Nutrition, Metabolism & Cardiovascular Diseases (2016) **26**, 239–245

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

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

C.J. Smith [a], K.K. Ryckman [a], V.M. Barnabei [b], B.V. Howard [c,d], C.R. Isasi [e], G.E. Sarto [f], S.E. Tom [g], L.V. Van Horn [h], R.B. Wallace [a], J.G. Robinson [a,*]

[a] University of Iowa Department of Epidemiology, College of Public Health, 145 N. Riverside Drive, Iowa City, IA, 52242, USA
[b] University at Buffalo, Department of Obstetrics and Gynecology, 219 Bryant Street, Buffalo, NY, 14221, USA
[c] Medstar Health Research Institute, Hyattsville, MD, USA
[d] Georgetown/Howard Universities Center for Clinical and Translational Research, USA
[e] Albert Einstein College of Medicine, Department of Epidemiology and Population Health, Bronx, NY, USA
[f] University of Wisconsin, Department of Obstetrics and Gynecology, Madison, WI, USA
[g] University of Maryland, School of Pharmacy, Baltimore, MD, USA
[h] Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Received 20 May 2015; received in revised form 14 October 2015; accepted 29 October 2015
Available online 18 November 2015

KEYWORDS
Risk prediction;
Proportional hazards model;
Barker hypothesis;
Self-reported birth weight;
Life course epidemiology;
Metabolic syndrome

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 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.

* Corresponding author.
E-mail address: jennifer-g-robinson@uiowa.edu (J.G. Robinson).

http://dx.doi.org/10.1016/j.numecd.2015.10.015
0939-4753/

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 g) 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 = 11,675), previous stroke (N = 2756), previous MI (N = 2632),