Birth Characteristics and Subsequent Risks of Maternal Cardiovascular Disease
Effects of Gestational Age and Fetal Growth

Anna-Karin Edstedt Bonamy, MD, PhD; Nisha I. Parikh, MD, MPH; Sven Cnattingius, MD, PhD; Jonas F. Ludvigsson, MD, PhD; Erik Ingelsson, MD, PhD

Background—Prior studies showing an inverse relationship between low birth weight in offspring and maternal risks of cardiovascular diseases (CVD) are limited by lack of information on gestational age and/or insufficient adjustment for confounders.

Methods and Results—In a nationwide Swedish study, we included information on 923,686 women and their first singleton births between 1983 and 2005. Cox proportional hazards models were used to study associations between gestational length, fetal growth, and maternal incident hospitalization or death from CVD (coronary heart disease, cerebrovascular events, and heart failure). Multivariable adjusted models accounted for birth year, income, education, country of birth, smoking, diabetes mellitus, hypertension, and preeclampsia.

The risk of maternal CVD increased with decreasing gestational age whereas the risk increase related to fetal growth appeared to be restricted to very small-for-gestational-age (SGA) infants. Compared with mothers of non-SGA infants born at term, the hazard ratio of CVD ranged from 1.39 (95% confidence interval 1.22–1.58) to 2.57 (95% confidence interval 1.97–3.34) among mothers to moderately and very preterm infants, respectively. There was a significant interaction between preterm birth and fetal growth with respect to mothers’ risk of CVD (P<0.001). Among mothers to very SGA infants, the hazard ratio of CVD ranged from 1.38 (95% confidence interval 1.15–1.65) to 3.40 (95% confidence interval 2.26–5.11) in mothers to term and very preterm infants, respectively.

Conclusions—Delivery of a preterm or SGA infant is associated with later life maternal hospitalization or death from CVD even after accounting for socioeconomic factors, smoking, and pregnancy-related complications. (Circulation. 2011;124:00–00.)

Key Words: cardiovascular diseases ▪ pregnancy ▪ premature birth ▪ risk factors ▪ women ▪ epidemiology

Mothers who deliver low–birth weight infants are at increased risks of cardiovascular diseases (CVD) later in life.1–8 Birth weight is a function of gestational age and fetal growth, and preterm birth is today the most common cause of low birth weight in developed countries. In previous studies, it is suggested that both mothers to preterm and small-for-gestational-age (SGA) infants are at increased risks of later CVD.1–9 However, it is not known whether the maternal risk of CVD increases with severity of prematurity or fetal growth restriction and whether there is an interaction between gestational age and fetal growth with respect to mothers’ CVD risk.

In addition, most previous studies have not been able to account for the possible influence of maternal characteristics (eg, smoking) and pregnancy complications (eg, hypertensive diseases), factors that are associated with fetal growth restriction, preterm birth, and mother’s long-term risks of CVD.7,9–11

Clinical Perspective on p ●●●

We undertook a study investigating the hypothesis that maternal risks of CVD increase both with severity of prematurity and fetal growth restriction. This hypothesis was investigated by large-scale record linkages of the nationwide Swedish health registries, adjusting for relevant confounders such as smoking, socioeconomic factors, and other pregnancy-related complications.

Methods

Data Sources

We accessed data from population-based registers maintained at the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se/en/) and Statistics Sweden (http://www.scb.se). Individual records were linked across registers using...
the unique personal identity number assigned to all Swedish resi-
dents (ie, individuals born in Sweden or those having a residence
permit for ≥1 year).12

The Swedish Medical Birth Register was initiated in 1973 as a
means to compile information on maternal, obstetric, and neonatal
factors. During the study period 1983 to 2005, 99% of all births in
Sweden were registered in the Medical Birth Register.13 The reason
for choosing 1983 as the start of the study was that information about
mothers’ smoking habits has been routinely collected since this year.

The National Patient Register started to collect data on inpatients at
hospitals in the 1960s. In 1983, all the major cities in Sweden and 90%
of the Swedish counties were covered, and from 1987 the coverage
was nationwide.14 The register contains information about dates of admis-
sion and discharge, hospital and clinic codes, and up to 8 discharge
diagnosis codes, the first representing the principal cause of hospital-
discharge, hospital and clinic codes, and up to 8 discharge
registration to antenatal care and is categorized into: none, current light
smoker (one to nine cigarettes per day), and current heavy smoker (at
least 10 cigarettes per day). The validity of self-reported smoking data
has been shown to be high.20

Assessment of Exposures and Covariates
Information about birth weight and gestational age (in completed
days) was collected from the Medical Birth Register. Information in
the Medical Birth Register has recently been validated, and the
quality of the variables included in the present investigation was
shown to be high.15

Birth weight for gestational age was based on the Swedish reference

Figure 1. Flow chart of the inclusion and exclusion criteria used
in the study.

