

# Association of High Birth Weight With Incident Heart Failure in the ARIC Study

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**Background**—Traditional risk factors for heart failure—coronary heart disease, hypertension, diabetes mellitus, obesity, and smoking—only account for about 50% of cases. Thus, the identification of novel risk factors is of significant public health importance. As high birth weight infants are at increased risk for obesity and diabetes mellitus later in life, which are both risk factors for the development of heart failure, we sought to assess the association of high birth weight with incident heart failure in the ARIC (Atherosclerosis Risk in Communities) study.

**Methods and Results**—The ARIC study is a biracial prospective community-based investigation of 15 792 individuals aged 45 to 64 years at baseline. Study participants who were born premature or born a twin were excluded from this analysis, resulting in 9820 participants who provided either their birth weight category (low, medium, high) or exact birth weight. After adjusting for differences in demographics, risk factors, and comorbidities, compared with medium birth weight, those with high birth weight had a significantly increased risk of incident heart failure (hazard ratio, 1.27; 95% CI, 1.05–1.54 [ $P=0.014$ ]). The hazard for all-cause mortality for high birth weight compared with medium birth weight was 1.16 (95% CI, 0.99–1.34;  $P=0.06$ ). There was no association of high birth weight with myocardial infarction (hazard ratio, 1.06; 95% CI, 0.84–1.34 [ $P=0.6$ ]).

**Conclusions**—High birth weight was associated with a significantly increased hazard of incident heart failure independent of traditional risk factors and a trend toward an increased hazard of death. A history of high birth weight should be ascertained in young adults for primordial prevention of heart failure and in older adults for primary prevention. (*J Am Heart Assoc.* 2019;8:e011524. DOI: 10.1161/JAHA.118.011524.)

**Key Words:** heart failure • obesity • pregnancy • prevention • risk factor

Heart failure (HF) is a global pandemic affecting more than 26 million patients worldwide<sup>1</sup> that is best addressed by intervening on risk factors for HF before the HF phenotype develops. The traditional risk factors for HF—hypertension, coronary heart disease (CHD), diabetes mellitus, smoking, and obesity—account for only about half of the population-attributable risk.<sup>2</sup> Thus, identification of novel risk factors for HF is of significant public health importance. One potential nontraditional risk factor is birth weight. The fetal origins of adult diseases hypothesis postulates that maladaptive changes in utero as a response to environmental stressors lead to permanent changes that persist

throughout life predisposing to the development of chronic diseases.<sup>3</sup>

Low birth weight (LBW) (<2.5 kg) has been considered a surrogate marker of fetal malnutrition.<sup>3</sup> Most studies on outcomes related to birth weight have focused on LBW with several studies linking LBW to the development of CHD<sup>4,5</sup> and hypertension.<sup>6–8</sup> High birth weight (HBW) (>4 kg) is commonly associated with maternal obesity, gestational diabetes mellitus, and greater maternal weight gain during pregnancy.<sup>9</sup> HBW infants are at increased risk of developing obesity<sup>10,11</sup> and type 2 diabetes mellitus<sup>12</sup> later in life, both of which are risk factors for HF.<sup>2</sup> We hypothesized that HBW would be associated with an increased risk of incident HF in a large biracial sample of community-dwelling adults enrolled in the ARIC (Atherosclerosis Risk in Communities) study.

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## Participants and Methods

### Data Source

The ARIC data set was obtained upon request from the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) of the National Heart, Lung, and

## Clinical Perspective

### What Is New?

- This study demonstrates an association between high weight at birth and subsequent development of heart failure as an adult.

### What Are the Clinical Implications?

- A history of high birth weight should be ascertained in young adults for primordial prevention of heart failure and in older adults for primary prevention.

Blood Institute under a data use agreement. The Washington University Human Research Protection Office granted this study an exemption from institutional review board oversight. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to BioLINCC (<https://biolincc.nhlbi.nih.gov>).

## Study Participants

The ARIC study is a prospective cohort trial investigating the etiology of atherosclerotic disease in biracial community-dwelling men and women between the ages of 45 and 64 years who were selected by probability sampling from 4 communities in the United States (Minneapolis, MN; Washington County, MD; Forsyth County, NC; Jackson, MS).<sup>13</sup> The institutional review boards at all participating centers approved the ARIC study protocol and all participants provided informed consent.

