

Association Between Infant Birth Weight and Maternal Cardiovascular Risk Factors in the Health, Aging, and Body Composition Study

JANET M. CATOV, PHD, MS, ANNE B. NEWMAN, MD, JAMES M. ROBERTS, MD, KIM C. SUTTON-TYRRELL, DRPH, SHERYL F. KELSEY, PHD, TAMARA HARRIS, MD, REBECCA JACKSON, MD, LISA H. COLBERT, PHD, SUZANNE SATTERFIELD, MD, DRPH, HILSA N. AYONAYON, PHD, AND ROBERTA B. NESS, MD, MPH

PURPOSE: Mothers who deliver a low-birth-weight (LBW) infant may themselves be at excess risk for cardiovascular disease. We investigated whether older women who bore LBW infants had higher blood pressure, lipid, glucose, insulin, interleukin 6 (IL-6), and C-reactive protein concentrations, and pulse wave velocity compared to women with normal-weight births.

METHODS: Participants were 446 women with a mean age of 80 years and 47% black. Women reported birth weight and complications for each pregnancy. Analysis was limited to first births not complicated by hypertension or preeclampsia.

RESULTS: Women who had delivered a first-birth infant weighing less than 2500 g had a lower body mass index (BMI) compared with women with a normal-weight (≥ 2500 g) infant (26.7 versus 28.4 kg/m²; $p = 0.02$), but they had a larger abdominal circumference for BMI (97.9 versus 95.5 cm; $p = 0.05$). They also were marginally more likely to be administered antihypertensive medication ($p = 0.06$). After adjustment for BMI, race, and age, women with a history of a small infant had elevations in systolic blood pressure ($p = 0.05$) and greater IL-6 levels ($p = 0.02$) and were more insulin resistant ($p = 0.05$) compared with women with a normal-weight infant.

CONCLUSIONS: These findings suggest that a history of LBW delivery identifies women with elevated cardiovascular risk factors.

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INTRODUCTION

Mothers who deliver a low-birth-weight (LBW) infant may themselves be at excess risk for cardiovascular disease (CVD). Large registry-based observational studies found that a LBW delivery increased maternal risk for cardiovascular death by 7- to 11-fold (1, 2), and risk for cardiovascular death was two to three times greater for women who delivered a preterm infant compared with those who delivered an

infant at term (3, 4). In two studies that related reproductive history to later occurrence of cardiovascular risk factors, bearing a LBW infant was related inversely to systolic blood pressure (5, 6) and maternal insulin resistance (6).

LBW and its components, idiopathic preterm delivery and intrauterine growth restriction, share many risk factors with CVD. These include black race (7, 8), young maternal age (8, 9), inflammation and infection (10), cigarette smoking (8, 11), hypertension (12, 13), and nongestational diabetes (14). It was proposed that unsuccessful adaptation to the profound biologic demands of pregnancy may result in growth restriction and perhaps other causes of LBW, and reasons for maladaptation to pregnancy could involve metabolic and vascular disease pathways (15).

Most studies of LBW and CVD to date used large registries of delivery data matched to mortality data. As such, they had limited ability to adjust for such potential confounders as lifetime smoking exposure and weight gain. Furthermore, they did not characterize outcomes beyond 10 to 20 years postpartum. We sought to assess the association between delivery of a LBW infant and increased cardiovascular risk among older women. Specifically, we investigated whether women who bore LBW infants had later elevations in blood pressure, pulse pressure, lipid profiles, glucose,

From the Department of Epidemiology, University of Pittsburgh Graduate School of Public Health (J.M.C., A.B.N., K.C.S.-T., S.F.K., R.B.N.); Magee Womens Research Institute and Department of OB/GYN and Reproductive Sciences, University of Pittsburgh (J.M.R.), Pittsburgh, PA; Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, MD (T.H.); Departments of Obstetrics and Gynecology (R.J.) and Epidemiology and Biostatistics (H.N.A.), University of California, San Francisco, CA; Department of Kinesiology, University of Wisconsin, Madison, WI (L.H.C.); and University of Tennessee, Memphis, TN (S.S.).

