation of diabetes.

A number of factors may explain why different fitted slopes for glucose measures were seen among the high birth weight women in our study. Compared to women in the low and normal birth weight groups, a larger proportion of the high birth weight women were born to older (≥ 30 years old) mothers (data not shown), and this may reflect a distinct, and possibly adverse, fetal experience and/or a shared genetic environment. Older maternal age is a risk factor for gestational diabetes [44, 45], and gestational diabetes is associated with larger babies at birth and higher levels of glucose and increased risk of type-2 diabetes later in life in both the mother and the offspring [29]. Barker has also proposed that high birth weight due to gestational diabetes may be one explanation for the association of fetal growth with increased risk for diabetes later in life [46].

Although steeper increases in glucose measures were observed in high birth weight women, the fitted slopes for insulin and insulin resistance did not differ by birth weight groups. This finding has several interpretations. First, while high birth weight women had increasing rates of glucose, this did not necessarily translate to adverse adult health. A critical period for muscle growth and liver development occurs in utero, and this muscle and liver development is the purported mechanism for the unfavorable adult health outcomes seen in low birth weight persons whereby slow fetal growth is associated with a disproportionate fat to muscle mass ratio and inefficient liver metabolism post

birth [7, 46-48]. By extension, the fetal growth in high birth weight individuals may be associated with a more favorable fat to muscle ratio and liver development after birth.

A number of studies have reported that high birth weight was associated with higher levels of lean mass later in life [21, 22]. Indeed, in Chapter 2, we reported that high birth weight MBHMS women had higher adult body composition measures compared to normal birth weight MBHMS women, especially of lean and skeletal muscle mass.

Muscle is important for glucose uptake and the liver is a site for glucose metabolism and enzymatic regulation of lipids and growth hormone. Potentially, the profile of increases in glucose in high birth weight women in the presence of similar insulin and HOMA-IR may be an indication of increasing dissonance in liver metabolism relative to muscle metabolism. The molecular mechanisms of insulin resistance are consistent with post-binding defects in insulin receptor-mediated signal transduction in adipocytes and skeletal muscle. It has been postulated that this signaling defect produces selective insulin resistance. Defects in glucose-stimulated insulin release may also be present. It is uncertain whether having greater muscle mass among those with a higher birth weight is an adequate explanation or whether the events leading to higher birth weight alters the timing of glucose-stimulated insulin release.

Evidence regarding associations between birth weight categories and cross-sectional measures of fasting glucose, insulin, and insulin resistance is inconsistent in the literature [30], although most studies suggest that lower weight at birth is correlated with higher levels of these measures. Indeed, in our cross-sectional analysis, we observed higher

glucose levels among the low and high birth weight group compared to the normal birth weight group. In a review of 25 studies that examined the relationship of birth weight to fasting glucose levels, 15 reported a negative association, while four reported no association and six reported a positive association [30]. When the authors reviewed studies of birth weight to levels of fasting insulin and insulin resistance, similar proportions were reported [30]. However, many of the reviewed studies reporting a negative association were based on data from older European populations and combined men and women [30]. Furthermore, different statistical methods were used across the studies and the review utilized only the direction of the association and not the magnitude of the statistical significance of the associations [30].

Few studies have described the relationship of birth weight to carbohydrate metabolism measures in U.S. female baby boomers [37, 38]. In a study of 228 Mexican American and 62 Non-Hispanic white women with a mean age of 32 years from the San Antonio Heart Study, significant mean differences in fasting glucose and insulin were seen only in the Mexican American women [37]. Although mean differences in fasting glucose and insulin were not seen among the Non-Hispanic white women, the highest mean glucose levels were observed among those in the highest birth weight tertile [37], which was consistent with our findings. In a report of 67 African American women with a mean age of 28 years, no association between birth weight and levels of fasting insulin were seen [38].

We identified a weak relationship between low birth weight and higher lipid levels. This is consistent with the existing literature which has described a weak inverse association between birth weight and lipids [31-33, 49]. In three reviews that encompassed more than 100 reports, the authors concluded that the lower levels of total cholesterol and LDL-c associated with higher birth weights was too weak to have any clinical or public health impact on adult chronic disease risk [31, 32, 49]. Additionally, we also showed that slopes fitted to the lipid measures did not differ across the birth weight categories.

We examined birth weight categories as risk factors for incidence and prevalence of diabetes and metabolic clustering. There were intriguing findings although the failure to achieve statistical significance probably reflects inadequate power in a relatively younger population. Although not significant, low birth weight women had a lower baseline risk of diabetes and high birth weight women had a higher baseline diabetes risk compared to normal birth weight women. Most prior literature has reported that low weight at birth was associated with an increased risk for diabetes, as described in a meta-analysis of 31 previously published studies [18]. However, the magnitude and direction of diabetes risk among high birth weight persons have been inconsistent, with reports of decreased risk in large population-based studies [25-27] and increased risk among the Native American population where gestational diabetes is prevalent [28, 29].

Several mechanisms have been proposed to explain the increased risk for diabetes among those with low birth weight, including maternal under-nutrition during pregnancy, which is speculated to cause metabolic and endocrine changes in utero resulting in slower fetal

growth [3, 46]. Although we could examine the actual occurrence of maternal under-nutrition in our population, these women, who were born in the post-WWII U.S., were much less likely to experience in utero maternal nutritional deprivation than women born during the worldwide economic depression of the 1930 and the ensuing world war where nutritional deprivation occurred in Europe, the Soviet Union, and parts of Asia.

We also described a non-significant increased risk for developing metabolic clustering, which represented a more sensitive measure of metabolic syndrome, in both low and high birth weight women compared to normal birth weight women. However, after adjustment for adult BMI, the risk was strengthened among the low birth weight, but became protective among the high birth weight, suggesting the risk for metabolic clustering is driven largely by adult BMI and less by birth weight.

A strength of this study was the capacity to evaluate the effect of birth weight on repeated measures of carbohydrate metabolism, lipids, and disease risk in the same women over a 15-year study period. To our knowledge, this is the first examination of birth weight in relation to longitudinal changes in glucose, insulin, and cholesterol measures and to the risk of type-2 diabetes. The ability to analyze data longitudinally provided new information about risk trajectories as women aged. An often cited limitation in studies that explore the relationship between birth weight and chronic disease risk is the inability to control for confounding variables, such as sex, age, race, and socioeconomic status; however, the MBHMS population is a relatively homogeneous cohort of Caucasian women with similar socioeconomic status.

The study has limitations. Though birth weight was self-reported, several investigations have identified the validity of self-reported birth weight data [50-52]. While 15 years of follow-up data were available, these were secured in adulthood and not during infancy or early childhood, the time period of rapid catch up growth, a characteristic that appears to exacerbate the association between low birth weight and disease risk [5, 7, 8, 13-15, 17]. The age and sample size of the population contributed minimal power to detect risk differences between birth weight groups with respect to disease outcomes such as type-2 diabetes.

In summary, this examination of birth weight in relation to longitudinal measures of carbohydrate metabolism and lipids provided new information about the contribution of birth weight to glucose trajectories. We observed steeper rates of change in glucose measures in the high birth weight group over 15 years, although we found no differences in the patterns of insulin, insulin resistance, and lipid measures over time as well as no differences on the risk for developing adult type-2 diabetes according to birth weight groups. These findings provide additional insight about the possible etiology and role of fetal growth and development of glucose metabolism and regulation in women. Additional studies with longitudinal data are needed in order to determine whether these findings continue to be seen in other populations.

Table 3.1. Baseline Mean Carbohydrate Metabolism and Lipid Measures by Birth Weight Category in Women from the Michigan Bone Health and Metabolism Study, n=587

	BIRTH WEIGHT CATEGORY		
	Low (<2500 g)	Normal (2500 - 4000 g)	High (>4000 g)
N (%)	54 (9.2%)	481 (81.9%)	52 (8.9%)
Birth weight (g)	2208.1 ± 259.2	3290.6 ± 352.1	4398.5 ± 363.5
Age (years)	37.7 ± 4.5	36.8 ± 4.9	36.0 ± 6.0
CARBOHYDRATE METABOLISM			
Glucose (mg/dL)	87.2 ± 8.6	85.0 ± 14.1	88.1 ± 17.7
Insulin (mIU/L)	14.0 ± 6.8	14.3 ± 10.1	18.4 ± 19.0 ^a
HOMA-IR	3.1 ± 1.8	3.1 ± 2.9	4.7 ± 8.6 ^a
BMI (kg/m ²)	26.1 ± 6.6	26.3 ± 5.6	30.0 ± 6.7
LIPIDS			
Total cholesterol (mg/dL)	224.0 ± 48.7 ^b	204.2 ± 44.3	195.5 ± 36.5
Triglycerides (mg/dL)	119.7 ± 85.6	114.3 ± 95.9	111.6 ± 52.7
LDL-c (mg/dL)	147.0 ± 43.2 ^a	130.6 ± 40.6	125.3 ± 32.7
HDL-c (mg/dL)	53.8 ± 15.1	50.6 ± 12.8	47.9 ± 12.3
^a p≤0.05 compared to Normal			
^b p≤0.01 compared to Normal			

Table 3.2. The Relationship of Low and High Compared to Normal Birth Weight on the Fifteen-Year Changes in Carbohydrate Metabolism and Lipids in 587 Adult Women from the Michigan Bone Health and Metabolism Study

	Overall Mean Difference						Interaction with Time					
	Low Birth Weight			High Birth Weight			Low Birth Weight			High Birth Weight		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Carbohydrate Metabolism												
Glucose (mg/dL)												
Model A ¹	1.42	1.88	0.45	2.02	1.83	0.27	-0.002	0.21	0.99	0.63	0.20	<0.01
Model B ²	1.56	1.82	0.39	0.28	1.80	0.88	-0.017	0.21	0.93	0.57	0.20	<0.01
log Insulin (mIU/L)												
Model A ¹	0.01	0.09	0.88	0.15	0.09	0.08	0.005	0.007	0.49	-0.002	0.006	0.77
Model B ²	0.03	0.07	0.70	-0.02	0.07	0.75	0.003	0.006	0.55	-0.010	0.005	0.06
log HOMA-IR												
Model A ¹	0.03	0.10	0.74	0.17	0.09	0.06	0.005	0.007	0.53	0.002	0.007	0.75
Model B ²	0.05	0.08	0.53	-0.02	0.08	0.83	0.003	0.006	0.59	-0.007	0.006	0.22
Lipids												
Cholesterol (mg/dL)												
Model A ¹	12.36	6.45	0.06	-10.40	6.39	0.10	-0.56	0.57	0.32	0.71	0.55	0.20
Model B ²	13.24	6.41	0.04	-18.87	6.42	<0.01	-0.60	0.55	0.27	1.21	0.54	0.02
log Triglycerides (mg/dL)												
Model A ¹	0.08	0.07	0.30	0.02	0.07	0.77	-0.005	0.005	0.30	-0.007	0.005	0.19
Model B ²	0.09	0.07	0.18	-0.14	0.07	0.04	-0.007	0.005	0.15	-0.004	0.005	0.38
LDL-c (mg/dL)												
Model A ¹	8.45	5.63	0.13	-7.81	5.56	0.16	-0.31	0.52	0.55	0.87	0.50	0.08
Model B ²	9.12	5.56	0.10	-13.17	5.54	0.02	-0.35	0.51	0.49	1.17	0.50	0.02
HDL-c (mg/dL)												
Model A ¹	2.12	1.89	0.26	-2.68	1.86	0.15	0.03	0.14	0.82	0.17	0.14	0.22
Model B ²	1.82	1.76	0.30	-0.67	1.74	0.70	0.06	0.14	0.68	0.25	0.13	0.06

¹Adjusted for Participant's Age at Baseline.