From 1987–1989, 15 792 participants attended the baseline clinical examination (visit 1). Subsequent visits were at  $\approx$ 3-year intervals (visit 2 in 1990–1992; visit 3 in 1993–1995; visit 4 in 1996–1998) except for visit 5 (2011–2013). Participants have been contacted annually (semiannually beginning in 2012) to obtain information about hospitalizations and for additional data collection. At visit 4, 11 656 participants were asked their birth weight in pounds and ounces. Recalled exact birth weight was converted to kilograms. Those who could not provide their exact birth weight were asked to categorize their birth weight as low, medium, or high. LBW was defined as  $<2.5$  kg, medium birth weight (MBW) as 2.5 to 4 kg, and HBW as  $\geq 4$  kg. Study participants who were born a twin or premature were excluded. This resulted in a total of 9820 participants who provided either their exact birth weight or birth weight category (complete cohort) included in this analysis, of whom 4776 provided their exact birth weight (exact birth weight subgroup). Additional information was obtained from the

baseline examination during visit 1 including anthropometric data, medical history, and cholesterol measurements.

## Outcomes

The primary outcome of interest was incident HF, defined as the first occurrence of a hospitalization with an HF diagnosis according to *International Statistical Classification of Diseases* codes in any position or a death certificate with death from HF in any position.<sup>14</sup> Secondary outcomes included all-cause mortality and myocardial infarction (MI). Follow-up time for outcome events was defined as the time from their baseline examination until the incident event.

Deaths were determined by annual (or later, semiannual) telephone calls, linkage to local hospital and state health department records, or, for those lost to follow-up, linkage to the National Death Index. MI was defined by  $\geq 1$  of the following: evolving diagnostic ECG changes, diagnostic ECG pattern and abnormal cardiac enzymes/biomarkers, or cardiac pain and abnormal enzymes/biomarkers and evolving ST-T pattern or equivocal ECG pattern.<sup>13</sup> Abstracted hospitalization events were classified by the ARIC Mortality and Morbidity Classification Committee.

The following methods were used for ascertainment of events in addition to the scheduled examinations: (1) patients were interviewed annually by phone about interim hospitalizations; (2) local hospitals provided lists of hospital discharges with cardiovascular diagnoses and were reviewed to identify ARIC cohort hospitalizations; and (3) health department death certificate files were continuously surveyed.<sup>15</sup>

## Covariates

The amount of ethanol use, level of education, and presence of left ventricular hypertrophy (LVH) as defined by the sex-specific Cornell voltage criteria on a 12-lead ECG were obtained during visit 1. Hypertension was defined as systolic blood pressure (BP)  $\geq 140$  mm Hg and diastolic BP  $\geq 90$  mm Hg or the use of antihypertensive medications. Diabetes mellitus was defined as a fasting plasma glucose level  $\geq 126$  mg/dL, a nonfasting plasma glucose level  $\geq 200$  mg/dL, or a self-reported history of diabetes mellitus diagnosed by a physician or treatment for diabetes mellitus. Information on prevalent CHD was obtained in visit 1 and defined as presence of MI from the adjudicated visit 1 ECG, by a history of MI, or revascularization such as coronary artery bypass surgery or percutaneous coronary intervention.

## Statistical Analysis

Continuous variables were summarized as mean $\pm$ SD. Categorical variables were summarized by frequency count

(percentage). Comparisons between birth weight groups were conducted using 2-sample Student *t* test and Fisher exact test for continuous and categorical variables, respectively. Variables with a non-normal distribution were summarized by the median (first quartile, third quartile) and compared with the Mann–Whitney *U* test. When comparing >2 groups, ANOVA, Fisher exact test, and Kruskal–Wallis test were used when evaluating continuous, categorical, and non-normal/ordinal data, respectively.

Crude outcome event rates were calculated and compared between birth weight groups using Fisher exact test.

Kaplan–Meier curves were created for each group and compared with the log-rank test. Unadjusted and adjusted Cox proportional hazards models were created for mortality, MI, and incident HF. Variables with *P*<0.10 in univariate birth weight group comparisons were included in the model as were variables selected based on clinical knowledge. The final model then included age, sex, body mass index (BMI), current and former smoking, ethanol intake, hypertension, diabetes mellitus, LVH, income, systolic BP, and high-density lipoprotein cholesterol. All analyses were conducted in SAS version 9.4 (SAS Institute Inc).

**Table 1.** Baseline Characteristics by Birth Weight Category in Complete Cohort

Variable	Overall (N=9820)	LBW (n=331)	MBW (n=8771)	HBW (n=718)	<i>P</i> Value
Age, y	53.9±5.7	53.8±5.7	53.8±5.7	54.1±5.6	0.38
Female	5477 (56)	261 (79)	4941 (56)	275 (38)	<0.001
Race					<0.001
Black	1920 (20)	91 (27)	1723 (20)	106 (15)	
White	7900 (80)	240 (73)	7048 (80)	612 (85)	<0.001
BMI, kg/m <sup>2</sup>					<0.001
BMI <25	3325 (34)	131 (40)	2996 (34)	198 (28)	
BMI 25 to 29.9	3930 (40)	104 (32)	3527 (40)	299 (42)	
BMI ≥30	2259 (26)	95 (29)	2244 (26)	220 (31)	
Smoking status					<0.001
Current	2098 (21)	76 (23)	1833 (21)	189 (26)	
Former	3308 (34)	82 (25)	2939 (34)	287 (40)	
Never	4407 (45)	172 (52)	3395 (46)	240 (34)	
Ethanol intake, g/wk	41.7±88.7	23.8±64.5	41.4±88.0	53.4±103.4	<0.001
Hypertension	2988 (31)	124 (38)	2660 (30)	204 (29)	0.009
CHD	360 (4)	6 (2)	324 (4)	30 (4)	0.16
Diabetes mellitus	679 (7)	29 (9)	597 (7)	53 (7)	0.32
LVH	143 (2)	7 (2)	126 (1)	10 (1)	0.54
Total cholesterol, mg/dL	215±41	218±44	215±41	213±39	0.16
HDL cholesterol, mg/dL	51.8±17	54.9±17	52.2±17	49.1±15	<0.001
Birth weight, kg*	3.50±0.71	2.15±0.32	3.36±0.41	4.80±0.56	<0.001
Income					<0.001
\$0 to \$15 999	1549 (17)	88 (28)	1385 (17)	76 (11)	
\$16 000 to \$34 999	3097 (33)	104 (34)	2767 (33)	226 (33)	
\$35 000+	4675 (50)	118 (38)	4176 (50)	381 (56)	
SBP, mm Hg	119±17	123±18	119±17	119±18	0.002
DBP, mm Hg	73±11	73±10	73±11	72±10	0.30
GFR MDRD, mL/min per 1.73 m <sup>2</sup>	67±11	68±12	68±11	68±11	0.24

Values are expressed as number (percentage) or mean±SD. BMI indicates body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; GFR MDRD, glomerular filtration rate as calculated in the Modification of Diet in Renal Disease study; HBW, high birth weight; HDL, high-density lipoprotein; LBW, low birth weight; LVH, left ventricular hypertrophy; MBW, medium birth weight; SBP, systolic blood pressure.

\*Includes only the 4776 participants who provided exact birth weight.

## Results

Of 9820 participants, 331 (3%) were born LBW, 8771 (89%) NBW, and 718 (7%) HBW (Table 1). Patients were predominantly white (80%) and female (56%), and mean age was  $53.9 \pm 5.7$  years at the time of enrollment. Median follow-up was 22.8 years (25th, 75th percentiles 20.9, 23.7 years). LBW individuals were more often female, had a BMI  $<25$ , and reported lower income. HBW infants were more often male, overweight or obese at ARIC study entry, current or former smokers, with higher ethanol intake and lower high-density lipoprotein cholesterol levels (Table 1). There were no

significant differences in hypertension, diabetes mellitus, LVH, and CHD between birth weight categories at the time of study enrollment. A separate analysis of the 4776 study participants who were able to provide their exact birth weight revealed that 215 (4.5%) were LBW, 3946 (82%) were MBW, and 616 (13%) were HBW (Table 2). LBW among these individuals was also more common in women, those with an adult BMI  $<25$ , and those of lower income. HBW individuals were more often current or former smokers and greater consumers of alcohol, with lower high-density lipoprotein cholesterol levels. Likewise, among participants with known birth weight, hypertension, diabetes mellitus, LVH, and CHD

**Table 2.** Baseline Characteristics by Birth Weight Category in Exact Birth Weight Subgroup

Variable	Overall (N=4776)	LBW (n=215)	MBW (n=3946)	HBW (n=616)	P Value
Age, y	53.3±5.7	53.1±5.4	53.2±5.7	54.2±5.6	<0.001
Female	2827 (59)	185 (86)	2396 (61)	246 (40)	<0.001
Race					0.27
Black	686 (14)	34 (16)	576 (15)	76 (12)	
White	4090 (86)	181 (84)	3370 (85)	539 (88)	
BMI (kg/m <sup>2</sup> )					0.007
BMI <25	1669 (35)	87 (40)	1398 (35)	184 (30)	
BMI 25 to 29.9	1845 (39)	66 (31)	1529 (39)	250 (41)	
BMI ≥30	1261 (26)	62 (29)	1019 (26)	180 (29)	
Smoking status					<0.001
Current	1039 (22)	42 (20)	829 (21)	168 (27)	
Former	1634 (34)	58 (27)	1331 (34)	245 (40)	
Never	2098 (44)	114 (53)	1784 (45)	200 (33)	
Ethanol intake	43.4±89.5	23.1±58.8	43.0±88.4	53.4±103.1	<0.001
Hypertension	1325 (28)	70 (33)	1083 (28)	172 (28)	0.25
CHD	149 (3)	3 (1)	121 (3)	25 (4)	0.15
Diabetes mellitus	332 (7)	21 (10)	265 (7)	46 (8)	0.20
LVH	60 (1)	3 (1)	47 (1)	10 (2)	0.51
Total cholesterol, mg/dL	213±41	217±46	213±40	213±40	0.33
HDL cholesterol, mg/dL	52.6±17	56.8±19	53.0±17	48.7±15	<0.001
Birth weight, kg	3.50±0.71	2.15±0.32	3.36±0.41	4.80±0.56	<0.001
Income					0.003
\$0 to \$15 999	642 (14)	42 (21)	538 (14)	62 (11)	
\$16 000 to \$34 999	1412 (31)	68 (33)	1155 (31)	189 (32)	
\$35 000+	2499 (55)	93 (46)	2074 (55)	332 (57)	
SBP, mm Hg	118±17	121±17	118±17	119±18	0.11
DBP, mm Hg	72±10	72±10	73±10	72±10	0.53
GFR MDRD, mL/min per 1.73 m <sup>2</sup>	67.5±11	66.5±11.6	67.4±11	68.4±10.9	0.039

Values are expressed as number (percentage) or mean±SD. BMI indicates body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; GFR MDRD, glomerular filtration rate as calculated in the Modification of Diet in Renal Disease study; HBW, high birth weight; HDL, high-density lipoprotein; LBW, low birth weight; LVH, left ventricular hypertrophy; MBW, medium birth weight; SBP, systolic blood pressure.

did not differ between birth weight groups at the time of enrollment.

The unadjusted crude outcome rates are displayed in Table 3. Among the complete cohort, there were 2411 (25%) deaths, 1000 (10%) MIs, and 1380 (15%) incident HF events, whereas among those with exact birth weight there were 1087 (23%) deaths, 467 (10%) MIs, and 637 (14%) incident HF events. In both the complete cohort and the exact birth weight subgroup, death and incident HF were significantly related to birth weight category, with numerically more deaths and incident HF in HBW individuals.

Figure 1A through 1C depict the survival curves for incident HF, MI, and all-cause mortality among the complete cohort. There was lower incident HF-free survival and overall survival in individuals with HBW. Analysis limited to the study participants who provided an exact birth weight (Figure 2A through 2C) did not alter the association of HBW with impaired overall survival and incident HF-free survival. Survival free of MI did not differ significantly between birth weight categories in the complete cohort or the subgroup with exact birth weights.

