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Preterm Delivery and Future Risk of Maternal Cardiovascular Disease: A Systematic Review and Meta-Analysis

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***Background*—**Preterm delivery (<37 weeks gestational age) affects 11% of all pregnancies, but data are conflicting whether preterm birth is associated with long-term adverse maternal cardiovascular outcomes. We aimed to systematically evaluate and summarize the evidence on the relationship between preterm birth and future maternal risk of cardiovascular diseases.

***Methods and Results*—**A systematic search of MEDLINE and EMBASE was performed to identify relevant studies that evaluated the association between preterm birth and future maternal risk of composite cardiovascular disease, coronary heart disease, stroke, and death caused by cardiovascular or coronary heart disease and stroke. We quantified the associations using random effects meta-analysis. Twenty-one studies with over 5.8 million women, including over 338 000 women with previous preterm deliveries, were identified. Meta-analysis of studies that adjusted for potential confounders showed that preterm birth was associated with an increased risk of maternal future cardiovascular disease (risk ratio [RR] 1.43, 95% confidence interval [CI], 1.18, 1.72), cardiovascular disease death (RR 1.78, 95% CI, 1.42, 2.21), coronary heart disease (RR 1.49, 95% CI, 1.38, 1.60), coronary heart disease death (RR 2.10, 95% CI, 1.87, 2.36), and stroke (RR 1.65, 95% CI, 1.51, 1.79). Sensitivity analysis showed that the highest risks occurred when the preterm deliveries occurred before 32 weeks gestation or were medically indicated.

***Conclusions*—**Preterm delivery is associated with an increase in future maternal adverse cardiovascular outcomes, including a 2-fold increase in deaths caused by coronary heart disease. These findings support the assessment of preterm delivery in cardiovascular risk assessment in women. **(*J Am Heart Assoc*. 2018;7:e007809. DOI: 10.1161/JAHA.117.007809.)**

Key Words: cardiovascular disease risk factors • coronary heart disease risk • long-term outcome • pregnancy and postpartum • stroke

Globally, preterm birth affects 11% of all pregnancies, with an estimated 14.9 million babies born before 37 weeks gestational age each year.[1] In addition to being the leading cause of neonatal mortality,[2] there is increasing evidence to show that preterm delivery is an adverse pregnancy outcome associated with an increased risk of future maternal cardiovascular health.[3–5] Cardiovascular disease is the leading cause of mortality worldwide,[6] most of which is preventable by altering behavioral risk profiles and lifestyle modifications, but there may be sex-specific cardiovascular risk factors that need to be recognized in women.[7]

Pregnancy is characterized by a challenge to the cardiovascular system with a doubling of blood volume, elevated coagulation and inflammatory factors, hyperlipidemia, and insulin resistance.[8,9] This physiological stress for most women is uncomplicated but for women who experience preterm birth,

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Accompanying Data S1, Tables S1 through S8, and Figure S1 are available at http://jaha.ahajournals.org/content/7/2/e007809/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Preterm delivery is associated with a 1.4- to 2-fold increase in maternal risk for future incident cardiovascular events, cardiovascular death, coronary heart disease events, coronary heart disease death, and stroke.
- This increased risk is greatest in preterm births that occur before 32 weeks in gestation or in those that are delivered for medical indications such as fetal growth restriction or pre-eclampsia.
- For cardiovascular disease and coronary heart disease outcomes, the risks are higher in women with a greater number of recurrent preterm births.

What Are the Clinical Implications?

- In keeping with current recommendations, our study highlights the importance of advising women with preterm births about their increased cardiovascular risk and advocating and supporting lifestyle and behavioral changes to control their modifiable risk factors.
- These findings support the evaluation of preterm delivery in cardiovascular risk assessment in postnatal women.

this adverse pregnancy outcome may serve to identify women at risk for cardiovascular disease who would not have been detected using traditional risk assessment tools at a time when it may be possible to alter their risk trajectory.[10–12]

It remains unclear whether preterm delivery is an independent risk factor for future cardiovascular disease or an early marker of women with background high-risk profiles for future cardiovascular disease. As preterm birth is a heterogeneous condition with multiple causes, the pathogenesis of preterm birth remains poorly understood. The main proposed mechanisms include increased systemic inflammation, infection, or vascular diseases.[13–15] The duration of pregnancy gestation has been inversely correlated to insulin resistance, blood pressure, and low-grade inflammation in women years after delivery.[16–18] In addition, women with previous preterm births, but without pre-eclampsia or small-for-gestational-age births, have higher atherogenic lipids and carotid arterial wall thickening in the decade after delivery compared with women who had term births.[19] Therefore, the dysregulation in cardiometabolic factors with their common pathways to cardiovascular diseases may provide a possible explanation for the link between preterm birth and future cardiovascular diseases.[20,21]

Previous studies, including a meta-analysis, have examined the relationship between preterm delivery and future incident cardiovascular disease.[3–5] The previous meta-analysis included studies published up to 2011.[3] Since then, there have been further studies including large sample sizes (ie, >100 000 participants).[22–24] Some newer studies also demonstrated results inconsistent with earlier literature showing no increased risk for future stroke events.[25,26] Furthermore, previous work did not differentiate between morbidity and mortality outcomes, nor examined clinically relevant factors such as gestation at delivery, recurrence and cause of preterm births. As recent guidelines from the United States[27,28] and European Union[29] recommend the inclusion of a history of preterm birth to evaluate the cardiovascular disease and stroke risk in women based on evidence from cohort studies published up to 2011,[30–35] there is a need for contemporary evidence. To this end, we conducted a systematic review and meta-analysis to quantify the risk of maternal cardiovascular events in later life following preterm birth and contribute to future recommendations for clinical practice.

Methods

Eligibility Criteria

The data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedure. The protocol was registered on PROSPERO an International prospective register of systematic reviews.[36] We selected studies investigating postnatal cardiovascular outcomes of women with preterm delivery. Preterm delivery was defined as birth any time before 37 weeks gestation. Primary cardiovascular outcomes were composite cardiovascular disease (defined as a combination of cardiac, cerebrovascular, and peripheral vascular disease), death caused by composite cardiovascular disease, coronary heart disease, death caused by coronary heart disease, stroke, and stroke death. The *International Classification of Diseases* (*ICD*) (versions 7-10) code definitions of the outcomes are specific to each study and are detailed in Table S2. The included studies had at least 2 groups (1 with preterm birth and 1 with term birth) and reported sufficient data to allow for accurate risk estimates to be calculated. There was no restriction based on language, cohort type, study design, or duration of follow-up.

Data Sources and Searches

MEDLINE and EMBASE were searched using OVID SP for studies from inception to October 2017. The detailed search terms are outlined in Methods S2. Manual searching for additional articles was also conducted by reviewing the bibliography of relevant review articles and published systematic reviews.[3–5,37]

Study Selection and Data Extraction

Two reviewers (P.W. and G.V.) screened all titles that met the inclusion criteria. This was followed by a screen of the remaining abstracts. The full articles were screened by

the same 2 reviewers and the final decision to include studies was made by P.W. Independent double data extraction was done by 4 reviewers (P.W., C.S.K., C.W., and A.N.). Data were collected on study design, year, country, number of participants, mean age, parity, cohort characteristics, definition and ascertainment of preterm birth, ascertainment of outcomes, timing of assessment, adequacy of follow-up, and results. The information was obtained from published data.

Study Quality Assessment

Study quality was assessed based on the recommendations of the Newcastle-Ottawa Quality Assessment Scale for cohort studies.[38] We evaluated studies that had the following characteristics as at low risk of bias: selection of exposed cohort from the general population of pregnant women; selection of nonexposed cohort from the same population; reliable ascertainment of exposure such that the likelihood of controls (term birth) being misclassified as having preterm birth when they did not or cases being wrongly classified as not having preterm birth was minimized; exclusion of women who had cardiovascular outcome of interest before or during pregnancy; comparable cohort where confounders, in particular age, pre-eclampsia, and diabetes mellitus/insulin resistance, or any other cardiovascular risk factors such as smoking, body mass index, and cholesterol, were accounted for; assessment of outcomes prospectively or through linkage of records and/or independent blind assessment; follow-up duration for at least 5 years postpartum; and <10% of the study participants in each cohort being lost to follow-up.

Data Synthesis and Analysis

We used RevMan Version 5.3.5 (Nordic Cochrane Centre) to conduct random effects meta-analysis using the inverse variance method for pooling log risk ratios (RRs). We used random effects because the studies were conducted in a wide range of settings in different populations, hence the need to take heterogeneity into account for the pooled effect estimate. Where possible, we chose to pool adjusted risk estimates from primary studies and when these data were not available, raw data were used to calculate unadjusted risk estimates. Studies were pooled in meta-analysis with subgroups based on whether or not the study used adjustments to account for confounders. Statistical heterogeneity was assessed using the I^2 statistic where I^2 values of 30% to 60% represented moderate level of heterogeneity.[39] Where there was greater than a moderate degree of heterogeneity, we performed leave-1-out analysis to identify studies that contributed to high degree of heterogeneity. In the case of an analysis where there are more than 10 studies and little evidence of heterogeneity, we planned to perform funnel plots to assess for publication bias.[40] Sensitivity analysis was performed to consider the follow-up duration of the studies (<10, 10–30, and >30 years), gestation (<32 weeks versus 32–37 weeks), and recurrence (1 recurrence versus ≥2 recurrence) of preterm births, and whether the preterm births occurred spontaneously or were medically indicated. For the sensitivity analysis on gestation, we excluded studies where the subgroups could not be categorized as either <32 weeks or 32 to 37 weeks gestation (eg, <34 weeks gestation).

Results

Description of Studies Included in Analysis

The initial MEDLINE and EMBASE search produced 653 titles and abstracts. After screening, 21 studies were included in the analysis (Figure 1) including 5 813 682 women in total (ranges from 446 to 923 686 women in each study). Studies recruiting patients from the same population were paired to avoid duplication of participant numbers.[31,32,41,42] Some studies assessed the same population over different time points.[24,31,32,41–45] In these cases, the study with the longest follow-up period was used for analysis in order to obtain the highest event rate.

Table 1 summarizes the study designs and participant characteristics. Out of the 16 studies that reported the number of women in study and control groups, 338 007 women delivered preterm while 5 261 933 delivered at term.* Data for women with singleton pregnancies were included in 15 studies.† At the index pregnancy, the participants had a mean or median age ranging from 23 to 31 years. The mean follow-up period ranged from 5.2 to 57 years.

Quality Assessment of Included Studies

The study quality was evaluated based on the recommendations of the Newcastle-Ottawa Quality Assessment Scale (Tables S1 and S2).[38] Fifteen studies were found to use reliable methods for ascertaining the preterm birth exposure, whereas 16 studies used reliable methods of obtaining cardiovascular outcomes.

Pooled Analysis of Preterm Birth and Cardiovascular Outcomes

Table 2 shows the results of the studies. A total of 8 studies were pooled and showed a 1.6-fold significantly increased

*References 5, 22, 23, 25, 26, 30, 31, 41, 43–51.
†References 22–24, 30–32, 35, 41–44, 47–50.

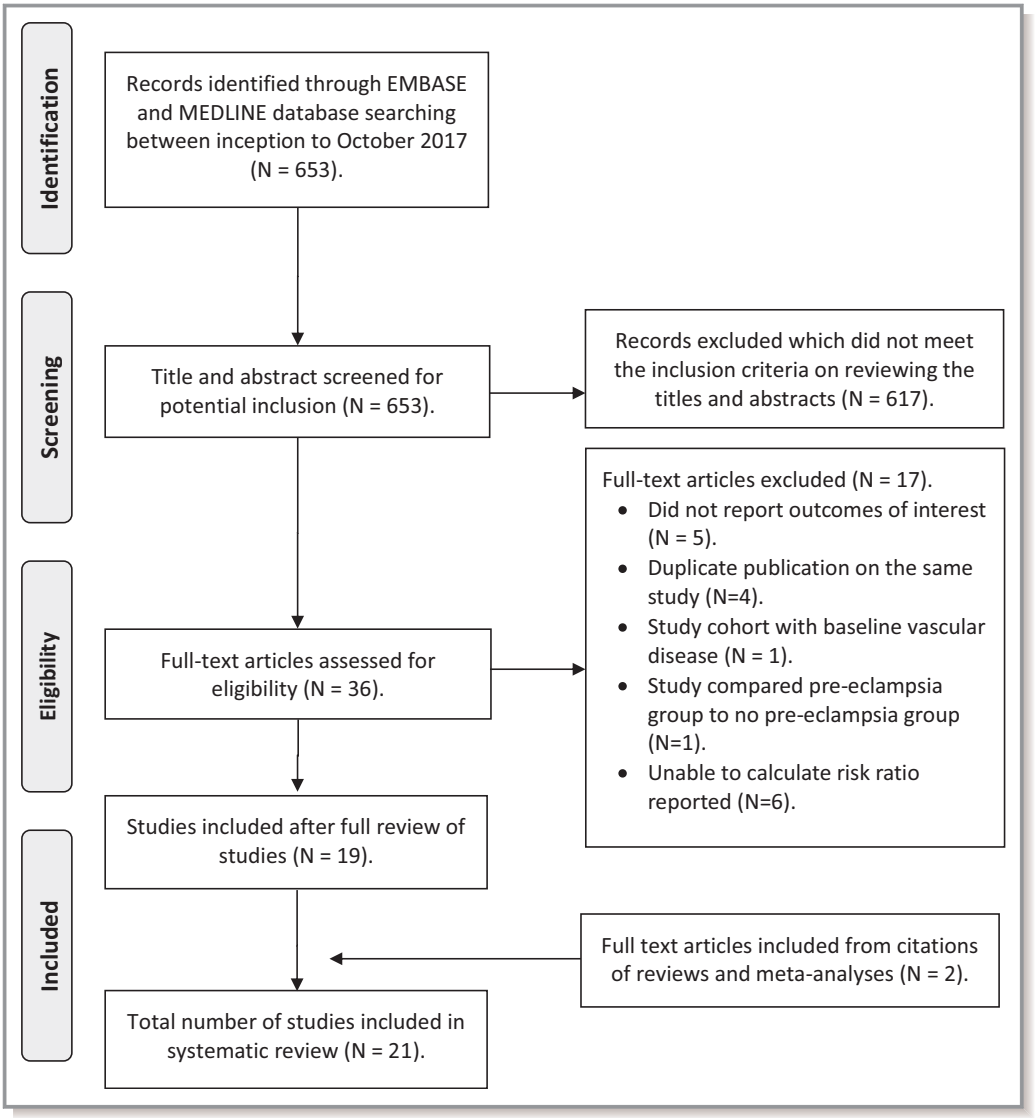

Figure 1. Flow diagram of study inclusion. Adapted from: Moher et al.[52]

maternal risk of composite cardiovascular disease in preterm birth (RR 1.56, 95% confidence interval [CI], 1.32, 1.84, I^2=93%) (Figure 2A).[22,23,25,30,43,46,48,51] Combining the 5 studies that adjusted for potential confounders,[23,25,43,46,48] the risk was 1.4-fold (adjusted risk ratio [aRR] 1.43, 95% CI, 1.18, 1.72; I^2=89%). The potential confounding factors evaluated in the studies are shown in Table S2. All 5 studies had adjusted for age. We performed leave-1-out analyses to explore the sources of heterogeneity. It was mainly driven by the Catov 2010 study.[43] By excluding this study, heterogeneity was reduced to 54% in the adjusted analysis (aRR 1.52, 95% CI, 1.31, 1.75). For composite cardiovascular disease death, the pooled results suggest a 1.8-fold increase in maternal cardiovascular disease death with preterm birth (RR 1.81, 95% CI, 1.55, 2.10, I^2=70%; aRR 1.78, 95% CI, 1.42, 2.21, I^2=77%) (Figure 2B).[24,31,35,41,43,53] There were no common confounders in the adjusted studies as they had adjusted for different confounding factors. The heterogeneity was mainly driven by the Davey-Smith 2005 study.[53] After excluding this study, heterogeneity reduced to 0% in both overall and adjusted analyses.

For coronary heart disease there was a 1.5-fold increase risk of events with preterm birth (RR 1.50, 95% CI, 1.39, 1.62, I^2=51%, aRR 1.49, 95% CI, 1.38, 1.60, I^2=54%) (Figure 3A). All of the 5 studies that used adjusted data had adjusted for age and socioeconomic status or education.[23,25,43,44,50] The heterogeneity was mainly driven by the Hastie 2011 study.[44] If this study was excluded, heterogeneity was reduced to 33% in the adjusted analysis (aRR 1.45, 95% CI, 1.33, 1.57). The 4 adjusted studies reporting coronary heart disease death showed a 2-fold increased risk with preterm birth (aRR 2.10, 95% CI, 1.87, 2.36, I^2=0%, Figure 3B).[24,44,47,53] There were no common confounders over these 4 studies as they had adjusted for different confounding factors.

Table 1. Study Design and Participant Characteristics

Study ID	Study Design, Country, Year	Total No. of Participants (Preterm/Term)	Mean Age at Pregnancy (y)	Parity	Participant Selection Criteria
Bonamy 2011[30]	Retrospective cohort study, Sweden, 1983–2005	923 686 (preterm 56 893/term 866 793)	Median 26.9	P	Women with a first singleton birth in Sweden between 1983 and 2005
Catov 2007[46]	Cross-sectional study, United States, 1997–2004	446 (preterm 27/term 419)	23.5	P	Women enrolled in the Health, Aging and Body Composition (Health ABC) study on 70- to 79-year-olds living in Pittsburgh during 1997 and 1998, who provided their past obstetric history
Catov 2010[43]	Retrospective cohort study, Denmark, 1973–2006	427 765 (preterm 26 588/term 401 177)	25.5	A	Women with singleton births in Denmark between 1973 and 1983
Cirillo 2015[47]	Prospective cohort study, United States, 1959–2011	10 310 (preterm 1251/term 9059)	Median 26	A	Women receiving prenatal care from the Kaiser Health Plan in California recruited to the Child Health and Development Studies (CHDS)
Smith 2000[35]	Cohort study, Finland, 1954–2000	3706	Unclear	P	A cohort of singleton live births between 1954 and 1963 in Helsinki
Smith 2005[53]	Cohort study, Finland, 1973–1997	10 368 mothers and 22 807 fathers	Unclear	A	Parents who had children born between 1973 and 1980 in Sweden
Freibert 2011[51]	Cross-sectional study, United States, 2006–2008	2882 (preterm 324/term 2558)	Unclear	A	Women from the Kentucky Women's Health Registry aged ≥50 y of age between 2006 and 2008, who provided their past obstetric history
Hastie 2011[44]	Retrospective cohort study, Scotland, 1969–2007	750 350 (preterm 44 743/term 705 607)	Median 24.5	P	Women with first singleton live births in Scotland between January 1969 and July 2007
Hovi 2014[22]	Retrospective cohort study, Finland, 1987–2012	152 219 mothers (preterm 8720/term 39–41 wks 143 499) and 190 996 fathers	Unclear	P	Women with first singleton births in the Finnish Medical Birth Register from 1987 to 1990
Irgens 2001[45]	Retrospective cohort study, Norway, 1967–1992	602 117 (preterm 26 018/term 576 099)	Unclear	P	Women with first deliveries recorded in the Norwegian medical birth registry from 1967 to 1992
Kessous 2013[48]	Retrospective cohort study, Israel, 1988–2010	47 908 (preterm 5992/term 41 916)	29	A	Women with singleton birth at the Soroka University Medical Center in Negev between 1988 and 1999
Lykke 2010[41] & Lykke 2010[31]	Retrospective cohort study, Denmark, 1978–2007	755 398 (preterm 41 659/term 713 739) in Lykke 2010[41] or 685 594 (preterm 41 659/term 643 935) in Lykke 2010[31]	26.8	P	Women with first singleton delivery in Denmark from 1978 to 2007
Nardi 2006[49]	Case–control study, France, 1990–2000	514 (preterm 76/term 438)	55 at enrollment	P	Women born between 1925 and 1950 who had a first MI between 1990 and 2000, matched with women of similar age, year and month of inclusion in study, educational level and area of residence. All women were in a health insurance scheme primarily covering teachers who had singleton pregnancies

Continued

Table 1. Continued

Study ID	Study Design, Country, Year	Total No. of Participants (Preterm/Term)	Mean Age at Pregnancy (y)	Parity	Participant Selection Criteria
Ngo 2015[23]	Retrospective cohort study, Australia, 1994–2012	797 056 (preterm 59 563/term 737 493)	Median 31	A	Women who had a singleton birth between July 1994 and December 2011 in New South Wales
Pell 2004[42] & Smith 2001[32]	Retrospective cohort study, Scotland, 1981–1999	199 668 (Pell 2004) or 129 920 (Smith 2001)	Median 23	P	Women with first singleton live births in Scotland between 1981 and 1985
Rich-Edwards 2015[24]	Retrospective cohort study, Norway, 1967–2009	688 662 (preterm 40 981 [spontaneous 33 230; indicated 7751]/term 647 681 [spontaneous 550 604; indicated 97 077])	24.6	P	Women with first singleton birth between 1967 and 1998 in the Medical Birth Registry of Norway
Tanz 2017[25]	Prospective cohort study, United States, 1989–2013	70 182 (preterm 6178, term 64 004)	27.4	P	Subset of women with pregnancies in the Nurses' Health Study II, that followed registered nurses aged 25 to 42 y in 1989
Wang 2011[26]	Retrospective cohort study, Taiwan, 2000–2008	4715 (preterm 1134/ term 3581)	27.8	P	Randomly selected, frequency-matched control women delivering in the same year as women with hypertensive disorders in pregnancy in the National Health Insurance program between 2000 and 2004
Wikstrom 2005[50]	Cross-sectional study; Sweden; 1973–1982	365 730 (preterm 17 860/term 347 870)	Median 48*	P	Women in the Swedish Medical Birth Register from 1973 to 1982 with singleton pregnancies

A indicates any parity; MI, myocardial infarction; P, primiparous.
*Age at follow-up.

Figure 4 shows the pooled analysis for studies on maternal preterm birth and stroke, and illustrate the risk to be increased by 1.7-fold in preterm birth (aRR 1.65, 95% CI, 1.51, 1.79, I^2=0%).[23,25,26,32,42,43] All studies had adjusted for potential confounders that included age and socioeconomic status or education or urbanization level. The pooled result on preterm birth and stroke death was not statistically significant (aRR 1.30, 95% CI, 0.94, 1.80, I^2=66%).[24,53] We did not perform funnel plots to assess for publication bias as <10 studies were included in each analysis.

Sensitivity Analysis for Follow-Up Time

We conducted sensitivity analyses to consider the effect of follow-up time for cardiovascular outcomes that were significant in the adjusted studies (Table 3). At <10 years following preterm birth, the risks for composite cardiovascular disease (RR 1.65, 95% CI, 1.49, 1.82), coronary heart disease (RR 1.61, 95% CI, 1.40, 1.86), and stroke (RR 1.67, 95% CI, 1.45, 1.93) were already significant and similar to longer follow-up times.

Sensitivity Analysis Considering Effect of Gestation of Preterm Birth, Recurrence of Preterm Birth, and Spontaneous Versus Medically Indicated Preterm Birth

Sensitivity analyses were performed to consider the effect of gestation, recurrence, and spontaneous onset of preterm birth in the 5 cardiovascular outcomes that were significant in the adjusted studies. These showed that the risks were higher when preterm deliveries occurred before 32 weeks gestation in all outcomes: composite cardiovascular disease (RR 1.85, 95% CI, 1.51, 2.28), composite cardiovascular disease death (RR 2.10, 95% CI, 1.61, 2.74), coronary heart disease (RR 1.62, 95% CI, 1.28, 2.04), coronary heart disease death (RR 2.30, 95% CI, 1.53, 3.46), and stroke (RR 2.00, 95% CI, 1.65, 2.43), compared with those occurring at 32 to 37 weeks gestation (Table 4).

When recurrence of preterm birth was studied, the risks for composite cardiovascular disease (RR 1.58, 95% CI, 1.17, 2.12) and coronary heart disease (RR 1.95, 95% CI, 1.53, 2.50) were higher if the preterm birth recurred in 2 or more pregnancies compared with recurring once only (Table 5). The

Table 2. Study Outcomes, Follow-Up and Results

Study ID	Definition of Preterm	Follow-Up Duration	Definition of Outcome	Results (Preterm vs Term)
Bonamy 2011[30]	Moderately preterm (32–36 wks), very preterm (28–31 wks), extremely preterm (≤27 wks)	11.8 y	CVD: unstable angina, acute MI, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack, acute stroke or heart failure	32 to 36 wks: 320/49 537 vs 3154/866 793. aHR 1.39 (1.22–1.58) 28 to 31 wks: 70/5259 vs 3154/866 793. aHR 2.57 (1.97–3.34) ≤27 wks: 24/2097 vs 3154/866 793. aHR 2.18 (1.33–3.57)
Catov 2007[46]	Delivery <37 wks gestation	57 y	CVD: MI, angina, coronary artery bypass surgery, percutaneous transluminal angioplasty, stroke or peripheral vascular disease	12/27 vs 120/491. aHR 2.85 (1.19–6.85)
Catov 2010[43]	Delivery <37 wks gestation	28 y	CVD: CHD, stroke, hypertension, atherosclerosis or thrombosis	Any preterm: 3454/26 588 vs 39 485/401 177. aHR 1.18 (1.10–1.25) 35 to 36 wks: aHR 1.26 (1.20–1.33) 33 to 34 wks: aHR 1.26 (1.16–1.37) ≤32 wks: aHR 1.36 (1.21–1.53) Recurrent 1 preterm birth: aHR 1.16 (1.09–1.25) Recurrent ≥2 preterm births: aHR 1.26 (1.05–1.51)
			CVD death*	Any preterm: aHR 1.98 (1.73–2.26) 35 to 36 wks: aHR 1.87 (1.59–2.14) 33 to 34 wks: aHR 2.10 (1.73–2.78) ≤32 wks: aHR 2.10 (1.47–3.00) Recurrent 1 preterm birth: aHR 1.70 (1.33–2.16) Recurrent ≥2 preterm births: aHR 2.12 (1.22–3.68)
			CHD*	Any preterm: 1272/26 588 vs 13 283/401 177. aHR 1.42 (1.34–1.52) 35 to 36 wks: aHR 1.41 (1.30–1.53) 33 to 34 wks: aHR 1.49 (1.32–1.68) ≤32 wks: aHR 1.38 (1.15–1.66) Recurrent 1 preterm birth: aHR 1.22 (1.09–1.36) Recurrent ≥2 preterm births: aHR 1.78 (1.40–2.27)
			Stroke*	Any preterm: 351/26 588 vs 3185/401 177. aHR 1.67 (1.48–1.89) 35 to 36 wks: aHR 1.73 (1.49–2.01) 33 to 34 wks: aHR 1.42 (1.10–1.84) ≤32 wks: aHR 1.92 (1.38–2.67) Recurrent 1 preterm birth: aHR 1.77 (1.44–2.17) Recurrent ≥2 preterm births: aHR 1.37 (0.75–2.49)
Cirillo 2015[47]	Delivery <37 wks gestation	40 y	CHD death	aHR 2.1 (1.40–3.01)
Smith 2000[35]	Delivery <37 wks gestation	Unclear	CVD death	aHR 2.06 (1.22–3.47)
Smith 2005[53]	Delivery <37 wks gestation	20.4 y	CVD (CHD and stroke) death	aHR 1.32 (1.09–1.61)
			CHD death	aHR 1.66 (1.20–2.29)
			Stroke death	aHR 1.07 (0.77–1.49)

Continued

Table 2. Continued

Study ID	Definition of Preterm	Follow-Up Duration	Definition of Outcome	Results (Preterm vs Term)
Freibert 2011[51]	Delivery between 20 and 36 wks gestation	Unclear	CVD	110/324 vs 573/2558
			CHD	37/324 vs 159/2558
Hastie 2011[44]	Delivery <37 wks gestation	22 y	CHD	Any preterm: aHR 1.58 (1.47–1.71) Spontaneous (n=29 965): aHR 1.46 (1.33–1.61) Medically indicated (n=14 747): aHR 1.81 (1.61–2.04)
			CHD death	Any preterm: aHR 2.26 (1.88–2.71) Spontaneous (n=29 965): aHR 2.14 (1.70–2.70) Medically indicated (n=14 747): aHR 2.49 (1.89–3.30)
Hovi 2014[22]	Delivery <37 wks gestation	22 y	CVD: CHD and stroke	Any preterm: 431/8720 vs 4127/143 499 34 to 36 wks: 303/6540 vs 4127/143 499. HR 1.55 (1.38–1.74) 32 to 33 wks: 50/954 vs 4127/143 499. HR 1.61 (1.22–2.13) 28 to 31 wks: 52/809 vs 4127/143 499. HR 2.12 (1.61–2.79) <28 wks: 26/417 vs 4127/143 499. HR 2.00 (1.36–2.94)
Irgens 2001[45]	Delivery between 16 and 36 wks gestation	13 y	CHD death	aHR 2.95 (2.12–4.11)
			Stroke death	aHR 1.91 (1.26–2.91)
Kessous 2013[48]	Delivery <37 wks gestation	10 y	CVD: hospitalization for CHD, stroke, peripheral vascular disease, hyperlipidemia, angina, hypertension, atherosclerosis, MI, heart failure, pulmonary heart disease, cardiac arrest, cardiac catheterization or cardiovascular stress test	Any preterm: aHR 1.4 (1.2–1.6) 34 to 37 wks (n=4596): OR 1.4 (1.2–1.6). <34 wks (n=1396): OR 1.7 (1.3–2.1) Spontaneous (n=41 669): OR 1.4 (1.2–1.6) Medically indicated (n=6239): OR 1.7 (1.3–2.4) Recurrent 1 preterm birth: 261/5217 vs 1467/41 916 Recurrent ≥2 preterm births: 43/775 vs 1467/41 916
Lykke 2010a[41] & Lykke 2010b[31]	Delivery <37 wks gestation	14.6 y (Lykke 2010a)	CHD	Any preterm: 589/41 659 vs 7257/713 739 32 to 36 wks: 500/35 255 vs 7257/713 739. aHR 1.32 (1.20–1.45) 28 to 31 wks: 63/4698 vs 7257/713 739. aHR 1.03 (0.80–1.34) 20 to 27 wks: 26/1706 vs 7257/713 739. aHR 1.61 (1.09–2.37) Recurrent 1 preterm birth: 71/4244 vs 4730/471 052. aHR 1.36 (1.02–1.81)
		14.8 y (Lykke 2010b)	CVD (CHD, stroke, hypertension, thromboembolic disease and type 2 diabetes mellitus) death	115/41 659 vs 824/643 935. aHR 1.98 (1.64–2.40)
Nardi 2006[49]	Delivery <8 mo gestation	5.2 y	CHD death	23/76 vs 86/438
Ngo 2015[23]	Delivery 20 to 36 wks gestation	7.5 y	CVD: hospitalization or death for CHD, stroke, and congestive heart failure	Any preterm: aHR 1.65 (1.50–1.83) 35 to 36 wks: aHR 1.53 (1.35–1.74) 33 to 34 wks: aHR 1.89 (1.55–2.31) 20 to 32 wks: aHR 1.83 (1.50–2.23)

Continued

Table 2. Continued

Study ID	Definition of Preterm	Follow-Up Duration	Definition of Outcome	Results (Preterm vs Term)
				Spontaneous: aHR 1.53 (1.35–1.72) Medically indicated: aHR 1.93 (1.66–2.25) 1 preterm birth: aHR 1.62 (1.46–1.79). Recurrent ≥2 preterm births: aHR 2.04 (1.56–2.67)
			CHD	Any preterm: aHR 1.61 (1.39–1.85) 35 to 36 wks: aHR 1.49 (1.24–1.78) 33 to 34 wks: aHR 1.89 (1.43–2.51) 20 to 32 wks: aHR 1.72 (1.29–2.29) Spontaneous: aHR 1.53 (1.29–1.81) Medically indicated: aHR 1.77 (1.41–2.21) 1 preterm birth: aHR 1.54 (1.33–1.79) Recurrent ≥2 preterm births: aHR 2.31 (1.61–3.33)
			Stroke	Any preterm: aHR 1.68 (1.46–1.95) 35 to 36 wks: aHR 1.49 (1.23–1.80) 33 to 34 wks: aHR 1.90 (1.41–2.56) 20 to 32 wks: aHR 2.13 (1.61–2.82) Spontaneous: aHR 1.49 (1.24–1.78) Medically indicated: aHR 2.12 (1.70–2.65) 1 preterm birth: aHR 1.68 (1.44–1.95) Recurrent ≥2 preterm births: aHR 1.76 (1.14–2.73)
Pell 2004[42] & Smith 2001[32]	Delivery 24 to 36 wks gestation	14 to 19 y (Pell 2004)	Stroke	aHR 1.91 (1.35–2.70).
		15 to 19 y (Smith 2001)	CHD death	HR 2.2 (0/9–5.7). aHR 1.9 (0.7–4.9)
Rich-Edwards 2015[24]	Delivery <37 w gestation	24.8 y	CVD (CHD and stroke) death	HR 1.9 (1.7–2.2) Spontaneous: Any preterm: HR 1.7 (1.5–2.0) 35 to 36 wks: aHR 1.4 (1.0–1.8) 32 to 34 wks: aHR 1.9 (1.3–2.7) 22 to 31 wks: aHR 2.1 (1.4–3.1) Medically indicated: Any preterm: HR 3.7 (2.4–4.5) Recurrent 1 preterm birth: aHR 3.3 (2.4–4.5)
			CHD death	Spontaneous: Any preterm: aHR 2.1 (1.7–2.5) 35 to 36 wks: aHR 2.1 (1.6–2.7) 32 to 34 wks: aHR 2.4 (1.7–3.4) 22 to 31 wks: aHR 2.3 (1.5–3.4) Medically indicated: 35 to 36 wks: aHR 6.2 (4.2–9.3) 32 to 34 wks: aHR 3.4 (1.7–6.9) 22 to 31 wks: aHR 4.7 (2.2–9.8)
			Stroke death	Spontaneous: Any preterm: 1.5 (1.2–1.8) 35 to 36 wks: aHR 1.3 (0.9–1.7) 32 to 34 wks: aHR 1.9 (1.3–2.8) 22 to 31 wks: aHR 1.8 (1.1–2.8) Medically indicated: Any preterm: aHR 3.0 (2.0–4.3) 35 to 36 wks: aHR 2.9 (1.7–5.1) 32 to 34 wks: aHR 1.9 (0.8–4.7) 22 to 31 wks: aHR 5.4 (2.8–10.4)

Continued

Table 2. Continued

Study ID	Definition of Preterm	Follow-Up Duration	Definition of Outcome	Results (Preterm vs Term)
Tanz 2017[25]	Delivery >20 and <37 wks gestation	32 y	CVD: MI and stroke	Without hypertensive disorders of pregnancy (preterm 4487 vs term 51 343): Any preterm: aHR 1.35 (1.06–1.72) 32 to <37 wks: aHR 1.12 (0.83–1.52) 20 to <32 wks: aHR 2.01 (1.38–2.93) Recurrent 1 preterm birth: aHR 1.63 (1.18–2.25)
			CHD	Any preterm: aHR 1.55 (1.19–2.01) 32 to <37 wks: aHR 1.36 (0.99–1.86) 20 to <32 wks: aHR 2.10 (1.38–3.21)
			Stroke	Any preterm: aHR 1.28 (0.95–1.71) 32 to <37 wks: aHR 1.09 (0.76–1.56) 20 to <32 wks: aHR 1.84 (1.15–2.95)
Wang 2011[26]	Unclear	6.4 y	Stroke	aHR 1.51 (0.77–2.93)
Wikstrom 2005[50]	Delivery <37 wks gestation	15 y	CHD	145/17 860 vs 1959/347 870. aRR 1.3 (1.1–1.5)

Data are HR/OR (95% confidence intervals). aHR indicates adjusted hazard ratio; aRR, adjusted risk ratio; CHD, coronary heart disease/ischemic heart disease; CVD, cardiovascular disease; MI, myocardial infarction; RR, risk ratio.
*Data not adjusted for diabetes mellitus.

risks for all available outcomes were greatest when the preterm birth occurred as a result of medically indicated compared with spontaneous preterm birth: composite cardiovascular disease (RR 1.88, 95% CI, 1.64, 2.16), composite cardiovascular disease death (RR 3.70, 95% CI, 2.88, 4.76), coronary heart disease (RR 1.80, 95% CI, 1.62, 2.00), coronary heart disease death (RR 3.56, 95% CI, 1.74, 7.25), and stroke (RR 2.12, 95% CI, 1.70, 2.65, Table 6).

The full cardiovascular risk factor profile of the preterm birth and the control term birth population is described in Table S3. Significant differences in age,[44,48] ethnicity,[48] education,[43] socioeconomic class,[44] obesity,[48] hypertension,[44] pre-eclampsia,[43,44] and small-for-gestational-age fetus[43] between the preterm and term birth groups were detected at the index pregnancy in 3 studies. Although these only contributed to 21% of total participant women, the cardiovascular risk factor profiles at the index birth were not available in the majority of participants within this systematic review and meta-analysis. Additional sensitivity analyses were performed where studies were stratified by singleton pregnancies, year of the study, quality of the study, location of the study, and pre-existing cardiovascular diagnosis in participants (Tables S4 through S8). We found that the results did not vary substantially.

Discussion

This meta-analysis examined 96 341 474 women years and included 338 007 women with preterm birth out of 5 813 682 study participants in 21 studies. We found that preterm delivery is associated with an increased maternal risk for future incident cardiovascular events, cardiovascular death, coronary heart disease events, coronary heart disease death, and stroke. The adjusted risk ranged between 1.4- and 2-fold compared with those without a history of preterm birth. This increased risk is greatest in preterm births that occur before 32 weeks in gestation or in those that are delivered for medical indications such as fetal growth restriction or pre-eclampsia. For the composite cardiovascular disease and coronary heart disease outcomes, the risks are higher in women with a greater number of recurrent preterm births. Preterm delivery is a significant event in a woman's reproductive history with a good recall rate including high specificity.[54–56] Therefore, it may be considered as a potential risk factor for future cardiovascular disease in women, as recommended by the current guidelines from the American Heart Association and European Society of Cardiology.[27–29]

By including an additional 1.7 million participants to the previous meta-analysis in this field, our results are consistent with earlier literature showing an increased risk in coronary heart disease, stroke, and composite cardiovascular disease.[3] Although our risk estimate for composite cardiovascular disease was lower than previously reported, this may be because of the difference in data analysis. In the previous meta-analysis, there was no distinction between adjusted and unadjusted data nor between morbidity and mortality outcomes. There are 2 other systematic reviews without meta-analysis of the literature, which also support our findings.[4,5] Unique to this study, we conducted sensitivity analyses to consider the duration of follow-up, gestation at birth,

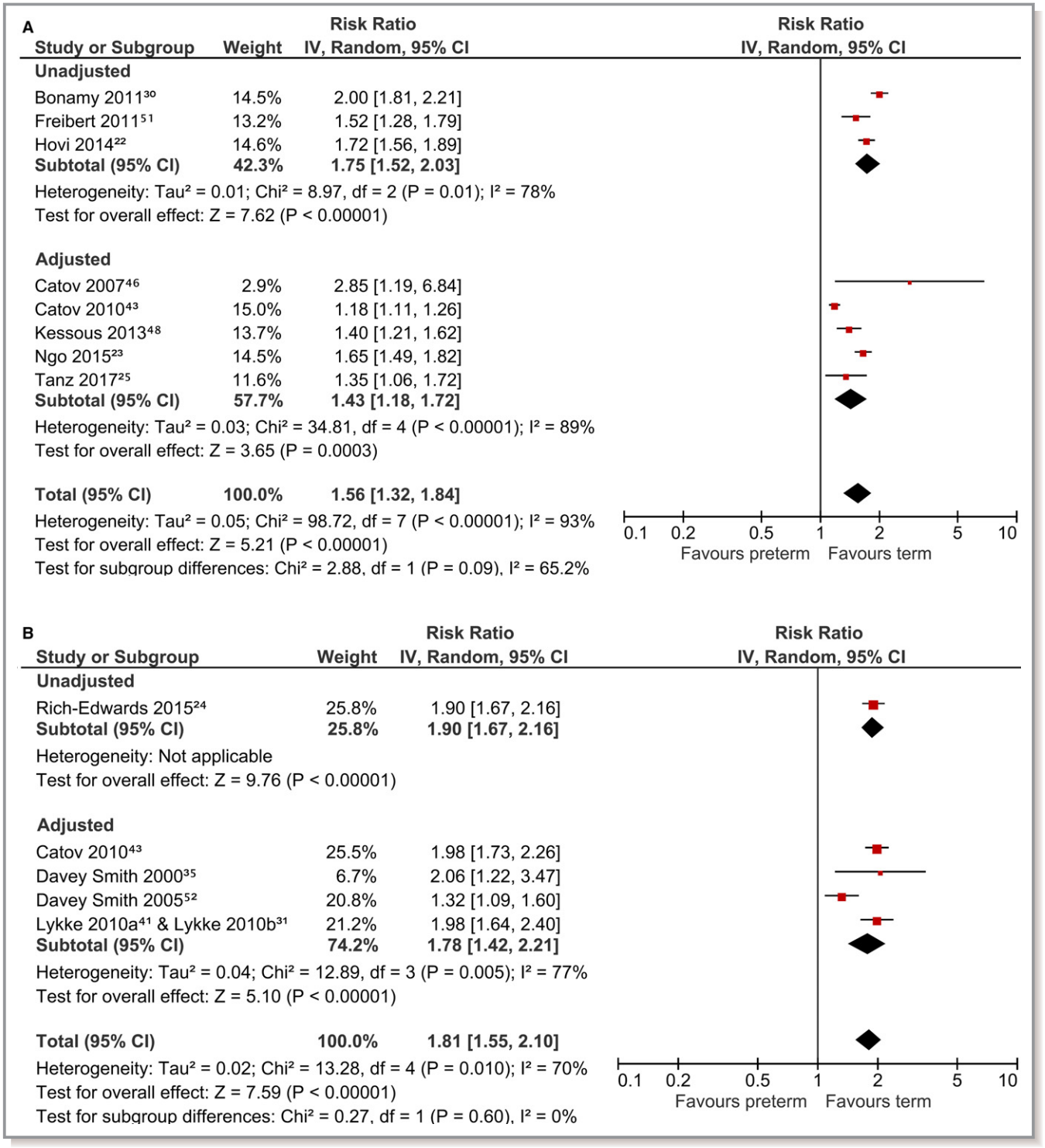

Figure 2. Risk of composite cardiovascular disease with preterm birth. A, Cardiovascular disease events. B, Cardiovascular disease death. CI indicates confidence interval.

recurrent preterm birth, and spontaneous or medically indicated preterm birth.

Because of the multifactorial nature of preterm birth causes, several pathognomonic mechanisms have been hypothesized.[13,57] These include vascular and metabolic factors,[58–60] as well as pre-eclampsia and fetal growth restriction that have both been independently associated with future adverse cardiovascular outcomes.[61–63] Moreover, preterm birth markers, such as proinflammatory cytokines, matrix metalloproteinase, fibrinolysis, prostaglandin cascade,[8,59,64–68] and dyslipidemia,[59,66,69] are also involved in atherosclerosis and endothelial dysfunction.[34,70–73]

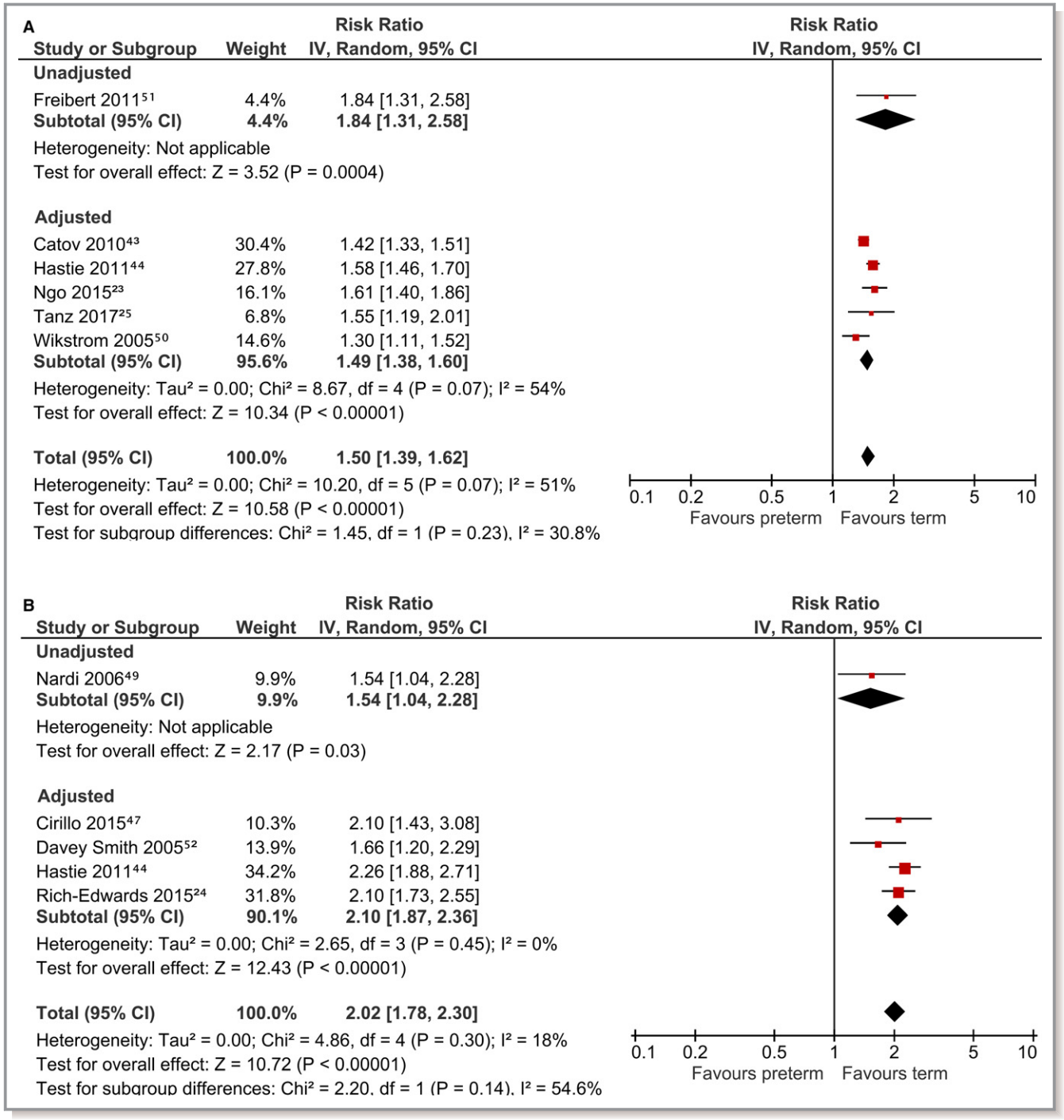

Figure 3. Risk of coronary heart disease with preterm birth. A, Coronary heart disease events. B, Coronary heart disease death. CI indicates confidence interval.

Therefore, preterm birth shares common risk factors with cardiovascular disease[74,75] and the association we identified may have been an epiphenomenon in women with high cardiovascular risk profiles that predispose them to both preterm birth and cardiovascular diseases. In contrast, other longitudinal studies have shown no difference in lipid profile, blood pressure, and inflammatory markers between preterm and term deliveries.[17,76]

There may also be other possible hypotheses for the association of preterm delivery and long-term adverse cardiovascular outcomes. One third of normotensive preterm births exhibit placental abnormalities commonly seen in pre-eclampsia and placental insufficiency,[77,78] while ≈17% of preterm births are medically indicated.[79] Common medical indications for preterm birth include pre-eclampsia and placental insufficiency causing fetal growth restriction, which

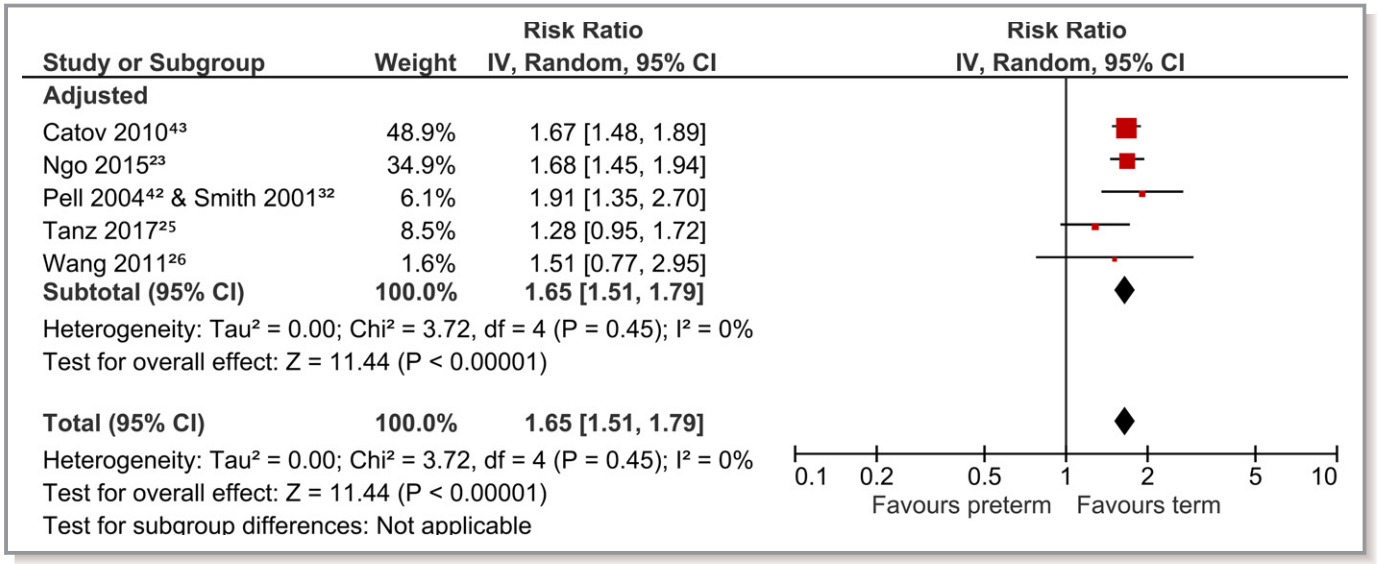

Figure 4. Risk of stroke with preterm birth. CI indicates confidence interval.

may have confounded any relationships reported in the literature. Moreover, diabetes mellitus is more common in women with previous preterm deliveries, which may have confounded our findings.[80] Although smoking has not been universally agreed upon as a risk factor for preterm birth,[81,82] the causative relationship between smoking and cardiovascular diseases is well established.[83–86] Other possible confounders include obesity and socioeconomic status, both of which have been linked to increased risks of preterm birth[32,87–89] and cardiovascular disease in women.[90–92]

Although the majority of the included studies (n=16) have attempted to adjust for some potential confounders,[‡] none of the studies have adequately adjusted for all relevant risk factors that form the basis of many of the established cardiovascular risk prediction scores (eg, cholesterol and family history of cardiovascular disease). There was also limited overlap between the adjusted confounding factors among the studies. As many key confounders for cardiovascular diseases were not adjusted for in the included studies, it is possible that the relationships that we have reported are entirely driven by differences in cardiovascular risk factor profiles at baseline. In the studies (48% of total participants) that presented the baseline cardiovascular risk factor profiles, the majority did not calculate whether there were any differences between the preterm and term birth groups. In the 3 studies (21% of total participants) that calculated this difference, all of them showed significant baseline risk factor profile differences between the preterm birth and the term birth populations.[43,44,48]

[‡]References 23–26, 30–32, 35, 41–48, 50, 53.

The 2011 American Heart Association guidelines for cardiovascular disease prevention in women advised healthcare professionals to inquire about adverse pregnancy outcomes, including preterm delivery, as a part of any cardiovascular risk assessment in women. However, there was a lack of additional specific guidance as preterm birth was not considered a major cardiovascular disease risk factor.[28] The 2014 guidelines from the American Heart Association and American Stroke Association for the prevention of stroke in women also recognized preterm birth as a factor associated with increased stroke risks after pregnancy, but did not make further recommendations because of the lack of evidence in the literature.[27] More recently, the 2016 European Society of Cardiology guidelines recommended the consideration of periodic screening for hypertension and

Table 3. Sensitivity Analyses With Regard to Duration of Follow-Up

Outcomes	<10 Y	10 to 30 Y	>30 Y
CVD	1.65 [1.49, 1.82], n=1	1.54 [1.19, 2.01], n=4	1.73 [0.87, 3.46], n=2
CVD death	…	1.79 [1.51, 2.11], n=4	…
CHD	1.61 [1.40, 1.86], n=1	1.45 [1.32, 1.60], n=3	1.55 [1.19, 2.01], n=1
CHD death	1.54 [1.04, 2.28], n=1	2.08 [1.80, 2.40], n=3	2.10 [1.43, 3.08], n=1
Stroke	1.67 [1.45, 1.93], n=2	1.70 [1.51, 1.90], n=2	1.28 [0.95, 1.72], n=1

Data are risk ratio [95% confidence intervals], number of pooled studies. CHD indicates coronary heart disease; CVD, cardiovascular disease.

Table 4. Sensitivity Analysis With Regard to Gestation of Preterm Birth

Outcomes	<32 Wks	32 to 37 Wks
CVD	1.85 [1.51, 2.28], n=6	1.40 [1.23, 1.59], n=5
CVD death	2.10 [1.61, 2.74], n=2	1.85 [1.58, 2.16], n=2
CHD	1.62 [1.28, 2.04], n=3	1.44 [1.35, 1.53], n=3
CHD death	2.30 [1.53, 3.46], n=1	2.20 [1.78, 2.71], n=1
Stroke	2.00 [1.65, 2.43], n=3	1.49 [1.22, 1.83], n=3

Data are risk ratio [95% confidence intervals], number of pooled studies. CHD indicates coronary heart disease; CVD, cardiovascular disease.

Table 6. Sensitivity Analysis With Regard to Spontaneous or Medically Indicated Preterm Birth

Outcomes	Spontaneous	Medically Indicated
CVD	1.47 [1.34, 1.62], n=2	1.88 [1.64, 2.16], n=2
CVD death	1.70 [1.47, 1.96], n=1	3.70 [2.88, 4.76], n=1
CHD	1.48 [1.36, 1.60], n=2	1.80 [1.62, 2.00], n=2
CHD death	2.12 [1.82, 2.45], n=2	3.56 [1.74, 7.25], n=2
Stroke	1.49 [1.24, 1.79], n=1	2.12 [1.70, 2.65], n=1

Data are risk ratio [95% confidence intervals], number of pooled studies. CHD indicates coronary heart disease; CVD, cardiovascular disease.

diabetes mellitus in women with a history of preterm birth.[29] In line with these recommendations, we suggest a detailed evaluation of a screening program for cardiovascular disease in women with a history of preterm birth, particularly in women who delivered because of any medical indications or before 32 weeks gestation (ie, the very or extremely preterm as defined by the World Health Organization). An opportune time for this screening is at the 6-week postpartum visit suggested in the World Health Organization recommendations on postnatal care.[93]

The strength of our study lies in the large sample size with a total of 96 341 474 patient-years follow-up. We used a search strategy without limiting the study design, language, and used independent reviewers for performing double data extractions and data analysis. All of the studies were designed to assess future cardiovascular diseases as their main outcome.

The limitations of this study include the risk of confounding and being unable to attribute causality of future cardiovascular disease to preterm delivery. These are because of the longitudinal nature of the epidemiological studies we included in this meta-analysis. As with any meta-analysis, there may be inherent publication bias, where studies with positive findings are more likely to be published compared with those showing neutral or negative outcomes. Over half of the included studies were retrospective in design. Therefore, there was limited control over the quality of data collected. As such, the preterm birth exposure could have been prone to recall bias or inaccuracies in historical data collection. Furthermore, the cardiovascular outcomes were determined by subjective self-reporting in 3 studies.[25,46,51] Heterogeneity may have arisen because of differences in the study population, research methodology, period of conducting the study, and inherent differences between the studies. Two studies were conducted in ethnically diverse populations[26,48] in contrast to the other studies that were performed in white populations. Six studies examined women of any parity,[23,43,47,48,51,53] while the others studied primiparous women. Specific populations were analyzed in 2 studies, which were Nardi et al[49] (women covered by a particular health insurance program) and Tanz et al[25] (nurses). As shown in Table 1, there was a mixture of retrospective, prospective, cross-sectional, and case–control studies. Because of the variation in duration of follow-up in the studies, the index preterm birth could have occurred in 1954 or in 2011. There has been both a change in obstetric practice, cardiovascular screening, and management of cardiovascular risk factors over these 57 years, which could have contributed toward differences between the studies. In the composite cardiovascular disease outcome, the heterogeneity was mainly driven by the Catov 2010 study.[43] Out of the pooled adjusted studies, this was the only study conducted in Europe as the others were conducted in the United States, Australia, or Israel.

Table 5. Sensitivity Analysis With Regard to Recurrence of Preterm Birth

Outcomes	Recurrent 1 Preterm Birth	Recurrent ≥2 Preterm Births
CVD	1.42 [1.17, 1.73], n=4	1.58 [1.17, 2.12], n=3
CVD death	2.35 [1.23, 4.50], n=2	2.12 [1.22, 3.68], n=1
CHD	1.36 [1.09, 1.71], n=2	1.95 [1.53, 2.50], n=2
Stroke	1.77 [1.44, 2.17], n=1	1.61 [1.13, 2.30], n=2

Data are risk ratio [95% confidence intervals], number of pooled studies. CHD indicates coronary heart disease; CVD, cardiovascular disease.

Our finding of an association between preterm delivery and the future development of incident cardiovascular disease has important implications for women and health policy. Women who experience a preterm delivery are at a higher risk of cardiovascular events and this suggests that a formal cardiovascular risk assessment using established risk scores should be considered in these women.[94,95] In addition, clinicians may find it pertinent to educate women regarding their increased cardiovascular risk and potentially motivate women toward controlling any modifiable risk factors. The perinatal period is a valuable time for opportunistic advice, education, intervention, and monitoring in at-risk women. However, there is little awareness regarding the long-term cardiovascular consequences of pregnancy complications

among healthcare professionals. A survey showed that only 5% of internists inquired about pre-eclampsia during history taking, while primary care data showed that 50% of women who had pre-eclampsia did not receive any further postnatal follow-up after 3 months.[96,97] Cardiovascular disease presents differently between men and women,[28,98] and most cardiac sudden deaths in women occur without prior history of heart disease.[99,100] Therefore, it would be appropriate to utilize past obstetric history to comprehensively assess cardiovascular risk profiles in women. Our findings support the current guidelines from the American Heart Association[27,28] and the European Society of Cardiology[29] to assess preterm delivery as part of the cardiovascular disease risk assessment in women.

Conclusions

Our large meta-analysis that included 5 813 682 women, 338 007 of whom had experienced a preterm delivery, demonstrated that preterm birth is associated with a 1.4- to 2-fold increase in future adverse cardiovascular outcomes. In keeping with current recommendations, our study highlights the importance of advising women with preterm births about their increased cardiovascular risk and advocating and supporting lifestyle and behavioral changes to control their modifiable risk factors. These findings support the assessment of preterm delivery in cardiovascular risk assessment in women, with the 6-week postpartum visit the ideal place for this to occur.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Search terms

Synonyms of preterm birth (‘preterm delivery’ or ‘preterm birth’ or ‘premature delivery’ or ‘premature birth’) AND ‘ischaemic heart disease’ or ‘ischemic heart disease’ or ‘coronary artery disease’ or ‘coronary heart disease’ or ‘myocardial infarction’ or ‘acute coronary syndrome’ or ‘heart failure’ or ‘cardiac failure’ or ‘left ventricular systolic dysfunction’ or ‘stroke’ or ‘cerebrovascular disease’ or ‘cerebrovascular accident’ or ‘cardiomyopathy’ or ‘peripheral vascular disease’ or ‘cardiovascular disease’ or ‘cardiovascular morbidity’ or ‘cardiovascular mortality’.

Table S1. Study quality assessment overview.

Study ID	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of preterm birth	Demonstration that outcome of interest was not present at start of study	Comparability of cohort	Assessment of outcome	Follow-up duration to capture outcomes	Adequacy of follow-up	Total score
Bonamy 2011[1]	*	*	*	*	**	*	*	*	9
Catov 2007[2]	*	*			**		*	*	6
Catov 2010[3]	*	*	*	*	**	*	*	*	9
Cirillo 2015[4]	*	*	*	*	*	*	*	*	8
Davey Smith 2000[5]	*	*	*	*	*	*			6
Davey Smith 2005[6]	*	*	*	*	*	*	*		7
Freibert 2011[7]	*	*						*	3
Hastie 2011[8]	*	*	*		*	*	*	*	7
Hovi 2014[9]	*	*	*			*	*	*	6
Irgens 2001[10]	*	*	*	*	*	*	*	*	8
Kessous 2013[11]	*	*	*	*	**	*	*	*	9
Lykke 2010a[12] & Lykke 2010b[13]	*	*	*	*	**	*	*	*	9
Nardi 2006[14]		*		*	*	*	*		5
Ngo 2015[15]	*	*	*	*	*	*	*	*	8
Pell 2004[16] & Smith 2001[17]	*	*	*		*	*	*		6

Rich-Edwards 2015[18]	*	*	*	*	*	*	*	*	8
Tanz 2017[19]		*		*	*		*		4
Wang 2011[20]	*	*	*	*	*	*	*	*	8
Wikstrom 2005[21]	*	*	*		*	*	*	*	7

Table S2. Study quality assessment in detail.

Study ID	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of preterm birth	Demonstration that outcome of interest was not present at start of study	Comparability of cohort	Reliable ascertainment of outcomes	Follow-up duration to capture outcomes	Adequacy of follow-up
Bonamy 2011[1]	General cohort of women.	Controls from the same cohort.	From the Swedish Medical Birth Register.	Excluded women with a CVD event before their first delivery.	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, pre-eclampsia/eclampsia and maternal smoking at beginning of pregnancy.	ICD-8 to 10 codes from the hospital discharge register or the cause of death register. ICD-8: 411, 427.00, 427.10. ICD-9: 411B, 428. ICD-8/9: 410, 430-436. ICD-10: G45, I20.0, I21-22, I50, I60-64.	Median 11.8 years.	Database study.
Catov 2007[2]	General cohort of women.	Controls from the same cohort.	Self-reported.	Excluded women who reported pre-eclampsia or hypertension during pregnancy.	Adjusted for race, age at study baseline, systolic BP, log pulse wave velocity (from simultaneous carotid and femoral artery Doppler flow signals), insulin resistance, log	Self-reported and validated using an algorithm that assesses medication, physical examination, blood tests and ECG.	Mean 57 years.	All women followed up.

					IL-6, HDL cholesterol and statin use.			
Catov 2010[3]	General cohort of women.	Controls from the same cohort.	From the Danish Medical Birth Registry.	Excluded women with hospitalization for CVD or diabetes before the first birth during study period and those dying during delivery.	Adjusted for maternal age at first birth, parity, education, birth year. Excluded pre-eclampsia, SGA offspring and diabetes.	ICD-8 and 10 codes from the National Hospital Discharge Register. ICD-8: 410-414, 430-438, 440, 444, 452, 453. ICD-10: I20-25.5, I60-69.8, I70-70.9, I74, I81, I82.	Mean 28 years.	Database study.
Cirillo 2015[4]	General cohort of women.	Controls from the same cohort.	From medical records.	Not applicable as death outcome.	Adjusted for age, race, parity, BMI and smoking. Excluded pre-existing heart disease, multiple births, gestations <20 weeks and missing parity data.	ICD-7 to 10 codes in data linkage to California Vital Statistics and National Death Index. ICD-7: 420.1. ICD-8: 410, 412. ICD-9: 410, 411, 414, 429. ICD-10: I21, I24, I25.	Median 40 years.	<10% loss to follow-up.

Davey Smith 2000[5]	General cohort of women.	Controls from the same cohort.	From previous study records.	Not applicable as death outcome.	Adjusted for age, height, marital status, visits to private doctor, BP and hormone use during pregnancy,	From Finnish Central Population and Cause of Death registers.	Unclear.	Unclear.
Davey Smith 2005[6]	General cohort of parents.	Controls from the same cohort.	From the Swedish Medical Birth Register.	Not applicable as death outcome.	Adjusted for birth weight.	ICD-9 codes in the Swedish Cause of Death register. ICD-9: 390-459.	Mean 20.4 years.	Unclear.
Freibert 2011[7]	General cohort of women.	Controls from the same cohort.	Self-reported.	No.	Unadjusted.	Self-reported.	Unclear.	92.3% of all eligible women had complete data.
Hastie 2011[8]	General cohort of women.	Controls from the same cohort.	From routine national electronic records.	No.	Adjusted for age at delivery, height, deprivation category, birthweight decile, essential hypertension and pre-eclampsia.	ICD-8 to10 codes from electronic records. ICD-8/9: 410-414. ICD-10: I20-25.	Mean 22 years.	Database study.
Hovi 2014[9]	General cohort of women.	Controls from the same cohort.	From the Finnish Medical Birth Register.	No.	Unadjusted.	ICD-9 and 10 codes from the Hospital Discharge Register data and non-primary	Up to 22 years.	<1% loss to follow-up.

						care outpatient visit data. No details on exact ICD codes used.		
Irgens 2001[10]	General cohort of women.	Controls from the same cohort.	From the Medical Birth Registry of Norway.	Not applicable as death outcome.	Adjusted for age at delivery and year of birth of baby. Excluded pre-eclampsia.	ICD-8 and 9 codes from the Registry of Causes of Death. ICD-8/9: 410-429.	Median 13 years.	<10% loss to follow-up.
Kessous 2013[11]	General cohort of women.	Controls from the same cohort.	From the hospital perinatal database.	Excluded women with known CVD before or during the index pregnancy.	Adjusted for diabetes, gestational diabetes, obesity, age, pre-eclampsia, ethnicity, anaemia and induction of labour.	ICD-9 codes from the hospitalization database. ICD-9: 272.2, 272.4, 401.9, 402, 404, 404.9, 410, 411, 411.8, 411.81, 413, 413.9, 414, 414.8, 414.9, 415, 415.0, 427.5, 428.0, 428.1, 428.9, 429.9, 429.2, 436, 437, 437.1, 440, 440.2, 443.8, 443.89, 443.9, V810, V812, Z0045-Z0047, Z005,	Mean 10 years.	Database study.

						Z0065, Z3721-Z3723, Z37211, Z3610, Z3619, Z8852-Z8857, Z8877, Z8941, Z8943, Z8944, Z895.		
Lykke 2010a[12] & Lykke 2010b[13]	General cohort of women.	Controls from the same cohort.	From the National Patient Registry in Denmark.	Excluded pre-existing diabetes, cardiovascular diagnosis and women who died or emigrated 3 months after delivery.	Adjusted for maternal age at delivery, year of delivery, hypertensive pregnancy disorders, SGA or large-for-gestational-age offspring, placental abruption and stillbirth (Lykke 2010a). Adjusted for maternal age at delivery and year of delivery (Lykke 2010b).	ICD codes from the National Patient Registry (Lykke 2010a) or from cause of death registry or first cardiovascular diagnosis within 1 week prior to death (Lykke 2010b). ICD-8: 39-44, 45.145.8, 41.0-41.4, 427.09-427.11, 427.19, 427.99, 428.99, 429.00, 429.08, 429.09, 430-438.	Median 14.6 years (Lykke 2010a) or 14.8 years (Lykke 2010b).	<10% loss to follow-up.

						ICD-10: G45, I0-9, I20-25, I50, I51.3, I51.9, I60-67.		
Nardi 2006[14]	Teachers covered by a health insurance scheme.	Controls from the same cohort.	Self-reported.	Not applicable as death outcome.	Unadjusted. Excluded pre-existing MI, angina, psychiatric disorders and unspecified other cardiac and non-cardiac diseases.	Death from CHD using ICD-9 codes from insurance and national databases. ICD-9: 410-414.	Mean 5.2 years from study enrolment.	19% loss to follow-up.
Ngo 2015[15]	General cohort of women.	Controls from the same cohort.	From the perinatal data collection.	Excluded chronic hypertension or hypertensive disorders of pregnancy, CVD event prior to last birth, CVD event within 42 days of last birth and death	Adjusted for age, country of birth, socioeconomic status, parity, SGA offspring, diabetes, gestational diabetes and smoking.	ICD-10 codes from national datasets. ICD-10: G45.0-45.2, G45.4, G45.8, G45.9, G46, I20-25, I25.2, I50, I60-66, I67.0-67.2, I67.4-67.9, I68.1, I68.2, I68.8, I69.	Median 7.5 years.	Linkage proportion for records >98%.

				before follow-up period.				
Pell 2004[16] & Smith 2001[17]	General cohort of women.	Controls from the same cohort.	From routine maternity hospital records.	No.	Excluded stillbirths. Adjusted for age, height, deprivation category, pre-eclampsia, lowest birth weight quintiles and previous spontaneous miscarriage (Pell 2004). Additional adjustment for essential hypertension, but not previous miscarriage (Smith 2001).	ICD-9 and 10 codes from the Scottish Morbidity Record system and General Registrar's Office. ICD-9: 410-414, 430-438. ICD-10: G44, I-20-25, I60-69,	14-19 years.	11.9% (Pell 2004) or 4.4% (Smith 2001) loss to follow-up.
Rich-Edwards 2015[18]	General cohort of women.	Controls from the same cohort.	From the Medical Birth Registry of Norway.	Not applicable as death outcome.	Adjusted for year of delivery, age and education at first birth.	ICD-8 to 10 codes in the National Cause of Death Registry. ICD-8/9: 410-414, 430-438. ICD-10: I20-25, I60-69.	Median 24.8 years.	8.3% loss to follow-up.
Tanz 2017[19]	Registered nurses.	Controls from the same cohort.	Self-reported.	Excluded pre-existing MI or stroke.	Excluded hypertensive disorders of pregnancy. Adjusted for age at first birth, age in 1989, ethnicity, parental education, pre-pregnancy BMI, smoking, Alternative	Self-reported then verified with medical records.	Median 32 years.	32% of eligible women had missing data.

					Healthy Eating Index score, alcohol intake, physical activity at 18 years of age, oral contraceptive use, chronic hypertension, hypercholesterolaemia, type 2 diabetes and family history of MI or stroke before 60 years of age.			
Wang 2011[20]	General cohort of women.	Controls from the same cohort.	From National Health Insurance program database.	Excluded pre-existing stroke or hypertension.	Adjusted for age, urbanization level, diabetes, hyperlipidaemia, CHD, abruption, lupus and thrombophilia.	ICD-9 codes from the national database. ICD-9: 430-437, 674.0, A290-294, A299.	Mean 6.4 years.	Database study.
Wikstrom 2005[21]	General cohort of women.	Controls from same cohort.	ICD codes from Swedish Medical Register.	Excluded hypertension and diabetes.	Adjusted for age, socio-economic level, category of hospital in which the first child was born.	ICD-9 and ICD-10 codes from hospital discharge register and cause of death register. ICD-9: 410-414. ICD=10: I20-25.	15 years.	3.15% died or emigrated.

BMI=body mass index, BP=blood pressure, CHD=coronary heart disease, CVD=cardiovascular diseases, ECG=electrocardiogram, HDL=high-density lipoprotein, IL=interleukin, MI=myocardial infarction, SGA=small-for-gestational age.

Table S3. Cardiovascular risk factor profile of preterm birth and term birth groups in the included studies. GDM=gestational diabetes, HBW=high birth weight >2500g, LBW=low birth weight <2500g, BMI=body mass index, N.S.=non-significant, SE=socio-economic, SEIFA=socio-economic indexes for areas, SGA=small-for-gestational age, wk=weeks gestation.

Study ID	**Risk factor profile**	**During pregnancy / study enrolment**			**At follow-up**		
		Preterm	**Term**	***p* value**	**Preterm**	**Term**	***p* value**
Bonamy 2011[1]	Not available	-	-	-	-	-	-
Catov 2007[2]	Age (year)	23.1	HBW 23.7 LBW 22.0	-	72.9	HBW 73.0 LBW 73.4	-
	Black race (%)	-	-	-	51.9	HBW 41.5 LBW 63.2	-
	Low SE status (%)	-	-	-	22.2	HBW 14.2 LBW 18.4	-
	Ever smoker (%)	-	-	-	66.7	HBW 41.7 LBW 47.4	-
	BMI (kg/m^2)	-	-	-	27.8	HBW 28.3 LBW 26.7	-
	Triacylglycerol (mg/dL)	-	-	-	139.5	HBW 141.3 LBW	-

						163.7	
	Fasting glucose (mg/dL)	-	-	-	104.0	HBW 101.4	-
						LBW 98.0	
	Fasting insulin (IU/mL)	-	-	-	9.8	HBW 8.2	-
						LBW 10.7	
	Hypertension (%)	-	-	-	70.4	HBW 59.8	-
						LBW 71.1	
	Diabetes (%)	-	-	-	7.7	HBW 9.5	-
						LBW 7.9	
Catov 2010[3]	Age (year)	25.2	25.7	-	-	-	-
	Basic education (%)	51.1	44.1	<0.001	-	-	-
	Pre-eclampsia (%)	5.0	3.2	<0.001	-	-	-
	SGA (%)	13.1	9.2	<0.001	-	-	-
Cirillo 2015[4]	Not available	-	-	-	-	-	-
Davey Smith 2000[5]	Not available	-	-	-	-	-	-
Davey Smith 2005[6]	Not available	-	-	-	-	-	-
Freibert 2010[7]	Age (year)	-	-	-	59.6	60.3	-
	Education ≤12 years (%)	-	-	-	38	36.4	-
	Ever smoker (%)	-	-	-	44	40	-

Hastie 2011[8]	Age (year)	24	25	<0.001	-	-	-
	High deprivation quintile using Carstairs index (%)	7.9	6.7	<0.001	-	-	-
	Hypertension (%)	0.4	0.1	<0.001	-	-	-
	Pre-eclampsia (%)	8.8	8.1	<0.001	-	-	-
Hovi 2014[9]	Not available	-	-	-	-	-	-
Irgens 2001[10]	Not available	-	-	-	-	-	-
Kessous 2013[11]	Age (years)	28.1	29.9	0.001	-	-	-
	Jewish (%)	52.6	70.4	0.001	-	-	-
	GDM and Diabetes (%)	8.3	8.2	N.S.	-	-	-
	Obesity (%)	1.1	2.0	0.001	-	-	-
Lykke 2010a[12] & Lykke 2010b[13]	Not available	-	-	-	-	-	-
Nardi 2006[14]	Not available	-	-	-	-	-	-
Ngo 2015[15]	High deprivation using SEIFA index (%)	24.0	20.9	-	-	-	-
	Ever smoker (%)	30.0	28.3	-	-	-	-
	Diabetes (%)	1.3	0.4	-	-	-	-
Pell 2004[16] & Smith 2001[17]	Not available	-	-	-	-	-	-
	Age (year)	23.7	23.9	-	-	-	-

Rich-Edwards 2015[18]	Education <high school (%)	53.6	46.4	-	-	-	-
Tanz 2017[19]	Age (year)	<32 wk 27.5	27	-	-	-	-
		≥32 to <37 wk 27.8					
	BMI≥30 (%)	<32 wk 4.0	3.1	-	-	-	-
		≥32 to <37 wk 3.4					
	Caucasian (%)	<32 wk 91.0	92.9	-	-	-	-
		≥32 to <37 wk 90.9					
	Ever smoker (%)	<32 wk 33.0	31.8	-	-	-	-
		≥32 to <37 wk 30.9					
Wang 2011[20]	Not available	-	-	-	-	-	-
Wikstrom 2005[21]	Not available	-	-	-	-	-	-

Table S4. Sensitivity analysis with regards to singleton and multiple pregnancies.

Outcomes	**Singleton pregnancies only**	**Singleton and multiple pregnancies**
CVD	1.56 [1.27, 1.93], n=5	1.56 [1.32, 1.84], n=8
CVD death	1.95 [1.79, 2.12], n=4	1.81 [1.55, 2.10], n=5
CHD	1.48 [1.36, 1.61], n=4	1.50 [1.39, 1.62], n=6
CHD death	2.07 [1.76, 2.44], n=3	2.02 [1.78, 2.30], n=5
Stroke	1.69 [1.54, 1.85], n=3	1.65 [1.51, 1.79], n=5

Table S5. Sensitivity analysis with regards to the year each study was commenced.

Outcomes	**Study year before 1990**	**Study year after 1990**	**Study year before 1970**	**Study year after 1970**
CVD	1.51 [1.20, 1.90], n=5	1.62 [1.46, 1.80], n=3	-	-
CVD death	-	-	1.91 [1.68, 2.16], n=2	1.74 [1.36, 2.23], n=3
CHD	1.46 [1.34, 1.59], n=4	1.64 [1.44, 1.87], n=2	-	-
CHD death	-	-	2.17 [1.92, 2.46], n=3	1.61 [1.26, 2.07], n=2
Stroke	1.60 [1.33, 1.93], n=3	1.67 [1.45, 1.93], n=2	-	-

Table S6. Sensitivity analysis with regards to study quality score.

Outcomes	**Study quality score ≤6**	**Study quality score ≥7**
CVD	1.59 [1.38, 1.83], n=4	1.53 [1.18, 1.97], n=4
CVD death	2.06 [1.22, 3.47], n=1	1.79 [1.51, 2.11], n=4
CHD	1.65 [1.34, 2.03], n=2	1.48 [1.36, 1.61], n=4
CHD death	1.54 [1.04, 2.28], n=1	2.10 [1.87, 2.36], n=4
Stroke	1.55 [1.05, 2.29], n=2	1.67 [1.52, 1.83], n=3

Table S7. Sensitivity analysis with regards to study location.

Outcomes	**Study location: Europe**	**Study location: U.S.**	**Study location: other**
CVD	1.54 [1.23, 1.92], n=5	1.73 [0.87, 3.46], n=2	1.65 [1.49, 1.82], n=1
CVD death	1.81 [1.55, 2.10], n=5	-	-
CHD	1.45 [1.32, 1.60], n=3	1.65 [1.34, 2.03], n=2	1.61 [1.40, 1.86], n=1
CHD death	1.98 [1.69, 2.33], n=4	2.10 [1.43, 3.08], n=1	-
Stroke	1.70 [1.51, 1.90], n=2	1.28 [0.95, 1.72], n=1	1.67 [1.45, 1.93], n=2

Table S8. Sensitivity analysis with regards to whether the study excluded women with pre-existing cardiovascular disease.

Outcomes	**Pre-existing CVD excluded**	**Pre-existing CVD not excluded**
CVD	1.54 [1.24, 1.92], n=6	1.65 [1.46, 1.85], n=2
CVD death	1.98 [1.77, 2.21], n=2	1.54 [1.02, 2.33], n=3
CHD	1.45 [1.33, 1.57], n=4	1.59 [1.48, 1.71], n=2
CHD death	-	2.02 [1.78, 2.30], n=5
Stroke	1.63 [1.49, 1.78], n=4	1.91 [1.35, 2.70], n=1

Figure S1. PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Preterm Delivery and Future Risk of Maternal Cardiovascular Disease: A Systematic Review and Meta-Analysis.	1
ABSTRACT			
Structured summary	2	*Background*: Preterm delivery (<37 weeks gestational age) affects 11% of all pregnancies, but data are conflicting whether preterm birth is associated with long-term adverse maternal cardiovascular outcomes. *Objectives*: To systematically evaluate and summarize the evidence on the relationship between preterm birth and future maternal risk of cardiovascular diseases. *Data sources*: A systematic search was conducted using MEDLINE and EMBASE from inception to October 2017. Manual searching for additional articles was also conducted by reviewing the bibliography of relevant review articles and published systematic reviews. Search terms were: Synonyms of preterm birth ('preterm delivery' or 'preterm birth' or 'premature delivery' or 'premature birth') AND 'ischaemic heart disease' or 'ischemic heart disease' or 'coronary artery disease' or 'coronary heart disease' or 'myocardial infarction' or 'acute coronary syndrome' or 'heart failure' or 'cardiac failure' or 'left ventricular systolic dysfunction' or 'stroke' or 'cerebrovascular disease' or 'cerebrovascular accident' or 'cardiomyopathy' or 'peripheral vascular disease' or 'cardiovascular disease' or 'cardiovascular morbidity' or 'cardiovascular mortality'. *Study selection*: The included studies had at least two groups (one with preterm birth and one with term birth) and reported sufficient data to allow for accurate risk estimates to be calculated. There was no restriction based on language, cohort type, study design or duration of follow-up. *Data extraction*: Independent double data extraction was done by four reviewers using predefined data fields, including study quality indicators. *Study appraisal and synthesis methods*: Study quality was assessed based on the recommendations of the Newcastle-Ottawa Quality Assessment Scale for cohort studies. We used RevMan Version 5.3.5 (Nordic Cochrane Centre) to conduct random effects meta-analysis using the inverse variance method for pooling log risk ratios (RRs).	5 6 7 8

		Results: Twenty-one studies with over 5.8 million women, including over 338,000 women with previous preterm deliveries, were identified. Meta-analysis of studies that adjusted for potential confounders showed that preterm birth was associated with an increased risk of maternal future cardiovascular disease (risk ratio (RR) 1.43, 95% CI 1.18, 1.72), cardiovascular disease death (RR 1.78, 95% CI 1.42, 2.21), coronary heart disease (RR 1.49, 95% CI 1.38, 1.60), coronary heart disease death (RR 2.10, 95% CI 1.87, 2.36), and stroke (RR 1.65, 95% CI 1.51, 1.79). Sensitivity analysis showed that the highest risks occurred when the preterm deliveries occurred before 32 weeks gestation or were medically indicated. *Limitations*: The limitations of this study include the risk of confounding and being unable to attribute causality of future cardiovascular disease to preterm delivery. There may be inherent publication bias, recall bias or inaccuracies in historical data collection. Heterogeneity may have arisen due to differences in the study population, research methodology, period of conducting the study, and inherent differences between the studies. *Conclusions*: Preterm delivery is associated with an increase in future maternal adverse cardiovascular outcomes, including a two-fold increase in deaths due to coronary heart disease. These findings support the assessment of preterm delivery in cardiovascular risk assessment in women. *Systematic review registration number*: PROSPERO CRD42017068455	16 17
INTRODUCTION			
Rationale	3	Preterm birth (<37 weeks gestational age) affects 11% of all pregnancies. Pregnancy is characterized by a challenge to the cardiovascular system. This physiological stress for most women is uncomplicated but for women who experience preterm birth, this adverse pregnancy outcome may serve to identify women at risk for cardiovascular disease who would not have been detected using traditional risk assessment tools at a time when it may be possible to alter their risk trajectory. It remains unclear whether preterm delivery is an independent risk factor for future cardiovascular disease or an early marker of women with background high-risk profiles for future cardiovascular disease. The pathogenesis of preterm birth remains poorly understood.	5
Objectives	4	To systematically evaluate and summarize the evidence on the relationship between preterm birth and future maternal risk of cardiovascular diseases, we reviewed studies that compared long-term adverse cardiovascular outcomes between women with and without preterm birth in postnatal women.	6
METHODS			
Protocol and registration	5	Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017068455 Protocol registration number: PROSPERO CRD42017068455	6
Eligibility criteria	6	*Participants*: postnatal women. *Comparisons*: Preterm birth versus term birth. *Outcome measures*: ischaemic heart disease, coronary artery disease, coronary heart disease, myocardial infarction, acute coronary syndrome, heart failure, cardiac failure, left ventricular systolic dysfunction,	6

		stroke, cerebrovascular disease, cerebrovascular accident, cardiomyopathy, peripheral vascular disease, cardiovascular disease, cardiovascular morbidity, cardiovascular mortality. *Study characteristics*: the included studies had at least two groups (one with preterm birth and one with term birth) and reported sufficient data to allow for accurate risk estimates to be calculated. There was no restriction based on language, cohort type, study design or duration of follow-up.	
Information sources	7	Searches were conducted using the databases MEDLINE and EMBASE from inception to present. Manual searching for additional articles was also conducted by reviewing the bibliography of relevant review articles and published systematic reviews. The last search was run on 7th October 2017.	7
Search	8	Synonyms of preterm birth ('preterm delivery' or 'preterm birth' or 'premature delivery' or 'premature birth') AND 'ischaemic heart disease' or 'ischemic heart disease' or 'coronary artery disease' or 'coronary heart disease' or 'myocardial infarction' or 'acute coronary syndrome' or 'heart failure' or 'cardiac failure' or 'left ventricular systolic dysfunction' or 'stroke' or 'cerebrovascular disease' or 'cerebrovascular accident' or 'cardiomyopathy' or 'peripheral vascular disease' or 'cardiovascular disease' or 'cardiovascular morbidity' or 'cardiovascular mortality'.	Supplemental methods 2.
Study selection	9	Eligibility assessment was performed independently by 2 reviewers. Disagreements between reviewers were resolved by using the eligibility assessment by PW, who is a more experienced researcher.	7
Data collection process	10	Independent double data extraction was done by 4 reviewers using predefined data fields, including study quality indicators. Disagreements between reviewers were resolved by consensus. If no agreement could be reached, the decision was made by PW. The information was obtained from published data.	7
Data items	11	Data were collected on study design, year, country, number of participants, mean age, parity, cohort characteristics, definition and ascertainment of preterm birth, ascertainment of outcomes, timing of assessment, adequacy of follow-up and results. Where possible, we chose to pool adjusted risk estimates from primary studies and when these data were not available, raw data were used to calculate unadjusted risk estimates.	7, 8
Risk of bias in individual studies	12	Each study was individually assessed for quality based on the recommendations of the Newcastle-Ottawa Quality Assessment Scale for cohort studies by independent reviewers. No studies were excluded following quality assessment.	7
Summary measures	13	We conducted random effects meta-analysis using the inverse variance method for pooling log risk ratios.	8
Synthesis of results	14	Studies were pooled in meta-analysis with subgroups based on whether or not the study used adjustments to account for confounders. Statistical heterogeneity was assessed using the I^2 statistic.	8
Risk of bias across studies	15	In the case for an analysis where there is more than 10 studies and little evidence of heterogeneity, we planned to perform funnel plots to assess for publication bias.	8
Additional analyses	16	Sensitivity analysis was performed to consider the follow-up duration of the studies (<10 years, 10-30 years, and >30 years), gestation (<32 weeks versus 32-37 weeks) and recurrence (1 recurrence versus ≥2	8

		recurrence) of preterm births, and whether the preterm births occurred spontaneously or were medically indicated.	
RESULTS			
Study selection	17	See flow diagram in figure 1.	Figure 1
Study characteristics	18	See table 1.	Table 1
Risk of bias within studies	19	See supplemental table 1 and 2.	Supplemental tables 1 and 2.
Results of individual studies	20	See table 2, figures 2-4.	Table 2, figures 2-4.
Synthesis of results	21	See figures 2-4.	Figures 2-4.
Risk of bias across studies	22	We did not perform funnel plots to assess for publication bias as less than 10 studies were included in each analysis.	11
Additional analysis	23	See table 3 and supplemental table 4.	Table 3 and supplemental table 4.
DISCUSSION			
Summary of evidence	24	We found that preterm delivery is associated with an increased maternal risk for future incident cardiovascular events, cardiovascular death, coronary heart disease events, coronary heart disease death and stroke. The adjusted risk ranged between 1.4 to 2–fold compared to those without a history of preterm birth. This increased risk is greatest in preterm births that occur before 32 weeks in gestation or in those that are delivered for medical indications such as fetal growth restriction or pre-eclampsia. For the composite cardiovascular disease and coronary heart disease outcomes, the risks are higher in women with a greater number of recurrent preterm births.	13
Limitations	25	*Outcome level*: The limitations of this study include the risk of confounding and being unable to attribute causality of future cardiovascular disease to preterm delivery. Heterogeneity may have arisen due to differences in the study population, research methodology, period of conducting the study, and inherent differences between the studies.	16

		Review level: There may be inherent publication bias, recall bias or inaccuracies in historical data collection.	
Conclusions	26	In keeping with current recommendations, our study highlights the importance of advising women with preterm births about their increased cardiovascular risk and advocating and supporting lifestyle and behavioural changes to control their modifiable risk factors. These findings support the assessment of preterm delivery in cardiovascular risk assessment in women, with the 6-week postpartum visit the ideal place for this to occur.	17
FUNDING			
Funding	27	This work was supported by a grant from the North Staffordshire Heart Committee. PW and CSK are funded by National Institute for Health Research Fellowships.	18

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