²Adjusted for Participant's Age at Baseline and Current Adult BMI at Time of Assessment.

Figure 3.1. Predicted Fasting Glucose (mg/dL) Trajectories for 54 Low Birth Weight Women (red dashed), 481 Normal Birth Weight Women (green solid), and 52 High Birth Weight Women (blue dotted) from the Michigan Bone Health and Metabolism Study, adjusted for Baseline Age (A) or Baseline Age and Adult Body Mass Index (B)

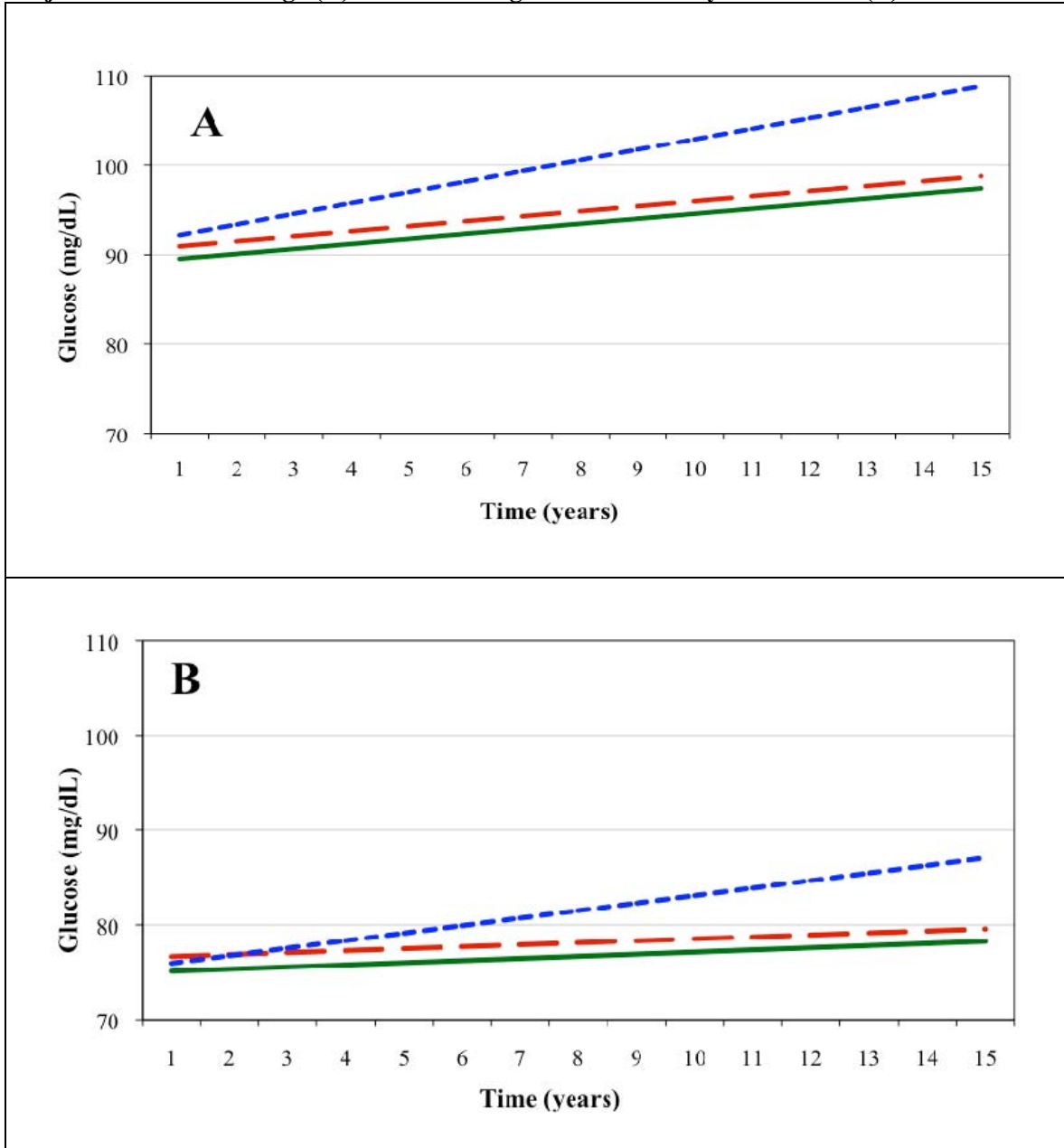


Table 3.3. Fifteen-Year Baseline and Annual Risk of Diabetes or Metabolic Clustering in 587 Women from the Michigan Bone Health and Metabolism Study, with a mean age of 37 years at 1992 Baseline

	<u>Unadjusted</u>		<u>Adjusted for Baseline Age Only</u>		<u>Adjusted for Baseline Age and Adult BMI</u>	
	Baseline Risk (95% CI)	Annual Risk (95% CI)	Baseline Risk (95% CI)	Annual Risk (95% CI)	Baseline Risk (95% CI)	Annual Risk (95% CI)
Type-2 Diabetes						
Low Birth Weight	0.36 (0.05-2.81)	1.07 (0.96-1.20)	0.34 (0.04-3.02)	1.07 (0.95-1.21)	0.33 (0.03-4.36)	1.08 (0.93-1.25)
Normal Birth Weight	Ref		Ref		Ref	
High Birth Weight	1.54 (0.35-6.83)	0.99 (0.90-1.09)	1.65 (0.38-7.11)	0.99 (0.90-1.08)	1.45 (0.35-5.98)	0.97 (0.88-1.07)
Metabolic Clustering						
Low Birth Weight	1.31 (0.41-4.21)	1.06 (0.96-1.16)	1.29 (0.40-4.18)	1.06 (0.96-1.16)	1.61 (0.40-6.53)	1.03 (0.92-1.15)
Normal Birth Weight	Ref		Ref		Ref	
High Birth Weight	1.60 (0.24-10.46)	1.02 (0.95-1.10)	1.59 (0.24-10.49)	1.02 (0.94-1.11)	0.66 (0.19-2.31)	1.00 (0.93-1.08)

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CHAPTER 4

Influence of Mother's Intrauterine Experience on Offspring Birth Weight

ABSTRACT

Much work has been done to understand the determinants of birth weight, with a primary focus on maternal factors, such as behavior during pregnancy and socioeconomic characteristics. However, little is known about intergenerational determinants on birth weight and the impact of the mother's own fetal environment on offspring birth weight. This study examined the association of a maternal grandmother's pregnancy characteristics on her grandchildren's birth weight.

Women of the Michigan Bone Health and Metabolism Study (MBHMS) provided information about their own birth history and the birth histories of their offspring. Participant's birth history included in utero smoking exposure, mother's age at their birth, birth weight, and birth order. Their offspring's birth history included birth weight, sex, birth order, and birth date. We evaluated the association of participant and offspring's birth history with offspring birth weight using generalized linear mixed models, adjusting for family clustering.

Women exposed to cigarette smoke in utero had offspring who were an average of 136 grams heavier than offspring whose mothers were not exposed to cigarette smoke in utero ($p=0.02$). The offspring of women whose mothers were between 25-29 years old at their birth were an average of 157 grams heavier than the offspring of women born to mothers who were between 20-24 years old at their birth ($p<0.01$). No association was seen between offspring birth weight and their mother's first born status or by whether their mother was from a singleton or multiple birth.

These findings suggest an intergenerational effect on birth weight along the maternal line. These results emphasize the importance of a healthful pregnancy, which may not only affect the long-term health of the immediate offspring, but may influence birth outcomes of future generations.

INTRODUCTION

The impact of maternal factors, including behavior during pregnancy, social factors, and physical characteristics, on offspring birth weight has been well examined [1-8]. Several studies have also examined intergenerational effects in order to understand how parental birth characteristics, such as birth order, gestational age, and birth weight, may influence their offspring's birth outcomes [9-17]. However, few studies have had the capacity to investigate grandparental pregnancy characteristics and a parent's fetal experience on birth weights in later generations.

A multigenerational cohort study of men and women born in 1958 in the United Kingdom found a positive association between grandchildren's birth weight and grandmother height [18] and grandmother smoking behavior during pregnancy [19]. A similar association between higher grandchild birth weights among grandmothers who smoked during pregnancy was also reported in a more recent study completed among women in the United States [20]. In a Danish study of women born between 1959 and 1961, the risk of women who were small for gestational age having children who are also small for gestational age was strongest among grandmothers with the shortest stature [13]. In addition, this same study showed that women with in utero smoking exposure were more likely to be born small-for-gestational-age, but were not at increased risk of delivering a child who was small for gestational age [13].

It has been proposed that the correlations in birth weight seen across generations, especially along the maternal line, may be due to an intrauterine programming effect

[21]. As oocytogenesis occurs during a female's fetal development, it is feasible that information from a grandmother's pregnancy can be transmitted to her grandchildren. Determining the extent to which pregnancy characteristics of earlier generations affect birth outcomes in subsequent generations may provide evidence of these potential programming effects. Furthermore, understanding intergenerational effects on birth outcomes would provide valuable information to women as they plan their future pregnancies, emphasizing the importance of achieving and maintaining a healthy pregnancy.

The purpose of this study was to further investigate the association of a mother's own fetal experience with the birth weight of her offspring. We hypothesized that grandmaternal behaviors and characteristics during pregnancy would be associated with grandchildren's birth weight, independent of pregnancy characteristics in the mother.