Address correspondence to: Janet M. Catov, PhD, MS, Department of Epidemiology, University of Pittsburgh, Graduate School of Public Health, 130 DeSoto Street, Pittsburgh, PA 15261. Tel.: (412) 383-2626; fax: (412) 383-1121. E-mail: jmcst43@pitt.edu

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Selected Abbreviations and Acronyms

LBW = low birth weight
BMI = body mass index
IL-6 = interleukin 6
IUGR = intrauterine growth restriction
CVD = cardiovascular disease
CRP = C-reactive protein
aPWV = aortic pulse wave velocity

insulin, interleukin 6 (IL-6), C-reactive protein (CRP), and pulse wave velocity.

METHODS

Participants

The Health, Aging, and Body Composition Study is a large ongoing epidemiologic study of how changes in body composition affect morbidity, disability, and mortality. A total of 3075 well-functioning community-dwelling participants (50% female) were enrolled in Pittsburgh, PA, and Memphis, TN, in 1997 to 1998. Recruitment procedures have been described elsewhere in detail (16). All participants signed an informed consent approved by the Institutional Review Board at the University of Pittsburgh. Eligibility criteria included age of 70 to 79 years, self-report of no difficulty walking one quarter mile or climbing 10 steps without resting, no difficulty performing basic activities of daily living, no use of assistive devices to ambulate, no history of active treatment for cancer in the prior 3 years, and no plans to move out of the area in the next 3 years.

For 608 women in the Pittsburgh cohort who were interviewed in 2003 and 2004 as part of the year 7 follow-up visit, we included questions about pregnancy history. Five hundred ninety-seven women (98%) provided pregnancy history details. Of 507 women (85%) who had at least one live birth, 466 women (92%) provided their firstborn's birth weight. Mean age at this interview was 80 years, and 47% of women were black.

Recalled Birth Characteristics

Women were asked to report the birth weight for each pregnancy lasting more than 6 months. Smoking status, preterm delivery (in weeks), and selected complications (hypertension during pregnancy and preeclampsia) also were assessed for each pregnancy. Analysis was limited to first births because birth weight and gestational age are recalled more accurately for first births compared with subsequent births (17). We validated the accuracy of the recall of infant birth weight for first births in a randomly selected group of women in our study (intraclass correlation coefficient, 0.96) and showed that these older women reported birth weight data reliably across race, age, income, and education strata

(18). In addition, our validation study indicated that mothers underestimated the birth weight of their first birth by 44 g compared with actual birth certificate or hospital records (18), and these results were remarkably consistent with other studies of maternal recall of infant birth weight (17, 19). We excluded women who reported hypertension during pregnancy ($n = 11$; 2.4%) or preeclampsia ($n = 11$; 2.4%) to describe maternal prognosis after delivery of a LBW infant beyond the well-known increase in CVD risk for women with these pregnancy complications (20–25).

Infant birth weight was converted to grams for the purposes of the analysis and evaluated as a continuous variable and a dichotomous LBW variable (< 2500 versus ≥ 2500 g). LBW also was stratified by preterm delivery (< 37 weeks gestation). This stratification allowed us to identify infants who were small and preterm versus infants small at term.

Cardiovascular Risk End Points

The primary end points were cardiovascular risk factors assessed at baseline (1997 to 1998). The average of two sitting blood pressures was used for analysis, measured in the right arm after a 5-minute rest by using a mercury sphygmomanometer (26). Pulse pressures were calculated (systolic blood pressure minus diastolic blood pressure). Total cholesterol, high-density lipoprotein, triglycerides, and glucose were assayed from fasting serum by using a colorimetric technique on a Johnson & Johnson Vitros 950 analyzer (New Brunswick, NJ). Fasting glucose was measured in all participants, including those with diabetes, and serum insulin (determined by using a radioimmunoassay kit; Pharmacia, Uppsala, Sweden) was measured in all participants except those with insulin-dependent diabetes. Insulin resistance was estimated by means of the homeostasis model assessment, the product of fasting glucose and insulin concentrations in millimolar divided by 22.5 (27). Low-density lipoprotein was estimated by using the Friedwald equation, and for hemoglobin A1C, ion-exchange high-performance liquid chromatography (Biorad [Hercules, CA] Variant analyzer) was used. Measures of the inflammatory markers IL-6, tumor necrosis factor α , and CRP were obtained from frozen stored serum collected by means of venipuncture after an overnight fast. Cytokines were measured in duplicate by using an enzyme-linked immunosorbent assay kit from R&D Systems (Minneapolis, MN). Serum CRP also was measured in duplicate by using an enzyme-linked immunosorbent assay based on purified protein and polyclonal anti-CRP antibodies. Blind duplicate analyses showed average interassay coefficients of variation of 10.3% (IL-6), 8.0% (CRP), and 15.8% (tumor necrosis factor α).

Aortic pulse wave velocity (aPWV) was assessed as an indicator of aortic stiffness and was measured from

simultaneous Doppler flow signals obtained from the right carotid and right femoral arteries by use of nondirectional transcutaneous Doppler flow probes (model 810A; 9.0- to 10-MHz probes; Parks Medical Electronics Inc. [Aloha, OR]). Replicate measures of aPWV showed intraclass correlations of 0.88 between sonographers and 0.84 between readers.

Covariates

Covariates considered included sociodemographic status (race, education, and income), pregnancy history (smoking status during pregnancy and age at first birth), smoking history (characterized as never, former, or current and measured in pack-years; average packs of cigarettes smoked daily multiplied by years smoking), presence of diabetes (physician diagnosed and confirmed with medication) or hypertension (physician diagnosed and medication use or systolic blood pressure >135 mm Hg and diastolic blood pressure >85 mm Hg), and current use of statins or antihypertensives. We also evaluated body composition variables, including body mass index (BMI; kilograms per square meter), abdominal circumference, and visceral fat (estimated by means of computed tomographic scans between the fourth and fifth lumbar vertebrae).

Statistical Analysis

Results are presented for 446 women with complete information on all birth weight variables. Student *t*-test or chi-square tests were used to detect differences in means (\pm SE) or proportions between women who delivered LBW versus normal-weight infants. Inflammatory markers, triglycerides, glucose, insulin, hemoglobin A1C, and aPWV were log-transformed for the purposes of analysis, and results are presented as geometric means.

Analysis of covariance was used to detect differences in mean values of body composition variables for women who delivered normal versus LBW infants, adjusted for race and age. Abdominal circumference and visceral fat were adjusted further for BMI. Analysis of covariance also was used to detect differences in mean values (adjusted for BMI, race, and age) for each cardiovascular risk factor dichotomized into LBW and normal-birth-weight groups. In secondary analysis, current smokers were removed. Moreover, women were stratified by race to determine whether results were consistent between black and white women. Deliveries also were stratified into LBW and preterm versus LBW and not preterm. Infant birth weight also was considered as a continuous linear and quadratic variable in regression models, adjusted for covariates associated with LBW or CVD, to determine an independent relationship with selected CVD risk factors. Curves produced by nonparametric regression smoothing with a locally weight regression

scatterplot smoother were inspected to observe the nature of the relationship modeled. All tests were two sided, and differences with $p < 0.05$ are considered significant; differences less than 0.1 are considered marginally significant.

RESULTS

For 446 women who recalled the birth weight of their first born, mean birth weight was 3117 ± 582 (SD) g, and 56 women (12.6%) recalled having a baby of birth weight less than 2500 g. Thirty first births were reported as premature (6.2%); 18 of these also were LBW. Mean age at the study baseline visit was 73.1 ± 2.8 (SD) years, average maternal age at first birth was 23.5 ± 4.4 (SD) years, and mean number of live births was 3.0 ± 1.5 (SD).

