

## Association between Birth weight and Metabolic Syndrome

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### Abstract

**Objective:** This study examined the effects of high birth weight (HBW), >4 kg and low birth weight (LBW), <2.5 kg, on an individual's risk of developing metabolic syndrome (MetS) later in life; with consideration of both maternal and individual lifetime behavioral, social, and environmental factors.

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

**Results:** The study population was 55% female, 22% African-American, with an average age of 63 years. The prevalence of reported LBW among males and females was 1.7% and 4.6%, respectively. The prevalence of reported HBW among males and females was 8.7% and 5.0%, respectively. A relationship between LBW and future risk of MetS was attenuated by pertinent socioeconomic and lifestyle-related risk factors that defined both the participant and their familial influence, particularly maternal age at the time of birth. An association between HBW and MetS was not found.

**Conclusions:** This work does not support an association between HBW nor LBW with adult MetS. The development of MetS may be associated with subject's socioeconomic and lifestyle factors.

**Keywords:** Obesity; Metabolic syndrome; Low Birth weight; High Birth weight

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## Introduction

Risk for developing metabolic abnormalities that later manifest as metabolic syndrome (MetS) may begin in utero and be first evidenced by an infant's weight at birth, long before developing any symptoms [1-3]. The relevance of these risks is of growing importance as the prevalence of MetS among adults continues to rise. A 2017 study indicated that MetS prevalence increased from 1988 to 2012 for every sociodemographic group with over one-third of adults in the United States meeting the criteria for MetS diagnosis in 2012 [4,5]. At the same time, the rates of high birth weight, low birth weight, and premature birth in the U.S continue to remain high and have all been linked to increased risk of infant mortality and continue to exceed rates seen in other developed countries [6-8]. In 2018, The Centers for Disease Control reported that among all U.S. births, 10% of births were considered pre-term (less than 37 completed weeks of gestation) and about 9% of births to be of Low Birth weight (LBW) or very low birth

weight [7]. Similarly, nearly 8% of U.S. infants were considered high birth weight (HBW) according to the National Vital Statistics Report for U.S. Births in 2015. Based on the National Health and Nutrition Examination Survey 1999-2006, an estimated 35% of Americans have MetS with the prevalence rising to an estimated 50% among U.S. adults over the age of 60 [8]. It should also be noted that HBW, LBW, pre-term birth and MetS all occur at disproportionately higher rates among minority and underserved populations [9]. Birth weight is the best available surrogate marker of the quality of the intrauterine environment and is known to be representative of the quality of maternal nutritional status during gestation [9,10]. LBW is considered less than 2.5 kg without consideration of gestational age [11]. Contrarily, HBW is considered any infant born at a weight greater than 4 kg, with consideration of gestational age [12]. A HBW may indicate an adverse fetal environment secondary to a mother's excess gestational weight gain, development of gestational diabetes, pre-pregnancy obesity, circulating triglyceride concentrations, or

degree of inflammation during pregnancy [12,13]. LBW may also indicate an adverse fetal environment. Risk of LBW increases with maternal history of premature births, with birthing multiples, African-American ethnicity, non-married mothers, maternal age above the age of 25 years or being a teen mother, lack of prenatal care, lack of health insurance, substance abuse, and maternal illnesses or infections such as genital or urinary tract infections, preeclampsia, or chronic health conditions such as hypertension [14]. Like high or low birth weight, MetS is linked to many of the same risk factors including, but not limited to, a parent's and child's educational attainment, Socioeconomic Status (SES), and lifetime health behaviors. The preliminary research suggests a variety of interrelated factors influence birth weight, familial upbringing, and the development of MetS [15]. This study sought to explore the possible association between birth weight and MetS in adulthood while controlling for factors that were believed to confound the hypothesized relationship.

## Methods

The study population includes 10,969 participants for the Atherosclerosis Risk in Communities (ARIC) Study that began in 1987 in four field centers: Washington County, MD, Forsyth County, NC; Jackson, MS; and Minneapolis, MN. Each cohort consisted of approximately 4,000 randomly selected and recruited individuals ages 45-64. Each of the 15,792 initial participants underwent a comprehensive examination in 1987-1989 that enabled researchers to gather baseline medical, social, and demographic data. The participants were then re-examined every three years thereafter: 1990-92, 1993-95, 1996-98. During the study's fourth exam the 10,969 participants' socioeconomic data, including participant's reported birth weight, were collected that informed this study's research question. The association between the variables of interest was examined retrospectively [16]. This article was prepared using ARIC Research Materials obtained from the National Heart Lung Blood Institute (NHLBI) Biologic Specimen and the Data Repository Information Coordinating Center. The Institutional Review Board of Appalachian State University approved the acquisition and use of this dataset. Details of the methodology of the ARIC study are described elsewhere [16]. The independent variables were derived using participant's responses to two sets of questions related to their birth weight. Participants self-reported their birth weight using a questionnaire provided by the ARIC study. In addition, participants who reported a "low" birth weight on a categorical scale from low to high were then combined with participants who reported a numerical birth weight value less than 5.5 lbs (2.5kg). These individuals were defined as LBW. The same method was used in identifying participants who reported a "high" birth weight or a reported numerical birth weight value greater than 8.8 lbs (4kg). These individuals were defined as HBW. Among the 10,969 participants, 3,631 reported their birth weight numerically, while 5,546 reported either a low, medium, high birth weight. Some 3,544 participants reported their birth weight using both methods. Overall, 5,771 participants answered either or both of the ARIC survey questions related to birth weight as "unknown" or not at all. The dependent variable was defined by the presence of MetS, or not, among participants