METHODS

Study Population. The source population were mothers from the Michigan Bone Health and Metabolism Study (MBHMS), a women's health study which has been previously described [22]. Briefly, the MBHMS is a prospective cohort study that investigates changes in women's health through the reproductive years to the menopause transition. Enrollment began in 1988 and included 543 women, who were aged 20-40 years and daughters of study participants in the Tecumseh Community Health Study (TCHS). In 1992, recruitment was expanded in order to include age-eligible women whose families were not in the TCHS, resulting in the enrollment of an additional 121 women.

Therefore, in 1992, a total of 664 women, aged 24-50 years, were participants in the MBHMS.

In 2008, 561 (84.5%) of the MBHMS participants who were still active were invited to participate in a supplemental telephone-based interview to more fully characterize their personal birth history and the birth histories of their children. Among these women, 82% (n=460) completed the supplemental interview, 4% (n=22) refused or could not be located and 14% (n=79) could not be reached. The collection of these data was approved by the University of Michigan Institutional Review Board.

This analysis included birth history data from 935 children of 397 MBHMS participants who experienced at least one live birth and who had at least one singleton offspring for whom birth weight information was available. The data from 22 MBHMS children were excluded from analyses because they were from a multiple birth (n=20) or had missing birth weights (n=2). Data also included pregnancy characteristics on 320 mothers of the MBHMS participants (grandmothers), which described the birth history of the MBHMS participant.

To allow for differentiation, the mothers of the MBHMS participants were labeled as “mother of index”, MBHMS participants were labeled “index respondent”, and children of MBHMS participants were characterized as “offspring”.

Birth Characteristic Measures. At the 1988 examination, 530 of the 543 enrolled women self-reported their weight at birth. During the 2008 supplemental interview, index respondents self-reported additional characteristics about their own birth and provided characteristics about their children's birth. For their own birth histories, index respondents self-reported their birth weight (in pounds and ounces), whether they were from a singleton or multiple birth, their birth order, their date of birth, their mother's date of birth, and if their mother's smoked during pregnancy. For their offspring's birth history, index respondents reported birth weights (in pounds and ounces), birthdates, sex, and the amount of weight gained (in pounds) during the pregnancy.

Index Respondent Birth Characteristics. To estimate the mother of index's age at time of birth, the index respondent's birth date was subtracted from mother of index's date of birth. This variable was grouped into five age categories: 19 years or less, 20-24 years, 25-29 years, 30-34 years, and 35 years or more. Four categories were used to describe the in utero smoking exposure: mother smoked before but not during pregnancy, mother smoked before and during pregnancy, mother did not smoke, and does not know. Since index respondent birth weights were collected in 1988 and there was little variation between the information gathered in 1988 compared to 2008, the 2008 index respondent birth weight data were used only if the birth weight data from 1988 were missing (n=78). Birth weight in grams (g) was categorized into three levels based on clinical cut-points: low, defined as less than 2500 g; normal, defined as 2500 to 4000 g; and high, defined as greater than 4000 g. Singleton birth was determined using birth date information and was a dichotomized variable.

Offspring Birth Characteristics. The outcome of this study was the birth weight in grams (g) of the offspring. Index respondent's age at each offspring's birth was calculated by subtracting the offspring's date of birth from the index respondent's birth date and was categorized into five age groups: 19 years or less, 20-24 years, 25-29 years, 30-34 years, and 35 years or greater. Amount of weight gained during each pregnancy was classified into three categories: 15 pounds or less, 15-45 pounds, and over 45 pounds. Smoking status at time of offspring's birth was constructed from the MBHMS annual interview data and categorized into four groups: ex-smoker and quit before pregnancy, smoker during pregnancy, never smoker, and undetermined. Offspring dates of birth determined first born and singleton birth status, which were also dichotomized variables.

A summary of the index respondent and offspring birth characteristics is provided in Table 4.1.

Smoking History Across Two Generations. The smoking history of the mother of index respondent and the index respondent was combined to create a variable that would capture different smoking exposures over two generations of pregnancies. Four categories were developed: mother of index respondent smoked during pregnancy and index respondent did not, mother of index respondent did not smoke during pregnancy and index respondent did, both smoked during pregnancy, and neither smoked during pregnancy.

Statistical Analysis. Offspring birth weight was examined for normality and contingency tables were used to evaluate frequency distributions on the index respondent and offspring birth characteristics. Least square means and trend tests evaluated statistically significant mean differences in offspring birth weight by the index respondent and offspring birth characteristics.

Since there were 935 offspring from 397 index respondents (mothers), who were daughters from 320 mothers of index (grandmothers), linear mixed models were used to estimate the change in offspring birth weight associated with index respondent and offspring birth characteristics, while accounting for correlated variances within both family and maternal clusters. Mother of index's age at time of index respondent's birth, index respondent's birth weight, index respondent's age at offspring's birth, and amount of index respondent's weight gain during pregnancy were also examined as continuous variables to investigate linear and quadratic relationships to offspring birth weight. Statistical significance was defined at $\alpha=0.05$ and analyses were completed using SAS v9.2.

RESULTS

Index Respondent Birth Characteristics in Relation to Offspring Birth Weight. Most offspring (37.6%) were born to index respondents whose mothers were 20-24 years old at the time of their birth, while 10.6% and 9.5% of offspring were born to index respondents whose mothers were teenagers or 35 years and older, respectively, at the time of their birth (Table 4.2A). Index respondents born to mothers aged 20-24 years gave birth to

offspring who weighed less than offspring born to index respondents whose mothers were aged 25-29 years (3410 ± 552 g vs. 3573 ± 509 g; $p < 0.01$) (Table 4.2A).

The majority of offspring (66.4%) were born to index respondents who self-reported that their mothers did not smoke while pregnant; however, 20.3% of offspring were born to index respondents who reported that mothers did smoke during their pregnancy. Index respondents who self-reported being exposed to smoking in utero gave birth to children who were an average of 90 g heavier compared to index respondents who self-reported no intrauterine smoking exposure, although these mean differences were not statistically significant.

Birth weights of index respondents tracked with those of their offspring - low birth weight index respondents had children with the lowest weights at birth, while high birth weight index respondents had children with the highest weights at birth ($p\text{-trend} < 0.01$).

Offspring Birth Characteristics in Relation to Offspring Birth Weight. The mean birth weight of male and female offspring, born between the years 1964 to 2006, was 3483 ± 559 g, with a range of 1332 to 5245 g. As age of the index respondent at delivery increased, the average offspring birth weight also increased ($p < 0.01$) (Table 4.2B).

Weight gain during pregnancy tracked with offspring birth weight, such that index respondents who gained the least weight had offspring with the lowest average birth weights and index respondents who gained the most weight during the pregnancy had, on average, the heavier offspring ($p\text{-trend} < 0.01$). Index respondents who were smokers at

the time of offspring birth had offspring who were, on average, lighter (3411 ± 572 g) than index respondents who never smoked (3519 ± 548 g), but these mean differences were not statistically significant ($p=0.07$) (Table 4.2B). Over 55% of the offspring were male and were an average of 151 g heavier at birth than their female counterparts ($p<0.01$).

Offspring Birth Weight in Relation to Smoking History Across Two Generations. A total of 791 offspring had information on smoking exposure over two generations of pregnancies (Table 4.3). For most offspring (57.5%), neither the mother of index respondent (grandmother) nor the index respondent (mother) smoked during pregnancy; however, in 20.2% of offspring, the mother of index respondent was not a smoker during pregnancy but the index respondent was, while in 16.4% of offspring, mother of index respondent smoked during pregnancy but index respondent did not. Mean offspring birth weight was highest among those whose mother of index respondent (grandmother) smoked while pregnant, regardless of the smoking status of the index respondent (mother) (Table 4.3); however, only those with discordant smoking histories were found to have statistically significant mean differences. Mean offspring birth weight was 3556 ± 608 g in those whose mother of index respondent (grandmother) smoked during pregnancy but index respondent (mother) who did not compared to a mean offspring birth weight of 3377 ± 567 g in those whose mother of index respondent (grandmother) did not smoke during pregnancy but index respondent (mother) did ($p=0.03$).

Adjusted Analysis. After accounting for the family and maternal clustering in offspring birth weights, the findings were consistent with those reported in the descriptive analyses (Table 4.4A and Table 4.4B). Index respondents born to mothers aged 25-29 years had offspring who were an average of 157 g heavier compared to index respondents born to mothers aged 20-24 years ($p<0.01$), and this association remained after adjustment for all other index respondent and offspring birth characteristics (Table 4.4A). As a continuous variable, offspring birth weight increased an average of 7 g for every 1-year increase in mother of index respondent's age ($p=0.10$), but this association attenuated to 5 g after adjustment for all other index respondent and offspring birth characteristics (data not shown). Index respondents who self-reported in utero smoking exposure gave birth to offspring who were an average of 136 g heavier relative to index respondents who self-reported being born to a mother who never smoked ($p=0.02$), and this association was strengthened after adjustment (Table 4.4A). Offspring birth weight increased by 21 g, on average, for every 1-kg increase in index respondent's birth weight ($p<0.01$) and these associations remained after adjustment for all other birth characteristics.

Index respondent's age at offspring birth showed a curvilinear relationship to offspring birth weight (Figure 4.1A). Offspring birth weight increased an average of 113 g for every 1-year increase in index respondent's age until approximately age 31 years, at which time mean offspring birth weight began to decrease ($p<0.01$). However, this association weakened to a 48 g average increase in offspring birth weight after adjustment for all other index respondent and offspring birth characteristics. Index respondents who gained less than 15 pounds during pregnancy had offspring who were

an average of 347 g lighter ($p < 0.01$), while index respondents who gained over 45 pounds during pregnancy had offspring who were, on average, 199 g heavier ($p < 0.01$) than index respondents who gained between 15-45 pounds during pregnancy (Table 4.4B). As a continuous variable, offspring birth weight increased by 253 g for every 10-lb. increase in index respondent weight gain until approximately 70 pounds when offspring birth weight began to decrease ($p < 0.01$). This association remained statistically significant even after adjustment (Figure 4.1B). Index respondents who were smokers at the time of offspring birth had offspring who were, on average, 114 g lighter than index respondent who were never smokers ($p = 0.04$), but this association was attenuated after adjustment for all other birth characteristics. First born offspring weighed an average of 186 g less than non-first born offspring ($p < 0.01$) and male offspring weighed an average of 158 g more than female offspring ($p < 0.01$) and adjustment did not affect these associations.

