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Cardiovascular disease risk in women with a history of spontaneous preterm delivery: A systematic review and meta-analysis

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Abstract

Background: Increasing evidence suggests a relation between having had spontaneous preterm delivery and cardiovascular disease in the future. We performed a systematic review and meta-analysis to assess the relation between a history of spontaneous preterm delivery and risk of ischaemic heart disease (IHD), stroke or overall cardiovascular disease (CVD).

Methods: We carried out a systematic search in Medline (from 1966 to 17 July 2014) and Embase (from 1980 to 17 July 2014). We included studies with a cohort design assessing the relation between spontaneous preterm delivery and fatal or nonfatal IHD, stroke, or overall CVD. IHD, stroke and CVD were assessed through linkage with national registries. Hazard ratios (HRs) were pooled using a random-effects model.

Results: Of the 10 cohort studies included; sample sizes ranged from 3706 to 923,686 women and follow-up ranged from 12–35 years. Spontaneous preterm delivery was related to an increased risk of developing or dying from IHD (HR 1.38, 95% confidence interval (CI) 1.22–1.57), stroke (HR 1.71, 95% CI 1.53–1.91) and overall CVD (relative risk (HR) 2.01, 95% CI 1.52–2.65). All studies found a positive effect, although substantial between-study heterogeneity was found for IHD and CVD.

Conclusion: Spontaneous preterm delivery is an independent risk factor for the development of IHD, stroke and overall CVD.

Keywords

Premature birth, stroke, ischaemic heart disease, cardiovascular disease, meta-analysis

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Introduction

Cardiovascular disease (CVD) is the most important cause of death in women in industrialised countries.[1] In the last decade it has become increasingly clear that pregnancy related disorders are associated with future cardiovascular morbidity and mortality.[2–4] Spontaneous preterm delivery is not only responsible for substantial perinatal mortality and morbidity;[5] it also appears to rank high among the pregnancy complications exposing the mother to an increased risk for CVD risk later in life, analogous to preeclampsia.[6–8]

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Preterm deliveries are those that occur before 37 weeks of gestation. In the USA, the rate of preterm birth is 12–13%, while in Europe and other developed countries these rates range from 5–11%.[9,10] The proportion of medically indicated preterm deliveries is rising during the last decades and is at least 30–35%.[11] The main reasons for these medically indicated deliveries include preeclampsia and intrauterine growth restriction,[11] both of which have been associated with increased maternal CVD risk.[2,12] The other 70% of all preterm births are the result of spontaneous labour or preterm prelabour rupture of membranes (PPROM).[11] Although the precise aetiology remains unknown in many cases, some of the spontaneous preterm births are the result of infection, uterine overdistension or uterine anomalies.

Mechanisms explaining the association between CVD and spontaneous preterm delivery are not well understood. However, classic CVD risk factors, such as hypertension, dyslipidaemia, type 2 diabetes, inflammation and thrombosis, which are evidently more often present in women after spontaneous preterm delivery, are likely to play a role.[3,13–15]

Studies that reported so far on the relationship between CVD and preterm delivery used different designs, outcomes and confounders.[7,8,12,16–24] Therefore, the aim of this study was to systematically review the literature on this topic for good quality studies with sufficient follow-up and to carry out a meta-analysis to obtain a quantitative estimate of the risk of fatal and non-fatal ischaemic heart disease (IHD), stroke and overall CVD after a spontaneous preterm delivery and to assess the degree of heterogeneity.

Methods

Literature search

The following search strategy was used to identify cohort studies reporting on the association between spontaneous preterm delivery and fatal and/or non-fatal IHD, stroke and overall CVD. We searched the electronic databases Ovid Medline (from 1966 to 17 July 2014) and Embase (from 1980 to 17 July 2014) using the following terms for the exposure: 'obstetric labor, premature' (MeSH), 'preterm delivery', 'preterm birth', 'premature birth', 'premature delivery', and search terms for the outcome were: 'cardiovascular disease' (MeSH), 'stroke', 'CVA', 'cerebrovascular', 'myocardial infarction', 'angina pectoris'. We restricted the search to the terms 'mothers' or 'maternal' in the title or abstract, since many articles have been published about cardiovascular disease among infants born preterm. For details of the search see Supplementary Material, Appendix 2. Furthermore, reference lists of original and review articles were reviewed to search for more studies. Only full-length articles in the English language were considered.

Inclusion and exclusion criteria

For inclusion, studies had to fulfil the following criteria: (a) original article or systematic review; (b) cohort design; (c) the study compared women with a spontaneous preterm delivery (<37 weeks) to women with uncomplicated pregnancies, or compared women with preterm birth by any cause to women with uncomplicated pregnancies and adjusted for preeclampsia and foetal growth restriction (d) inclusion of >10 subjects with a history of preterm birth; (e) fatal or non-fatal IHD, stroke or overall CVD recorded as outcome; (f) adult population. If multiple published reports from the same study were available, we included the one with the largest cohort and most detailed information on both exposure and outcome. We excluded studies of ≤3 year follow-up and studies with low event rates (≤10 cases) because of the risk of under or overestimation of the true effect.

Data extraction

Two investigators (FMvD and BKV) independently screened titles and abstracts of all retrieved studies. Eligible full text reports were obtained to determine whether they met inclusion criteria. Differences were resolved by discussion and consensus. Extracted relevant data included the first author's surname, year of publication, study design, population studied, country of origin of the population studied, recruitment year, number of participants, subjects' age, duration of follow-up, method used to ascertain preterm delivery and reference category, outcome assessment, number of events in each group, measures of association of fatal and non-fatal IHD, stroke of total CVD in women with history of preterm delivery vs reference category, corresponding 95% confidence interval (CI), and the number and type of covariates that were used in the analysis to adjust the association between preterm delivery and the outcome.

Assessment of study quality

The methodological quality of the studies included in the meta-analysis was evaluated by Newcastle-Ottawa quality assessment scale (Table 1), a validated checklist for assessing the quality of both cohort studies and case-control studies.[25] It consists of several items distributed between three subscales: selection, comparability and outcome. For the assessment of cohort studies, the maximum score is four stars for selection, two for comparability and three for outcome.

Table 1. Summary of critical appraisal of included studies using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Exposure (max 3 stars)
Bonamy et al., 2011[16]	****	**	***
Catov et al., 2010[2,3]	****	**	***
Hastie et al., 2011[1,7]	***	**	***
Irgens et al., 2001[1,8]	***	*	***
Lykke et al., 2010a[1,9]	****	**	***
Lykke et al., 2010b[8]	****	*	***
Pell et al., 2003[21]	***	**	***
Smith et al., 2000[1,2]	***	*	**
Smith et al., 2001[22]	**	**	**
Wikstrom et al., 2005[20]	***	**	***

Statistical analysis

In each study we identified the reference category. Women with a term delivery (after 37 weeks of gestation) were the reference category in the majority of studies.[8,12,16–19] Other reference categories were a normotensive pregnancy and a term delivery,[20] or a delivery after 36 weeks.[21,22]

Hazard ratios (HRs) were extracted from the selected publications and were used to measure the relationship between a history of preterm delivery and fatal or non-fatal IHD, stroke or overall CVD. When available, the results of the most complete multivariate models to adjust for potential confounders were used. For individual studies where the association of interest was distinguished in different categories, such as gestational age, we first combined these stratified results in an overall association for a particular study using a fixed effect approach. A pooled or summary estimate of the HRs across all studies was calculated together with a 95% CI using a random effects model. Different random effects models were used for the different outcomes (i.e. fatal or non-fatal IHD, stroke or overall CVD).

The heterogeneity in results among studies was evaluated by I^2-statistics and by prediction intervals. The I^2-statistic is a measure of inconsistency that describes the percentage of observed variability in results, which reflects real differences in effects rather than variation that can be expected due to chance. Values of $I^2 > 50\%$ indicate significant heterogeneity.[26] A 95% prediction interval shows the likely range of values for the HR that can be expected if a new and large study were to be performed similar to ones included in this review. The prediction interval provides insight in the variability or consistency between the results of individual studies whereas a 95% CI around the pooled estimates provides insight as to how certain we are about the size of the pooled estimate. The amount of between-study variation (the tau-squared estimate of a random effects model) is a key factor determining the width of a 95% prediction interval: large values of between-study variation will result in a large prediction interval, even if a large number of studies is included in a review.[27]

Funnel plot asymmetry was examined to detect whether smaller studies had systematically different results than larger studies. Random effect models were performed using Review Manager 5.2.

Results

Characteristics of the studies

Based on the selection criteria, 10 studies were included (Figure 1). Table 2 summarises the characteristics of the included studies. The sample sizes of the individual studies ranged from 3706 to 923,686 and populations were from five north western European countries (Denmark, Finland, Norway, Scotland, Sweden). Follow-up ranged from 12–35 years. Preterm delivery was assessed by record linkage in all studies. Gestational age at delivery was based on last menstrual period,[18,23] a combination of last menstrual period and in later years ultrasound,[8,16,19] or was not specified.[12,17,20–22] In five studies cases of preeclampsia and/or small-for-gestational-age were excluded.[8,17,18,20,23] In five studies adjustment was made for preeclampsia and small-for-gestational-age.[12,16,19,21,22] Non-fatal incident cases of IHD, stroke and overall CVD were ascertained through disease registers. Death was assessed through death certificates. Cause of death was assessed by ICD codes in all studies.

Overall the quality score of the included studies was high with three studies achieving the maximum of nine stars,[16,19,23] four were eight-star studies,[8,17,20,21] one was a seven-star study[19] and two were six-star studies.[12,22]

Meta-analysis

IHD. Five studies assessed the relation between preterm delivery and IHD.[17,19,20,22,23] Since two studies used the same Danish cohort[19,23] and two studies the same

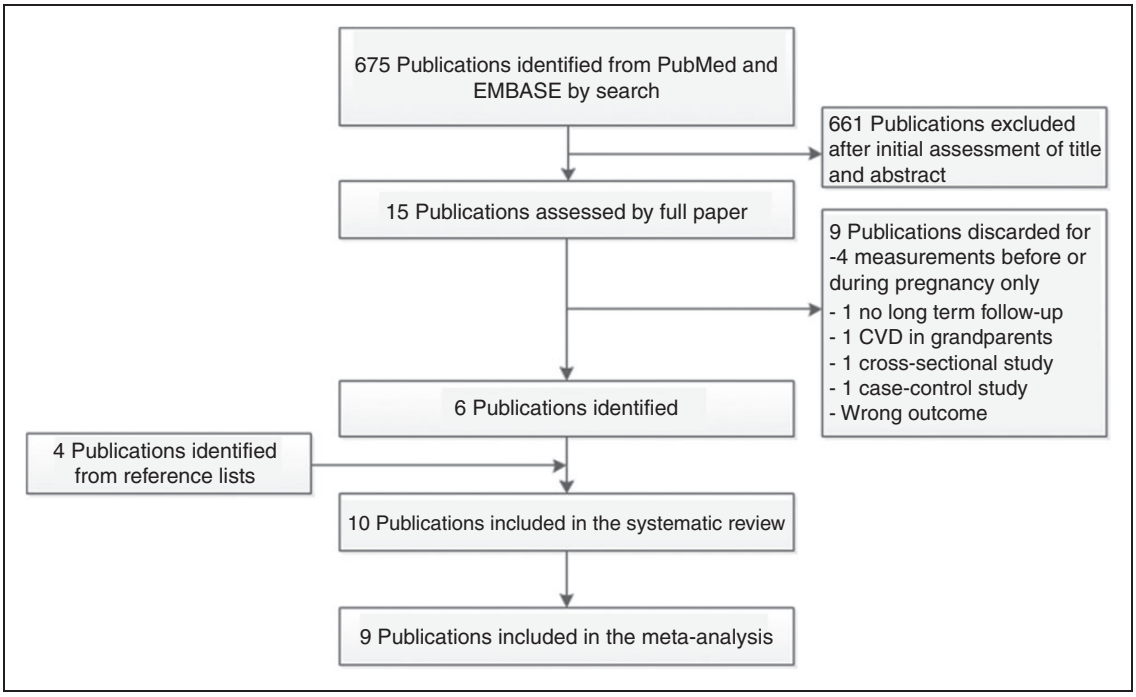

Figure 1. Flow chart of literature search for studies reporting on the association of spontaneous preterm birth and cardiovascular disease (CVD).

Scottish cohort,[17,22] we included the studies of Lykke et al.[19] and Hastie et al.[17], in the meta-analysis because those were the largest cohorts. In the pooled analysis an increased risk was observed for nonfatal or fatal IHD (HR 1.38, 95% CI 1.38–1.57) with no evidence for publication bias (Figure 2(a)). There was a considerable amount of heterogeneity in results between the studies ($I^2 = 74\%$). The 95% prediction interval (range of likely values of a new and large study) ranged between 1.09–1.74 for IHD.

Stroke. Three studies assessed the relation between preterm delivery and stroke.[18,21,23] In the pooled analysis an increased risk was observed for nonfatal or fatal stroke (HR 1.71, 95% CI 1.53–1.91,) with no evidence of publication bias (Figure 2(b)). Evaluation of heterogeneity in results is difficult with only three studies, but differences between the three studies were small. The 95% prediction interval for stroke ranged from 1.53–1.92.

Overall CVD. Five studies assessed the relation between preterm delivery and CVD.[8,12,16,18,23] Since there was overlap between the cohorts of Catov et al.[23] and Lykke et al.[8], we included the study of Lykke et al. because this was the largest cohort. In the pooled analysis an increased risk was observed of nonfatal or fatal CVD (HR 2.01, 95% CI 1.52–2.65), with no evidence of publication bias (Figure 2(c)). Heterogeneity in results between studies was considerable ($I^2 = 72\%$); the 95% prediction interval for overall CVD ranged from 1.15–3.51.

Discussion

In this meta-analysis of high quality cohort studies we found that women with a history of preterm delivery have a two-fold increased risk for IHD, stroke and overall CVD over time. This increased risk was observed consistently for different outcomes in women with a history of spontaneous preterm delivery compared to women with a term delivery. Although the exact height of the strength of the association varied substantially between studies, the prediction intervals of the different meta-analysis indicate that finding of a positive association is a robust one.

Although several systematic reviews and meta-analysis have examined the association between pregnancy complications and CVD, most of them focused on preeclampsia.[2,28,29] One review has been published on preterm birth and subsequent CVD but this review included fewer cohort studies and lacked a meta-analysis.[30]

Preterm delivery can be divided in spontaneous and medically indicated preterm delivery due to pregnancy complications such as preeclampsia and/or intrauterine growth restriction (IUGR). Especially preeclampsia is associated with an increased maternal risk of CVD.[2] We only included studies that either excluded cases of preeclampsia and IUGR, or adjusted for hypertension/

Table 2. Characteristics of included studies assessing risk of ischaemic heart disease (IHD), stroke or total cardiovascular disease (CVD).

Author, year published	Country, baseline year	Cohort	Follow-up, years	Mean age at baseline, years	Sample size cohort, *n*	Sample size SPTB, *n*	Definition SPTB, GA	Outcome	Outcome assessment	Events SPTB, *n*	HR (95% CI)	Adjustment
Catov et al., 2010[2,3]	Denmark, 1973–1983	National registry-based	28	25.2–25.7	427,765	26,588	<37	Fatal and non-fatal CVD	ICD-8: 390–459; ICD-10: I00–99	3454	1.18 (1.10–1.25)	maternal age at first birth, parity, education
								Fatal CVD		NR	1.98 (1.73–2.26)	
								IHD	ICD-8: 410–414; ICD-10: I20–25.5	1272	1.42 (1.34–1.52)	
								Stroke	ICD-8: 430–438; ICD-10: I60–69.8	124	1.67 (1.48–1.89)	
Lykke et al., 2010a[1,9]	Denmark, 1978–2007	National registry-based	14.6	26.8	782,287	41,659	≤36	Fatal and non-fatal IHD	ICD-8: 410–414; ICD-10: I20–25	589	1.30 (1.19–1.42)	Maternal age, year of delivery, hypertensive pregnancy disorders, small- and large-for-gestational-age offspring, placental abruption and stillbirth
						35,255	32–36			500	1.32 (1.20–1.45)	
						4698	28–31			63	1.03 (0.80–1.34)	
						1706	20–27			26	1.61 (1.09–2.37)	
Lykke et al., 2010b[8]	Denmark, 1978–2007	National registry-based	14.6	26.8	782,287	31,132	<37	Fatal CVD	ICD-8: 39–44, 451–458; ICD-10: D10–I9	70	1.90 (1.49–2.43)	Maternal age and year of delivery
Smith et al., 2000[12]	Finland, 1954–1963	Exposure of exogenous hormones during pregnancy on birth outcomes	35	25	3706	NR	<37	Fatal CVD	ICD not specified	NR	2.06 (1.22–3.47)	Maternal age, hormone use, maternal height, marital status, visit to private doctor, blood pressure during pregnancy.
Irgens et al., 2001[1,8]	Norway, 1967–1992	National registry-based	13	NR	626,272	26,018	16–36	Fatal CVD[a]	ICD-8/9: 410–429	NR	2.95 (2.14–4.11)	Age at delivery, year of birth of baby
								Fatal stroke	ICD not specified	NR	1.91 (1.26–2.91)	
Hastie et al., 2011[1,7]	Scotland, 1969–2007	National registry-based	22	24–25	750,350	29,965	<37	Non-fatal IHD	ICD-8/9: 410–414; ICD-10: I20–25	445	1.46 (1.33–1.61)	Age at delivery, maternal height, deprivation category, birthweight decile, essential hypertension and pre-eclampsia
								Fatal IHD		79	2.14 (1.70–2.70)	
Pell et al., 2003[21]	Scotland, 1981–1985	National registry-based	14–19	23	119,668	6768	24–36	Fatal and non-fatal stroke	ICD-9: 430–438; ICD-10: I60–69, G45	NR	1.91 (1.35–2.70)	Maternal age, maternal height, deprivation category, preeclampsia, lowest birth weight quintile, previous spontaneous abortion

(continued)

Table 2. Continued

Author, year published	Country, baseline year	Cohort	Follow-up, years	Mean age at baseline, years	Sample size cohort, *n*	Sample size SPTB, *n*	Definition SPTB, GA	Outcome	Outcome assessment	Events SPTB, *n*	HR (95% CI)	Adjustment
Smith et al., 2001[22]	Scotland, 1981–1985	National registry-based	15–19	23	129,920	7315	24–36	Fatal and non-fatal IHD	ICD-9: 410–414; ICD-10: I20–I25	NR	1.8 (1.3–2.5)	Maternal age, maternal height, socioeconomic deprivation category, essential hypertension, lowest birthweight quintile and pre-eclampsia
								Fatal IHD		NR	1.9 (0.7–4.9)	
Bonamy et al., 2011[16]	Sweden, 1983–2005	National registry-based	11.8	NR	923,686	56,893	≤36	Fatal and non-fatal CVD	ICD-8: 410–411, 430–436, 427.00, 427.10; ICD-9: 410, 411B, 430–436, 428; ICD-10: I20–I22, I60–I64, G45, I50	414	1.59 (1.42–1.78)	Maternal age, birth year, highest income, highest education before first delivery, country of birth, pregestational hypertension, pregestational diabetes, gestational diabetes, gestational hypertension and preeclampsia / eclampsia, antenatal smoking
						49,537	32–36			320	1.39 (1.22–1.58)	
						5259	28–31			70	2.57 (1.97–3.34)	
						2097	≤27			24	2.18 (1.33–3.57)	
Wikstom et al., 2005[20]	Sweden, 1973–1982	National registry-based	14.7	NR	403,550	17,860	<37	Fatal and non-fatal IHD	ICD-9: 410–314; ICD-10: I20–I25	145	1.3 (1.1–1.5)	Maternal age, socioeconomic level and category of hospital in which the first child was born

CI: confidence interval; GA: gestational age; HR: hazard ratio; NR: not reported; SPTB: spontaneous preterm birth. [a]Cardiovascular mortality was defined as all deaths in which the cause was registered as being related to the heart.