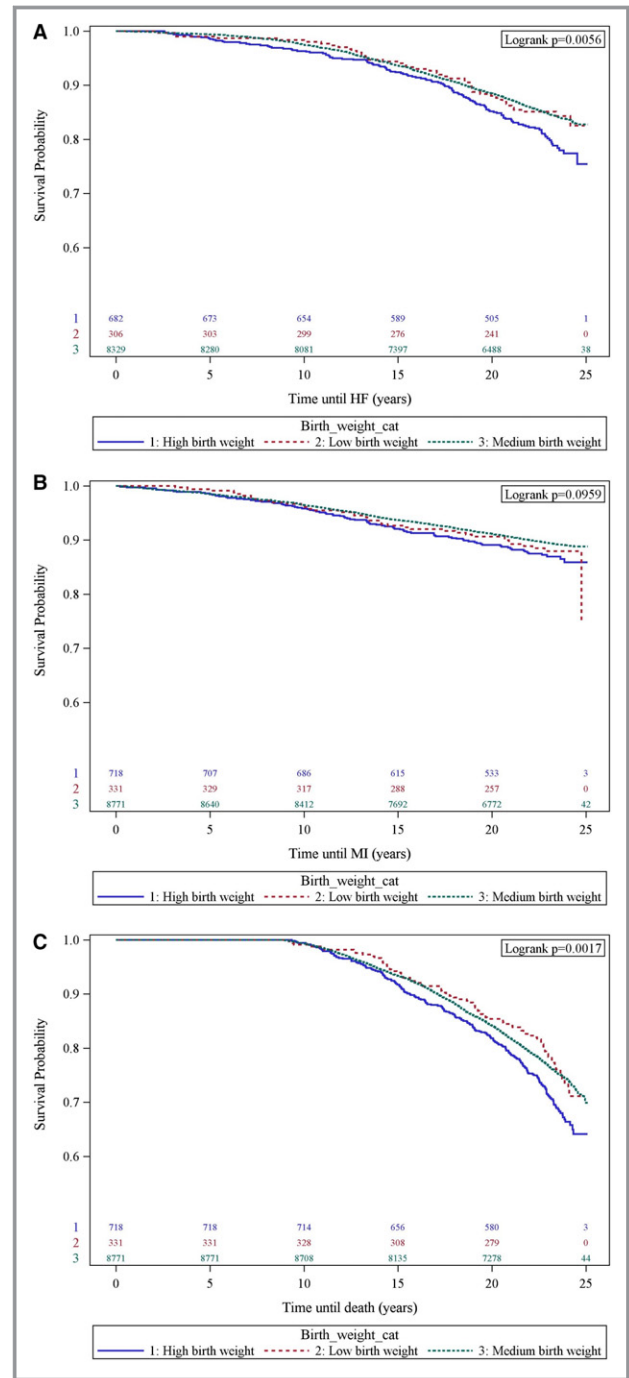
On Cox proportional hazards analysis of the complete cohort, HBW compared with MBW was positively associated with a significantly increased hazard of incident HF (hazard ratio [HR], 1.27; 95% CI, 1.05–1.54 [ $P=0.014$ ]) (Table 4). Other variables independently associated with incident HF included age, female sex, overweight or obesity, current or former smoking, higher ethanol intake, hypertension, diabetes mellitus, LVH, greater income, systolic BP, and high-density lipoprotein cholesterol. LBW was not associated with incident HF. HBW was also associated with a trend toward an increase

in mortality (HR, 1.16; 95% CI, 0.99–1.34 [ $P=0.06$ ]) but not with an increased hazard of incident MI (HR, 1.06; 95% CI, 0.84–1.34 [ $P=0.60$ ]). In the individuals who provided exact

**Table 3.** Outcomes in the Complete Cohort and Exact Birth Weight Subgroup

Outcomes in Complete Cohort					
Variable	Overall (N=9820)	LBW (n=331)	MBW (n=8771)	HBW (n=718)	P Value
Death	2411 (25)	76 (23)	2119 (24)	216 (30)	0.001
MI	1000 (10)	38 (11)	874 (10)	88 (12)	0.11
HF	1380 (15)	45 (15)	1207 (14)	128 (19)	0.010
Outcomes in Exact Birth Weight Cohort					
Variable	Overall (N=4776)	LBW (n=215)	MBW (n=3946)	HBW (n=616)	P Value
Death	1087 (23)	43 (20)	863 (22)	181 (29)	<0.001
MI	467 (10)	26 (12)	368 (9)	73 (12)	0.07
HF	637 (14)	28 (14)	498 (13)	111 (19)	0.002

Values are expressed as number (percentage). HBW indicates high birth weight; HF, heart failure; LBW, low birth weight; MBW, medium birth weight; MI, myocardial infarction.



**Figure 1.** A, Kaplan–Meier estimates of incident heart failure (HF) hospitalization by birth weight category in the complete cohort. B, Kaplan–Meier estimates of incident myocardial infarction (MI) by birth weight category in the complete cohort. C, Kaplan–Meier estimates of all-cause mortality by birth weight category in the complete cohort. The graphs show the unadjusted Kaplan–Meier estimates of the primary end points in the total cohort (HF hospitalization, MI, and all-cause mortality).

birth weights, HBW was also positively associated with an increased hazard of incident HF (HR, 1.36; 95% CI, 1.09–1.69 [ $P=0.006$ ]) (Table 4) compared with MBW but not death (HR,

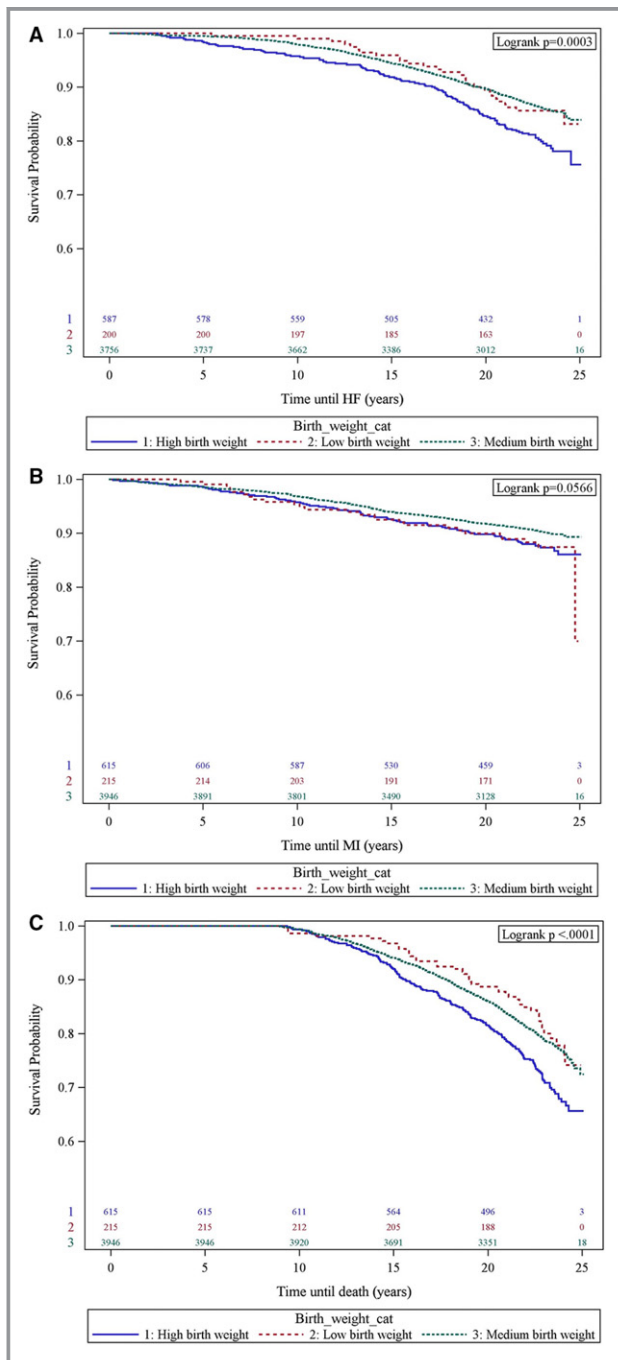
1.14; 95% CI, 0.96–1.35 [ $P=0.13$ ]) or MI (HR, 1.06; 95% CI, 0.81–1.39 [ $P=0.67$ ]).

## Discussion

In this prospective cohort of biracial community-dwelling adults in the United States we observed that, after adjusting for differences in demographics and comorbidities, HBW is significantly associated with a 27% to 36% increased hazard of incident HF, a trend toward increased mortality, and no association with MI compared with MBW. Notably, the association of HBW with incident HF persisted after adjustment for traditional risk factors for HF including age, male sex, BMI, hypertension, diabetes mellitus, overweight or obesity, and smoking, suggesting that HBW may be a novel, independent risk factor for the development of HF.

An estimated 6.5 million American adults have HF with projections that its prevalence will increase 46% from 2012 to 2030, resulting in over 8 million adults with HF. It is estimated that 1 000 000 new cases of HF are diagnosed annually.<sup>16</sup> Data from Olmstead County, MN, indicate that CHD, hypertension, diabetes mellitus, obesity, and smoking are responsible for only 52% of incident HF cases in the population.<sup>2</sup> Thus, although greater adherence to the American Heart Association's Life's Simple 7 guidelines (better profiles in smoking, BMI, physical activity, diet, cholesterol, BP, and glucose) would be expected to lower the incidence of HF<sup>17</sup> associated with traditional risk factors, even strict adherence would not prevent the development of HF in the approximately one half of cases unrelated to traditional risk factors. Thus, the identification of new risk factors is of significant public health importance so that new interventions can be developed to reduce the toll of HF on patients.

The precise mechanism by which HBW is positively associated with incident HF and, possibly, mortality is not known. HBW was not associated with an increased hazard of MI, suggesting that the mechanism of HF associated with HBW is not mediated through myocyte loss caused by MI. The metabolic syndrome represents a cluster of cardiometabolic risk factors including hypertension, insulin resistance, dyslipidemia, and obesity that are associated with an increased risk of HF.<sup>18</sup> Insulin resistance and inflammation are thought to be critical mediators of the syndrome.<sup>19,20</sup> However, numerous studies indicate that LBW, as opposed to HBW, infants are at increased risk for the development of metabolic syndrome.<sup>21–23</sup> Similarly, inflammatory markers are increased in adults born at LBW rather than HBW.<sup>24–27</sup> Thus, the available data suggest that although LBW predisposes to metabolic syndrome and inflammation, LBW is not an independent risk factor for HF. On the other hand, HBW is associated with an increased risk for obesity and type 2 diabetes mellitus,<sup>10–12</sup>



**Figure 2.** A, Kaplan–Meier Estimates of incident heart failure (HF) hospitalization by birth weight category in the exact birth weight subgroup. B, Kaplan–Meier estimates of incident myocardial infarction (MI) by birth weight category in the exact birth weight subgroup. C, Kaplan–Meier estimates of all-cause mortality by birth weight category in the exact birth weight subgroup. The graphs show the unadjusted Kaplan–Meier estimates of the primary end points in the exact birth weight cohort (HF hospitalization, MI, and all-cause mortality).

**Table 4.** Cox Proportional Hazards Model for Incident HF

Variable	Complete Cohort			Exact Birth Weight Subgroup		
	HR	95% CI	P Value	HR	95% CI	P Value
HBW (vs MBW)	1.27	1.05–1.54	0.014	1.36	1.09–1.69	0.006
LBW (vs MBW)	0.98	0.71–1.35	0.89	1.25	0.84–1.86	0.27
Age (per 1-y increase)	1.09	1.08–1.10	<0.001	1.08	1.07–1.10	<0.001
Female	0.76	0.67–0.88	<0.001	0.80	0.65–0.98	0.033
White	1.07	0.91–1.25	0.43	0.96	(0.75–1.23)	0.76
BMI 25 to 29.9 (vs BMI <25)	1.21	1.04–1.41	0.014	1.28	1.02–1.61	0.035
BMI ≥30 (vs BMI <25)	1.94	1.65–2.28	<0.001	1.95	1.53–2.49	<0.001
Current smoking (vs never)	2.87	2.48–3.33	<0.001	3.20	2.57–3.97	<0.001
Former smoking (vs never)	1.34	1.16–1.55	<0.001	1.40	1.14–1.73	0.002
Ethanol intake (per 1-unit increase)	0.99	0.99–1.00	0.024	1.00	0.99–1.00	0.34
Hypertension	1.51	1.31–1.73	<0.001	1.37	1.11–1.69	0.003
Diabetes mellitus	2.36	2.01–2.76	<0.001	2.56	2.04–3.22	<0.001
LVH	1.96	1.43–2.69	<0.001	2.52	1.62–3.92	<0.001
Income \$16 000 to 34 999 (vs \$0–15 999)	0.85	0.73–0.99	0.038	0.88	0.69–1.11	0.28
Income \$35 000+ (vs \$0–15 999)	0.65	0.54–0.76	<0.001	0.65	0.51–0.84	<0.001
SBP (per 1-mm Hg increase)	1.008	1.00–1.01	<0.001	1.01	1.00–1.02	0.001
HDL-C (per 1-mmol/L increase)	0.75	0.63–0.89	<0.001	0.80	0.63–1.02	0.07