DISCUSSION

In this examination of middle-class, Caucasian women from the midwestern United States, a woman's own fetal experience was associated with the birth weight of her offspring. Women who had self-reported in utero smoking exposure or who were born to older mothers had heavier offspring than women who did not self-report exposure to cigarette smoke in utero or who were born to younger mothers. These findings suggest an intergenerational relationship along the maternal line, specifically that the characteristics and behaviors during the grandmother's pregnancy were associated with her grandchildren's birth weight.

Since women have a finite number of oocytes at birth, it has been proposed that the intrauterine growth of females may be implicated in generational associations along the maternal line [18, 21]. It is also speculated that generational effects are associated with shared genetic and environmental factors [23]. Studies have reported that parental [4, 6, 7, 24] as well as grandparental stature [7, 18], representing a shared genetic and social environment, is positively associated with birth weight in subsequent generations.

Emanuel showed that grandmaternal height and grandpaternal social class was positively associated with the birth weights in the offspring of their daughters [18], suggesting that the health and socioeconomic conditions of grandparents influenced the birth outcomes of the grandchildren. Although we could not directly test this hypothesis, we speculate that investigations in the MBHMS would yield similar findings because the families from the MBHMS were from and continue to live in a similar geographic environment (Tecumseh, Michigan) and there is little variation in social position.

Our finding that women with fetal exposure to tobacco tended to have heavier offspring was consistent with the few published studies that have evaluated pregnancy and smoking behavior across multiple generations [13, 19, 20]. Misra et al reported that offspring of non-smoking women who had in utero smoking exposure were an average of 244 grams heavier than offspring of non-smoking women who did not have in utero tobacco exposure [20]. Similarly, women from a 1958 birth cohort study in the United Kingdom described a positive relationship between grandmaternal smoking during pregnancy and grandchildren birth weight [19]. Klebanoff et al report that grandmaternal smoking does not increase risk for small-for-gestational age grandchildren [13]. Misra et al suggested

that the increased birth weights seen in grandchildren among grandmothers who smoked during pregnancy may be due to unmeasured confounding in which smoking behavior may reflect a higher socio-economic status [20]. However, this hypothesis is unlikely to fully explain our study's findings because our sample population is so homogenous with respect to social position. Rather, the higher birth weight seen in offspring of mothers with fetal smoking exposure may represent a protective adaptive response consistent with an intergenerational programming effect on female germ cells. Further, our finding that mean offspring birth weight from grandmothers who smoked during pregnancy but mothers who did not was significantly higher than mean offspring birth weight from grandmothers who did not smoke during pregnancy but mothers who did was consistent with Misra et al who described an interaction between mother's smoking and mother's in utero smoking exposure on offspring birth weight [20].

Women born to mothers who were in their late twenties at their birth tended to have offspring with higher birth weights, particularly compared to women born to mothers who were in their early twenties - a relationship not described in the existing literature. Since most MBHMS participants were born in the late 1940s to 1950's, this may reflect a baby boomer cohort effect, when women were marrying and starting families at a relatively early age [25].

A few studies have described an inverse relationship between maternal birth order and offspring birth weight [16, 26]. These studies suggested that the association of higher maternal birth order to lower offspring birth weight was contradictory because maternal

birth order is positively related to the mother's own birth weight which, in turn, is positively associated to her offspring's birth weights [16, 26]. An evaluation of offspring birth weights to index respondent birth order in the MBHMS revealed no significant findings (data not shown); however, the relationship of maternal birth order and offspring birth weight in MBHMS was strengthened after adjustment for grandmaternal age at time of index respondent birth, a characteristic strongly associated with maternal birth order. This suggests the need to control for grandmaternal age in an analysis of maternal birth order and offspring birth weight.

We also reported a significant positive association between a mother's birth weight and her child's birth weight, a finding that has been consistently confirmed in a number of prior generational studies [9-15, 17, 18]. Our findings that mother's age, amount of weight gained during the pregnancy, sex and birth order of the offspring were related to offspring birth weight replicates findings reported in the literature [2, 9, 14, 15, 18, 27]. Furthermore, identifying that the relationship of maternal age and amount of weight gain during pregnancy on offspring birth weight is not a linear but quadratic function may provide additional evidence for use in clinical recommendations regarding optimal age for and nutrition during pregnancy.

The ability to examine characteristics across two generations was a strength of this study. Many generational studies have been limited to associations between parents and children, with relatively few studies able to evaluate birth and pregnancy characteristics contributed about grandmother, mother, and children. Moreover, using linear mixed

modeling permitted us to account for variability arising from family and maternal clusters, sustained our statistical power and sample size and enabled us to maintain a population-based sample thus improving overall generalizability. While Misra et al used generalized estimating equations to account for the maternal clustering, only the eldest daughter was used from the second generation of families [20] as did the multigenerational examination of the 1958 United Kingdom birth cohort [18]. In addition, the MBHMS participants were interviewed about the birth characteristics of their offspring in 2008, when they were between 66 and 41 years of age and most had completed their childbearing. In contrast, women in the study by Emanuel et al were only followed until aged 23 years, well before they may have completed their childbearing [18]. Finally, the MBHMS participants represented a population-based sample of middle-class, Caucasian women, the majority of whom were born and continue to live in Tecumseh, Michigan. The homogeneity across the generation of families in this study allowed analysis of generational influences on offspring birth weight without the need to control for confounding factors such as race, socioeconomic status, and social environment – characteristics associated with variability in birth weights.

Despite these strengths, there are some limitations. All index respondent and offspring birth characteristic data were self-reported. However, several studies have reported on the ability of women to validly report their own birth weight [28, 29] as well as the birth weights of their children [30-32]. In addition, women's self-reported fetal smoking exposure has been shown to be a reliable measure [33]. We were also limited to grandmaternal pregnancy information and were unable to examine other grandmaternal

characteristics, such as stature, body size, or socioeconomic position, which may provide more insight about shared environmental or genetic factors. However, a few studies have already described a positive association between grandchildren birth weight and grandparental stature and socioeconomic status [7, 18].

In conclusion, this study provides support for a matrilineal effect on birth weight. Since oocyteogenesis begins in gestation and is finished well before birth, it is feasible that programming effects may be occurring at a follicular level. These findings emphasize the importance of healthful pregnancies, which may affect birth and health outcomes across multiple generations. Although we speculate that the increase in grandchildren birth weight seen among women who had in utero smoking exposure is a beneficially adaptive response, studies that can investigate the health outcomes of these grandchildren would be worth pursuing.

Table 4.1. Summary of Birth Characteristics by Mother (Index Respondent) and Offspring

	Variable	Variable Characterization
Index Respondent (n = 397)	Mother's Age at Index Respondent Birth	Continuous, in years, and Five categories: <ul style="list-style-type: none"> • 19 years or less • 20 - 24 years • 25 - 29 years • 30 – 34 years • 35 years or more
	In Utero Smoking Exposure	Four categories: <ul style="list-style-type: none"> • Mother smoked before but not during pregnancy • Mother smoked before and during pregnancy • Mother did not smoke • Does not know
	Birth Weight	Continuous, in grams, and Three categories: <ul style="list-style-type: none"> • Low (<2500 grams) • Normal (2500–4000 grams) • High (>4000 grams)
	Singleton Birth Status	Two categories: <ul style="list-style-type: none"> • From a singleton birth • From a multiple birth
	Birth Order	Two categories: <ul style="list-style-type: none"> • First born • Not first born

Table 4.1. Summary of Birth Characteristics by Mother (Index Respondent) and Offspring (cont.)

Offspring of Index (n = 935)	Mother's Age at Offspring's Birth	Continuous, in years, and Five categories: <ul style="list-style-type: none"> • 19 years or less • 20 - 24 years • 25 - 29 years • 30 – 34 years • 35 years or more
	Amount of Weight Mother Gained during Pregnancy	Continuous, in pounds, and Three categories: <ul style="list-style-type: none"> • <15 pounds • 15-45 pounds • >45 pounds
	Mother's Smoking Status at Time of Birth	Four categories: <ul style="list-style-type: none"> • Ex-smoker and quit prior to pregnancy • Smoker during pregnancy • Never smoker • Undetermined
	Birth Weight	Continuous, in grams
	Birth Order	Two categories: <ul style="list-style-type: none"> • First born • Not first born
	Sex	Two Categories: <ul style="list-style-type: none"> • Male • Female

Table 4.2A. Distribution and Mean Offspring Birth Weight, in grams, by Mothers' (Index Respondent) Birth Characteristics, Michigan Bone Health and Metabolism Study, n=935^a

Index Respondent Birth Characteristics	n (%)	Mean ± SD
<u>Grandmother's Age at Mother's Birth</u>		
19 years or less	98 (10.6%)	3482 ± 571
20 - 24 years ^b	348 (37.6%)	3410 ± 552
25 - 29 years	249 (26.9%)	3573 ± 509
30 - 34 years	143 (15.4%)	3473 ± 614
35 years and older	88 (9.5%)	3545 ± 556
<u>Grandmother's Smoking History</u>		
Smoked before but not during pregnancy	65 (7.0%)	3487 ± 542
Smoked before and during pregnancy	190 (20.3%)	3561 ± 568
Did not smoke	621 (66.4%)	3455 ± 547
Does not know	59 (6.3%)	3521 ± 658
<u>Mother's Birth Weight^{c,d}</u>		
Low (<2500 grams)	86 (9.8%)	3297 ± 547
Normal (2500 - 4000 grams)	718 (81.6%)	3496 ± 545
High (>4000 grams)	76 (8.6%)	3702 ± 475
<u>Mother Singleton Birth</u>		
Yes	909 (97.2%)	3477 ± 561
No	26 (2.8%)	3680 ± 459
<u>Mother First Born</u>		
Yes	259 (27.7%)	3469 ± 566
No	676 (72.3%)	3488 ± 557
^a Values do not sum to totals because of missing data. ^b p<0.01 mean difference compared to 25-29 year olds ^c p<0.01 mean difference across all categories ^d p<0.01 test for trend		

Table 4.2B. Distribution and Mean Offspring Birth Weight, in grams, by Offspring Birth Characteristics, Michigan Bone Health and Metabolism Study, n=935^a