Women who delivered a LBW infant (<2500 g.) were significantly more likely to be black compared with women who delivered a normal-weight infant, and among smokers, women who delivered LBW infants had greater lifetime exposure to cigarettes, measured in pack-years (Table 1). They also were more likely to have been younger than 20 years at the time of their first births and, as expected, were more likely to deliver preterm compared with women who delivered a normal-weight infant. Women who delivered a LBW infant also were marginally more likely to be administered antihypertensive medication at the baseline visit compared with women who delivered a normal-weight first birth.

After adjustment for race and age (Table 2), women who delivered a LBW infant had a lower average BMI at baseline compared with women with a normal-weight infant (26.7 versus 28.4 kg/m²; $p = 0.02$), but average abdominal circumferences of both groups of women were not different ($p = 0.64$). However, after additional adjustment for BMI, women who delivered small infants had a larger mean abdominal circumference (97.9 versus 95.5 cm; $p = 0.05$) and borderline greater visceral fat content ($p = 0.07$) compared to women with normal-weight first births.

Women with a prior LBW baby had significantly greater IL-6 levels compared to women with normal-weight infants after adjustment for race, age, and BMI ($p = 0.02$). CRP levels showed a similar, but weaker, trend ($p = 0.06$). Systolic blood pressure was elevated in this group of women after adjustment for race, age, and BMI (143.1 versus 137.3 mm Hg; $p = 0.05$), and pulse pressure was marginally elevated ($p = 0.07$). For women who delivered LBW versus normal infants, fasting insulin ($p = 0.06$) and triglyceride levels ($p = 0.07$) were marginally elevated after adjustment for BMI, race, and age, and they were more insulin resistant ($p = 0.05$). These results did not change when current smokers ($n = 37$) were excluded. Additional adjustment for lifetime cigarette exposure measured in pack-years had no substantial effect on most estimates, with the exception

TABLE 1. Maternal characteristics according to birth weight of first birth

	Normal birth weight (≥2500 g) (n=390)	Low birth weight (<2500 g) (n=56)	<i>p</i> ^a
Age at baseline (years)	73.0 ± 0.1	73.3 ± 0.3	0.477
Black (%)	41.3%	62.5%	0.003
Education (%)			
<High school	15.4	12.5	0.760
High school graduate	48.0	46.4	
Postsecondary	36.7	41.1	
Family income (%)			
<\$10,000	12.1	18.9	0.070
\$10,000–\$25,000	42.1	52.8	
\$25,000–\$50,000	34.2	17.0	
\$50,000+	11.5	11.3	
Smoking (%)			
Never	57.7	46.4	0.218
Former	34.6	41.1	
Current	7.7	12.5	
Pack-years smoking	12.6 ± 1.1	19.6 ± 3.5	0.036
Smoked during pregnancy (%)	21.2	29.1	0.185
Age at first birth (years)	23.6 ± 0.2	22.5 ± 0.6	0.065
Younger than 20 years at first birth (%)	16.2	30.4	0.010
Premature delivery (<37 weeks) (%)	2.3	32.1	<0.0001
Diabetes mellitus (%)	9.3	9.1	0.969
Antihypertensives (%)	50.9	64.3	0.061
Hypertension (%)	60.3	69.6	0.177
Statins (%)	20.3	19.6	0.908

Values expressed as percentage or mean ± SE.
^aChi-square or *t*-test.

that it attenuated results for the inflammatory markers, but IL-6 levels (2.21 versus 1.83 pg/mL; *p* = 0.04) remained significantly elevated in women who delivered a LBW infant compared to women with a normal-weight infant. CRP levels were no longer significantly different between groups. Adjustment for abdominal circumference significantly attenuated only the elevation in triglyceride levels in women who had delivered a prior LBW infant compared with women who delivered normal-weight infants (133.8 versus 127.8 mg/dL; *p* = 0.48). Additional adjustment for family income did not alter any estimates (results not shown).

Considering white (*n* = 249) and black women (*n* = 195) separately, those in both groups with LBW infants had larger abdominal circumferences and greater elevations in systolic blood pressure and levels of triglycerides, IL-6, and CRP (adjusted for BMI and age) compared to women with normal-weight infants. The one race-specific finding related to fasting insulin levels. There was no difference in fasting insulin levels among black women who delivered LBW infants compared to black women with normal-weight infants (8.76 versus 8.25 IU/mL; *p* = 0.57); however, fasting insulin levels were significantly elevated in white women

with a LBW versus normal-birth-weight infant (8.17 versus 6.23 IU/mL; *p* = 0.02).

Despite small numbers (*n* = 18), the subgroup of women who delivered an infant that was both preterm and LBW had greater average lifetime cigarette smoking exposure (25.4 versus 12.7 pack-years; *p* = 0.02), larger adjusted abdominal circumferences (99.6 versus 95.3 cm; *p* = 0.03), and marginally greater adjusted systolic blood pressures (146.9 versus 137.3 mm Hg; *p* = 0.06) compared to women with normal-weight infants. Women with term LBW infants (*n* = 38) had greater adjusted triglyceride levels (148.9 versus 126.7 mg/dL; *p* = 0.03) and visceral fat content (129.3 versus 110.4 cm²; *p* = 0.01) compared with women who delivered normal-weight infants.

We also explored the relationship between infant birth weight as a continuous variable and maternal systolic blood pressure. Each kilogram decrease in infant birth weight was associated with a 16.1 ± 7.2 (SE) mm Hg increase in maternal systolic blood pressure (*p* = 0.027) after adjustment for age at study baseline, race, smoking, diastolic blood pressure, and BMI. A quadratic birth weight term also was borderline significant (*p* = 0.075), suggesting the possibility of a curvilinear relationship (Fig. 1). That is, systolic blood pressure was highest at low birth weights, dipped at normal birth weights, and was elevated again at high birth weights. Infant birth weight as a continuous variable did not have an independent linear or quadratic relationship with any other CVD risk factors.

DISCUSSION

In this group of older women, those who delivered a infant who weighed less than 2500 g had elevations in levels of vascular, inflammatory, and metabolic markers independent of age, race, BMI, and lifetime exposure to cigarette smoking. These associations were present in women evaluated up to 60 years postpartum. These data support a small, but emerging, body of evidence that LBW pregnancies, because of either fetal growth restriction or preterm delivery, may involve pathways that lead to poor pregnancy outcomes during the reproductive years and greater cardiovascular risk later in life.

Our findings are consistent with those from the only two comparable studies that related cardiovascular risk factors to reproductive history. Fifty years after a LBW first pregnancy, Lawlor et al. (6) reported that systolic blood pressure was elevated and insulin resistance was more common. Walker et al. (5) also reported an inverse association between maternal systolic blood pressure and infant birth weight 19 years after delivery.

Maternal prepregnancy BMI is positively correlated with infant birth weight (28–30), and, as expected, small women

TABLE 2. Comparison of selected maternal characteristics according to delivery of a low birth weight (<2500 g) versus normal-weight (≥2500 g.) infant (adjusted for race, age, and BMI)

	Adjusted for age and race			Adjusted for BMI, age, race		
	Normal birth weight (g) ≥2500 (n = 390)	Low birth weight (g) <2500 (n = 56)	p	Normal birth weight (g) ≥2500 (n = 390)	Low birth weight (g) <2500 (n = 56)	p
Body composition						
BMI, study baseline ^a (kg/m ²)	28.4	26.7	0.018	28.4	26.7	0.018
Abdominal circumference (mm)	95.8	94.9	0.640	95.5	97.9	0.048
Visceral fat (cm ²)	111.9	110.7	0.875	110.4	121.9	0.070
Lipids						
Total cholesterol (mg/dL)	218.5	220.9	0.661	220.3	218.5	0.618
High-density lipoprotein (mg/dL)	60.0	63.0	0.232	60.2	61.3	0.611
Low-density lipoprotein (mg/dL)	130	127.3	0.600	129.9	128.1	0.726
Triglycerides (mg/dL)	127.4	137.0	0.262	126.7	142	0.071
Vascular						
Systolic blood pressure (mm Hg)	137.4	142.5	0.088	137.3	143.1	0.048
Diastolic blood pressure (mm Hg)	72.2	73.3	0.468	72.2	73.5	0.359
Pulse pressure (mm Hg)	65.1	69.2	0.106	65.1	69.7	0.069
Pulse wave velocity (cm/s)	776.7	757.6	0.682	772.8	780.6	0.854
Metabolic						
Fasting glucose (mg/dL)	98.2	97.1	0.727	97.9	99.2	0.723
Fasting insulin ^b (IU/mL)	7.13	7.60	0.446	7.07	8.10	0.064
Insulin resistance ^b (HOMA)	1.61	1.76	0.342	1.60	1.88	0.045
Hemoglobin A _{1c} (%)	6.24	6.22	0.708	6.23	6.25	0.881
Inflammatory						
Interleukin 6 (pg/mL)	1.82	2.28	0.016	1.82	2.26	0.021
Tumor necrosis factor α (pg/mL)	3.26	3.07	0.312	3.27	3.02	0.194
C-Reactive protein (μg/mL)	1.96	2.50	0.047	1.96	2.48	0.059

BMI = body mass index; HOMA = homeostasis model assessment.

^aAdjusted for race and age.

^bPersons without diabetes.

in our study had smaller babies. However, our results suggest that women who delivered a LBW infant had a distinct body composition in older adulthood, with low BMI, high abdominal circumference for BMI, and somewhat greater visceral fat for BMI. The concept of a “metabolically obese, normal weight” individual has been described as an individual with a relative preponderance of visceral fat, modest overall weight gain, insulin resistance, and greater risk for type 2 diabetes (31–33). Women who deliver a LBW infant could be at greater risk to develop these attributes. We were unable to determine whether these women had larger abdominal circumferences before their first births, although there is evidence that prepregnancy waist-hip ratio correlated positively with infant birth weight (29), suggesting that abdominal adiposity in these women with small babies may occur postpartum. Interestingly, women in our study with a LBW infant did not have greater rates of diabetes.

Women in our study who delivered a LBW infant were more likely to have higher systolic blood pressures and somewhat more likely to be administered antihypertensive medications. Previous studies showed that women with elevated blood pressure before or during pregnancy, without superimposed preeclampsia, have smaller babies and an elevated risk

for preterm delivery (24, 25). In addition, small blood pressure elevations during pregnancy in women who remain normotensive may modestly restrict fetal growth (34), although there is conflicting evidence in this area. These data suggest that occult vascular disease, preexisting before the first birth, could lead to pregnancies complicated by placental insufficiency, resulting in smaller babies or preterm delivery (23, 35–39) and manifesting later in life as hypertension.

Levels of the inflammatory markers IL-6 and CRP also were elevated in women with a LBW infant, suggesting that these women may be predisposed to upregulation of inflammation that has been associated with growth-restricted pregnancies (40, 41) and increased CVD risk (42, 43). Alternatively, or additionally, elevated levels of inflammatory markers could reflect the increased central adiposity and visceral fat accumulated in these women as they age (44, 45); however, additional adjustment for abdominal circumference did not alter these estimates.

Women in our study who delivered a LBW infant had greater fasting insulin levels than women with normal-weight infants, were more insulin resistant, but were not more likely to have diabetes. These findings exactly replicate the study by Lawlor et al. (6). Although visceral fat

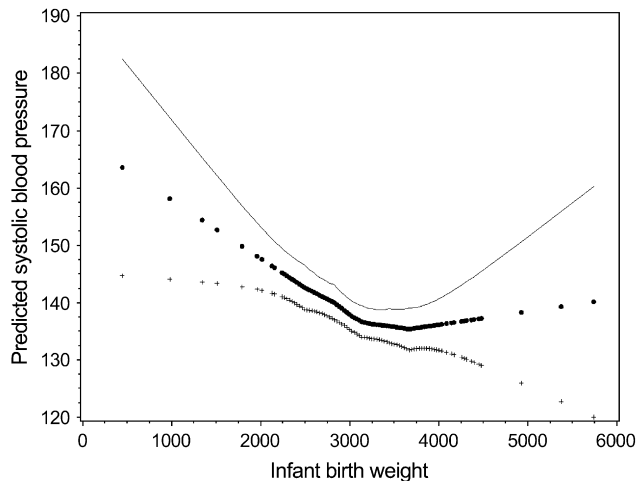


FIGURE 1. Unadjusted association between infant birth weight and predicted maternal systolic blood pressure (dark line), with 95% confidence intervals.

independent of BMI is a particularly strong marker of insulin resistance in middle-aged (46) and elderly adults (47), it may have developed later in adulthood in women with a LBW delivery. This suggestion derives from the observation that diabetes mellitus before pregnancy increases the risk for preterm delivery, but not typically LBW (30, 48). Furthermore, the presence of insulin resistance without diabetes mellitus may reflect a recent pathophysiologic state that has not progressed. Our findings also suggest that elevated insulin levels may be limited to white women, a finding consistent with other reports of racial differences in measures of insulin resistance (49).

There are several strengths to our study. The strong representation of black women in the Health, Aging, and Body Composition Study cohort made it an ideal population to study because rates of LBW and CVD in black women are almost twice those in white women (50, 51). In addition, we were able to investigate a variety of cardiovascular risks and had extensive data for body composition.

Our study also has limitations. Because pregnancy history data were collected through recall, our results may be imprecise. We validated both the accuracy and reliability of maternal recall of birth-weight data in a sample of women in our study (18), and our results were consistent with the one other study that investigated the validity of maternal recall of infant birth weight, preterm status, and cigarette smoking compared with hospital records reflecting actual events that occurred an average of 32 years after delivery (19). That several characteristics of women in our study who delivered a LBW infant were consistent with well-known attributes associated with this outcome (low socioeconomic status, black race, greater rates of smoking, and young maternal age) is reassuring. Nonetheless, assuming

the presence of misclassification, it is unlikely that women would overreport or underreport infant birth weight systematically based on CVD risk; thus, the impact of recall bias likely would be that our observed associations were attenuated.

Although we excluded women who reported pregnancies complicated by preeclampsia or hypertension in our study, it is possible that these conditions were misreported and our findings could be caused by misclassification. The rate of preeclampsia in women in our study (2.4%) is consistent with national estimates (52). In addition, one study showed that maternal recall of preeclampsia had a 97% negative agreement compared with hospital records (53), providing some reassurance that preeclampsia cases were not grossly misclassified in our study. We also have no way to know whether the increased CVD risk that we observed was the result of earlier risk preexisting before the first birth or something about the birth itself.

Community-dwelling well-functioning women who survive to age 80 with reasonable cognitive function are healthier than the general population, thus limiting the generalizability, but not the validity, of our findings. Previous studies identified an association between infant birth weight and maternal cardiovascular death in relatively young women (1-4), suggesting that the impact of survival bias in our study would be to underestimate the true magnitude of an effect.

Our ability to distinguish between preterm and growth-restricted LBW infants was limited, although our results suggest there may be long-term differences in women with one versus both pregnancy complications. One study found that women who delivered small and preterm infants had a four-fold increase in risk for ischemic heart disease later in life: LBW or preterm delivery considered separately each conferred about a twofold increase in risk (2). This area requires further investigation in a population in which gestational age can be precisely characterized and small-for-gestational-age infants can be identified. In addition, it would be important in future studies to adjust infant birth weight for maternal prepregnancy weight; these data were not available to us.

Our results confirm that older women who had a first-pregnancy complicated by LBW had elevations in systolic blood pressure, IL-6, CRP, and fasting insulin compared to women with normal-weight infants. They also had lower BMIs compared with women who delivered normal-weight infants, but larger abdominal circumferences adjusted for BMI. Our study provides epidemiologic evidence of an inverse association between infant birth weight and maternal risk for CVD. These findings need to be replicated and extended, but raise the possibility that subclinical maternal chronic disease risk may contribute to the persistent public health challenges of LBW and preterm delivery. LBW may

mark women who could benefit from screening and intervention to delay the onset of CVD.

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