BMI indicates body mass index; HBW, high birth weight; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LBW, low birth weight; LVH, left ventricular hypertrophy; MBW, medium birth weight; SBP, systolic blood pressure.

both of which are risk factors for HF.<sup>2</sup> However, after adjustment for obesity and diabetes mellitus, both of which are associated with an increased hazard of HF in this study, HBW remains independently associated with incident HF.

Although the fetal origins of disease hypothesis initially focused on fetal deprivation in LBW infants,<sup>3</sup> its implications extend beyond the LBW population and include babies exposed to other forms of metabolic stress during different critical periods of development, which ultimately result in a disease state. Mothers with gestational diabetes mellitus are at increased risk for delivering a neonate at HBW. Gestational diabetes mellitus results in increased delivery of glucose and other macronutrients to the fetus, resulting in increased fetal production of insulin, the dominant fetal growth hormone. The in utero environment thus promotes the deposition of adipose tissue and increased insulin secretion early in life, thereby setting the fetus up for an abnormal body composition and future disease.<sup>3</sup> It remains to be determined how the fetal milieu imparts a susceptibility to HF in adulthood.

Over 300 000 HBW infants are born in the United States annually.<sup>28</sup> Nonmodifiable risk factors for HBW include parental height, parity, ethnicity, maternal age, infant sex, and previous delivery of an HBW infant. Maternal weight, gestational weight gain, and glycemic control are the risk factors for HBW that are most amenable to intervention

through diet, exercise, and lifestyle modification.<sup>9</sup> Recent data suggest that genetic factors also contribute to birth weight and may drive the development of cardiometabolic diseases in later life.<sup>29</sup>

### Study Limitations

This analysis has certain limitations. First, echocardiographic data were not available to characterize HF as a function of left ventricular structure or function. Second, self-reported birth weight and birth weight categories were used without verification of their accuracy. However, recalled birth weight data obtained in the ARIC study followed expected patterns. Specifically, recalled exact birth weight was higher in males than females, and positively correlated with adult height, weight, and BMI.<sup>30</sup> Furthermore, the characteristics and outcomes of the complete cohort and the exact birth weight subgroup were concordant, suggesting that estimates of birth weight categories were as reliable as measures of exact birth weight. Third, incident HF events not requiring hospitalization were not captured. However, community surveillance reports have demonstrated that 74% of outpatients with HF are hospitalized within 1.7 years.<sup>31</sup> Given the extended follow-up of this cohort, it is likely that most patients diagnosed with HF in the outpatient setting would have been admitted to the

hospital and captured as an incident HF admission. Fourth, as with all observational studies, unmeasured and residual confounding of the relationship between birth weight and cardiovascular outcomes cannot be completely addressed by Cox proportional hazards analysis. Finally, without formal causal mediation analysis we are unable to state precisely how much of the increased hazard of HF is mediated directly by HBW. Given the lack of information on maternal health during the pregnancy, it is possible that HBW is a marker of maternal weight gain or the development of gestational diabetes mellitus.

## Conclusions

In this analysis of biracial community-dwelling adults in the United States, HBW was independently associated with incident HF and may represent a novel risk factor, although the mechanisms remain to be defined. At this time, the most effective intervention would appear to be at the level of maternal nutrition and weight gain. In addition, a history of HBW should be ascertained in young adults for primordial prevention of HF and in older adults for primary prevention.

## Author Contributions

Mr Novak had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Rashid, Brown; acquisition, analysis, or interpretation of data: all authors; drafting of the article: Rashid, Brown; critical revision of the article for important intellectual content: all authors; statistical analysis: Novak; administrative, technical, or material support: all authors; supervision: Brown.

## Disclosures

None.

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