Offspring Birth Characteristics	n (%)	Mean ± SD
<u>Mother's Age at Offspring Birth^b</u>		
19 years or less ^c	85 (9.1%)	3314 ± 519
20 - 24 years ^{d,e}	307 (32.8%)	3414 ± 556
25 - 29 years	304 (32.5%)	3539 ± 533
30 - 34 years	172 (18.4%)	3586 ± 565
35 years and older	67 (7.2%)	3497 ± 643
<u>Mother's Weight Gain During Pregnancy^{b,f}</u>		
15 pounds or less	31 (3.5%)	3066 ± 546
15 - 45 pounds	717 (81.4%)	3476 ± 538
Over 45 pounds	133 (15.1%)	3651 ± 615
<u>Mother's Smoking History</u>		
Ex-Smoker and quit before pregnancy	119 (12.7%)	3484 ± 557
Smoker during pregnancy	233 (24.9%)	3411 ± 572
Never Smoked	494 (52.8%)	3519 ± 548
Undetermined	89 (9.5%)	3473 ± 579
<u>Offspring First Born^f</u>		
Yes	391 (41.8%)	3365 ± 546
No	544 (58.2%)	3568 ± 553
<u>Offspring Sex^f</u>		
Male	516 (55.2%)	3551 ± 578
Female	419 (44.8%)	3400 ± 523
^a Values do not sum to totals because of missing data. ^b p<0.01 test for trend ^c p<0.01 mean difference compared to 25-29 year olds and 30-34 year olds ^d p<0.01 mean difference compared to 30-34 year olds ^e p<0.05 mean difference compared to 25-29 year olds ^f p<0.01 mean difference across all categories		

Table 4.3. Frequency and Mean Offspring Birth Weights by Grandmother’s and Mother’s Smoking Behavior during Pregnancy, Michigan Bone Health and Metabolism Study, n=791

		Grandmother (Mother of Index Respondent) Smoked During Pregnancy	
		Yes	No
Mother (Index Respondent) Smoked During Pregnancy	Yes	46 (5.8%) offspring Mean birth weight = 3570 ± 496 g	160 (20.2%) offspring Mean birth weight = 3377 ± 567 g ^a
	No	130 (16.4%) offspring Mean birth weight = 3556 ± 608 g ^a	455 (57.5%) offspring Mean birth weight = 3490 ± 524 g

^ap<0.05 mean difference

Table 4.4A. Change in Offspring Birth Weight, in grams, associated with Mothers' (Index Respondent) Birth Characteristics, Michigan Bone Health and Metabolism Study, n=935

	Unadjusted		Adjusted ^a	
	β (SE)	p-value	β (SE)	p-value
Index Respondent Birth Characteristics				
<u>Grandmother's Age at Mother's Birth</u>				
19 years or less	70 (79)	0.37	96 (79)	0.22
20 - 24 years	Referent		Referent	
25 - 29 years	157 (57)	<0.01	145 (58)	0.01
30 - 34 years	64 (68)	0.35	12 (68)	0.86
35 years and older	133 (83)	0.11	96 (82)	0.25
<u>Grandmother's Smoking History</u>				
Smoked before but not during pregnancy	37 (90)	0.68	118 (88)	0.18
Smoked before and during pregnancy	136 (59)	0.02	154 (57)	<0.01
Did not smoke	Referent		Referent	
Does not know	31 (95)	0.74	75 (98)	0.45
<u>Mother's Birth Weight</u>				
Low (<2500 grams)	-187 (79)	0.02	-201 (78)	0.01
Normal (2500 - 4000 grams)	Referent		Referent	
High (>4000 grams)	210 (82)	0.01	225 (83)	<0.01
<u>Mother Singleton Birth</u>				
Yes	-185 (142)	0.19	-186 (137)	0.17
No	Referent		Referent	
<u>Mother First Born</u>				
Yes	-27 (50)	0.59	-56 (55)	0.31
No	Referent		Referent	

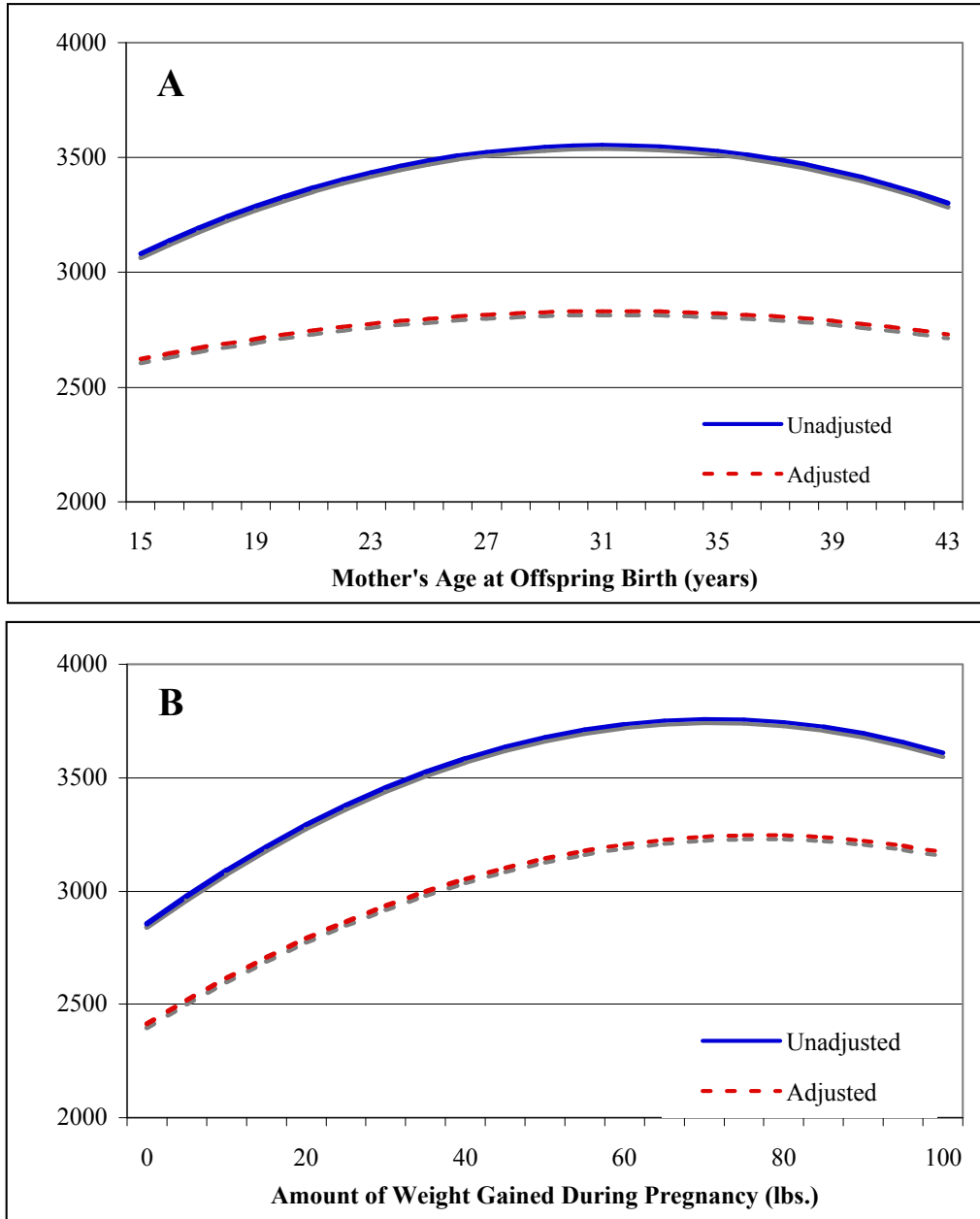
^aAdjusted for all other mother and offspring birth characteristics shown in Table 4.4A and Table 4.4B.

Table 4.4B. Change in Offspring Birth Weight, in grams, associated with Offspring Birth Characteristics, Michigan Bone Health and Metabolism Study, n=935

	Unadjusted		Adjusted ^a	
	β (SE)	p-value	β (SE)	p-value
Offspring Birth Characteristics				
<u>Mother's Age at Offspring Birth</u>				
19 years or less	-94 (61)	0.12	-32 (61)	0.60
20 - 24 years	Referent		Referent	
25 - 29 years	110 (40)	<0.01	35 (41)	0.38
30 - 34 years	159 (50)	<0.01	55 (52)	0.29
35 years and older	56 (70)	0.42	12 (70)	0.86
<u>Mother's Weight Gain During Pregnancy</u>				
15 lbs or less	-347 (99)	<0.01	-332 (93)	<0.01
15 - 45 lbs	Referent		Referent	
Over 45 lbs	199 (52)	<0.01	187 (52)	<0.01
<u>Mother's Smoking History</u>				
Ex-Smoker and quit before pregnancy	31 (68)	0.65	-77 (67)	0.25
Smoker during pregnancy	-114 (54)	0.04	-52 (54)	0.33
Never Smoked	Referent		Referent	
Undetermined	-60 (81)	0.46	-50 (80)	0.53
<u>Offspring First Born</u>				
Yes	-186 (30)	<0.01	-196 (34)	<0.01
No	Referent		Referent	
<u>Offspring Sex</u>				
Male	158 (33)	<0.01	157 (32)	<0.01
Female	Referent		Referent	

^aAdjusted for all other mother and offspring birth characteristics shown in Table 4.4A and Table 4.4B.

Figure 4.1. Relationship of Offspring Birth Weight to Mother's Age at Offspring Birth (A) and Amount of Weight Gained During Pregnancy (B).



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CHAPTER 5

Conclusions

SUMMARY OF FINDINGS

This dissertation expands the scope of research on the developmental origins of health and disease by examining the relationship of birth weight to trajectories in body composition, carbohydrate metabolism, and lipids and to the risks of type-2 diabetes and metabolic clustering in a population of middle-class, middle-aged midwestern Caucasian women. These women were born between 1942 and 1967 and were followed annually from 1992 to 2007. We also evaluated the determinants of birth weight across two generations of pregnancies in order to understand the extent to which a woman's own fetal experience may affect her children's birth outcomes.

Early research on the developmental origins of health and disease focused on the association between low birth weight and adult disease in English and Scandinavian populations born either early in the 20th century [1-3] or during wartime famine [4-6]. However, this study examined categories of birth weight in adult women, and included high birth weight – a birth characteristic that may also represent a unique fetal experience, but has not been examined as frequently as low birth weight. The burden of collecting both birth history information and adult health outcome data in study populations over time often precludes the opportunity to investigate effects on longitudinal outcomes of health and across generations. Thus, earlier studies have

typically used retrospective historical data that collected adult health measures at one point or period in time. The availability of birth history information from two generations, along with annually collected measures of adult health and disease, permitted us to examine the effects of birth weight on changes in health over time as well as the determinants of birth weights across generations. Investigating longitudinal changes in health as well as generational determinants of birth weight in women may provide insight about the etiology of chronic disease in this population. It may also inform the development of clinical recommendations, behavioral interventions, and public health policies aimed at reducing chronic disease incidence and improving the general health of women across the life span.

