

# Preterm Delivery and Later Maternal Cardiovascular Disease Risk

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**Background:** Women who have delivered a preterm infant are at elevated risk for cardiovascular disease (CVD), but mechanisms for this association are not understood.

**Methods:** In a cross-sectional study we investigated whether older women with a history of preterm birth (<37 weeks) had a higher prevalence of CVD. Participants were 446 women (mean age 80 years; 47% black) enrolled in the Pittsburgh, PA field center of The Health, Aging and Body Composition Study. Women reported preterm status, birth weight, smoking status, and selected complications for each pregnancy. CVD status was determined by self-report and hospital records. Analysis was limited to first births not explicitly complicated by hypertension or preeclampsia.

**Results:** Women who had delivered a preterm infant (on average 57 years in the past) had a higher prevalence of CVD. After adjustment for race, age, blood pressure, pulse wave velocity, interleukin-6, high-density lipoprotein cholesterol, and statin use, the odds ratio for CVD among women who delivered a preterm infant was 2.85 (95% confidence interval = 1.19–6.85) compared with women who had delivered term infants weighing more than 2500 g. This relationship was not altered by lifetime smoking history. There was evidence of negative confounding by statin use and high-density lipoprotein cholesterol. Among women delivering infants who were both preterm and low birth weight (<2500 g), the odds ratio was 3.31 (1.06–10.37) for CVD compared with women with term, normal weight infants.

**Conclusions:** These results suggest that vascular and metabolic factors account for some but not all of the increased prevalence of CVD among women many years after a preterm birth.

(*Epidemiology* 2007;18: 733–739)

Women who have delivered a preterm infant may be at elevated risk for later cardiovascular disease (CVD). Large registry-based observational studies have found that women who had delivered a preterm infant had a 2- to 3-fold higher risk for cardiovascular death compared with those who delivered at term.<sup>1–3</sup> Delivery of a low birth weight (LBW) infant (60% of whom are probably also preterm<sup>4</sup>) has been associated with a 7- to 11-fold higher risk for cardiovascular death.<sup>2,5</sup> In the few studies that have related pregnancy outcome to later maternal cardiovascular risk factors, infant birth weight was inversely related to maternal systolic blood pressure,<sup>6–8</sup> insulin resistance,<sup>7,8</sup> and inflammation.<sup>8</sup> To our knowledge, no studies have investigated the biologic mechanisms that may link preterm birth with maternal cardiovascular risk.

Underlying risk factors for CVD may affect a woman's ability to successfully adapt to the vascular or metabolic demands of pregnancy, leading to poor pregnancy outcomes during the reproductive years and higher cardiovascular risk later in life.<sup>9</sup> Abnormal placentation, perhaps due to preexisting, subclinical vascular abnormalities, has been associated with preterm birth<sup>10,11</sup> and growth restriction,<sup>12</sup> even in non-preeclamptic pregnancies. In addition, infection or inflammation has been implicated in preterm birth<sup>10,13,14</sup> and fetal growth restriction,<sup>13,15</sup> as well as CVD risk.<sup>16</sup>

In a cross-sectional study of older women, we investigated the relationship among recalled pregnancy characteristics, biologic markers of cardiovascular risk, and CVD status. Specifically, we examined whether women without explicit preeclampsia or hypertension in pregnancy, who reported that they had borne preterm infants (<37 weeks gestation) with or without LBW (<2500 g), had an increased prevalence of CVD compared with women who had term births  $\geq$ 2500 g. Our goal was to identify risk factors that could be elevated

Submitted 18 December 2006; accepted 25 July 2007.

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Supported by grants N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106.

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ISSN: 1044-3983/07/1806-0733

DOI: 10.1097/EDE.0b013e3181567f96

many years after a preterm birth and to determine how these might affect CVD status.

## METHODS

### Participants

The Study of Health, Aging and Body Composition (Health ABC) is a large on-going epidemiologic study of changes in body composition, morbidity, disability, and mortality. A total of 3075 community-dwelling participants (50% women) were enrolled in Pittsburgh, Pennsylvania and Memphis, Tennessee in 1997–1998. Recruitment procedures have been described elsewhere in detail.<sup>17</sup> All participants signed an informed consent agreement approved by the institutional review board at the University of Pittsburgh. Eligibility criteria included: age 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 subsequent 3 years. Based on these criteria, participants were considered to be functioning well.<sup>18</sup>

The 608 women in the Pittsburgh cohort who were interviewed in 2003 and 2004 as part of the year 7 follow-up visit, were asked questions about pregnancy history. Pregnancy history details were provided by 597 women (98%). Of the 507 (85%) women who had at least 1 live birth, 466 (92%) provided their first-born's term/preterm birth status and birth weight. Mean age at this interview was 80 years, and 47% of the women were black. We excluded women who reported hypertension or preeclampsia during pregnancy ( $n = 20$ ), to describe maternal prognosis beyond the well-known increase in cardiovascular risk for women with these pregnancy complications.<sup>19–24</sup> Our analysis was based on the recalled birth characteristics of 446 women and their CVD status at the time of the interview.

### Recalled Birth Characteristics

Women were asked to report the preterm birth status (<37 weeks) for each pregnancy lasting more than 6 months. Smoking during pregnancy, birth weight, and selected complications (hypertension during pregnancy and preeclampsia) were also assessed for each pregnancy. Analysis was limited to first births, as birth characteristics are recalled more accurately for first births compared with subsequent births.<sup>25,26</sup> We validated the accuracy of the recall of infant birth weight for first births among a randomly selected group of women in our study (intraclass correlation coefficient, 0.96), and found that these older women reported birth weight data reliably at 2 time points across race, age, income, and education strata.<sup>25</sup> Mothers underestimated the birth weight of their first birth by an average of 44 g when compared with actual birth certificate or hospital records<sup>25</sup>; these results were remarkably

consistent with other studies of maternal recall of infant birth weight among younger women.<sup>26,27</sup>

Infants reported as having been born at <37 weeks were considered preterm. Infant birth weight was converted to grams for the purposes of the analysis, and was evaluated as both a continuous and dichotomous (<2500 g vs.  $\geq 2500$  g) variable. LBW was stratified by preterm delivery to identify 2 subsets of deliveries that were either small and preterm, or small and term. Women with term births  $\geq 2500$  g were the referent group.

### CVD Status

Prevalent CVD was ascertained at baseline (1997–1998) via self-report and was validated with algorithms that included selected medications and electrocardiogram (ECG) results.<sup>28</sup> There were 101 participants with the following prevalent conditions: myocardial infarction, angina, coronary artery bypass surgery, or percutaneous transluminal angioplasty (70 participants); ECG evidence of myocardial infarction (3 participants); stroke (22 participants); or peripheral vascular disease (6 participants). Incident events that occurred after baseline were ascertained by phone contact or at the clinic examination every 6 months (1998 to 2002), and validated by medical record review.<sup>29</sup> Among 31 participants with incident cardiovascular events, 30 had a myocardial infarction or angina and 1 had a stroke. Overall, 132 women (30%) were identified with CVD at the time of the interview.

### Potential Confounders

Potential confounders included characteristics that have an established association with preterm birth or CVD. Socio-demographic and lifestyle variables included age, race, education, income, and smoking status (characterized as ever vs. never; and measured in pack-years [the average packs of cigarettes smoked daily multiplied by years smoking]). Participants reported annual family income at study baseline, and also described how well their income fit their needs (poorly, fairly well, very well). Due to the high number of missing values for family income ( $n = 63$ , 14%), a low socioeconomic indicator variable was calculated for women who reported either the lowest quartile of family income or the lowest level of income adequacy.

High-density lipoprotein (HDL) cholesterol and triglycerides were measured on fasting serum by a colorimetric technique on a Johnson and Johnson Vitros 950 analyzer (New Brunswick, NJ). Low-density lipoprotein (LDL) cholesterol was estimated with the Friedewald calculation. Vascular measures included systolic blood pressure<sup>28</sup> and pulse wave velocity<sup>30</sup> (measured from simultaneous Doppler flow signals obtained from the right carotid and right femoral arteries by use of nondirectional transcutaneous Doppler flow probes). Hypertension was defined via self-report and medication use, or as systolic blood pressure above 135 and diastolic blood pressure above 85. Presence of diabetes mel-

litus (self-report and medication) or metabolic syndrome (National Cholesterol Education Program III definition<sup>31</sup> as 3 or more of the following: abdominal circumference  $>88$ ; blood pressure  $\geq 130/85$  or taking antihypertensive medication; fasting glucose  $\geq 110$  or taking insulin or oral antidiabetic agents; HDL cholesterol  $<50$ ; or triglycerides  $\geq 150$ ) was also considered. Other metabolic markers were serum insulin (nondiabetics only) and glucose (determined using a radioimmunoassay kit [Pharmacia, Uppsala, Sweden]). Insulin resistance was estimated with the homeostasis model assessment (the product of fasting glucose and insulin concentrations in mmol/L divided by 22.5).<sup>32</sup> Body composition variables included body mass index (BMI) ( $\text{kg}/\text{m}^2$ ), abdominal circumference, and visceral fat (estimated with computed tomography scans between fourth and fifth lumbar vertebrae).<sup>33</sup> Inflammatory markers considered were interleukin (IL)-6 and C-reactive protein (measured in duplicate from overnight fasting serum by an enzyme-linked immunosorbent assay kit from R&D Systems [Minneapolis, MN]).

Subclinical CVD (characterized according to previously published protocol<sup>34–36</sup> as abnormal ECG findings, positive results on the Rose questionnaire for intermittent claudication, or ankle-brachial index  $<0.9$ ) was also considered as a potential mediator between birth infant characteristics and maternal CVD status.

### Statistical Analysis

Maternal characteristics were compared according to characteristics of the first birth (term births  $\geq 2500$  g, term births  $<2500$  g, and preterm births). Analysis of covariance was used to examine group differences in means for body composition variables (adjusted for race and age) and vascular, metabolic, and inflammatory measures (adjusted for race, age, and BMI). Inflammatory markers, triglycerides, glucose, insulin, hemoglobin A1c, and a pulse wave velocity were log-transformed for the purposes of analysis as they were not normally distributed, and results are presented as geometric means. Multinomial logistic regression was used to assess the association between a woman's CVD status and a first birth that was either preterm or term  $<2500$  g. In a separate model we also estimated the combined effect of delivering an infant both preterm and  $<2500$  g. Women with term births  $\geq 2500$  g were the referent for all models. We computed odds ratios (ORs) and 95% confidence intervals (CIs).

The models were adjusted a priori for age and race; other covariates were considered confounders if they changed the  $\beta$ -coefficient associated with the infant characteristics by more than 10%. Covariates considered included low socioeconomic status, young maternal age, smoking status, subclinical CVD, waist circumference, visceral fat, LDL and HDL cholesterol, use of statins, systolic blood pressure, hypertension, pulse wave velocity, diabetes, glucose, insulin resistance, and inflammatory markers.

### RESULTS

Among the 446 women who recalled the preterm status and birth weight of their first-born, 27 women (6%) reported delivering a preterm infant and 38 women (9%) reported having a term infant weighing less than 2500 g. A total of 18 births (4%) were reported as both preterm and LBW. Average  $\pm$  SD maternal age at first birth was  $23.5 \pm 4.4$ , and mean number of live births was  $3.0 \pm 1.5$ .

Women with preterm births or small term births tended to have higher rates of CVD, higher systolic blood pressures, and higher rates of hypertension compared with women who reported term births  $\geq 2500$  g (Table 1). Women with preterm births had higher HDL cholesterol, lower LDL cholesterol, and a lower reported prevalence of statin use. Women with small term births tended to have more visceral fat, higher triglyceride concentrations, and higher concentrations of IL-6. In terms of pregnancy characteristics, women with preterm births or small term births were more likely to have been younger than age 20 at the time of their first birth, compared with women with larger term births. When the analysis was restricted to women without CVD, these results were attenuated but the group differences generally persisted.

As compared with delivery of a term infant  $\geq 2500$  g, a preterm delivery was associated with a higher prevalence of CVD (OR = 2.05; 95% CI = 0.93–4.52; Table 2). Delivery of a small term infant produced an unadjusted odds ratio of CVD of 1.33 (0.66–2.70) and delivery of a preterm and  $<2500$  g infant was associated with an odds ratio of 2.55 (0.99–6.60). Adjustment for age and race modestly altered these results. After additional adjustment for systolic blood pressure, pulse wave velocity, insulin resistance, IL-6, HDL cholesterol, and use of statins, the OR for CVD among women who reported that their infant was born preterm vs. term  $\geq 2500$  g was 2.85 (95% CI = 1.10–6.85). The OR was 3.31 (1.06–10.37) for women with infants that were both  $<2500$  g and preterm compared with women having normal weight infants at term. In these data, adjustment for relevant covariates attenuated the relationship between delivery of a small term infant and CVD to the null (0.84; 0.37–1.89). Additional adjustment for smoking status or subclinical CVD did not alter these estimates.

The fully adjusted models produced increased odds ratios associated with preterm delivery when compared with crude estimates, suggesting negative confounding.<sup>37</sup> For example, statin use was associated with an increased prevalence of CVD (2.2; 1.3–3.5), and was less common among women with preterm delivery (0.30; 0.07–1.3). Thus, controlling for statin use strengthened the association between preterm delivery and CVD in our models. There was also evidence of negative confounding associated with HDL cholesterol.

### DISCUSSION

Among this group of older women, those who had delivered preterm infants had a higher prevalence of subse-

**TABLE 1.** Selected Maternal Characteristics\* According to Characteristics of the First Birth

	Term Births > 2500 g (n = 381)	Term Births < 2500 g (n = 38)	Preterm Births (n = 27)
Maternal characteristics			
Age at baseline	73.0 ± 2.8	73.4 ± 2.8	72.9 ± 2.3
Black; no. (%)	158 (41.5)	24 (63.2)	14 (51.9)
Education; no. (%)			
Less than high school	58 (15.2)	3 (7.9)	6 (22.2)
High school graduate	183 (48.0)	22 (57.9)	8 (29.3)
Postsecondary	140 (36.8)	13 (34.2)	13 (48.2)
Low socioeconomic status; no. (%)	54 (14.2)	7 (18.4)	6 (22.2)
Ever-smoked (former or current); no. (%)	159 (41.7)	18 (47.4)	18 (66.7)
Pack-years smoked (among smokers)	29.0 ± 24.8	36.5 ± 29.2	45.7 ± 30.1
Clinical cardiovascular disease; no. (%)	107 (28.1)	13 (34.2)	12 (44.4)
Subclinical cardiovascular disease <sup>†</sup> ; no. (%)	92 (33.6)	9 (36.0)	3 (20.0)
Body composition			
BMI, age 73 (kg/m <sup>2</sup> ) <sup>‡</sup>	28.3 ± 5.3	26.7 ± 4.9	27.8 ± 6.7
Abdominal circumference (cm) <sup>§</sup>	95.3 ± 13.7	97.4 ± 12.2	98.1 ± 15.1
Visceral fat (cm <sup>2</sup> ) <sup>§</sup>	110.1 ± 58.0	129.4 ± 51.5	112.9 ± 66.6
Lipid markers			
HDL (mg/dL) <sup>§</sup>	59.9 ± 16.9	61.4 ± 18.7	65.5 ± 20.8
LDL (mg/dL) <sup>§</sup>	130.2 ± 34.8	133.1 ± 40.3	116.4 ± 32.5
Triglycerides (mg/dL) <sup>§</sup>	141.3 ± 71.6	163.7 ± 74.3	139.5 ± 68.1
Statin use; no. (%)	78 (20.5)	10 (11.1)	2 (7.4)
Vascular markers			
Systolic blood pressure <sup>§</sup>	136.8 ± 20.6	142.4 ± 23.8	148.4 ± 25.2
Pulse wave velocity (cm/s) <sup>§</sup>	774.3 ± 419	741.6 ± 427	825.3 ± 393
Hypertension; no. (%)	228 (59.8)	27 (71.1)	19 (70.4)
Metabolic markers			
Fasting glucose (mg/dL) <sup>§</sup>	101.4 ± 33.1	98.0 ± 21.0	104.0 ± 35.3
Fasting insulin (IU/mL) <sup>¶</sup>	8.2 ± 5.8	10.7 ± 13.2	9.8 ± 6.1
Insulin resistance (Homeostasis Model Assessment) <sup>¶</sup>	1.59 ± 1.9	1.83 ± 2.1	1.94 ± 1.8
Diabetes mellitus; no. (%)	36 (9.5)	3 (7.9)	2 (7.7)
Metabolic syndrome; no. (%)	154 (40.6)	14 (36.8)	12 (44.4)
Inflammatory markers			
IL-6 (pg/mL) <sup>§</sup>	1.82 ± 1.9	2.24 ± 1.9	2.11 ± 1.84
C-reactive protein (μg/mL) <sup>§</sup>	1.96 ± 2.3	2.31 ± 1.95	2.51 ± 2.77
First birth			
Infant birth weight (g)	3268 ± 448	2283 ± 224	2159 ± 703
Smoked during pregnancy; no. (%)	78 (20.9)	10 (27.0)	9 (33.3)
Age at first birth	23.7 ± 4.4	22.0 ± 4.0	23.1 ± 4.9
Younger than 20 years of age at first birth; no. (%)	60 (15.8)	12 (31.6)	8 (29.6)

\*Mean ± SD, unless otherwise indicated.

<sup>†</sup>Abnormal ECG, positive Rose questionnaire, intermittent claudication or ankle-brachial index <0.9.<sup>‡</sup>Adjusted for race.<sup>§</sup>Adjusted for race and BMI.<sup>¶</sup>Nondiabetics only, adjusted for race and BMI.

quent CVD independent of age, race, and vascular, inflammatory, and metabolic factors. Large registry-based observational studies, with limited ability to adjust for confounding, have found a high risk for maternal cardiovascular death in relatively young women after preterm birth<sup>1-3</sup> or LBW.<sup>5,38</sup> Our findings among older women suggest that this risk may persist in women who survive to age 80, and that vascular and

metabolic factors account for some but not all of this relationship.

Infant birth weight has been found to be inversely related to maternal systolic blood pressure and insulin resistance measured in women age 34 to 79 years.<sup>6-8</sup> Similarly, pulse wave velocity (a marker of arterial stiffness), systolic blood pressure, and insulin resistance substantially altered the

**TABLE 2.** Crude and Multivariate Assessment of Cardiovascular Disease Risk and Characteristics of the First Birth

	Unadjusted Prevalence (No. CVD Cases/ Total No.)	Odds Ratio (95% CI)
Unadjusted		
Term >2500 g*	28.1 (107/381)	1.0
Term <2500 g	34.2 (13/38)	1.33 (0.66–2.70)
Preterm (<37 wk)	44.4 (12/27)	2.05 (0.93–4.52)
Preterm <2500 g <sup>†</sup>	50.0 (9/18)	2.55 (0.99–6.60)
Adjusted for maternal characteristics <sup>‡</sup>		
Term >2500 g*		1.0
Term <2500 g		1.12 (0.54–2.31)
Preterm (<37 wk)		1.95 (0.87–4.37)
Preterm <2500 g <sup>†</sup>		2.24 (0.85–5.91)
Adjusted for maternal characteristics and vascular, metabolic, and inflammatory markers <sup>§</sup>		
Term >2500 g*		1.0
Term <2500 g		0.92 (0.38–2.20)
Preterm (<37 wks)		2.07 (0.86–5.02)
Preterm <2500 g <sup>†</sup>		2.52 (0.84–7.62)
Adjusted for maternal characteristics and vascular, metabolic, inflammatory and lipid markers <sup>¶</sup>		
Term >2500 g*		1.0
Term <2500 g		0.84 (0.37–1.89)
Preterm (<37 wks)		2.85 (1.19–6.85)
Preterm <2500 g <sup>†</sup>		3.31 (1.06–10.37)

\*Reference category.

<sup>†</sup>Separate model where referent group is women with term infants >2500 g.<sup>‡</sup>Adjusted for race and maternal age at study baseline.<sup>§</sup>Adjusted for race, maternal age at study baseline, systolic blood pressure, pulse wave velocity (log), insulin resistance (Homeostasis Model Assessment), and IL-6 (log).<sup>¶</sup>Adjusted for race, maternal age at study baseline, systolic blood pressure, pulse wave velocity (log), insulin resistance (Homeostasis Model Assessment), and IL-6 (log), HDL cholesterol, and statin use.

relationship between preterm birth and CVD in our study, suggesting that vascular and metabolic pathways may in part explain this relationship. Davey Smith et al reported a 2.5-fold increased risk for CVD among women who had delivered preterm—results consistent with our findings.<sup>3</sup> The magnitude of this association was attenuated when adjusted for infant birth weight, suggesting that extreme premature delivery or growth restriction in conjunction with preterm birth was an important component of this relationship. In our data, delivery of a small term infant (<2500 g) did not appear to be independently associated with CVD, suggesting that birth weight alone may not be as relevant as gestational age in explaining this relationship. This possibility, however, warrants further study.

Previous studies have shown that women with elevated blood pressure before or during pregnancy, even without superimposed preeclampsia, have an elevated risk for preterm birth and also tend to deliver smaller babies.<sup>22–24</sup> In addition, maternal decidual or myometrial vascular changes have been associated with preterm delivery,<sup>14</sup> as well as intrauterine growth restriction,<sup>12</sup> in pregnancies not complicated by pre-

eclampsia or hypertension. These findings suggest that occult maternal vascular disease may contribute to preterm delivery, and over the course of a woman's lifetime, could lead to hypertension or arterial stiffness that ultimately increases risk for CVD.

Statin use and HDL cholesterol negatively confounded the relationship between preterm delivery and CVD. This less-atherogenic lipid profile of women after preterm birth could be due to the association of lean body composition with preterm birth, with persistence of leanness into older adulthood.<sup>39–41</sup> Previous work by our group indicated that the older women in the Health ABC Study who had delivered LBW infants had a distinct body composition, with low BMI but high waist circumference adjusted for BMI.<sup>8</sup> Our findings related to preterm birth are similar. Women who had delivered preterm infants <2500 g had the highest odds of CVD compared with women with uncomplicated births, and they also had the lowest BMI (26.3 vs. 28.2 kg/m<sup>2</sup>,  $P = 0.11$ ) and the largest waist circumferences (99.7 vs. 95.4 cm,  $P = 0.02$ ).

There are several strengths to our study. We were able to examine extensive physical and biologic variables associ-

ated with preterm birth and CVD. In addition, we were able to study a racially diverse cohort, which is important as the rates of preterm birth,<sup>42,43</sup> LBW,<sup>44,45</sup> and CVD<sup>46</sup> among black women are twice that of white women. The association between CVD and preterm birth was similar in black and white women, although we cannot rule out the possibility that exclusion of women at highest risk of developing CVD (because of death or disability) may have occurred more for blacks than for whites.

Several limitations of our study may affect the interpretation of our results. Our sample size is modest and this limits the precision of our estimates. In addition, our work should be considered preliminary, as the data were collected in the context of a study designed for other purposes. Because pregnancy data were collected via recall, our exposure variables are subject to misclassification. Mothers have, however, been found to reliably recall certain pregnancy characteristics, including preterm status, many years postpartum,<sup>27</sup> and we confirmed the validity and the reliability of maternal recall of infant birth weight among this cohort of older women.<sup>25</sup> Nonetheless, assuming the presence of misclassification, it is unlikely that women would systematically over- or under-report preterm status or infant birth weight based on CVD status, and so the impact of recall bias would likely be that our observed associations were attenuated.

Community-dwelling, well-functioning women who survive to late old age with reasonable cognitive function are healthier than the general population. This may limit the generalizability, although not the validity, of our findings. Preexisting CVD was not an exclusion criterion for participation in our study, but the impact of survival bias would be to underestimate the true magnitude of an effect. The fact that our odds ratios are a bit lower than those of studies involving younger women suggests the possibility of such bias.<sup>2,5</sup>

Our ability to distinguish between preterm and growth-restricted infants was limited. In addition, we may have underestimated preeclampsia or hypertension during pregnancy due to imprecise maternal recall, and therefore we may have included persons who were at greater risk secondary to these conditions. Additional studies are needed in which these pregnancy complications are more precisely characterized. In addition, both adverse pregnancy outcomes and CVD are associated with socioeconomic status; we cannot rule out residual confounding by unmeasured or misclassified factors.

Our results suggest that older women who delivered a preterm first birth had an increased prevalence of CVD after adjusting for demographics, smoking, and cardiovascular risk factors. This effect was greater in women who delivered infants both small and preterm, suggesting that earlier preterm delivery or preterm birth with growth restriction are associated with more profound risk for CVD. Although these results need to be replicated and expanded, they suggest that

delivery of a preterm infant may identify women who could benefit from cardiovascular risk screening and intervention.

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