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History of preterm birth and subsequent cardiovascular disease: a systematic review

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Abstract

A history of preterm birth (PTB) may be an important lifetime risk factor for cardiovascular disease (CVD) in women. We identified all peer-reviewed journal articles that met study criteria (English language, human studies, female, and adults ≥19 years old), that were found in the PubMed/MEDLINE databases, and that were published between Jan. 1, 1995, and Sept. 17, 2012. We summarized 10 studies that assessed the association between having a history of PTB and subsequent CVD morbidity or death. Compared with women who had term deliveries, women with any history of PTB had increased risk of CVD morbidity (variously defined; adjusted hazard ratio [aHR] ranged from 1.2e2.9; 2 studies), ischemic heart disease (aHR, 1.3e2.1; 3 studies), stroke (aHR, 1.7; 1 study), and atherosclerosis (aHR, 4.1; 1 study). Four of 5 studies that examined death showed that women with a history of PTB have twice the risk of CVD death compared with women who had term births. Two studies reported statistically significant higher risk of CVD—rerelated morbidity and death outcomes (variously defined) among women with —2 pregnancies that ended in PTBs compared with women who had at least 2 births but which ended in only 1 PTB. Future research is needed to understand the potential impact of enhanced monitoring of CVD risk factors in women with a history of PTB on risk of future CVD risk.

Keywords

cardiovascular disease; death; preterm birth

Preterm birth (PTB), defined as delivery of an infant at <37 weeks' gestation, is the leading cause of long-term neurologic disabilities in children and the most common cause of infant death.[1] PTB not only poses risks for the child, but also it may identify women with elevated lifetime risks for cardiovascular disease (CVD).[2]

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In 2011, for the first time the American Heart Association identified 3 pregnancy complications (preeclampsia, gestational diabetes mellitus, and pregnancy-induced hypertension) as risk factors for CVD and 2 adverse birth outcomes (PTB and delivery of a small-for-gestational age infant) as possible risk factors for CVD. [2] CVD typically refers to a host of diseases that affect the cardiovascular system and includes atherosclerosis, hypertension, coronary heart disease, stroke, heart failure and other conditions. CVD is the leading cause of death among women overall and the third leading cause of death among women 18-44 years old.[3,4] Several systematic reviews have examined associations of pregnancy complications and future CVD,[5-8] but none have provided an in-depth review of the studies that investigated the risk of CVD in mothers with a history of PTB. Some proportion of PTBs is caused by hypertension (with and without preeclampsia), infection, congenital anomalies, diabetes mellitus, prenatal smoking, and placental abnormalities, but the cause of PTB remains unknown in most cases.[9] It is plausible that similar alterations in inflammatory mediators and immune function might be acting in the pathogenesis of both CVD and PTB.[10,11] Assessment of the current evidence of the association between PTB and future CVD may identify a group of women who possibly could benefit from enhanced clinical screening and monitoring.

The aim of this systematic review was to summarize the evidence that is related to PTB and subsequent CVD in the mother.

Methods

We used a multistage search strategy to conduct a systematic review of the literature to address whether having a PTB is associated with increased risk of future CVD morbidity or death. Three investigators (C.L.R., Y.H., P.M.D.) developed the electronic search strategies using a combination of free text terms and controlled vocabulary concepts that were derived from PubMed's "All Field" searches and "Medical Subject Headings" and "Title/Abstract" field (Table 1). Additional filters that were applied to the searches included limiting the searches to English language, human studies, female, and adults who were ≥19 years old and to articles that were published from Jan. 1, 1995—Sept. 17, 2012. A 2000 Lancet article claimed that no previous studies had examined the association between PTB and cardiovascular death,[12] and we found no relevant articles before 2000. For the systematic review search, the additional filters "Meta-analysis" and "Review" were applied. First, we searched the PubMed/MEDLINE and Cochrane Library databases to identify relevant systematic reviews or metaanalyses. Next, we searched PubMed/MEDLINE for relevant peer-reviewed individual studies.

Data collection entailed study selection and data extraction. Two researchers (C.L.R., Y.H.) examined the abstracts with titles that appeared to be relevant and selected all articles that examined the association between PTB and future CVD morbidity and/or death in the mother. We used researcher agreement to reconcile questions about eligibility. Finally, we reviewed reference lists of selected articles to identify any missed articles. We did not search unpublished or gray literatures. We considered all study designs. Data abstraction was performed by 1 investigator (Y.H.) with Table 2 and was verified by another (C.L.R.).

We used the Community Guide's methods and a structured tool to assess the quality of bias in individual studies because this tool offered flexibility in the evaluation of articles with different study designs (available at: http://www. thecommunityguide.org/library/ajpm 355_d.pdf).[13] This method evaluates validity threats by assessing points for each of 6 categories: study description (1), sampling (1), measurement (2), data analysis (1), interpretation of results (3), and other (ie, limitations not identified in the other 5 categories; 1). Pairs of investigators (Y.H/C.L.R., Y.H/P.M.D., C.L.R/P.M.D.) independently assessed the quality of studies by summing the number of possible flaws and categorizing the study accordingly: good (0-1 flaws), fair (2-4), or poor (>4). Differences between independent assessments were discussed by 3 investigators (Y.H., C.L.R., P.M.D.) and were resolved by consensus. This study was exempt from institutional review board approval because it did not involve human subjects.

Results

We identified 185 possible titles of systematic reviews or metaanalyses in PubMed/ MEDLINE, but none of the articles focused on the association between PTB and future CVD in the mother. Additionally, we found no relevant reviews in the Cochrane library. The initial search for individual studies generated 4828 articles. Many reports were deemed not relevant based on title (n = 4432). We identified 10 of the remaining 396 abstracts (2.5%) that addressed PTB as a primary exposure for CVD-related outcomes (Figure 1).

Study designs and samples

Table 2 describes exposures, outcomes, and other individual study details in ascending chronologic order of publication date. Study designs included case-control (n = 1), cohort (n = 8), and cross sectional (n = 1). Study populations were from Denmark (3), Finland (1), France (1), Scotland (3), Sweden (1), and the United States (1). Follow-up time from delivery to onset of morbidity or death ranged from 12-35 years (Table 3). All but 1 study omitted details about the racial composition of their study samples, but most were conducted in countries with predominantly white populations.

Exposure

Definitions and sources of PTB varied among the studies (Tables 2 and 4). Most came from registries that relied on International Classification of Diseases codes (n = 7)[14-20] or medical records systems (n = 1)[12]; 2 studies relied on validated self-report histories among women 55[21] or 80[22] years old (on average). Some studies restricted their study population to women who gave birth to babies at 24 weeks' gestation at least[16,19,20]; some studies used 20 weeks' gestation,[18] and other studies had no minimum number of weeks' gestation.[12,14,15,17,21,22] All but one study used 36 weeks' gestation to define the upper gestation limit of preterm; Nardi et al[21] defined PTB as ≤8 months' gestation. In the 8 studies that used vital records or birth registries, gestational age was based on last menstrual period,[12,15] estimated date of delivery,[19,20] or a combination of last menstrual period and ultrasound dating[14,17,18]; 1 study did not specify how gestational age was determined.[16]

Outcomes

Outcomes that were examined were CVD morbidity (n = 3),[15,18,22] CVD death (n = 5),[12,15-17,20] and either CVD hospitalization or death (as a single outcome; n = 5)[14,16,19-21] (Tables 3 and 4). Morbidity outcomes included CVD,[15,22] ischemic heart disease (IHD; which is the same as coronary heart disease),[15,18] stroke,[15] and atherosclerosis.[15] Death outcomes included CVD or IHD death. The definitions of outcomes are shown in Table 4. CVD definitions varied from broadly defined CVD (ie, any CVD, atherosclerosis, hypertensive disease, IHD stroke, myocardial diseases stroke, thromboembolic diseases, and type 2 diabetes mellitus)[15,17] to consideration of few major CVD categories: IHD, stroke, and peripheral vascular disease[22] or IHD, stroke, and heart failure.[14] Definition of IHD varied from inclusion of all IHD (acute myocardial infarction, other acute and subacute forms of IHD, old myocardial infarction, angina pectoris, or other forms of chronic IHD)[12,14,16,18] to the consideration of myocardial infarction with unstable angina only.[14] All studies used vital records, except 2 studies that relied on self-reported histories.[21,22]

Quality

The method quality of included studies was good (n = 3), fair (n = 6), and poor (n = 1). The most common validity threats were noted in measurement and interpretation of results. Specifically, 6 studies did not report evidence that exposure measures were valid.[12,15,19-22] Additionally, 4 studies did not specifically exclude women with CVD before pregnancy,[12,19,20,22] and all but 2 studies failed to adjust for smoking, which is an important potential confounder.[14,21] All studies adjusted for, or otherwise controlled for, age and hypertension/preeclampsia; 7 studies adjusted for socioeconomic status (SES)[12,14-16,19-21]; 5 studies adjusted for birthweight/fetal growth restriction,[15,16,18-20] and 2 studies examined interactions with birthweight.[14,17]

Findings

CVD morbidity—Two fair-quality studies reported positive associations with CVD morbidity: a US based cross-sectional study[21] and a cohort study conducted in Denmark[15] (Tables 2 and 3). The US study was based on a subsample of women who lived in Pittsburgh (n = 446) and who had participated in a large cohort epidemiologic study called The Study of Health, Aging, and Body Composition. This subsample had an average age of 80 years; 47% of the participants were black. Overall, women who self-reported history of PTB had an adjusted odds ratio of 2.9 (95% confidence interval [CI], 1.2–6.9) for self-reported CVD incident events that occurred from 1998-2002.[22] That study did not exclude women with heart disease before first delivery. The other study (n = 427,765) included all Danish women with deliveries that occurred from 1973-2006 and also reported excess risk that was associated with a history of PTB for CVD among women without previous CVD (adjusted hazard ratio [aHR], 1.2; 95% CI, 1.1–1.3). Registry data were used for that study with follow-up time that ranged from 23–33 years (mean, 28 years).[15]

IHD morbidity—We reviewed 2 studies that examined IHD morbidity (Tables 2 and 3).[14,17] The fair-quality cohort study that was conducted in Denmark and investigated the association of PTB and CVD also reported a statistically significant association for IHD

morbidity (aHR, 1.4; 95% CI, 1.3–1.5).15 An even larger, good-quality cohort study (1978-2007; n = 782,287) followed Danish women with singleton deliveries for 15 years (median). Those investigators conducted stratified analyses by degree of preterm, controlling for age, year of delivery, and several adverse pregnancy outcomes. They reported a 60% increased risk of IHD (95% CI, 1.1e2.4) for the most severe PTB (20-27 weeks' gestation), no statistically significant association for PTB at 28-31 weeks' gestation, and 30% increased risk for PTB at 32-36 weeks' gestation (95% CI, 1.2e1.6).[18]

CVD/IHD death—Women with a history of PTB had approximately twice the risk of CVD or IHD-related death as women with term births (Figure 2; Table 1).[12,15-17,20] A poor-quality study reported a similar association (aHR, 2.1; 95% CI, 1.2e3.5) based on 35 years of follow up (mean) on a Finnish sample of 3706 women with PTB and singleton deliveries documented in their Helsinki maternity records between 1954 and 1963.[12] Four fair- or good-quality cohort studies reported similar levels of risk (aHR range, 1.9–2.2),[15-17,20] although the association (aHR, 1.9; 95% CI, 0.7–4.9) was not statistically significant in 1 study.[20] The nonsignificant findig was reported in a fair quality study that included 129,920 women with singleton first births in Scotland between 1981 and 1985 (follow up ranged from 15–19 years).[20] In the previously mentioned Danish study that investigated numerous morbidity outcomes (fair quality; n = 427,765), Catov et al[15] followed women for 28 years (mean) and reported that women with PTB had excess CVD death compared with women with term deliveries (aHR, 2.0; 95% CI, 1.7–2.3). Another Danish study (n = 782,287) included women from 15-50 years old with a first, singleton delivery from January 1978 to October 2007 (median follow up time, 15 years) and reported an increased risk of CVD death that was associated with history of PTB (aHR, 2.0; 95% CI, 1.6–2.4).[17] A large fair-quality cohort study (n = 551,488) of all women with first singleton live births from January 1969 to July 2007 in Scotland reported a positive association of any PTB and subsequent maternal death from IHD (aHR, 2.3; 95% CI, 1.9e2.7).[16] Registry data were used for that study with a mean follow-up period of 22 years.

IHD hospitalization or death (combined)—Three fair-quality studies reported excess risk associated with a history of PTB and subsequent maternal hospitalizations or death that was related to IHD (Table 3).[16,20,21] The previously mentioned Scottish study on IHD death outcomes (n = 129,920) also investigated the association of PTB (24-36 weeks' gestation inclusive) with any IHD event (ie, death or hospital admission because of IHD) and reported increased risk (aHR, 1.8; 95% CI, 1.3e2.5).[20] A nested case-control study (n = 504) reported a positive association between PTB and subsequent diagnosis of or death from IHD (aHR, 2.1; 95% CI, 1.1e4.1).[21] That fair-quality study was based on a subsample from a French prospective cohort study that investigated cancer risk factors in 98,997 women who belonged to a major health insurer of teachers and who were born from 1925-1950.[21] Control subjects were matched to medically verified cases on birth year, cohort study enrollment date, education, and residence. A history of PTB was self-reported for births that had occurred from 42-68 years earlier and were defined as delivery at ≤8 months' gestation. Self-reported IHD was validated with medical records. The large study (n = 551,488) that was conducted in Scotland that investigated the association of PTB and IHD death also reported an association for PTB and any IHD event (fatal or nonfatal; aHR, 1.6; 95% CI,

1.5–1.7).[16] Those investigators separately analyzed the data, stratifying PTB by spontaneous (defined as vaginal delivery without induction or cesarean delivery after onset of labor) and elective (ie, induced delivery without onset of labor). Compared with term births, associations for elective PTB (aHR, 1.8; 95% CI, 1.6–2.0) were greater than associations between spontaneous PTB and IHD death (aHR, 1.5; 95% CI, 1.3–1.6; P = .005).

CVD/cerebrovascular disease hospitalization or death (combined)—Two studies reported excess risk associated with a history of PTB and subsequent maternal hospitalizations or death from CVD or cerebrovascular disease (Table 3).[14,19] A fair-quality Scottish study reported excess risk associated with a history of PTB (24-36 weeks' gestation inclusive) and subsequent maternal hospitalizations or death (combined) from cerebrovascular disease only.[19] Those researchers used vital records data from 119,668 women with deliveries (1981- 1985). They controlled for confounding by SES and preeclampsia and examined interactions with birthweight. They reported an increased risk of 1.9 (95% CI, 1.4–2.7) but no evidence of interaction. In a good-quality study, Bonamy et al[14] used vital records data from 923,686 women with first singleton births in Sweden from 1983-2005 and observed them through December 2005 (median, 12 years) to assess risk of first occurrence of maternal hospitalization or death from IHD stroke or heart failure. In addition to controlling confounding from SES, they also adjusted for hypertension, preeclampsia, diabetes mellitus, and smoking and examined interactions with birthweight. Compared with mothers of term infants with normal weight for gestational age, those investigators reported increased risk of subsequent CVD for mothers who delivered infants at ≤27 weeks' (aHR, 2.2; 95% CI, 1.3–3.6), 28-31 weeks' (aHR, 2.6; 95% CI, 2.0–3.3), and 32-36 weeks' gestation (aHR, 1.4; 95% CI, 1.2–1.6).[14]

Associations with recurrent PTBs—Two Danish studies (1 fair- and 1 goodquality) examined the associations of recurrent PTBs and CVD outcomes (Table 5).[15,18] The fair-quality cohort study is the same one that also investigated the association of PTB and CVD, IHD, stroke, atherosclerosis, and CVD death.[15] For their analysis of the association between recurrent PTB and CVD, Catov et al[15] used a subsample of women with ≥2 births (n = 182,146) and compared those with only term births to women with ≥1 PTBs. Among women with 1 PTB (aHR, 2.7; 95% CI, 1.7–4.4) and with ≥2 PTBs (aHR, 8.7; 95% CI, 4.4–17.3), the strongest association was with atherosclerosis. As seen with atherosclerosis, the risk of IHD was higher among women with ≥2 PTBs (aHR, 1.8; 95% CI, 1.4–2.3) compared with women who had ≥2 births but only 1 PTB (aHR, 1.2; 95% CI, 1.1–1.4). Confidence intervals for risk estimates of CVD, stroke, and CVD death by recurrent PTB status (only 1 vs ≥2 PTBs) overlapped. The 2 studies reported 1.4-1.8 times increased risk of IHD among women with ≥2 PTBs.[15,18] Investigators from those 2 studies also examined CVD risk by timing of PTB among a subsample of women who had ≥2 births but ≥1 PTB, and no clear pattern was evident.[15,18]

Comment

This systematic review provides a comprehensive overview of the current state of research examining CVD risk in mothers who have histories of PTB. Metaanalysis was not performed and can be misleading when observational studies are used because of

heterogeneity of available studies.[23] All included studies found that having a PTB was associated with a statistically significant increase in future CVD. The results were consistent, despite the fact that these studies examined a variety of CVD outcomes and included morbidity or death or both. The 2 studies that examined CVD risk among women with ≥2 births reported higher risks among subsamples with ≥2 PTBs compared with women who had only 1 PTB.

Elucidating the strengths and weaknesses of the included studies is important for translation of the evidence from this review. All but 2 studies linked data from large registries that enabled population level analyses and minimized selection bias.[21,22] Sample sizes of the individual studies ranged from 446e 923,686. Unmeasured risk factors that were associated with PTB and with CVD in the mother may confound observed associations if they are not adjusted for in the analyses. However, most studies adjusted for or examined interactions with hypertension/preeclampsia, birth- weight, and SES. Smoking was left unmeasured in 8 studies, possibly resulting in overestimated associations. In the 2 studies that controlled for smoking, the adjustment had no influence on the associations.[14,21] For the outcome of IHD hospitalization or death, the association remained even after adjustment for smoking[21] and was similar in magnitude to 3 other studies that did not control for smoking.[16,20,21] Only one-half of the studies excluded women with CVD before the first birth in the study period,[14,15,17,18,21] yet, estimates of risk in those studies were comparable with estimates from studies that did not have this exclusion criterion. All but one study focused predominantly on white populations; thus, whether associations are consistent across other racial and ethnic groups remains unknown.[22] Finally, we acknowledge the possibility of a cardioprotective effect for term pregnancy, rather than risk because of PTB.[24]

This review has several strengths that include manual review of reference lists for the identification of relevant studies, a report of study flow that detailed the selection of studies, and geographic breadth of studies that spanned the globe. Additionally, we used a quality assessment instrument that is based on methods that were used in other systematic reviews. Although that instrument offers flexibility for evaluation of articles with different study designs, it is intended as a measure of how well the selected study design was executed. Therefore, the type of study design was not weighted in the quality assessments. Despite our efforts to thoroughly and fairly evaluate the evidence, the possibility of publication bias and exclusion of reports in non-English language may have led to the exclusion of relevant studies. Given that this systematic review included studies that were published over a time span of 17 years and that we identified only 10 relevant articles, the amount of literature that examined this research question is relatively small. Moreover, we found major overlap in 2 articles,[19,20] and we found minor overlap in 2 articles that used the same datasets.[17,18]

CVD is a result of a complex interplay of multiple factors that span the life course, and some of the many pathways that lead to PTB may share common physiologic processes with CVD. Although the pathophysiologic processes that are responsible for the consistently reported associations between a history of PTB and subsequent CVD are uncertain, common inflammatory processes and genetic determinants have been posited as possible mechanisms of action for both.[11,25] Levels of risk were particularly high for atherosclerosis, which may provide insight into underlying mechanisms and support etiologic hypotheses of

inflammatory processes.[11,26] Inflammation may also play a key role in the explanation of the pathophysiologic process underlying the association between preeclampsia and future CVD.[5-7,27] Although preeclampsia can lead to PTB, all studies that were included in the review adjusted for or excluded pregnancies that were complicated by preeclampsia and gestational hypertension. Thus, our results suggest that the association between PTB and future CVD is independent of hypertensive disorders in pregnancy. In fact, emerging evidence supports our thinking. A 2013 study reported a linear association between the number of previous PTBs and a risk of future CVD hospitalization.[28]

Studies rarely account for the heterogeneity that is inherent in the PTB syndrome.[29] For example, only one study differentiated between spontaneous and indicated PTB. Most PTBs occur as a result of spontaneous onset of labor and/ or rupture of fetal membranes before term,[9] and there are likely inflammatory, vascular, and/or neuroendocrine pathways involved in these births. The current literature cannot distinguish among these pathways, and the degree to which specific pathophysiologic spontaneous preterm labor presentations might be associated with subsequent CVD cannot be determined.[9] However, the associations for both types of PTB with CVD are biologically plausible. The leading causes for indicated PTB are hypertensive disorders in pregnancy, which include preeclampsia and/or intrauterine growth retardation, although spontaneous PTB may be initiated by multiple factors.[9] Nevertheless, increased systemic inflammation, increasing stimulation of the infection or inflammation pathways,[30] and oxidative stress, which are well-known promoters of atherogenesis, also have been reported to be present in preeclampsia, fetal growth restriction, and spontaneous preterm labor.[31] It remains to be determined whether the associations of these pregnancy complications and CVD are due to pregnancy acting as a stress test that exposes a predilection for antiinflammatory and antioxidative dysfunction or whether these complications cause long-lasting subclinical damage to these antiatherosclerotic mechanisms that later contribute to the development of CVD.

Despite comparability and measurement challenges, nearly all included studies reported statistically increased risk of CVD outcomes that are associated with PTB. Although the magnitude of the risk may be modest, on a population level, PTB can identify a nontrivial number of women who are at increased risk of CVD (approximately one-half million women each year in the United States). Because most cardiac sudden deaths in women occur in the absence of a previous diagnosis of heart disease,[32,33] having comprehensive information about a woman's risk profile, which would include a history of reproductive health outcomes, enables optimal risk-appropriate screening, monitoring, and treatment. Delivery of a preterm infant may be the first indication that a woman has increased risk of the development of CVD. The American Heart Association's 2011 update on effectiveness-based guidelines for CVD prevention in women suggests that women with a history of gestational diabetes mellitus, hypertensive disorder in pregnancy, PTB, and/or delivery of a small-for-gestationalage infant may benefit from having their CVD risk factors carefully monitored.[2]

The current systematic review confirms that a history of PTB is an important CVD risk factor that is unique to women. Additional high-quality, longitudinal studies of racially and ethnically heterogeneous younger age women are needed to augment this systematic review.

Positive findings from such studies may tilt the weight of evidence toward institutionalized incorporation of PTB into CVD risk calculation in women. Given the accumulating evidence for such an association, clinicians may consider educating women about their increased risk, because this could motivate women to control their modiflable risk factors. Future research is needed to understand the potential impact of enhanced monitoring of CVD risk factors in women with a history of PTB on the risk of future CVD.

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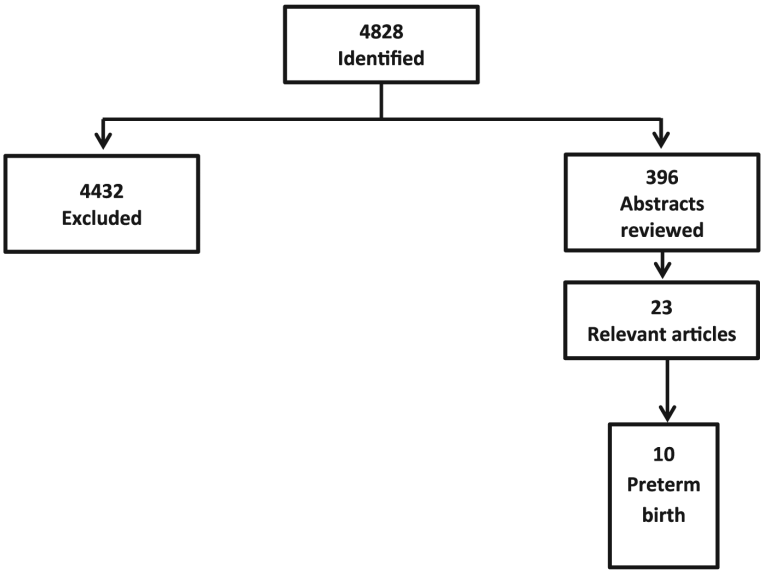

FIGURE 1.

Flow chart illustrates the selection of individual studies

Selection of studies that examined the association of preterm birth and/or fetal growth restriction with cardiovascular disease.

Robbins. Preterm birth and cardiovascular disease. Am J Obstet Gynecol 2014.

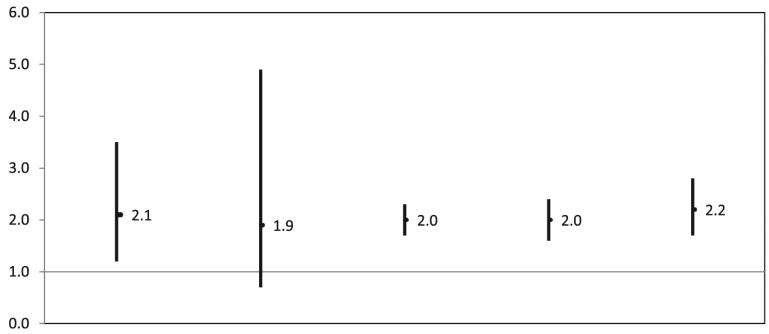

FIGURE 2.

Association of PTB and subsequent maternal death from CVD or IHD

Graph depicts the association.

CVD, cardiovascular disease; IHD, ischemic heart disease; PTB, preterm birth.

Robbins. Preterm birth and cardiovascular disease. Am J Obstet Gynecol 2014.

TABLE 1

PubMed/MEDLINE search strategy

All fields and title abstract	Topic[a]
Predictors	Fetal growth restriction
	Fetal growth retardation
	Low birthweight
	Low birthweight infant
	Small for gestational age
	Very low birthweight infant
	Extremely low birthweight infant
	Intrauterine growth restriction
	Intrauterine growth retardation
	Premature infant
	Prematurity
	Premature birth
	Birthweight
	Newborn
	Preterm delivery
	Pre-term delivery
	Newborn infant
	Complicated pregnancies
	Pregnancy complications
	Preterm birth
	Adverse pregnancy events
Cardiovascular-related outcomes	Cardiovascular disease
	Cardiovascular pregnancy complications
	Hypertension
	Dyslipidemia
	Hypercholesterolemia
	LDL cholesterol
	HDL cholesterol
	High blood pressure
	Hyperlipemia
	Hyperlipidemia
	Lipemia
	Lipidemia
	Lipid disorders
	Cholesterol
	Low density lipoprotein cholesterol

All fields and title abstract	Topic[a]
	High density lipoprotein cholesterol
	Triglycerides
	Cerebrovascular accident
	Cerebrovascular disease
	Ischemic heart disease
	Ischaemic heart disease
	Myocardial ischemia
	Myocardial ischaemia
	Thromboembolism
	Coronary heart disease
	Arteriosclerosis
	Cardiovascular death
	Cardiovascular morbidity
	Cardiovascular risk factors
	Cardiovascular risk
	Vascular risk
Morbidity and death-related outcomes	Mortality
	Death
	Cause of death
	Fatal outcome
	Survival rate
	Premature death
	Hospital death
	Maternal death
	Maternal risk
	Mothers' risk
	Death risk
	Death of mothers

LDL, low-density lipoproteins.

[a] Also entered as MeSH database terms.

TABLE 2

Individual preterm birth studies

Study	Study design/country	Eligible population and description of sample	Assessment of gestational age	Assessment of outcome
Smith et al, 2000[12]	Cohort study/Finland	Women with live, singleton births from 1954-1963 in Helsinki; analytic sample, 3706 women	Preterm: <37 weeks' gestation; source: Helsinki maternity care records	Cardiovascular disease death; source: Finnish central population and cause-of-death registers
Smith et al, 2001[20]	Cohort study/Scotland	Women with singleton first births in Scotland from 1981-1985 (n = 137,094); exclusions: stillbirths, infants born alive at <24 weeks' gestation and those with birthweight <500 g, women with previous pregnancies; analytic sample, 129,920 women (94.8%)	Based on estimated date of delivery; preterm: 24-36 weeks' gestation; source: Scottish Morbidity Record System	Death because of ischemic heart disease or any ischemic heart disease hospitalization or death per ICD-9 or 10 codes; source: Scottish Morbidity Record System
Pell et al, 2004[19]	Cohort/Scotland	Women with singleton first births in Scotland from 1981-1985 (n = 137,094 women); exclusions: stillbirths, infants born alive at <24 weeks' gestation and those with birthweight <500 g, women with previous pregnancies; analytic sample = 119,668 (87.3%)	Based on estimated date of delivery; preterm: 24-and 36 weeks' gestation; source: Scottish Morbidity Record System	Death or hospital admission because of a principal diagnosis of stroke (ischemic stroke, intracranial hemorrhage, or transient ischemic attack) per ICD-9 codes; source: Scottish Morbidity Record System
Nardi et al, 2006[21]	Retrospective nested case control study from the E3N study cohort/France	Cases were women born 1925-1950 who self-reported having had a first myocardial infarction from 1990-2000 and had a singleton live birth (n = 144); exclusions: previous cardiovascular problems, psychiatric disorders, and other noncardiac diseases; analytic sample = 504 women: 109 cases (75.7%), and 395 randomly selected control subjects matched on birth year, month/year of E3N enrollment, education, and residence area	Preterm: self-reported length of pregnancy at ≥8 months; source: survey	Self-reported ischemic heart disease; source: survey responses validated by review of hospital discharge records or death because of ischemic heart disease per ICD-9 code
Catov et al, 2007[22]	Cross-sectional study (the study of health, aging and body composition -health ABC)/Pittsburgh, PA	Women 70-79 years old in 1997-1998 who reported having had ≥1 live birth, were well-functioning, had ongoing plans for community-dwelling (n = 507 women); exclusion: women who did not provide pregnancy history details at the interview; analytic sample = 446 (88.0%)	Preterm: self-reported length of pregnancy at <37 weeks; source: survey	Self-reported cardiovascular disease: ischemic heart disease, stroke; or peripheral vascular disease; ischemic heart disease included myocardial infarction, angina, coronary artery bypass surgery, or percutaneous transluminal angioplasty; source: survey responses validated by medications and electrocardiogram results
Catov et al, 2010[15]	Cohort study/Denmark	Women with no previous cardiovascular disease or diabetes mellitus diagnoses who delivered a singleton live or still birth in Denmark from 1973-1983 (n =	Based on last menstrual period; preterm: <37 weeks' gestation; categorized as: ≥32, 33-34,	Composite endpoint per ICD-8 or ICD-10 code was first cardiovascular disease outpatient visit, hospitalization, or death (because of atherosclerosis; hypertensive

Study	Study design/country	Eligible population and description of sample	Assessment of gestational age	Assessment of outcome
		453,337); exclusions: children who were adopted or could not be matched to mothers, women with missing information related to gestational age, previous hospitalization for cardiovascular disease or diabetes mellitus, death during delivery, missing information on education; analytic sample = 427, 765 (94.4%); analytic subsample of women with ≥2 births = 182,146	or 35-36 weeks' gestation; source: the Danish Medical Birth Registry	disease; ischemic heart disease; stroke; and thrombosis); ischemic heart disease, stroke, hypertension, atherosclerosis, or thrombosis examined separately; source: the National Hospital Discharge Register
Lykke et al, 2010[18]	National registry-based cohort study/Denmark	Women 15-50 years old with no previous cardiovascular or diabetes mellitus diagnoses who delivered a first singleton in Denmark from January 1978 to October 2007 (n = 796,915); exclusions: women with previous cardiovascular or diabetes mellitus diagnoses and those who died or emigrated within 3 months of delivery; analytic sample for cohort 1 = 782,287 (98.2%); cohort 2 = subpopulation of cohort 1, defined as women who had a first delivery at >15 years old and second singleton delivery at <50 years old (n = 550,809); exclusions: women with cardiovascular or diabetes mellitus diagnoses before the second delivery and those who died or emigrated within 3 months of the second delivery Analytic sample for cohort 2 = 536,419 (97.4%)	Preterm: <37 weeks' gestation; categorized as: 20-27, 28-31, or 32-36 weeks' gestation; source: the National Patient Registry	First diagnosis of ischemic heart disease per ICD-8 and 10 codes; source: linked data from the National Patient Registry, the Danish Central Person Registry, and the Cause of Death Registry
Lykke et al, 2010[17]	National cohort study/Denmark	See description for cohort 1 [18]	Preterm: <37 weeks' gestation; source: National Patient Registry	Death from any cardiovascular disease per ICD-8 or 10 codes or a first cardiovascular disease diagnosis reported at ≤1 week before death (caused by any cardiovascular disease, hypertensive disease; ischemic heart disease; myocardial diseases, stroke; and thromboembolic diseases, or type 2 diabetes mellitus); sources: linked data from the National Patient Registry, the Danish Central Person Registry, and the Cause of Death Registry
Bonamy et al, 2011[14]	National cohort study/Sweden	Resident women with a first singleton birth in Sweden from 1983-2005 and no previous cardiovascular event (n = 957,412); exclusions: missing information on birthweight or gestational age or missing record in	Term: ≥37 weeks' gestation; moderately preterm: 32-36 weeks' gestation; very preterm: 28-31 weeks' gestation;	Cardiovascular disease incidence or death (defined as primary diagnosis for first hospitalization or underlying cause of death caused by coronary heart disease, unstable angina or acute myocardial infarction), stroke

Study	Study design/country	Eligible population and description of sample	Assessment of gestational age	Assessment of outcome
		the medical birth register; analytic sample = 923,686 (96.5%)	extremely preterm: ≤27 weeks' gestation; source: ultrasound scan or last menstrual period	(cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack, or other acute stroke), or heart failure per ICD-8 and 9 codes; sources: the Hospital Discharge Register, the Cause of Death Registry
Hastie et al, 2011[16]	Cohort study/Scotland	Women with first singleton live-births from January 1969 to July 2007 and 35-65 years old at the time of their first ischemic heart disease event or at the end of follow-up (n = 750,350); exclusions: women with maternal age at delivery of <12 years, birthweight <500 g, and gestational age <24 weeks or >43 weeks; analytic sample = 551,488 (73.5%)	Preterm: <37 weeks' gestation; term: ≥37 weeks' gestation; mild-moderate preterm:33-36 weeks' gestation; extreme preterm: 24-32 weeks' gestation; source: Scottish Morbidity Record System	Ischemic heart disease death or event per ICD-8, ICD-9, or ICD-10 code; source: linked data from the Scottish Morbidity Records and Scotland's Registrar General

ICD, International Classification of Diseases, 8th, 9th, or 10th revision.

TABLE 3

At-a-glance: individual preterm birth studies

				Statistically significant association[a]			Adjustment[b]								
Study	**Sample, n**	**Outcome**	**Follow up,y**	**Yes**	**No**	**95% CI**	**Age**	**Race**	**Socioeconomic status**	**Hypertension or preeclampsia**	**Diabetes mellitus**	**Birthweight**	**Tobacco**	**other**	**Ouality**
Smith et al, 2000[12]	3706	CVD death	35	2.1		1.2–3.5	x		x	x				x	Poor
Smith et al, 2001[20]	129,920	IHD death	15-19		1.9	0.7–4.9	x		x	x		x		x	Fair
		IHD hospitalization or death	15-19	1.8		1.3–2.5	x		x	x		x		x	Fair
Pell et al, 2004[19]	119,668	Stroke hospitalization or death	14-19	1.9		1.4–2.7	x		x	x		x		x	Fair
Nardi et al, 2006[21]	504	IHD hospitalization or death	N/A[c]	2.1		1.1–4.1	x		x	x	x		x	x	Fair
Catov et al, 2007[22]	446	CVD morbidity	N/A[d]	2.9[e]		1.2–6.9	x	x		x	x			x	Fair
Catov et al, 2010[15]	427, 765	CVD hospitalization	28	1.2		1.1–1.3	x		x	x	x	x		x	Fair
		IHD	28	1.4		1.3–1.5	x		x	x		x		x	
		Stroke	28	1.7		1.5–1.9	x		x	x		x		x	
		Atherosclerosis	28	4.1		3.3–5.1	x		x	x		x		x	
		CVD death	28	2.0		1.7–2.3	x		x	x	x	x		x	
Lykke et al,	782,287	IHD hospitalizations	15	1.6[f]		1.1–2.4	x			x		x		x	Good

Study	Sample, n	Outcome	Follow up,y	Statistically significant association[a]			Adjustment[b]								
				Yes	No	95% CI	Age	Race	Socioeconomic status	Hypertension or preeclampsia	Diabetes mellitus	Birthweight	Tobacco	other	Ouality
2010[18]															
			15		1.0[g]	0.8–1.3	x			x		x		x	
			15	1.3[h]		1.2–1.5	x			x		x		x	
Lykke et al, 2010[17]	782,287	CVD death	15	1.9		1.5–2.4	x			x		x		x	Good
Bonamy et al, 2011[14]	923,686	CVD hospitalization or death	12	2.2[i,j]		1.3–3.6	x		x	x	x		x	x	Good
			12	2.6[g,i]		2.0–3.3	x		x	x	x		x	x	
			12	1.4[h,i]		1.2–1.6	x		x	x	x		x	x	
Hastie et al, 2011[16]	750,350	IHD death	22	2.3[j]		1.9–2.7	x		x	x		x		x	Fair
			22	2.2[k]		1.7–2.7	x		x	x		x		x	
			22	2.5[l]		1.9–3.3	x		x	x		x		x	
		IHD hospitalization or death	22	1.6[j]		1.5–1.7	x		x	x		x		x	Fair
			22	1.5[k]		1.3–1.6	x		x	x		x		x	
			22	1.8[l]		1.6–2.0	x		x	x		x		x	

CVD, cardiovascular disease; *IHD*, ischemic heart disease; *N/A*, not available.

[a] Adjusted hazard ratios, unless otherwise noted;

[b] Adjustments noted if variable was included in model, if stratified analyses were conducted, or if exclusions were made based on the variable;

[c] Not reported; women recruited at 55 years old on average; mean time from recruitment to event was 5.2 years;

[d] Not reported; women interviewed at 80 years old on average;

[e] Adjusted odds ratios;

[f] Preterm, <27 weeks' gestation;

[g] Preterm, 28-31 weeks' gestation;

[h] Preterm, 32-36 weeks' gestation;

[i] Excludes small for gestational age;

[j] Any preterm;

[k] Spontaneous preterm (defined as vaginal delivery without induction or caesarean delivery after onset of labor);

[l] Elective preterm (induced delivery without onset of labor).

TABLE 4

Definitions of outcomes used in individual studies

		Source code				
Reference	**Definition details**	**ICD-7**	**ICD-8**	**ICD-9**	**ICD-10**	**Other**
Atherosclerosis						
Catov et al, 2010[15]	Atherosclerosis hospitalization or death		440		170-170.9	
Cerebrovascular disease						
Pell et al, 2004[19]	Stroke hospitalization or death			430-438	160-169, G45	
Catov et al, 2010[15]	Stroke hospitalization or death		430-438		160-169.8	
Cardiovascular disease						
Smith et al, 200[12]	Cardiovascular disease deaths					Not specified
Catov et al, 2007[22]	Cardiovascular disease morbidity: myocardial infarction, stroke, peripheral vascular disease, angina, coronary artery bypass surgery, or percutaneous transluminal angioplasty					Self-reported and validated with algorithms that included selected medications and electrocardiogram
Catov et al, 2010[15]	Cardiovascular disease outpatient visit, hospitalization, or cardiovascular disease deaths from atherosclerosis; hypertensive disease; ischemic heart disease; stroke; and thrombosis; NOTE: ischemic heart disease, stroke, hypertension, atherosclerosis, or thrombosis also examined separately		390-459		100-199	
Bonamy et al, 2011[14]	Cardiovascular disease deaths or hospitalizations: coronary heart disease, stroke, or heart failure		410, 411, 430-436, 427, 427.10	410, 411B, 430-436, 428	120.0, 121-122, G45, 1160-1164, 150	
Lykke et al, 2010[17]	Cardiovascular disease deaths: any cardiovascular disease or ischemic heart disease, stroke, myocardial infarction, hypertension, thromboembolic disease, or type 2 diabetes mellitus					
Ischemic heart disease						
Smith et al, 2001[20]	Ischemic heart disease hospitalization or death			410-414	120-125	
Nardi et al, 2006[21]	Myocardial infarction					Self-reported and validated with information on diagnosis, ECC, and

		Source code				
Reference	**Definition details**	**ICD-7**	**ICD-8**	**ICD-9**	**ICD-10**	**Other**
						enzymatic dosages via interviews with general practitioners and review of hospital and ischemic heart disease death records
Catov et al, 2010[15]	Ischemic heart disease hospitalization or death		410-414		120-125.5	
Lykke et al, 2010[18]	Ischemic heart disease hospitalization		410-414		120-125	
Hastie et al, 2011[16]	Ischemic heart disease hospitalization or death		410-414	410-414	120-125	

ECC, electrocardiogram; ICD, International Classification of Diseases, 7th, 8th, 9th, or 10th revision.

TABLE 5

Studies that examined associations between PTB and CVD outcomes, stratified by the number of PTBs

			1 PTB		≥2 PTBs	
Study	**Sample, n**[a]	**Outcome**	**Adjusted hazard ratio**	**95% CI**	**Adjust hazard ratio**	**95% CI**
Catov et al, 2010[15, b]	182,146	Cardiovascular disease	1.2	1.1–1.3	1.4	1.2–1.6
		Ischemic heart disease	1.2	1.1–1.4	1.8	1.4–2.3
		Stroke	1.8	1.4-2.2	1.4	0.8-2.5
		Atherosclerosis	2.7	1.7–4.4	8.7	4.4–17.3
		Cardiovascular disease death	1.7	1.3–2.2	2.1	1.2–3.7
Lykke et al, 2010[18, c]	536,419	Ischemic heart disease	1.1[d]	0.9–1.2	1.4	1.0–1.8
			1.2[e]	1.0–1.4		

CI, confidence interval; *CVD*, cardiovascular disease; *PTB*, preterm birth.

[a] Sample limited to women with ≥2 singleton births in the study period;

[b] Adjusted for age, socioeconomic status, parity, education;

[c] Adjusted for age, year of delivery, hypertensive pregnancy disorders, small or large for gestational age, placental abruption, stillbirth;

[d] PTB in first pregnancy;

[e] PTB in second pregnancy.