In Chapter 2, we examined whether groups of low and high birth weight women had different trajectories in their body composition measures compared to women classified as having normal weight at birth. We saw no significant differences between the groups of low and normal birth weight women, but we found that women classified as high birth weight continued to be heavier into adulthood. Compared to normal birth weight women, high birth weight women had, on average, higher weight, height, BMI, hip and waist circumferences, and higher fat, lean, and skeletal muscle mass. Notably, these differences were constant over time. Waist-to-hip ratio was not different across the birth weight groups, suggesting that although high birth weight women had higher levels of fat mass, this excess adipose tissue was not centrally distributed.

In Chapter 3, we evaluated the risk profiles of diabetes and metabolic clustering - a condition similar to metabolic syndrome - across the birth weight categories. We also investigated the longitudinal changes of cardiometabolic risk factors across the birth weight groups. Compared to women in the normal birth weight group, women classified as high birth weight had an increased overall risk for type-2 diabetes and metabolic clustering. Women categorized as low birth weight appeared to be less likely to develop type-2 diabetes, but more likely to develop metabolic clustering. The low incidence of these diseases in this relatively young population of women likely decreased our power to detect statistically significant associations. In our examination of cardiometabolic risk factors, no differences in the trajectories of insulin, insulin resistance, total cholesterol, triglycerides, and low- and high-density lipoprotein cholesterol by birth weight group were observed. However, women who were categorized as high birth weight had steeper fitted slopes in their glucose measures, with levels that increased at an average rate of 0.63 mg/dL per year relative to women in the normal birth weight women group.

In Chapter 4, we shifted focus to intergenerational associations of birth weight, specifically examining whether a woman's intrauterine environment can influence the birth weights of her offspring. Using birth weight data collected about the MBHMS participants' offspring, women who self-reported being exposed to cigarette smoke in utero or women born to older mothers (25 to 35 years) gave birth to offspring who were, on average, heavier than women who self-reported having no in utero smoking exposure or who were born to younger mothers (20 to 24 years). We saw evidence of effect modification between grandmaternal and maternal smoking status during pregnancy on

offspring birth weight. Specifically, offspring birth weight was lowest among mothers who were smokers and grandmothers who were nonsmokers, but offspring birth weight was highest among grandmothers who smoked during pregnancy regardless of maternal smoking status. This evaluation of pregnancy data about mothers and their daughters provided support for an intergenerational effect on birth weight along the maternal line. These findings suggest that the behavior and health of women who are pregnant with daughters may affect not only the offspring from that immediate pregnancy, but also the offspring from their daughters' future pregnancies.

Critics of the developmental origins of health and disease paradigm describe a number of analytical problems prompting debate about whether the associations between early life growth and development and adverse health in adulthood are real [7-11]. Jaddoe et al provides a summary of the points most commonly made, which include inconsistencies in the findings, inadequate statistical methods, inappropriately addressed confounding, selection bias, satisfying the criteria for causal associations, the biological mechanisms, and the strength of public health impact [10]. In the next section, I address some of these criticisms within the context of this dissertation research. In the section that follows, I discuss the implications of some of these criticisms to general developmental origins of disease research and offer suggestions for future research in evaluating the developmental origins of health and disease. I conclude with a discussion of how the findings from this dissertation may be used to inform clinical guidelines and public health policy and interventions.

STRENGTHS AND LIMITATIONS

Inconsistencies in the Findings. Our findings that low birth weight women in the MBHMS did not have higher levels of body composition, carbohydrate metabolism, lipids nor increased risk for developing type-2 diabetes seems discordant with prior studies that have described associations between lower weights at birth and higher levels of fat mass [12, 13], glucose [14], total and low-density lipoprotein cholesterol [15-18], and increased risk for diabetes [19-23]. However, most of the previous research has been undertaken in populations whose early life experience differs substantially from the population of women in the MBHMS. Many of the earlier research studies used retrospective historical cohorts in populations born prior to or during the World Wars, when family size, family dynamics, and the overall social environment were different [24]. For instance, the men in the studies from Hertfordshire, England were born between 1911 and 1930 [1], men and women of the Helsinki Birth Cohort were born from 1924 to 1944 [20, 21], and women of the Nurses Health Study were born from 1921 to 1946 [25]. The majority of cohorts from these earlier studies would have come from larger families and be born to women who were smaller and less educated [24]. These period effects would likely result in differences in the association between early life experiences and adult health. The women of MBHMS were born during a post-WWII era, from 1942 to 1967, to mothers who were of middle-class status. In turn, present-day women in Michigan are heavier than their own mothers, more educated, and having children at later ages. Acknowledging these period differences, emphasizes the importance of evaluating development origins of disease studies within the context of the

birth cohorts [24]. Law and Baird suggest that the evidence from developmental origins research should be interpreted in consideration of changes within generations [24].

Therefore, the findings of low birth weight and adverse adult health reported in earlier studies and our finding that high birth weight was associated with higher body composition levels and steeper rates of change in glucose may be legitimate when considered within the context of secular trends and the birth cohort.

Incomplete Statistical Analysis. A primary strength of our study was the ability to examine the same population of women using 15 years of annually collected data. Despite the three-level hierarchical structure of the data, we were able to employ statistical approaches that included linear mixed modeling and generalized estimating equations to account for the family and subject clustering as well as the within-subject variance inherent in longitudinally-collected data. Our adjustment for random effects at both the family and maternal level in our examination of intergenerational effects permitted us to use the birth weights of all offspring from a given MBHMS participant, thus curtailing the loss of statistical power. Prior intergenerational studies used first-born children only or randomly selected a single offspring [26-28].

Confounding. Another major strength of our study was the homogeneity of our study population. All the MBHMS women (and therefore their mothers) were Caucasian. Most of the MBHMS women were born in Tecumseh, Michigan and continue to reside there. Although it is possible that their offspring may be of mixed-Caucasian descent, we

believe this is unlikely in the majority of these births because Tecumseh continues to be an area with a racial composition of primarily Caucasians.

Confounding due to socioeconomic factors is a criticism of many studies of the developmental origins of disease, including inability to adjust for socioeconomic status (SES) in adulthood as well as at birth [9]. The MBMHS population is a relatively homogeneous with respect to SES. The city of Tecumseh, Michigan was and continues to be largely rural middle-class community. The participants of the Tecumseh Community Health Study (TCHS), the study that comprised of the parents of the MBHMS women, were middle-class and the MBHMS participants were also middle-class. Further, when we evaluated the education levels of the MBHMS participants, most had some college-level education, which is an indicator of middle-class status. Thus, women in the MBHMS likely retained the same SES from birth through adulthood.

The appropriateness of adjusting for measures of adult body composition (primarily, adult body mass index) in analyses of birth weight on adult lipid measures and risk for metabolic diseases is controversial because these measures may be in the causal pathway of birth outcomes to adult disease [9, 10, 15]. Indeed, our findings reported in Chapter 2 provided evidence that high birth weight resulted in higher adult body size. Lucas et al observed that the inclusion of adult body size in examinations of birth size on adult disease is not an adjustment, but rather alters the exposure from birth outcomes to post-birth growth patterns [9-11]. Therefore, we analyzed the effect of birth weight on

measures of carbohydrate metabolism and lipids and risk for diabetes and metabolic clustering with and without the adjustment for adult BMI.

Critics have suggested that the association between low birth weight and adverse health is not a result of development in a sub-optimal fetal environment, but rather continued exposure to an unhealthy environment during childhood and adulthood [29]. Therefore, characteristics and behaviors that contribute to an unhealthy environment, such as smoking and alcohol use, sedentary lifestyle, poor nutrition, and poverty, should be controlled for in studies that examine early life factors and adult health. Our relatively small sample limited the ability to control for these behavioral characteristics in our analysis. However, prior studies with larger sample sizes, and thus statistical power, have reported that adjustment for these factors attenuates, but does not eliminate the association between restricted fetal growth and subsequent disease [3, 9, 25, 29, 30]. For example, research from the Nurses Health Study showed that adjustment for smoking and alcohol use, poor diet, ethnicity, physical activity levels, and socioeconomic status had little effect on the association of low birth weight on the risk for cardiovascular disease [25].

Selection Bias. Critics have argued that developmental origins studies that used large historical cohorts may be susceptible to selection bias because these cohorts had significant loss to follow-up and/or investigators used only a small proportion of the entire cohort [8, 10]. We believe, however, that our study was less likely to be prone to selection bias. We were able to use birth weight and adult health measures on 587

(88.4%) out of the 664 women who were enrolled in 1992, 21 (3.2%) of whom were excluded because they were from a multiple birth. Although selection bias can occur with a small percentage of loss to follow-up, we saw no evidence that women without birth weight data experienced different adult health outcomes than those with birth weight data.

In contrast, the birth history data, including birth weights, of the MBHMS participants and their offspring were self-reported and may be subject to recall bias. We see some evidence of this in our comparison of birth weights collected in 1988 and 2008. While mean differences were similar between the 1988 self-reported birth weight data and the 2008 documented birth weight data, there were statistically significant mean differences between the 1988 data and the 2008 data that were collected from memory (Table 1.3). Mean birth weights collected from the memories of participants' parents were higher than the 1988 mean birth weights; however, mean birth weights recalled from the participant's own memory were lower than the 1988 mean birth weights. Therefore, we minimized the use of the 2008 birth weight data by using it only when it was missing from the 1988 dataset, comprising of only 12.8% (n=78) of the cohort.

Additional Strengths of the Study. The ability to prospectively examine body composition, carbohydrate metabolism, and lipid measures as well as risk for diabetes and metabolic clustering in adulthood is a strength of this study. The women in the MBHMS were well into middle age at the end of the 15 years of follow-up, the time frame in which diabetes and metabolic conditions are more likely to be present. Since

these health outcomes have a long latency period, their frequent follow-up is often a limitation in many cohort studies because of the cost and potential loss to follow-up in study populations followed over long periods of time.

This study has good external validity. The use of a population-based study sample was a good representation of U.S. middle-class Caucasian women. The offspring of the MBHMS participants were not limited to those who were first born or were randomly selected from one child in the family, which has been done in other intergenerational studies [26-28]. This improved the study's generalizability because many U.S. families have more than one child.

FUTURE DIRECTION OF DEVELOPMENTAL ORIGINS RESEARCH

Causality and Biological Mechanisms. Birth weight is recognized as a crude marker of the fetal experience, since different genetic environments and maternal characteristics can give rise to the same weight at birth [19, 31, 32]. Therefore, comprehending what birth weight truly represents with respect to the intrauterine environment is challenging. Law et al describe birth weight as a “summary measure of growth over a specified period reflecting length, body mass and head size, which in turn reflects skeletal and muscle growth, fat mass, and organ size” [33]. Langer describes four determinants of normal fetal growth: 1) genetics; 2) fetal hormones (e.g. insulin); 3) uterine constraints (e.g. placental function) and; 4) maternal risk factors (e.g. pre-pregnancy body size and amount of weight gained during pregnancy) [34]. Consistent with the concepts underlying the developmental origins paradigm, a change in the intrauterine milieu (i.e. a

developmental insult) that causes an alteration in any of these four determinants of normal fetal growth would give rise to abnormal fetal growth. Indeed, risk factors associated with macrosomic or large for gestational age infants include excessive weight gain in pregnancy, tall maternal height, mother being multiparous, ethnicity, maternal history of type-2 diabetes and/or gestational diabetes, maternal history of a macrosomic birth, and high pre-pregnancy BMI [34-36]. In contrast, determinants of low birth weight and small for gestational age infants include insufficient weight gain in pregnancy, short maternal height, mother being nulliparous, ethnicity, smoking in pregnancy, maternal history of low birth weight infant, and low pre-pregnancy weight [37, 38].

The inclusion of maternal characteristics and additional birth outcomes would contribute greatly to describing the quality of the fetal environment and to understanding the mechanisms by which intrauterine and early life development cause disease [8-11, 19, 32]. Furthermore, the continued promotion of research that focuses on the identification of additional developmental insults as well as epigenetic research, including understanding the mechanisms by which these insults or gene-environment interactions operate, is important. Along with animal models, clinical trials, and observational studies, study populations should continue to include twins and multiple generations of families, which can better control for shared genetic and social factors. Given the influence of period effects previously discussed, research should proceed to include various populations, in both developed and developing countries, and across different social classes and racial/ethnic groups, while considering the context of time that generations were born. Of note, current medical advances have improved the likelihood

of survival in very low birth weight and/or extremely premature infants, as well as the safe delivery of infants who are large for gestational age [24]. What the fetal experience of these infants represents and their potential influence on adult disease remains to be seen.

For this dissertation research, we did not include information on maternal characteristics, and their investigation could provide additional understanding of the MBHMS women's fetal experience. However, future research on developmental factors and health in this study population could involve the incorporation of data from the TCHS, which would provide information about the health and behaviors about the parents of the MBHMS participants, including characteristics and risk factors in mother's of the MBHMS women. Furthermore, our collection of birth history data among MBHMS offspring included information about the MBHMS participants' pregnancies, including amount of weight gain and presence of maternal disease (Appendix A). Therefore, if data on the postnatal health outcomes of the MBHMS offspring were to be collected, future studies could evaluate the developmental origins of health and disease in the MBHMS offspring.

We also recognize that the relatively small sample size of the MBHMS is a limitation for much developmental origins research. However, there are a number of research studies in different study populations and from developing and developed countries that can be used to further investigate these relationships. These include the continued use of historical birth cohorts such as the Helsinki Birth Cohort, which is comprised of nearly 16,000 subjects whose data includes birth outcomes, childhood growth, and multiple

measures of adult health [39]. Studies of U.S. populations include the Nurses Health Studies, which comprise of three age cohorts of nearly 240,000 female nurses with longitudinally collected adult health measures, birth outcomes, and intergenerational data [40], the Health Professionals Follow-Up Study, a cohort study of over 50,000 U.S. men that began in 1986 and also includes birth weight and longitudinal adult health data [41], and the Framingham Heart Study, which has followed over 5,200 adults since 1948 and, in 1971 and 2002, recruited and enrolled the children and grandchildren, respectively, of the original cohort [42]. Research should also continue to examine diverse populations, including investigations in developing nations, such as the New Delhi Birth Cohort Study [42], and in minority groups, such as the Native American Indian tribes, which may have birth and adult health measures through medical record data from the Indian Health Service.

In addition, newly established longitudinal cohort studies in pregnant women and infants aimed at examining multiple aspects and exposures that may influence growth and development include the Generation R Study in Rotterdam, The Netherlands, which recruited nearly 10,000 pregnant women who delivered between April 2002 and January 2006 [43], and the National Children's Study in the United States, which intends to follow approximately 100,000 U.S. children from birth to age 21 years and began recruitment of pregnant women from select locations in 2009 [44]. Although the availability of the data from the Generation R Study and the National Children's Study as they relate to health and disease later in life will not be ready for several years, these

studies would potentially provide valuable insight about the developmental origins of health.

Replication of Findings. In addition to research aimed at understand the biological mechanisms and causal associations of the developmental origins of health and disease, research should confirm our findings that high birth weight is associated with steeper adult glucose trajectories. This observation is new and efforts to replicate these results in other study populations are needed. The differences in the risks of type-2 diabetes and metabolic clustering by birth weight group that was observed in our study should be also confirmed using larger study populations that have greater statistical power. This requires the use of large cohorts with longitudinally collected data, such as the Nurses Health Study or the Framingham Heart Study. Further, the replication of research in these larger study populations may also generate new ideas about biological and social mechanisms and may help to explain how early life development affects disease later in life.

The investigation of the role of intergenerational effects on health and disease in subsequent generations should also be pursued. We found an association of intergenerational effects on birth weight along the matrilineal side of the family; however, the information about the pregnancy characteristics in the mothers of the MBHMS participants was limited in this body of work. Moreover, our analysis of maternal age and weight gain during pregnancy on offspring birth weight maybe suggestive of an optimal amount of weight gain and an ideal age to reproduce. These

findings should be replicated in other studies, especially among other racial/ethnic groups. In addition, whether and how these intergenerational influences affect health when the offspring are adults is not known. While there is some evidence in studies of offspring whose mothers were prenatally exposed to the affects from the Dutch Hunger Winter famine [45-47], studies such as the Nurses Health Study or the Framingham Heart Study, which have collected health data among their study subject's offspring, could be extended to families who were not exposed to extreme maternal malnutrition.

SUGGESTIONS FOR CLINICAL RECOMMENDATIONS AND PUBLIC HEALTH POLICIES AND INTERVENTIONS

While more research on the developmental origins of disease is needed, the evidence that early life experiences affect adult health and disease is compelling. In fact, within the context of this dissertation, we showed that in Caucasian women high weight at birth tracks to high weight in adulthood. Further, these high birth weight women are at an increased risk for delivering high birth weight children. Given the continued rise in obesity prevalences in the United States [44], a break in this perpetual cycle of high birth weight across generations may aid in curbing the obesity epidemic. In addition, the general understanding that the health of women prior to conception and the growth and development of offspring through early adolescence, which likely extends across multiple generations, may have important public health significance. Thus, clinical recommendations and public health programs and policies are proposed.

Clinical Recommendations. Our finding that grandmaternal pregnancy characteristics may be associated with birth outcomes in grandchildren demonstrates the need to collect parental health histories from pregnant women and women who are planning a pregnancy. This may include information such as parental smoking behavior and alcohol use, body size, and socioeconomic indicators. In addition to grandparental risk factors, maternal risk factors should also be more thoroughly gathered, including history of birth weights, disease and infection, and amount of weight gain in previous pregnancies, the presence of current chronic disease, smoking behavior, and body size. With this information, clinicians may be better equipped to identify women who are at an increased risk for delivering a low or high birth weight infant and to create tailored health guidelines that include the ideal amount of weight that should be gained in pregnancy and the optimal age for childbearing. In addition, as the technology of fetal monitoring becomes more advanced and with the collection of these grandparental and maternal risk factors, clinicians may be better informed about the need to induce labor, particularly among pregnancies with prolonged gestation, in an effort to prevent the birth of very heavy infants.

When the delivery of a low or high birth weight infant occurs, grandparental and parental risk factors should also be collected in an effort to determine the possible explanations for the birth outcome. If, for example, genetics likely explains the birth outcome (e.g. grandparents had small stature and mother was short), then further monitoring or recommendations for changes in behavior may not be warranted. However, if the presence of maternal diabetes likely explains the birth outcome, clinicians may

recommend different feeding protocols to minimize birth weight tracking or may desire special monitoring for adverse health outcomes later in life.

Public Health Interventions. In addition to clinical recommendations aimed at preventing adverse birth and adult health outcomes, public health interventions targeted to women planning a pregnancy, women already pregnant, or new mothers could be developed or more strongly reinforced. By considering the familial risk factors and the woman's reproductive history, these programs could all be tailored specifically for women who are at an increased risk for delivering offspring with an adverse birth outcome (e.g. high or low birth weight infant). For women planning a pregnancy, these programs may involve recommendations for behavioral changes in diet or physical activity in order to achieve the ideal body size prior to becoming pregnant. For pregnant women, interventions may include targeted prenatal care for dietary changes in order to achieve optimal weight gain. While for new mothers, particularly those with a low or high birth weight infant, programs may involve becoming educated about specialized feeding protocols and monitoring the infant's weight in an effort to limit rapid catch-up growth [in low birth weight babies] or to minimize obesity in early life tracking into adulthood.

Public Health Policy. The transparency and availability of one's own birth outcomes as well as parental health histories may be valuable for all individuals interested in risk factor identification for adult disease. This may be achieved with a public health policy that includes the standardization of the collection of these data on all birth certificates.

Furthermore, the inclusion of parental health information, such as weight, height, and smoking behavior, on birth certificates will serve as grandparental health histories when the given individual is ready to begin his/her childbearing.

CONCLUSIONS

The developmental origins of health and disease research has expanded beyond low birth weight and maternal malnourishment to include maternal and birth characteristics, experiences, and insults that better represent the quality of early life growth and development. This dissertation further extends the current developmental origins research to investigate adult risk factor trajectories, risk profiles of chronic disease over time, and intergenerational effects. As this research continues to evolve and progress, we anticipate a greater understanding of the biological and social mechanisms of chronic disease and an increase in the general awareness of the importance of early life experiences on health later in life. This knowledge will continue to have important implications in the development of public health policies and interventions as well as clinical recommendations aimed at improving women and children's health across the lifespan and preventing adult chronic disease.

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APPENDIX A

MICHIGAN BONE HEALTH AND METABOLISM STUDY PROTOCOL FOR THE COLLECTION OF BIRTH HISTORY DATA

The Michigan Bone Health and Metabolism Study (MBHMS) is a prospective cohort study that was established to examine changes in women's health through the menopause transition. A total of 664 women were enrolled into MBHMS at baseline, which began in 1988. Participation in MBHMS comprises of health evaluations and interviews and subjects are currently completing their 13th evaluation over the past 19 years.

MBHMS will continue to examine the effect of the menopause transition on changes in women's health. However, in 2008, a new study aim will be implemented to examine the effect of the women's birth and pregnancy characteristics on her subsequent development of select chronic disease in adulthood. For this aim, participants will be asked to provide information about their birth and, if applicable, their pregnancies and the births of their children.

Study Participants

Participants for this new study aim will comprise of all women who are currently participating in MBHMS. There are no exclusion criteria - all women who are willing to participate will be eligible. Women who are lost to follow-up or who have asked to no longer participate in the study will not be pursued to contribute. Of the 664 women who were enrolled at baseline, 12 are deceased and 521 participated in the 2006 evaluation, resulting in a participation rate of 79.9%.

Methodology

Data Collection

Participants will be sent a letter about this new study aim (Appendix A). To collect data that are as accurate as possible, this data collection effort will encourage participants to use their birth certificate information for birthweight and gestational age and, if applicable, the birth certificate information of their children for the same information. Within 1 month of receiving this letter, participants will be contacted via telephone and, upon consent, asked to complete a telephone-based interview (Appendix B). In addition to the letter, the information packet will include the interview and a description of what is being consented to by participating in the telephone interview. Trained staff who have an established rapport with the participants will administer the phone interviews. The phone interviews are anticipated to take between 10-20 minutes to complete.

Measures

Data gathered from the interview comprise of information about the participant's own birth, her pregnancy history, and the birth history of her children. Specific measures include:

Birth Characteristics of Participant

- Birthweight
- Gestational Age
- Singleton or Multiple birth
- Age of mother at birth
- Birth order
- Mother's smoking status at birth

Participant's Pregnancy History

- Ever pregnant
- Number of live births

Birth Characteristics of Participant's Children

- Date of birth
- Birthweight
- Gestational age

- Type of delivery
- If pregnancy occurred due to infertility treatment
- Occurrence of pregnancy-related conditions (i.e., gestational diabetes, pre-eclampsia)

Data Management

To ensure the participant's anonymity, no personal identifiers will be included on the interviews. The same MBHMS identification number that has been used in prior evaluations will be used to differentiate all participants. This will also ensure that the data collected for this aspect of the study can be linked to data already collected in previous examinations. A data entry system will be created using Epi-Info 6 and all data will be entered by trained staff. All forms and questionnaires completed will be secured in locked files and be accessible to only qualified staff.

Anticipated Timeline

- January 2008: Pretest and finalize phone interview questionnaire and create data entry system
- February 2008: Finalize and send letter to all currently active participants
- March – April 2008: Begin and complete phone interviews to all currently active participants
- April – May 2008: Complete data entry

Date

Participant's Address
City, State Zip Code

Dear Participant:

Thank you for your continued participation and dedication to the Michigan Bone Health and Metabolism Study. With your help, we are able to better understand what causes and risk factors are associated with the development of adult chronic diseases, such as osteoporosis, osteoarthritis, diabetes, cardiovascular disease, and cognitive functioning. In addition to this research, we are now also interested in learning how certain characteristics of your birth, such as birth weight or whether or not you were premature, may relate to the development of these chronic diseases as an adult. We are hoping you are willing to participate in this new area of study!

For this study, we plan to complete a phone interview with you in which we ask you a series of questions about your birth and, if you have children, the birth of your children. To ensure the birth information you give us is as precise as possible, we are asking you to refer to your birth certificate. We plan to begin these phone interviews in March 2008 and we anticipate they will take between 10-15 minutes to complete. We have enclosed a consent form which describe your rights as a study participant and a copy of the phone questionnaire, so that you will be aware of the information we will be asking you.

If you have questions about this new phase of the Michigan Bone Health and Metabolism Study, please feel free to contact us at.....

If there is a specific day and time you wish to be contacted for your phone interview, please feel free to call....to set up an appointment.

Thank you again for your dedication and we look forward to talking to you this spring!

Sincerely,

BIRTH HISTORY QUESTIONNAIRE

Respondent MBHMS ID: _____

Respondent DOB: ____ / ____ / _____

Date of Interview: ____ / ____ / _____

We are interested in learning more about how birth characteristics relate to health and disease as an adult. This first series of questions are related to your own birth.

SECTION A: BIRTH CHARACTERISTICS

A1. What was your birthweight, in pounds and ounces? _____ lbs. _____ oz.

A2. How many weeks was your mother pregnant with you when she delivered you?

_____ weeks

A3. Were you a single birth or from a set of twins, triplets, or more? (Please select.)

_____ Single birth (go to A4)

_____ Multiple birth (specify) _____ (go to A3a)

A3a. Where you born first, second, third, or more? Birth order:

A4. How old was your mother when you she delivered you? _____ years old

SECTION B: BIRTH HISTORY VALIDATION

B1. Were all of the above questions answered using information on your birth certificate?

_____ Yes (go to SECTION C)

_____ No (go to B1a)

B1a. Please explain your source of information for the answers to the above questions:

The following questions ask about your mother's health when she was pregnant with you.

SECTION B: MOTHER'S PREGNANCY HISTORY

B1. How many children did your mother already give birth to before she gave birth to you?

_____ previous live births

B2. Did your mother smoke cigarettes before or during her pregnancy with you? (Please select.)

_____ smoked before pregnancy but stopped during pregnancy

_____ smoked before and during pregnancy

_____ did not smoke before or during pregnancy

_____ don't know

This next section asks about your pregnancies and about the birth of your children.

SECTION D. PREGNANCY CHARACTERISTICS

D1. According to previous interviews, you have been pregnant _____ times. Is this correct?

If zero, STOP! END OF QUESTIONNAIRE.

If greater than zero, go to D2.

D2. We also show that, of these pregnancies, _____ resulted in a live birth. Is this correct?

If zero, STOP! END OF QUESTIONNAIRE.

If greater than zero, go to SECTION E.

I am now going to ask you a series of questions about your pregnancies and the births of your children, starting with your oldest child and finishing with your youngest child.

INTERVIEWER: For each live birth reported, please ask the above questions and complete the following grid with the responses provided.

SECTION E. BIRTH HISTORY OF CHILDREN

E1. What is his/her year of birth?

E2. What is his/her sex?

E3. Do you have a copy of his/her birth certificate to refer to for the next set of questions?

E4. What was his/her birthweight, in pounds and ounces?

E5. How many weeks were you pregnant when you delivered him/her?

E6. Did you have any pregnancy-related health conditions, such as extreme nausea, hypertension/preclampsia, gestational diabetes, infection, pre-term labor, or depression?

E7. How much weight, in pounds, did you gain during this pregnancy?

E8. Did you become pregnant because of fertility treatments?

E9. Did you deliver vaginally or did you have a Cesarean/C-section?

	E1. Year of birth	E2. Sex	E3. Used birth certificate	E4. Birthweight	E5. Gestational age	E6. Maternal conditions during pregnancy (check all that apply)	E7. Weight gain during pregnancy	E8. Used infertility treatments	E9. Type of Delivery
1st Child		<input type="checkbox"/> Male <input type="checkbox"/> Female	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/> lbs <input type="text"/> oz	<input type="text"/> wks	<input type="checkbox"/> Extreme Nausea <input type="checkbox"/> HTN/Preclampsia <input type="checkbox"/> Gestational Diabetes <input type="checkbox"/> Infection <input type="checkbox"/> Pre-term labor <input type="checkbox"/> Depression <input type="checkbox"/> Other, specify:	<input type="text"/> lbs	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Vaginal <input type="checkbox"/> Cesarean
2nd Child		<input type="checkbox"/> Male <input type="checkbox"/> Female	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/> lbs <input type="text"/> oz	<input type="text"/> wks	<input type="checkbox"/> Extreme Nausea <input type="checkbox"/> HTN/Preclampsia <input type="checkbox"/> Gestational Diabetes <input type="checkbox"/> Infection <input type="checkbox"/> Pre-term labor <input type="checkbox"/> Depression <input type="checkbox"/> Other, specify:		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Vaginal <input type="checkbox"/> Cesarean
3rd Child		<input type="checkbox"/> Male <input type="checkbox"/> Female	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/> lbs <input type="text"/> oz	<input type="text"/> wks	<input type="checkbox"/> Extreme Nausea <input type="checkbox"/> HTN/Preclampsia <input type="checkbox"/> Gestational Diabetes <input type="checkbox"/> Infection <input type="checkbox"/> Pre-term labor <input type="checkbox"/> Depression <input type="checkbox"/> Other, specify:		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Vaginal <input type="checkbox"/> Cesarean
4th Child		<input type="checkbox"/> Male <input type="checkbox"/> Female	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/> lbs <input type="text"/> oz	<input type="text"/> wks	<input type="checkbox"/> Extreme Nausea <input type="checkbox"/> HTN/Preclampsia <input type="checkbox"/> Gestational Diabetes <input type="checkbox"/> Infection <input type="checkbox"/> Pre-term labor <input type="checkbox"/> Depression <input type="checkbox"/> Other, specify:		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Vaginal <input type="checkbox"/> Cesarean

5th Child		<input type="checkbox"/> Male <input type="checkbox"/> Female	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/> lbs <input type="text"/> oz	<input type="text"/> wks	<input type="checkbox"/> Extreme Nausea <input type="checkbox"/> HTN/Preclampsia <input type="checkbox"/> Gestational Diabetes <input type="checkbox"/> Infection <input type="checkbox"/> Pre-term labor <input type="checkbox"/> Depression <input type="checkbox"/> Other, specify:		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Vaginal <input type="checkbox"/> Cesarean
6th Child		<input type="checkbox"/> Male <input type="checkbox"/> Female	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/> lbs <input type="text"/> oz	<input type="text"/> wks	<input type="checkbox"/> Extreme Nausea <input type="checkbox"/> HTN/Preclampsia <input type="checkbox"/> Gestational Diabetes <input type="checkbox"/> Infection <input type="checkbox"/> Pre-term labor <input type="checkbox"/> Depression <input type="checkbox"/> Other, specify:		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Vaginal <input type="checkbox"/> Cesarean
7th Child		<input type="checkbox"/> Male <input type="checkbox"/> Female	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/> lbs <input type="text"/> oz	<input type="text"/> wks	<input type="checkbox"/> Extreme Nausea <input type="checkbox"/> HTN/Preclampsia <input type="checkbox"/> Gestational Diabetes <input type="checkbox"/> Infection <input type="checkbox"/> Pre-term labor <input type="checkbox"/> Depression <input type="checkbox"/> Other, specify:		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Vaginal <input type="checkbox"/> Cesarean

These are all the questions we have for you. Thank you for your time and willingness to talk with us!

END OF INTERVIEW.

Interviewer Notes: