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The impact of birth weight on cardiovascular disease risk in the Women's Health Initiative

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Abstract

Background and Aims—Cardiovascular disease (CVD) is among the leading causes of morbidity and mortality worldwide. Traditional risk factors predict 75-80% of an individual's risk of incident CVD. However, the role of early life experiences in future disease risk is gaining attention. The Barker hypothesis proposes fetal origins of adult disease, with consistent evidence demonstrating the deleterious consequences of birth weight outside the normal range. In this study, we investigate the role of birth weight in CVD risk prediction.

Methods and Results—The Women's Health Initiative (WHI) represents a large national cohort of post-menopausal women with 63 815 participants included in this analysis. Univariable proportional hazards regression analyses evaluated the association of 4 self-reported birth weight categories against 3 CVD outcome definitions, which included indicators of coronary heart

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Disclosures

The authors have nothing to disclose.

For a list of all the investigators who have contributed to WHI science, please visit: <https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf>

disease, ischemic stroke, coronary revascularization, carotid artery disease and peripheral arterial disease. The role of birth weight was also evaluated for prediction of CVD events in the presence of traditional risk factors using 3 existing CVD risk prediction equations: one body mass index (BMI)-based and two laboratory-based models. Low birth weight (LBW) (< 6 lbs.) was significantly associated with all CVD outcome definitions in univariable analyses (HR=1.086, $p=0.009$). LBW was a significant covariate in the BMI-based model (HR=1.128, $p<0.0001$) but not in the lipid-based models.

Conclusion—LBW (<6 lbs.) is independently associated with CVD outcomes in the WHI cohort. This finding supports the role of the prenatal and postnatal environment in contributing to the development of adult chronic disease.

Keywords

risk prediction; proportional hazards model; Barker hypothesis; self-reported birth weight; life course epidemiology; metabolic syndrome

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide.¹ Traditional risk factors such as age, gender, lipid levels, smoking, hypertension, and diabetes predict 75-80% of an individual's risk of incident CVD. Several risk prediction models that include these traditional risk factors are clinically useful.²

Recently, more attention is being given to early life exposures, including the prenatal environment and its impact on birth weight, and their role in the development of adult chronic disease. The “Barker hypothesis” proposes fetal origins of adult disease and is increasingly supported by many epidemiological studies demonstrating the deleterious consequences of birth weight outside the normal range.³⁻⁵ The premise of this hypothesis maintains that an inadequate intrauterine environment shapes fetal organ systems such that the nervous system receives more nutrients at the expense of other systems.³ This deficiency may result in altered metabolism and cardiovascular function postnatally and into adult life. In particular, low birth weight (LBW) (< 6 lbs.) is consistently associated with increased risk for adult chronic disease, including cardiovascular disease, type 2 diabetes, and metabolic syndrome.^{4,6,7} However, the role of birth weight in predicting incident CVD risk has yet to be explored. According to the Centers for Disease Control and Prevention (CDC), 8.0% of babies born in 2012 were born LBW (<2500 grams) in the United States. Thus, over 300,000 infants in one year alone are potentially susceptible to adverse adult outcomes due to LBW. Large-for-gestational-age (LGA) is also associated with increased risk for adult chronic disease, including cardiovascular disease and metabolic disturbances.^{8,9} Increasing prevalence of maternal obesity has resulted in an increasing incidence of LGA,¹⁰ representing another population that is at risk for adverse adult outcomes in response to the intrauterine environment.

The Women's Health Initiative (WHI) began as a clinical investigation of prevention strategies for breast and colorectal cancer, cardiovascular disease, and osteoporotic fractures, common sources of morbidity and mortality among post-menopausal women.¹¹ Since its

inception in 1991, the WHI has been a valuable resource for additional analytical studies investigating the role of exposures in chronic disease outcomes. In this study, we investigated the role of birth weight in the prediction of incident CVD in the WHI participants.

Methods

Study Population

The WHI consists of clinical trial (CT) and observational cohorts (OS).¹¹ Because only the observational cohort provided information on birth weight, our analyses evaluate only this cohort of approximately 100 000 subjects. This cohort included a baseline questionnaire to gather demographic and health history information and a baseline screening visit, at which clinical laboratory values were measured.¹¹ Women self-reported their own birth weight as one of four categories: <6 pounds, 6 – 7 pounds 15 ounces, 8 – 9 pounds 15 ounces, and 10 pounds. Women also self-reported if they were born before 37 weeks completed gestation, i.e., they were born preterm. Inclusion and exclusion criteria for the WHI-OS cohort have been described previously.¹¹ Briefly, inclusion criteria for all WHI participants included age 50-79 years, ability to provide written informed consent and the expectation of maintaining residence in the study recruitment area for at least three years following enrollment. Exclusion criteria included medical conditions with a predicted survival time < 3 years, competing risks for cancer or cardiovascular disease, or inability to complete the baseline study requirements, such as the baseline questionnaire or clinical visit(s).¹¹ Additionally, for our analyses, subjects with self-reported high cholesterol ever requiring medication or a medical record history of stroke or myocardial infarction (MI), carotid artery disease, peripheral arterial disease, or coronary revascularization at baseline were excluded. Subjects were excluded for prior events as our analyses were intended to predict the risk of incident cardiovascular events.

Outcome Definition

Outcome adjudication in the WHI study has been described previously.¹² OS participants were contacted annually by mail to provide updated medical histories. Hospitalized events were adjudicated using all available information, including medical history, ECG readings and cardiac enzyme/troponin levels.¹³ Fatal events were adjudicated based on review of medical records and death certificate.

Three outcome definitions were used in the univariable analyses. “Hard atherosclerotic cardiovascular disease (ASCVD)” included coronary heart disease (consisting of clinical MI, definite silent MI or death due to coronary heart disease; CHD) and ischemic stroke. “Any CVD” included CHD, ischemic stroke, coronary revascularization (consisting of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty), carotid artery disease, and peripheral arterial disease. “Major CVD” included CHD, ischemic stroke and coronary revascularization. These three outcome definitions encompass the outcomes included in the three risk prediction models, although the combinations differ slightly from the risk prediction models as the univariable outcomes were established *a*

priori, whereas the outcomes for the risk prediction models were the same as the studies in which they were developed.

Statistical Analyses

The sample size of subjects with complete baseline questionnaire data was 81,355. Subjects were then excluded for existing CVD, including high cholesterol (N=11675), previous stroke (N=2756), previous MI (N=2632), carotid artery disease (N=716), peripheral artery disease (N=1763), and coronary revascularization (N=1469). Given that many subjects had more than one pre-existing condition, 17,540 unique individuals were excluded for existing CVD, resulting in a final sample size of 63,815 participants.

Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 (Cary, NC, USA). OS cohort participants with complete data for birth weight were included in the univariate analyses and the body mass index (BMI)-based equation analysis; the subset with baseline lipid measures (n=3368) were included in the evaluation of the lab-based equations. Survival analysis, specifically, proportional hazards regression, was used for all analyses given the nature of the study question, which involved the addition of a biomarker to existing CVD risk prediction models. The results of proportional hazards models are reported in this study as beta coefficients (β) and hazard ratios (HR).

Univariable analyses were performed for four self-reported birth weight categories (<6 pounds, 6 – 7 pounds 15 ounces, 8 – 9 pounds 15 ounces, and 10 pounds) and ‘hard ASCVD’, ‘major CVD’ and ‘any CVD’ outcomes for the entire OS cohort (N=63,815). To assess the role of preterm birth, independent of birth weight, univariable analyses were adjusted for preterm birth. Sensitivity analyses were performed in which preterm subjects were excluded to assess the role of birth weight and CVD among full term subjects.

Three CVD risk prediction models were applied to the WHI population with and without birth weight as a covariate. The purpose of this analysis was two-fold: first, to assess additive predictive value of birth weight as a covariate and second, to assess the utility of three established CVD risk prediction models in the WHI cohort. The BMI-based Gaziano model included the following covariates: current smoking, history of diabetes, history of hypertension treatment and the natural logarithm of age, systolic blood pressure and body mass index (BMI).¹⁴ The outcomes included in the Gaziano analysis included CHD, ischemic stroke, CHF, and coronary revascularization, consisting of CABG and PTCA.¹⁴

We used two risk prediction models containing lipid measurements as covariates, the Reynolds Risk Score and the Pooled Cohort risk equation. Lipid measurements were only available for a subset of African American (N=2278) and Hispanic subjects (N=1090) and no eligible Caucasian subjects. The lipid-based Reynolds Risk Score model included the following covariates: age, current smoking, parental history of MI, and the natural logarithm of systolic blood pressure, HDL-C and total cholesterol.¹⁵ A parental history of MI prior to a parental age of 55 years was used based on the categorization of this question in the WHI baseline questionnaire to account for family history of CVD. Hemoglobin-A1C, as an indicator of diabetes, and C-reactive protein (CRP) were not included due to low availability among subjects. The outcomes included in the Reynolds analysis included CHD, ischemic

stroke and coronary revascularization.¹⁵ Note that this outcome definition is the same as ‘hard ASCVD’ used in the univariable analysis. The Pooled Cohort risk equations for African Americans were used for African American WHI participants and the equations for white individuals were used for Hispanic WHI participants. These models included the smoking status, diabetes status, and the natural logarithm of age, total cholesterol, HDL cholesterol, and systolic blood pressure.¹⁶ The outcomes included in the Pooled Cohort analysis included nonfatal or fatal stroke, nonfatal MI or CHD death.¹⁶

For all risk prediction models, CVD risk was calculated using the respective published beta coefficients for model covariates.¹⁴⁻¹⁶ C indices were calculated for each of the three models, with and without birth weight to assess discrimination.¹⁷ Calibration and reclassification of the addition of birth weight to existing risk prediction models were assessed according to Hosmer & Lemeshow methods.¹⁸

Forward selection methods were used to generate a regression model for ‘hard ASCVD’ outcomes in the WHI population in accordance with Hosmer & Lemeshow methods¹⁸. The study population was randomly split in half for validation (N=31,907 per group). Variables included for evaluation included age, smoking status, systolic blood pressure, diastolic blood pressure, diabetes status, hypertension treatment status, body mass index (BMI), income, education level, marital status, prior cancer, waist circumference, waist-to-hip ratio, children, no insurance, and employment status. Positive smoking status included both current and prior smoking. Categorical variables were evaluated using a chi-square test and continuous variables were evaluating using a t-test. Variables with a p-value greater than 0.20 were eliminated. Remaining variables were included in a model and eliminated with a p-value less than 0.05.

Results

Demographic and risk factor characteristics of the study population are reported in **Table 1**. In the full WHI analysis group (n=63 815), there were 819 events for “hard ASCVD,” 2457 events for “any CVD” and 2205 events for “major CVD.” For the analyses of subjects with lipid values, which was comprised of only African American and Hispanic subjects (n=3368), there were 104 events for “hard ASCVD,” 150 events for “any CVD,” and 133 events for “major”.

The results of univariable analyses of birth weight are reported in **Table 2**. For all 3 composite CVD outcomes, birth weight less than six pounds was associated with cardiovascular disease events ($p<0.05$) even after adjustment for preterm delivery ($p<0.001$, data not shown). LBW was also associated with all 3 composite CVD outcomes in the sensitivity analyses among subjects born full term ($p<0.0001$, data not shown). Taken together, this suggests that LBW, independent of preterm birth, is associated with future CVD.

The results of the established risk prediction model analyses are reported in **Table 3**. Birth weight less than six pounds was a significant covariate only in the BMI-based Gaziano model ($p=0.0004$). Birth weight was not a significant covariate in the two lipid-based

models, Reynolds and Pooled Cohort. Without birth weight, all model covariates were significant ($p < 0.05$, data not shown). In all models, the C index did not change significantly with the addition of birth weight (**Table 3**). Of note, discrimination based on the C-index was poor for all 3 models. Discrimination was no better than chance for the Gaziano model (with or without birth weight) and somewhat worse than chance in the Pooled Cohort models. Discrimination was best for the Reynolds Score, although still suboptimal (data not shown). Results of the within-population fitted model are reported in **Supplemental Table 1**. This model contained age, smoking status, systolic blood pressure, diabetes, hypertension treatment and prior cancer.

Discussion

LBW (<6 lbs.) was associated with increased CVD risk in a univariate model and in a multivariate model that did not include laboratory measures of lipids or glucose. The association between LBW and increased CVD risk in WHI is consistent with previous research.^{4,6,7} Our study included over 63 000 women, over 7000 of whom reported that they were born less than six pounds. The only similar study of this magnitude was the Nurses' Health Study cohort, consisting of 70 297 women, fewer than 5000 of whom were born LBW (< 5.5 lbs.).¹⁹ Among this population, women who were born LBW and had a high adulthood BMI had an especially increased risk for CVD.²⁰ However, these studies did not investigate the univariate role of birth weight on incident CVD risk, nor did they use clinical risk prediction models.

Birth weight was a significant covariate in the BMI-based Gaziano model but not in the lipid-based models. This is likely due to the limited sample size of subjects with available lipid values. However, evidence from human studies and studies using animal models demonstrate that endothelial dysfunction in response to LBW and intrauterine growth restriction result in excess lipid accumulation in vascular walls.²¹ This may be exacerbated by a state of dyslipidemia.²¹ The significance of LBW in the BMI-based Gaziano prediction model suggests its value in the prediction of CVD risk when lipid values are not available. Although birth weight did not improve prediction in combination with traditional risk factors, the finding that it is independently associated with cardiovascular disease risk highlights the importance of proper management of LBW infants. In particular, studies have demonstrated the beneficial effects of managing postnatal diet and weight gain in LBW infants to maximize development while reducing the risk of metabolic syndrome in later life.²²⁻²⁴

Limitations of this study include the lack of lipid levels in the vast majority of WHI OS participants. The small number and low rate of events of African American and Hispanic participants in WHI limits the conclusions that can be drawn regarding the contribution of birth weight to ASCVD risk prediction for these racial/ethnic groups. In addition, since Pooled Cohort Equations were not available specific to Hispanic women in the US, we used the equations for Caucasian women which may have been inadequately calibrated for this group. Nonetheless, the poor performance of the Pooled Cohort equations in the African American and Hispanic WHI participants requires further investigation. However, our study is ultimately strengthened by the inclusion of African American and Hispanic subjects, as

the majority of life course epidemiology studies have primarily focused on Caucasian populations. Another limitation of this study is the use of self-reported birth weight as the exposure of interest. However, studies have demonstrated the validity of self-reported birth weight among middle-aged and elderly women and their concordance with birth certificate data.^{25,26}

Previous studies investigating the effect of birth weight on cardiovascular disease risk have included prevalent CVD as the outcome of interest. By restricting our outcomes to incident CVD events, we demonstrate that birth weight is independently associated with incident CVD risk. Although our analyses were confined to women, previous studies demonstrate an increased risk for cardiovascular disease among males born LBW.^{27,28} The fitted model developed in the WHI-OS population included traditional risk factors but birth weight was not significant in the presence of these factors. However, this model represents the first risk prediction model to be developed among the WHI population and is the first risk prediction model to be developed in a population specific to women.

In conclusion, although LBW was independently and significantly associated with incident CVD, the addition of birth weight to traditional CVD risk factors does not appear to meaningfully contribute to existing CVD risk prediction in post-menopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- ❑ Epidemiologic studies demonstrate an increased risk of CVD for LBW individuals
- ❑ We evaluate the predictive value of birth weight in CVD risk prediction among WHI participants
- ❑ Self-reported birth weight was analyzed for association with three composite CVD outcomes
- ❑ LBW (<6 lbs.) is independently associated with increased risk for CVD in the WHI population
- ❑ Low birth weight is a significant predictor of CVD risk in a model using BMI as a proxy for lipids