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women (Figure 1). Women who had missing information on off-
spring birth weight or gestational age (N = 33 726) more often had
stillbirths, smoked during pregnancy, were born outside Sweden,
had lower income, had higher prevalence of diabetes mellitus, and
had higher incidence of gestational hypertension compared with
women included in the study sample. The incidence rate of CVD in
women with missing information on offspring birth weight or
gestational age was also higher: 0.55/1000 person years at risk (95%
confidence interval [CI] 0.47–0.64/1000 person years) compared
with 0.34/1000 person years at risk (95% CI 0.33–0.35/1000 person
years in the study sample). The study was approved by the Ethics
Committee of Uppsala University, Uppsala, Sweden.

Study Population
All women who had a first singleton birth in Sweden between 1983
and 2005 were eligible for the present study (N = 1 052 771). After
exclusion of immigrating women (because we could not be sure that
we ascertained data from their first delivery), women with a CVD
event before having their first delivery, and women with missing
record or missing information on birth weight and gestational age in
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pean countries, and non-European countries. Information on total parity up to 2005 was derived from the Multi-Generation Register.

Weight at delivery and pregnancy weight gain were recorded in the Medical Birth Register between 1982 and 1989. From 1992, maternal prepregnancy weight is recorded at registration for antenatal care. The prepregnancy weight was calculated for a subset of women giving birth 1983 to 1989 by subtracting the pregnancy weight gain from the maternal weight at delivery (N=495,257). In 175,677 women, prepregnancy weight was recorded at registration for antenatal care. The prepregnancy body mass index (BMI) was calculated by dividing the maternal prepregnancy weight (recorded or derived) by the maternal height in meters squared. In total, prepregnancy BMI data were available for 670,934 women (online-only Data Supplement Table I).

Follow-Up and Outcomes

Follow-up started at the time of the first delivery. End of follow-up was December 31, 2005, or the date of first occurrence of the following: first CVD event (as defined below), emigration from Sweden, or death.

Incidence in CVD was defined as the first hospitalization (assessed from the Hospital Discharge Register) or death (assessed from the Cause of Death Register) caused by coronary heart disease (CHD), cerebrovascular events, or heart failure. Coronary heart disease was defined as unstable angina (ICD-8 code 411, ICD-9 code 411B, ICD-10 code I20.0) or acute myocardial infarction (ICD-8 and ICD-9 code 410, ICD-10 codes I21-I22). Cerebrovascular events were defined as cerebral infarction (ICD-8 codes 432–434, ICD-9 codes 433–434, ICD-10 code I63), cerebral hemorrhage (ICD-8 code 431, ICD-9 codes 431–432, ICD-10 codes I61-I62), subarachnoid hemorrhage (ICD-8 and ICD-9 code 430, ICD-10 code I60), transient ischemic attack (ICD-8 and ICD-9 code 435, ICD-10 code G45), or other acute stroke (ICD-8 and ICD-9 code 436, ICD-10 code I64). Heart failure was defined by ICD-8 codes 427.00 and 427.10, ICD-9 code 428, ICD-10 code I50. We only considered hospitalizations or deaths with the above diagnoses as primary diagnosis of the hospitalization or underlying cause of death. The positive predictive values of the myocardial infarction and stroke diagnoses in the Swedish Hospital Discharge Register have been demonstrated to be around 95% when only primary diagnoses are considered.7

Statistical Methods

Gestational age was analyzed as a categorical variable with 4 levels as defined above: term, moderately preterm, very preterm and extremely preterm. Birth weight for gestational age was analyzed as a categorical variable with 5 levels as defined above: very small, moderately small, normal (reference), moderately large, and very large. The separate analyses of gestational age and birth weight for gestational age were restricted to live births.

Mothers’ birth year was stratified into 5 categories (1932–1941; 1942–1951; 1952–1961; 1962–1971; 1972 or later) and analyzed as a categorical variable. Highest income before first delivery and maternal prepregnancy BMI were analyzed as a continuous variable whereas educational level and country of birth were analyzed as dichotomous variables.

The baseline characteristics of the study sample of women giving their first delivery between 1983 and 2005 are given in Table 1. The median follow-up time was 11.8 years (range 0–23.0 years; 25th–75th percentiles 5.5–16.9) contributing to 10,500,000 person years at risk. During this period, 3568 women developed a first CVD event (CHD, n=937; cerebrovascular event, n=2372; and heart failure, n=259). The overall unadjusted incidence rate was 0.34 cases/1000 person years at risk (95% CI 0.33–0.35/1000 person years).

Compared with women who had a term first delivery, women with a preterm first delivery had an increased risk of hospitalization or death from CVD later in life even after adjustment for potential confounders, including preeclampsia and smoking. The risk was 39% higher in women delivering moderately preterm infants and more than doubled in women delivering very (28–32 weeks) and extremely (<28 weeks) preterm infants (Table 2).

Compared with women having an infant with normal birth weight for gestational age, women giving birth to an infant that was very SGA had an 83% increased risk of developing CVD in the multivariate model, which was reduced to a 60% increase in risk when we also adjusted for smoking (Table 2). However, giving birth to a moderately small or a large-for-gestational-age infant did not essentially influence risk of CVD. There was a significant multiplicative interaction between gestational age and birth weight for gestational age (P<0.001) with regard to maternal risk for hospitalization or death from CVD. In analyses of the joint effects of preterm birth and fetal growth, there were strong associations between preterm
Table 1. Baseline Characteristics of the Study Sample; Women Giving First Singleton Births in Sweden, 1983 to 2005 (N=923,686)

<table>
<thead>
<tr>
<th>Confounders</th>
<th>Birth weight for gestational age, n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term, ≥37</td>
<td>866,793 (93.8)</td>
</tr>
<tr>
<td>Moderately preterm, 32–36</td>
<td>49,537 (5.4)</td>
</tr>
<tr>
<td>Very preterm, 28–31</td>
<td>5259 (0.6)</td>
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<tr>
<td>Extremely preterm, &lt;28</td>
<td>2097 (0.2)</td>
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<tr>
<th>Categories of SGA and preterm births, n (%)†</th>
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<tbody>
<tr>
<td>Not SGA and term</td>
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<tr>
<td>Not SGA and moderately preterm</td>
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<tr>
<td>Not SGA and very preterm</td>
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<tr>
<td>Not SGA and extremely preterm</td>
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<tr>
<td>Moderately small and term</td>
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<tr>
<td>Moderately small and moderately preterm</td>
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<td>Very small and term</td>
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<td>Very small and moderately preterm</td>
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<tr>
<td>Very small and very preterm</td>
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<tr>
<td>Very small and extremely preterm</td>
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<tr>
<td>Stillbirth</td>
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Potential confounders

<table>
<thead>
<tr>
<th>Maternal birth year, n (%)</th>
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<tr>
<td>1932–41</td>
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<td>1942–51</td>
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<tr>
<td>1952–61</td>
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<tr>
<td>1962–71</td>
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<tr>
<td>1972 or later</td>
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<table>
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<tr>
<th>Maternal age at first delivery, y, median (interquartile range)</th>
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<tbody>
<tr>
<td>26.9 (23.6–30.3)</td>
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<tr>
<th>Maternal age at incident CVD, y, median (interquartile range)</th>
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<tr>
<td>40.5 (34.5–46.6)</td>
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<table>
<thead>
<tr>
<th>Highest income before first delivery, USD/y, median (interquartile range)‡</th>
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<tr>
<td>33,211 (25,984–41,978)</td>
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<tr>
<th>Educational level, n (%)</th>
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<tr>
<td>0–9 y of primary and secondary school</td>
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<tr>
<td>2 y of high school</td>
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<td>3 y of high school</td>
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<td>College or university studies</td>
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<tr>
<th>Country of birth, n (%)</th>
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<tbody>
<tr>
<td>Sweden</td>
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<td>Other Nordic countries§</td>
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<td>Other European countries</td>
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<tr>
<td>Countries from rest of the world</td>
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(Continued)
Table 2. Incidence Rates and Hazard Ratios* of CVD in Women by Gestational Age† or Birth Weight for Gestational Age‡ in Offspring

| No. of CVD Events | Rate/1000 PYAR (95% CI) | Age Adjusted, HR (95% CI) | Multivariable Adjusted, HR (95% CI) § | Smoking Adjusted, HR (95% CI) ||
|------------------|------------------------|--------------------------|--------------------------------------|----------------------------------|
| Term             | 3154                   | 0.32 (0.31–0.33)         | Referent                             | Referent                         |
| Moderately preterm| 320                    | 0.56 (0.50–0.62)         | 1.68 (1.50–1.88)                     | 1.45 (1.28–1.64)                 | 1.39 (1.22–1.58) |
| Very preterm      | 70                     | 1.17 (0.93–1.48)         | 2.32 (2.55–4.09)                     | 2.62 (2.04–3.36)                 | 2.57 (1.97–3.34) |
| Extremely preterm | 24                     | 1.09 (0.73–1.63)         | 3.06 (2.05–4.57)                     | 2.58 (1.70–3.93)                 | 2.18 (1.33–3.57) |
| Birth weight for gestational age‡ | | | | |
| Very small        | 246                    | 0.74 (0.65–0.83)         | 2.13 (1.87–2.44)                     | 1.83 (1.59–2.11)                 | 1.60 (1.38–1.86) |
| Moderately small  | 950                    | 0.39 (0.36–0.41)         | 1.23 (1.13–1.33)                     | 1.16 (1.07–1.27)                 | 1.09 (1.00–1.19) |
| Normal            | 1824                   | 0.30 (0.29–0.32)         | Referent                             | Referent                         | Referent          |
| Moderately large  | 460                    | 0.30 (0.28–0.33)         | 1.02 (0.92–1.12)                     | 0.97 (0.88–1.09)                 | 1.03 (0.92–1.15) |
| Very large        | 62                     | 0.38 (0.30–0.49)         | 1.26 (0.98–1.62)                     | 0.88 (0.66–1.16)                 | 0.90 (0.66–1.21) |

Women in Sweden giving first singleton births from 1983 to 2005 (N=923686) were included. Follow-up started at delivery and ended at first event of CVD, death, emigration, or December 31, 2005.

*Values are Cox proportional hazard ratios (95% CIs) for different categories of birth weight for gestational age or gestational age.

†Term is defined as ≥37 completed weeks; moderately preterm, 32–36 weeks; very preterm, 28 to 31 weeks; and extremely preterm, <27 weeks.

‡Birth weight for gestational age was based on the Swedish reference curve for intrauterine growth.16 A normal birth weight ratio was defined as 0.90 to 1.09 (approximately between 1 SD above the mean to 1 SD below the mean), very small as <0.75 (approximately 2 SD below the mean), moderately small as 0.75 to 0.89 (approximately between 1 and 2 SD below the mean), moderately large as 1.10 to 1.24 (approximately between 1 and 2 SD above the mean), and very large as >1.25 (approximately 2 SD above the mean).

§Adjusted for maternal age, birth year, highest income and highest education level before first delivery, country of birth, pregestational hypertension, pregestational diabetes mellitus, gestational diabetes mellitus, gestational hypertension, and preeclampsia/eclampsia.

‖Adjusted for all of the variables above and maternal smoking at antenatal booking.

CVD indicates cardiovascular disease; PYAR, person years at risk; HR, hazard ratio; and CI, confidence interval.

is also associated with an increased risk of maternal CVD, which is consistent with previous studies of low birth weight in relation to maternal CVD risk and mortality.1–8,22

Preterm birth is positively associated with maternal cardiovascular morbidity and mortality1,5,7,23,24 and it has been suggested that preterm birth and CVD share common antecedents.5,25 Possible causes of spontaneous preterm birth include infection and inflammation involving proinflammatory cytokines, the prostaglandin cascade, and matrix metalloproteinases.26 The process of atherosclerosis is also largely inflammatory in its origin. Biochemical markers of inflammation are correlated to risk of plaque rupture and endothelial dysfunction and thus CVD risk32 and also to risk of preterm birth.28 Further, there are other pathways that may be common to risks of both preterm birth and CVD, such as differences in thrombin expression. Thrombin can be activated by vascular lesions in the placenta and stimulates both smooth muscle contractions and degradation of fetal membranes, 2 of the key elements in spontaneous preterm birth.26 Thrombin is also a key component in the atherosclerotic process.29

During pregnancy, the maternal cardiovascular system undergoes hemodynamic changes to facilitate placental circulation in order to guarantee fetal oxygen and nutrient supply. Women at risk of CVD may have an impaired ability to adjust to this hemodynamic challenge and be at higher risk of placental dysfunction, the most common cause of intrauterine growth restriction and stillbirth.30,31 Even in normal pregnancies, birth weight is correlated to maternal CVD risk markers such as arterial stiffness and endothelial dysfunction.32 Moreover, endocrine signaling is important for normal fetal growth. There is a complex interplay between maternal, placental, and fetal hormones to regulate growth, notably involving the growth hormone/insulin-like-growth factor axis. Interestingly, low levels of insulin-like growth factor 1 are found in pregnancies complicated by intrauterine growth restriction, and are also associated with an increased risk of CVD.33,34

One major causal factor behind preterm birth and growth restriction is maternal preeclampsia, present in ~25% of preterm births and in 3% of all births.35,36 The risk of CVD is known to be higher in women exposed to early preeclampsia than in women diagnosed with preeclampsia later in pregnancy.7 In many spontaneous preterm births and in some pregnancies complicated by intrauterine growth restriction, there are placental vascular abnormalities similar to those seen in preeclampsia.37,38 Preeclampsia might thus be the tip of the iceberg of subclinical defects in placentation, characterized by endothelial dysfunction and systemic inflammation, related to preterm birth, intrauterine growth restriction, stillbirth, and CVD risk in the mothers. In the present study, we were able to adjust for maternal hypertensive diseases, including both pregestational and pregnancy-induced hypertensive diseases. As expected, the increased risk for CVD associated with a preterm and/or SGA delivery was slightly attenuated in the multivariable-adjusted model.

Most prior large studies have not been able to adjust for confounding by maternal smoking.3,5,7,9 We found that the association between low birth weight for gestational age and later maternal CVD was attenuated when adjusted for smoking, which is consistent with the finding by Smith et al in the British 1958 birth cohort.1 However, the association between preterm birth and later maternal CVD remained largely unchanged when adjusted for smoking.
Preterm birth has been associated with higher blood pressure and structural changes in the developing vascular tree in the offspring. It has been hypothesized that preterm birth is a risk factor for adult offspring CVD although this has not yet been confirmed. Twenty-five percent of the variance in CVD risks. Another limitation is that we did not study birth characteristics in relation to paternal CVD risk, which would be a way to investigate shared familial risk factors and genetic paternal effects. However, 2 previous studies of offspring preterm birth in relation to paternal cardiovascular mortality were not able to show any association between preterm birth and paternal CVD. In line with our findings, Davey-Smith et al then proposed that “the association between offspring prematurity and maternal cardiovascular mortality also suggests that there exist risk factors that influence her reproductive outcome, as well as her own cardiovascular health”.

Table 3. Incidence Rates and Hazard Ratios† of Cardiovascular Disease in Women Categorized by Birthweight for Gestational Age† and Preterm Birth§ in Their First Deliv ery

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of CVD Events</th>
<th>Rate/1000 PYAR (95% CI)</th>
<th>Age Adjusted, HR (95% CI)</th>
<th>Multivariable Adjusted, HR (95% CI)§</th>
<th>Smoking Adjusted, HR (95% CI)</th>
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<tbody>
<tr>
<td>Not SGA and term</td>
<td>2131</td>
<td>0.29 (0.28–0.31)</td>
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<td>Referent</td>
</tr>
<tr>
<td>Not SGA and moderately preterm</td>
<td>176</td>
<td>0.45 (0.39–0.52)</td>
<td>1.49 (1.27–1.73)</td>
<td>1.35 (1.15–1.59)</td>
<td>1.33 (1.13–1.57)</td>
</tr>
<tr>
<td>Not SGA and very preterm</td>
<td>28</td>
<td>1.11 (0.77–1.61)</td>
<td>3.36 (2.32–4.88)</td>
<td>2.93 (1.97–4.34)</td>
<td>2.64 (1.70–4.10)</td>
</tr>
<tr>
<td>Not SGA and extremely preterm</td>
<td>11</td>
<td>0.97 (0.54–1.75)</td>
<td>2.97 (1.64–5.37)</td>
<td>2.52 (1.31–4.86)</td>
<td>2.22 (1.06–4.67)</td>
</tr>
<tr>
<td>Moderately small and term</td>
<td>843</td>
<td>0.36 (0.34–0.39)</td>
<td>1.20 (1.10–1.30)</td>
<td>1.17 (1.08–1.27)</td>
<td>1.09 (1.00–1.19)</td>
</tr>
<tr>
<td>Moderately small and moderately preterm</td>
<td>87</td>
<td>0.70 (0.57–0.86)</td>
<td>2.18 (1.76–2.71)</td>
<td>1.66 (1.31–2.10)</td>
<td>1.35 (1.04–1.75)</td>
</tr>
<tr>
<td>Moderately small and very preterm</td>
<td>14</td>
<td>0.79 (0.47–1.34)</td>
<td>2.34 (1.38–3.97)</td>
<td>1.84 (1.07–3.19)</td>
<td>1.95 (1.13–3.37)</td>
</tr>
<tr>
<td>Moderately small and extremely preterm</td>
<td>6</td>
<td>1.02 (0.46–2.27)</td>
<td>2.96 (1.33–6.60)</td>
<td>2.78 (1.25–6.20)</td>
<td>2.16 (0.81–5.77)</td>
</tr>
<tr>
<td>Very small and term</td>
<td>158</td>
<td>0.61 (0.52–0.71)</td>
<td>1.83 (1.55–2.15)</td>
<td>1.63 (1.37–1.93)</td>
<td>1.38 (1.15–1.65)</td>
</tr>
<tr>
<td>Very small and moderately preterm</td>
<td>54</td>
<td>1.04 (0.80–1.36)</td>
<td>2.97 (2.27–3.89)</td>
<td>2.38 (1.79–3.16)</td>
<td>2.22 (1.66–2.96)</td>
</tr>
<tr>
<td>Very small and very preterm</td>
<td>27</td>
<td>1.63 (1.12–2.38)</td>
<td>4.72 (3.23–6.90)</td>
<td>3.59 (2.44–5.27)</td>
<td>3.40 (2.26–5.11)</td>
</tr>
<tr>
<td>Very small and extremely preterm</td>
<td>7</td>
<td>1.53 (0.73–3.22)</td>
<td>4.63 (2.21–9.73)</td>
<td>3.14 (1.49–6.62)</td>
<td>2.45 (1.01–5.91)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>26</td>
<td>0.68 (0.46–0.99)</td>
<td>2.47 (1.66–3.64)</td>
<td>2.27 (1.52–3.40)</td>
<td>1.95 (1.26–3.03)</td>
</tr>
</tbody>
</table>

Women in Sweden giving first singleton births from 1983 to 2005 (N=923,686) were included. Follow-up started at delivery and ended at first event of CVD, death, emigration or December 31, 2005.

*Values are Cox proportional hazards ratios (95% CIs) for different categories of birth weight for gestational age or gestational age.
†Birth weight for gestational age was based on the Swedish reference curve for intrauterine growth. A normal birth weight ratio was defined as 0.90 to 1.09 (approximately between 1 SD above the mean to 1 SD below the mean), very small as <0.75 (approximately 2 SD below the mean), moderately small as 0.75 to 0.89 (approximately between 1 and 2 SD below the mean), moderately large as 1.10 to 1.24 (approximately between 1 and 2 SD above the mean), and very large as ≥1.25 (approximately 2 SD above the mean).
‡Term is defined as ≥37 completed weeks; moderately preterm, 32 to 36 weeks; very preterm, 28 to 31 weeks; and extremely preterm, ≤27 weeks.
§Adjusted for all of the variables above and maternal smoking at antenatal booking.

CVD indicates cardiovascular disease; PYAR, person years at risk; HR, hazard ratio; CI, confidence interval; and SGA, small for gestational age.
The incidence of preterm birth is only 6% in our study, which is low from an international perspective. It is not known if our results are generalizable to other settings where preterm birth is more common and gestational age is distributed differently.

In conclusion, we show that women delivering preterm are at high risk for later CVD, and that this risk is even higher when the infant is both preterm and growth restricted. Because of recent advances in assisted reproduction and obstetric care, the number of women having a history of very-or-extremely-preterm birth will continue to increase. Pregnancy may be viewed as a cardiovascular stress test and a preterm and/or SGA delivery might be the first sign of CVD susceptibility in a woman. Obstetric history is easy to collect in the clinical situation and could be of potential use for CVD risk stratification in women. Unfortunately, it was not possible to evaluate the additional value of these factors to the Framingham Risk Score or other risk stratification instruments as part of the present study because individual measurements of cholesterol or blood pressures are not registered in the nationwide registers. Therefore, we suggest further studies in longitudinal cohort studies with available data on all Framingham Risk Score variables to evaluate whether obstetric history has an incremental value in assessment of cardiovascular risk in women.

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Disclosures
None.

References
Previous studies show that low birth weight is associated with an increased risk of later maternal cardiovascular disease (CVD). Earlier studies also indicate that preterm delivery (ie, before 37 weeks) may be associated with an increased maternal CVD risk. We examined the association between severity of preterm birth, fetal growth restriction, and later maternal incident hospitalization or death from coronary heart disease, heart failure, and cerebrovascular events taking measured potential confounders into account. We included 923,863 Swedish women giving their first singleton birth between 1983 and 2005. After accounting for maternal age, birth year, income, education, smoking, hypertension, and diabetes mellitus, we found that the risk for CVD was more than doubled in women delivering very or extremely preterm (before 32 and 28 weeks, respectively) compared with women delivering a term, non-small-for-gestational-age infant. In women delivering a small-for-gestational-age infant, the CVD risk was doubled if the infant was born at 32 to 36 weeks and tripled if the infant was born before 32 weeks of gestation compared with women delivering a nonsmall infant at term. In analyses restricted to women for whom prepregnancy body mass index data were available (N=670,934), additional adjustment for body mass index did not attenuate the CVD risk. Our findings suggest that a preterm or small-for-gestational-age birth is an early indicator of later maternal CVD risk. If primary cardiovascular prevention measures are undertaken in women with a history of a preterm or small-for-gestational age birth, it might lower their CVD risk and improve the outcome of the next pregnancy.
Birth Characteristics and Subsequent Risks of Maternal Cardiovascular Disease: Effects of Gestational Age and Fetal Growth
Anna-Karin Edstedt Bonamy, Nisha I. Parikh, Sven Cnattingius, Jonas F. Ludvigsson and Erik Ingelsson

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**SUPPLEMENTAL MATERIAL**

**Supplementary Table 1.** Incidence rates and hazard ratios (HR) of cardiovascular disease in women categorized by presence of small for gestational age† and preterm births‡ in their first delivery. Analyses restricted to 670,934 women with information on weight and height in the Swedish Medical Birth Register.§ Follow-up started at delivery and ended at first event of CVD, death or December 31, 2005.

<table>
<thead>
<tr>
<th>Birth Weight Category</th>
<th>Rate/1000 PYAR</th>
<th>Age-adjusted</th>
<th>Multivariable-adjusted ‡</th>
<th>Smoking+BMI-adjusted 1‡</th>
<th>Smoking+BMI-adjusted 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate/1000 PYAR</td>
<td>(95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Not SGA and term</td>
<td>1,110</td>
<td>0.28 (0.27-0.30)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Not SGA and moderately preterm</td>
<td>73</td>
<td>0.41 (0.33-0.51)</td>
<td>1.47 (1.21-1.79)</td>
<td>1.35 (1.10-1.66)</td>
<td>1.39 (1.13-1.71)</td>
</tr>
<tr>
<td>Not SGA and very preterm</td>
<td>16</td>
<td>1.23 (0.75-2.00)</td>
<td>3.34 (2.04-5.48)</td>
<td>2.91 (1.72-4.93)</td>
<td>2.74 (1.58-4.73)</td>
</tr>
<tr>
<td>Moderately small and term</td>
<td>575</td>
<td>0.37 (0.34-0.40)</td>
<td>1.23 (1.12-1.36)</td>
<td>1.24 (1.12-1.37)</td>
<td>1.18 (1.06-1.32)</td>
</tr>
<tr>
<td>Moderately small and moderately preterm</td>
<td>45</td>
<td>0.59 (0.44-0.79)</td>
<td>1.96 (1.46-2.63)</td>
<td>1.48 (1.06-2.07)</td>
<td>1.32 (0.93-1.88)</td>
</tr>
<tr>
<td>Moderately small and very preterm</td>
<td>11</td>
<td>0.94 (0.52-1.71)</td>
<td>2.95 (1.62-5.36)</td>
<td>2.44 (1.30-4.55)</td>
<td>2.24 (1.16-4.33)</td>
</tr>
<tr>
<td>Very small and term</td>
<td>119</td>
<td>0.70 (0.58-0.83)</td>
<td>2.19 (1.81-2.64)</td>
<td>1.98 (1.62-2.42)</td>
<td>1.71 (1.39-2.11)</td>
</tr>
<tr>
<td>Very small and moderately preterm</td>
<td>37</td>
<td>1.23 (0.89-1.69)</td>
<td>3.71 (2.68-5.15)</td>
<td>3.05 (2.17-4.30)</td>
<td>2.85 (2.01-4.03)</td>
</tr>
<tr>
<td>Very small and very preterm</td>
<td>17</td>
<td>1.56 (0.97-2.51)</td>
<td>5.17 (3.20-8.33)</td>
<td>3.92 (2.41-6.39)</td>
<td>3.72 (2.25-6.14)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>19</td>
<td>0.75 (0.48-1.17)</td>
<td>2.82 (1.79-4.43)</td>
<td>2.64 (1.64-4.26)</td>
<td>2.24 (1.32-3.79)</td>
</tr>
</tbody>
</table>

*Values are Cox proportional hazards ratios (95% confidence intervals) for different categories of birth weight and gestational age.

†Birth weight for gestational age was based on the Swedish reference curve for intrauterine growth†. Not SGA was defined as a birth weight ratio of ≥0.9 (approximately -1 SD below the mean or above), moderately small as 0.75-0.89 (approximately <1 to 2 SD below the mean) and very small as <0.75 (approximately <2 SD below the mean).

‡Term ≥37 completed weeks of pregnancy, moderately preterm 32-36 weeks, very preterm <32 weeks.
Pre-pregnancy BMI was defined as (maternal weight at delivery - weight gain during pregnancy)/height$^2$ for 495,257 women (data available 1982-1989). The remaining 175,677 women had BMI calculated from a pre-pregnancy weight registered in the Swedish Medical Birth Register (data available from 1992).

Adjusted for maternal age, birth year, highest income and highest education level before first delivery, country of birth, pre-gestational hypertension, pre-gestational diabetes, gestational diabetes, gestational hypertension and preeclampsia/eclampsia.

Adjusted for all of the variables above + maternal smoking at registration for antenatal care and BMI.

Analyses restricted to 175,677 women having a pre-pregnancy weight registered in the Swedish Medical Birth Register (data available from 1992).

Abbreviations: HR, hazard ratio; CVD, cardiovascular disease; CI, confidence interval; BMI, body mass index;
**Supplementary Table 2. Incidence rates and hazard ratios (HR)* for coronary heart disease and cerebrovascular events in women categorized by presence of small for gestational age† and preterm births‡ in their first delivery. Women in Sweden giving first singleton births from 1983 to 2005 (N=923,686) were included. Follow-up started at delivery and ended at first event of CVD, death or December 31, 2005.**

<table>
<thead>
<tr>
<th>No. of events</th>
<th>Rate/1000 PYAR</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Smoking-Adjusted§ HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not SGA and term</td>
<td>388</td>
<td>0.07 (0.06-0.08)</td>
<td>Referent</td>
</tr>
<tr>
<td>Not SGA and moderately preterm</td>
<td>40</td>
<td>0.14 (0.10-0.19)</td>
<td>1.74 (1.30-2.33)</td>
</tr>
<tr>
<td>Not SGA and very preterm</td>
<td>13</td>
<td>0.45 (0.26-0.78)</td>
<td>4.93 (2.95-8.24)</td>
</tr>
<tr>
<td>Moderately small and term</td>
<td>225</td>
<td>0.10 (0.09-0.11)</td>
<td>1.31 (1.12-1.53)</td>
</tr>
<tr>
<td>Moderately small and moderately preterm</td>
<td>35</td>
<td>0.28 (0.20-0.39)</td>
<td>3.53 (2.50-4.97)</td>
</tr>
<tr>
<td>Moderately small and very preterm</td>
<td>7</td>
<td>0.30 (0.14-0.62)</td>
<td>3.44 (1.63-7.26)</td>
</tr>
<tr>
<td>Very small and term</td>
<td>55</td>
<td>0.21 (0.16-0.27)</td>
<td>2.50 (1.90-3.31)</td>
</tr>
<tr>
<td>Very small and moderately preterm</td>
<td>20</td>
<td>0.39 (0.25-0.60)</td>
<td>4.21 (2.69-6.59)</td>
</tr>
<tr>
<td>Very small and very preterm</td>
<td>11</td>
<td>0.52 (0.29-0.94)</td>
<td>5.93 (3.26-10.77)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>22</td>
<td>0.28 (0.18-0.42)</td>
<td>3.71 (1.92-7.16)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not SGA and term</td>
<td>1,157</td>
<td>0.2 (0.19-0.21)</td>
<td>Referent</td>
</tr>
<tr>
<td>Not SGA and moderately preterm</td>
<td>68</td>
<td>0.24 (0.19-0.30)</td>
<td>1.30 (1.07-1.59)</td>
</tr>
<tr>
<td>Not SGA and very preterm</td>
<td>18</td>
<td>0.63 (0.40-1.00)</td>
<td>2.48 (1.60-3.86)</td>
</tr>
<tr>
<td>Moderately small and term</td>
<td>571</td>
<td>0.25 (0.23-0.27)</td>
<td>1.19 (1.08-1.31)</td>
</tr>
<tr>
<td>Moderately small and moderately preterm</td>
<td>43</td>
<td>0.34 (0.26-0.46)</td>
<td>1.60 (1.18-2.17)</td>
</tr>
<tr>
<td>Category</td>
<td>N</td>
<td>HR    (95% CI)</td>
<td>HR    (95% CI)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Moderately small and very preterm</td>
<td>12</td>
<td>0.51 (0.29-0.90)</td>
<td>2.24 (1.27-3.97)</td>
</tr>
<tr>
<td>Very small and term</td>
<td>97</td>
<td>0.37 (0.30-0.45)</td>
<td>1.68 (1.36-2.06)</td>
</tr>
<tr>
<td>Very small and moderately preterm</td>
<td>31</td>
<td>0.60 (0.42-0.85)</td>
<td>2.58 (1.81-3.68)</td>
</tr>
<tr>
<td>Very small and very preterm</td>
<td>21</td>
<td>0.99 (0.65-1.53)</td>
<td>4.36 (2.83-6.71)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>41</td>
<td>0.51 (0.38-0.70)</td>
<td>1.92 (1.13-3.25)</td>
</tr>
</tbody>
</table>

*Values are Cox proportional hazards ratios (95% confidence intervals) for different categories of birth weight and gestational age.

†Birth weight for gestational age was based on the Swedish reference curve for intrauterine growth. Not SGA was defined as a birth weight ratio of ≥0.9 (approximately -1 SD below the mean or above), moderately small as 0.75-0.89 (approximately <1 to 2 SD below the mean) and very small as <0.75 (approximately <2 SD below the mean).

‡Term ≥37 completed weeks of pregnancy, moderately preterm 32-36 weeks, very preterm <32 weeks.

§Adjusted for maternal age, birth year, highest income, highest education level before first delivery, country of birth, pre-gestational hypertension, pre-gestational diabetes, gestational diabetes, gestational hypertension and preeclampsia/eclampsia, and smoking at registration for antenatal care.

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease