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Original article

Birth weight was longitudinally associated with cardiometabolic risk markers in mid-adulthood

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ABSTRACT

Purpose: Birth weight (BW) is associated with risk of cardiovascular (CV) disease. The findings from studies examined the association of BW with metabolic markers of CV risk were inconsistent and controversial. We examined the association of BW with insulin resistance and blood lipids using repeated measures up to mid-adulthood.

Methods: Data from seven screenings of the Bogalusa Heart Study—a longitudinal study of cardiovascular risk factors in Bogalusa, LA—are analyzed using generalized estimation equations method. Participants with birth data and at least one measurement of study outcomes between 18 and 44 years ($n = 2{,}034$) were included.

Results: BW is inversely associated with insulin resistance, triglycerides, and total cholesterol ($P < .01$ for all). For 1-kg decrease in BW, insulin resistance increased by 2.3 units, 95% confidence interval (CI) = 0.7–3.9; triglycerides by 8.7 mg per dL, 95% CI = 4.9–12.4, and total cholesterol by 5.4 mg per dL, 95% CI = 1.8–9.1. The association of body mass with adult blood lipids levels is weaker in persons with low versus normal BW.

Conclusions: The study provides strong evidence of an inverse relationship of BW with adulthood cardiometabolic risk profile. Persons born with low BW are maybe less responsive to preventive interventions aiming at weight reduction.

Introduction

A large body of evidence has accumulated indicating a relationship between in utero growth restriction (IUGR) and the development of many disorders later in life, including increased insulin resistance and type 2 diabetes mellitus, hypertension, and adverse blood lipid profile [1–4]. According to the hypothesis of early origins of adult disease, adverse prenatal pressures stimulate fetal responses that permanently alter the "programming" of many of its physiological systems, thus predisposing the individual to various diseases later in life [5,6]. Low birth weight (BW) at or near term is the most commonly used surrogate measure of IUGR and has been related to increased cardiovascular mortality, presumably due to its adverse effect on many cardiovascular risk factors acting later in life [6–8]. The epidemiologic evidence clearly points to an inverse association between BW and many hemodynamic CV risk markers, especially systolic blood pressure and pulse pressure [9–11]. The findings are less consistent, however, for markers of cardiometabolic risk, such as blood lipids and lipoproteins and insulin resistance [12–17].

Additionally, some authors questioned these findings citing the lack of adjustment for important confounders, such as socioeconomic status and lifestyle variables [12,18]. Others have questioned the interpretation of an effect of BW from statistical models concurrently relating birth and current body mass to later CV risk factors, arguing that these models actually test the effect of change of body mass from birth rather than the effect of size at birth [18]. This notion has profound public health implications as it shifts the emphasis from prenatal to postnatal growth.

In this article, we examine the association of BW with levels of markers of cardiometabolic risk (serum lipids and lipoproteins and insulin resistance), using repeated measurements from young to

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mid-adulthood that were collected by the Bogalusa Heart Study (BHS). To address the aforementioned points, three analytical approaches are used: (1) testing the associations of BW with later markers of cardiometabolic risk without adjusting for body mass index (BMI); (2) testing the associations of BW with later markers of cardiometabolic risk adjusting for BMI and other important socioeconomic, behavioral, and familial variables; and (3) testing the association of repeated measures of BMI with later markers of cardiometabolic risk in persons with low BW (BW $<$ 2500g) versus those with normal BW (BW $\geq$ 2500g). Modeling the association of BW and repeated measures of body mass with metabolic markers of CV risk allows assessing the effect of the total burden of the change of body mass over time on various risk factors. Additionally, comparing the association of BMI with the outcomes in individuals of low versus normal BW allows assessing the heterogeneity, or lack of, of the effect of weight gain over time on CV risk factors in the two groups.

This study aims to reexamine the hypothesized association of low BW with an adverse metabolic CV risk profile later in life, while addressing the issues of adjusting for BMI and adequate controlling for important confounding factors such as lifestyle and familial variables.

Materials and methods

Participants

The BHS is a longitudinal study after a bi-ethnic cohort (65% white and 35% African American) from Bogalusa, LA, to examine the natural development of CV disease. A detailed description of the demographic characteristics of the community and the overall design of the study has been published elsewhere [19]. This study used data of seven screenings of BHS performed during participants' early to mid-adulthood (age range, 18–44 years). Birth data were collected from birth certificates that were obtained from the Office of Health Statistics in New Orleans, LA. Of the 2301 participants who were eligible to be included in this analysis, BW was available on 2274 (98.8%) of them. Singletons with complete birth data and at least one measurement of markers of CV risk after 18 years were eligible for the study (n = 2274). Birth data were obtained from birth certificates. Exclusion criteria included having type 1 diabetes mellitus (n = 6); having congenital heart disease (n = 4); failed to fast (n = 3) and premature birth (n = 226) leaving 2034 participants (89.4%) who were included in this analysis.

Informed consent was obtained from the parents during childhood screenings and from the participants during adulthood screenings. The study was approved by the institutional review board at Tulane University in New Orleans, USA.

Procedures

Height was measured manually to the nearest 1 mm and weight to the nearest 0.1 kg, both as the mean of two measurements. Body mass index (BMI) was calculated from the formula = weight (kg)/height^2 (meter). Birth weights were obtained from birth certificates and were then converted into kilograms (1 ounce $\approx$ 0.028 kg).

All laboratory tests were done after overnight fasting. Serum total cholesterol and triglycerides measurements were performed using enzymatic procedures on Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were determined by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis. Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas, Pharmacia Diagnostics, Piscataway, NJ). Serum glucose level was measured as part of a multiple chemistry profile. Homeostasis model assessment (HOMA-IR)—calculated as [fasting insulin (μU/mL) $\times$ fasting glucose (mmol/L)/22.5]—was used to measure insulin resistance [20]. The World Health Organization definition for low BW, less than 2500 g, was adopted for this study. Prematurity was defined as gestational age less than 37 weeks.

Income was defined as the last self-reported annual income and was classified into two categories: $<$\$45,000 and $\geq$\$45,000. Smoking status was defined as the last information available about smoking and was coded into two categories: non/former smokers and current smokers. Alcohol consumption was defined as the last information available about drinking and was coded into three categories: none/less than one drink per week, 2–4 drinks per week, and more than 4 drinks per week. Family history of cardiovascular disease was defined as having a parent who had a heart attack, a stroke, a bypass surgery, or an angioplasty or who died of a heart attack or stroke. This variable was coded as 2 if both parents had a history of CV disease, as 1 if one parent had a history of CV disease, and as 0 if neither parent had a history of CV disease. Available information on the familial and lifestyle variables ranged from 70 percent for income to 99 percent for smoking status.

Statistical analyses

De-identified data of the outcome and the independent variables from the seven files pertaining to the seven Bogalusa Heart Study screenings of young adults between 1988 and 2001 were linked to the file containing birth outcomes data, indexed on the unique ID number, and keeping the chronological order of the data.

The outcome variables were HOMA-IR, triglycerides, total cholesterol, LDL-C, or HDL-C. The generalized estimation equation method was used to analyze the data. Generalized estimation equation methods account for within-subject correlation due to repeated measurements and between-subject variation due to the individual differences among the participants. For each outcome, the correlation structure between the repeated measures was examined using Pearson's correlation. Based on this analysis, exchangeable working correlation matrix was defined for all models. All the dependent variables deviated from normality and were skewed to the right. Therefore, the inverse Gaussian distribution was selected for all models, resulting in much better fits to the data than the normal distribution, as measured by quasi likelihood under independence criterion. Two models were run for each outcome: the minimally adjusted model included BW, age, sex, and race as the independent variables, whereas the full model additionally included BMI, income, smoking status, alcohol drinking, and parental history of CV disease. BW was entered in the models as a continuous variable. Age and BMI were entered as time-variant variables to adjust for their effect as they changed over time. To examine whether BW interacts with body mass, the models were rerun in those with BW $<$ 2500 g versus $\geq$2500 g, and the coefficients of BMI in the two groups were compared. Two-tailed tests were used in all analyses with a significance level set to 0.01 to control for multiple testing. All analyses were conducted by using SPSS statistical package, version 21.0 (SPSS, Inc., Chicago, Illinois).

Results

The mean number of screenings per subject is 2.5 (range, 1–7). The sample is 65% white and 45% men. Table 1 shows the comparison of main birth outcomes by gender and race.

In minimally adjusted models, BW is borderline associated with later serum triglycerides and total cholesterol levels (b = −5.0,