Table 1

Demographic characteristics of study population

Variable	CVD N=819	No CVD N=62,996	P Value *	Entire Sample N=63,815
Age (years)	66.36 (7.80)	62.57 (7.30)	<0.0001	62.61 (7.32)
BMI (kg/m ²)	28.90 (6.64)	26.99 (5.85)	<0.0001	27.01 (5.87)
Smoking status			0.077	
<i>Prior or Never smoker</i>	385 (48%)	31841 (51%)		32226 (51%)
<i>Current smoker</i>	417 (52%)	30412 (49%)		30829 (49%)
Diabetes			<0.0001	
<i>Yes</i>	107 (13%)	2476 (4%)		2583 (4%)
<i>No</i>	712 (87%)	60464 (96%)		61176 (96%)
Systolic BP	132.39 (19.02)	125.29 (17.54)	<0.0001	125.38 (17.58)
HTN treatment			<0.0001	
<i>Yes</i>	279 (38%)	13017 (22%)		13296 (22%)
<i>No</i>	450 (62%)	45741 (78%)		46191 (78%)
Race			<0.0001	
<i>Caucasian</i>	617 (76%)	53853 (86%)		54470 (86%)
<i>African American</i>	119 (15%)	4489 (7%)		4608 (7%)
<i>Hispanic</i>	48 (6%)	2160 (3%)		2208 (3%)
Birth weight			0.373	
<6 lbs	116 (14%)	7155 (11%)		7271 (11%)
6 – 7 lbs 15 oz	512 (63%)	41414 (66%)		41926 (66%)
8 – 9 lbs 15 oz	161 (20%)	12342 (20%)		12503 (20%)
10 lbs	30 (3%)	2085 (3%)		2115 (3%)

*
T-test of variable vs. CVD event

Table 2

Results of univariable association between birth weight and CVD risk

Outcome [*]	β	SE	HR (95% CI)	P Value	Test for trend P value
Hard ASCVD[†]					0.753
<6 lbs	0.312	0.129	1.367 (1.061, 1.759)	0.015	
8 – 9 lbs 15 oz	0.174	0.108	1.190 (0.963, 1.472)	0.110	
10 lbs	0.344	0.220	1.410 (0.915, 2.171)	0.110	
Any CVD[†]					0.066
<6 lbs	0.288	0.063	1.334 (1.178, 1.510)	<0.0001	
8 – 9 lbs 15 oz	0.027	0.056	1.027 (0.921, 1.146)	0.235	
10 lbs	0.174	0.116	1.191 (0.949, 1.494)	0.132	
Major CVD[†]					0.104
<6 lbs	0.275	0.068	1.316 (1.153, 1.502)	<0.0001	
8 – 9 lbs 15 oz	0.013	0.059	1.013 (0.901, 1.138)	0.831	
10 lbs	0.202	0.121	1.223 (0.965, 1.552)	0.096	

N=63,815 for all analyses; β , beta coefficient of proportional hazards analysis; SE, standard error; HR, hazard ratio; CI, confidence interval^{*} Reference group = birth weight 6 – 7 lbs 15 oz[†] Hard ASCVD includes coronary heart disease events, consisting of clinical MI, definite silent MI or death due to coronary heart disease, and ischemic stroke. Any CVD includes coronary heart disease, ischemic stroke, coronary revascularization (consisting of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty), carotid artery disease, and peripheral arterial disease. Major CVD includes coronary heart disease, ischemic stroke and coronary revascularization.

Table 3

Results of the addition of birth weight to CVD risk prediction models

Model	β	SE	HR (95% CI)	P Value	C Index without BW	C Index with BW
Gaziano[‡]						
<6 lbs	0.218	0.062	1.244 (1.101, 1.405)	0.0004	0.5150	0.5149
8 - 9 lbs 15 oz	-0.005	0.054	0.995 (0.895, 1.106)	0.924		
10 lbs	-0.138	0.104	1.147 (0.936, 1.406)	0.185		
Reynolds[*]						
<6 lbs	0.060	0.260	1.061 (0.637, 1.768)	0.812	0.6508	0.6506
8 - 9 lbs 15 oz	0.138	0.236	1.148 (0.723, 1.823)	0.560		
10 lbs	0.449	0.463	1.566 (0.632, 3.879)	0.332		
Pooled[*]						
<6 lbs	0.060	0.417	1.061 (0.469, 2.403)	0.886	0.4378	0.4388
8 - 9 lbs 15 oz	0.476	0.349	1.609 (0.812, 3.189)	0.173		
10 lbs	-0.453	1.020	0.636 (0.086, 4.699)	0.657		

Reference group = birth weight 6 - 7 lbs 15 oz; β , beta coefficient of proportional hazards analysis; SE, standard error; HR, hazards ratio[‡]N=63,815^{*} Population contains only Hispanic (N=1,090) and African American (N=2,278) subjects