as reported during the study's fourth exam, the same point in time at which participant's reported birth weight was collected. Unlike the self-reported birth weight data and socioeconomic data, metabolic syndrome criteria data were physically measured by ARIC study investigators. The variable was derived by first identifying participants who met the diagnostic criteria for each of the five MetS factors using the criteria defined by the National Institutes of Health [17]. The diagnostic criteria included: 1) large waistline (waist measurement of 35 inches or more for women or 40 inches or more for men), 2) a high triglyceride level (triglyceride level of 150 mg/dL or higher or being on medicine to treat high triglycerides), 3) a low HDL cholesterol level (a cholesterol level of less than 50 mg/dL for women or less than 40 mg/dL for men or being on medicine to treat low HDL cholesterol), 4) high blood pressure/hypertension (a blood pressure of 130/85 mmHg or higher, or taking medicine to treat high blood pressure), and 5) a high fasting blood sugar (a fasting blood sugar level of 100 mg/dL or higher or being on medicine to treat high blood sugar). This last criterion can also include a diagnosis of prediabetes (fasting blood sugar level between 100-125 mg/dL) or diabetes (a fasting blood sugar of 126 mg/dL or higher). Each of the MetS criteria was coded dichotomously (0, 1) for each participant. The total number of MetS diagnostic criteria a given participant met equaled their MetS severity score, scaled 0-5. Those with 3 or more factors were considered to have MetS [17]. MetS data was available for 10,763 of the 10,969 total participants (98.1%). Alternate covariates were included in the analysis to control for environmental, social, and behavioral differences among the participants. Demographic factors controlled for included age, race, and sex. Social and familial factors included age of mother at participant's birth (in years), parents' years of education, participant's years of education, participant's household income, participant's Medicaid enrollment status, drinking status, smoking status, and level of physical activity. SPSS version 24 (IBM Company, Chicago, IL) software was used to calculate the descriptive statistics of the ARIC population and to conduct binomial logistic regression modeling to analyze the derived independent and dependent variables and relevant covariates.

## Results

The study population was made up of 45% males and 55% females with an average age of 62.8 years of age at the time of ARIC study's fourth examination. A summary of the study population's defining characteristics is shown in **Table 1**. Upon examining the association between birth weight and MetS, neither HBW nor LBW were significant predictors of MetS, in either of two independent univariate analyses nor in subsequent full multivariate analyses, when controlling for demographic and social factors shown in **Tables 2-5**. Sex, age, mother's age at birth, participant's years of education, physical activity level, and current drinking/smoking behaviors, however, were significantly associated with MetS based on binomial logistic regression modeling. Females were 0.78 times as likely as males to have MetS ( $p < 0.001$ ) in these models. Mother's age at birth, but not mother's educational attainment, was significantly associated with participants' MetS diagnosis. With each additional year of age, a woman's risk of delivering a child with an eventual MetS

**Table 1:** Study population characteristics, male versus female (% or mean ± standard deviation).

Participant Characteristics	N	Male	Female
Sex	4771	45%	55%
Age (in years)	4771	61.4 (52-75)	60.6 (53-73)
Black race	4771	15%	20%
Medicaid Enrollment	4771	7.2%	3.9%
Average Household Size	4768	2.4 ± 0.9	2.3 ± 1.0
Mother's Age at Time of Birth	4771	25.3 ± 5.6	25.1 ± 5.5
Mother High School Graduate or Higher	4530	43%	38%
Participant College Educated or Higher	4771	47%	38%
Current Drinker	4771	61%	48%
Current Smoker	4771	16%	15%
<b>Metabolic Syndrome Risk Factors</b>	<b>N</b>		
Average BMI (kg/m <sup>2</sup> )	4770	28.5 ± 4.5	28.9 ± 6.4
Metabolic Syndrome Average Score (0-5)	4771	2.6 ± 1.4	2.5 ± 1.4
Metabolic Syndrome Prevalence	4771	53%	50%
<b>Metabolic Syndrome Diagnostic Criteria</b>	<b>N</b>		
Elevated Waist Circumference	4771	53%	75%
Elevated Blood Pressure	4771	56%	56%
Low HDL	4771	50%	40%
Elevated Triglycerides	4771	43%	37%
Elevated Blood Glucose/Diabetes Diagnosis	4771	61%	43%
<b>Birthweight Risk Factors</b>			
Average Birthweight (lbs.)	1805	8.1 ± 1.7	7.3 ± 1.5
Cohort Classified LBW	4771	2.0%	5.0%
Cohort Classified HBW	4771	10.0%	5.0%

**Table 2:** Univariate association between birthweight and metabolic syndrome in adulthood.

Predictor Variables	p	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
N= 10763				
Low Birthweight	0.090	1.206	0.971	1.498
High Birthweight	0.182	0.902	0.775	1.050

**Table 3:** Association between birthweight and metabolic syndrome, controlling for demographic factors.

Predictor Variables	p	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
N= 10758				
Low Birthweight	0.041	1.256	1.009	1.562
High Birthweight	0.356	0.931	0.799	1.084

**Table 4:** Full Model for association between low birth weight and metabolic syndrome.

Predictor Variable	p	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
N=4771				
Low Birthweight	0.774	1.049	0.756	1.457
Female Sex	<0.001	0.775	0.687	0.875
Black Race	0.916	1.010	0.846	1.204
Age (per year)	0.011	1.016	1.004	1.028
Mother Age at Birth	<0.001	0.981	0.971	0.992
Mother's Education	0.512	0.989	0.956	1.023
Father's Education	0.718	0.995	0.967	1.023
Medicaid Enrolled	0.764	1.043	0.792	1.373
Household Income	0.059	0.960	0.920	1.002
Education (per year)	<0.001	0.968	0.952	0.983
Activity Level	<0.001	0.817	0.757	0.881
Current Smoker	0.005	0.793	0.674	0.933
Current Drinker	<0.001	0.749	0.661	0.849

**Table 5:** Full Model, association between high birth weight and metabolic syndrome.

Predictor Variable	p	Odds Ratio	95% C.I for Odds Ratio	
			Lower	Upper
N=4771				
High Birthweight	0.896	0.985	0.790	1.230
Female Sex	<0.001	0.776	0.687	0.876
Black Race	0.925	1.008	0.846	1.203
Age (per year)	0.011	1.016	1.004	1.028
Mother's Age at Birth	<0.001	0.981	0.971	0.991
Mother's Education	0.516	0.989	0.956	1.023
Father's Education	0.713	0.995	0.967	1.023
Medicaid Enrolled	0.762	1.043	0.793	1.373
Household Income	0.060	0.960	0.920	1.002
Education (per year)	<0.001	0.968	0.952	0.983
Activity Level	<0.001	0.817	0.757	0.881
Current Smoker	0.005	0.794	0.675	0.934
Current Drinker	<0.001	0.749	0.661	0.849

diagnosis decreased by 1.9% ( $p < 0.001$ ) in models for both LBW and HBW. In both full models being a current smoker and drinker was protective. Additional years of education and additional physical activity at work, leisure, or sports were also associated with lower risk.

## Discussion

No significant association between LBW or HBW and MetS was identified in the study and may indicate a lack of association between birth weight and future risk of developing MetS. Analysis of literature and significance of covariates, however, may suggest certain demographic and socioeconomic factors confound the hypothesized relationship. An interesting inverse relationship was observed between mother's age at participant's birth and MetS diagnosis in offspring. Other covariates such as being a drinker, more years of education, and more physical activity were associated with lower risk. The observational and retrospective nature of some epidemiological studies can limit the ability of such studies to infer causal inference; this study was no different. Recall bias was the most prominent as participants were relied upon to accurately report their birth weight either numerically or categorically many years later. Also, a true measure of socioeconomic status at the participants time of birth was not available when controlling for covariates in the various regression models. Instead, surrogate markers were used; Medicaid enrollment and household income were used to measure SES at the time of data collection, while mother's and father's educational attainment and participant's educational attainment was used to estimate participant SES at the time of birth. The study cohort consisted of an average number of individuals with MetS and a below average number of individuals born at high or low birth weights compared to the U.S. population. The prevalence of MetS was near the expected prevalence rate (56%) reported in the literature, considering the advanced age of the study population [18]. The prevalence of MetS was similar among females and males (56%) in this population, consistent with the literature [19]. HBW rates among males (9%) were comparable to prevalence rates reported in the literature (8%). All other instances of HBW and LBW occurred less frequently and

disproportionate by sex among this population than others cited in the literature [20]. A key limitation of this study was the use of birth weight as the only indicator of an adverse fetal environment or insult in utero. It cannot be assumed that infants born at "normal" birth weights were not subjected to a significant insult that may have affected metabolic programming and their future disease risk [11]. The ARIC dataset lacks information regarding maternal behaviors prior to pregnancy, during pregnancy, and post-natal factors (i.e. breast feeding and the rate of post-natal growth) that have been found to significantly influence birth weight, fetal programming, and metabolic development in the early stages of infancy [21]. The range of findings in previous studies [22-27] and lack of significant findings in this study indicate the shortcomings in both this study and others, in answering this complex research question. Another limitation of the study is the large number of subjects that simply reported their birth weight as low, medium, or high. In sum, limitations of the study include recall bias, reliance on surrogate measures, and a study population that may not be representative of the U.S. population.

## Conclusion

This analysis did not support the hypothesis that birth weight influences an individual's risk of developing MetS later in life. Certain factors showed lower risk in the predictive models for MetS, such as participant's years of education, activity level, current drinking, and smoking status, and mother's age at which she gave birth.

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