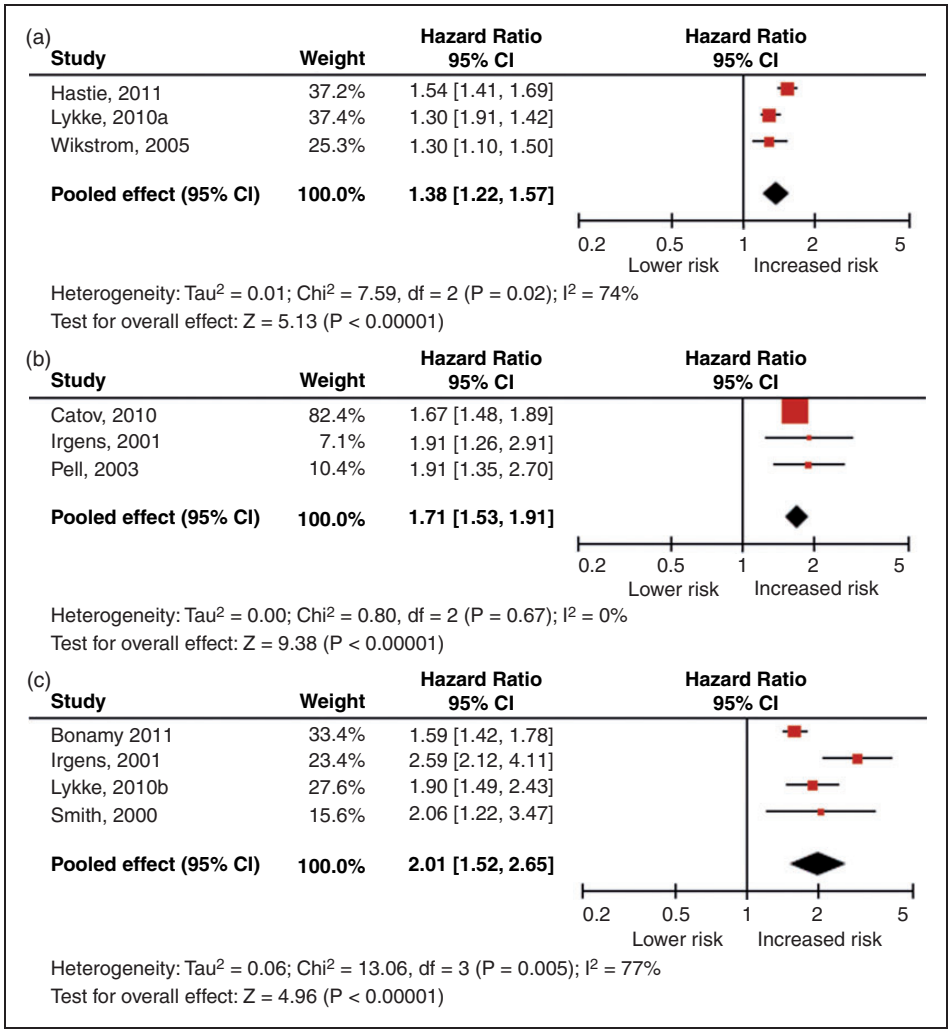

Figure 2. Forest plots of studies investigating spontaneous preterm delivery in relation to the risk of fatal and nonfatal cardiovascular disease, (a) ischaemic heart disease (b) stroke (c) overall cardiovascular disease. CI: confidence interval.

preeclampsia and birth weight. Other reasons for induced preterm labour are rare. Therefore, the assumption was made that the results of this meta-analysis represent the relation between CVD and spontaneous preterm delivery.

Mechanisms explaining the relation of CVD with spontaneous preterm delivery are not well understood, mostly because the aetiology of preterm birth is multifactorial. A potential mechanism may be the inflammatory pathway. It is known that inflammatory mediators in the cervix, placenta and foetal membranes play a central role in human parturition.[31] Inflammatory phenomena are especially observed in women with preterm delivery, even in the absence of infection. These women are considered to have a 'proinflammatory' phenotype.[15] Inflammatory processes also play an important role in the pathogenesis of vascular disease. Inflammation is one of the key factors in the development of atherosclerosis, from the initial lesion to the progression resulting in thrombotic complications.[32] Furthermore, the conventional cardiovascular risk factors of hypertension and diabetes are more prevalent in women with a history of preterm birth.[19,23] Unfortunately, only three studies were adjusted for hypertension present before pregnancy.[16,17,22] It would be interesting to explore how hypertension and diabetes influence the risk of developing CVD in women with spontaneous preterm birth.

Socio-economic status, which is related to a risk for both spontaneous preterm delivery[33] as well as CVD,[34] was included as a confounder in several studies.[16,17,20,21] The results of these studies did not differ from those without an adjustment for socio-economic status.

The strength of our study is that we only included high quality cohort studies and all studies used record-linkage or medical records for the assessment of CVD. To correct for possible confounding, we used the most extensive adjusted HR in the meta-analysis. However confounders differed between the studies and this may

have caused residual confounding and variation in the reported values of the HR between studies.

Nevertheless, the same relations were found, whether studies were adjusted for confounders such as socio-economic status or hypertension or not. Only an individual participant data meta-analysis might further explore this issue.

Some limitations also need to be addressed. First, we could not analyse the influence of smoking during pregnancy, an important confounder. Smoking is associated with both an increased risk for preterm delivery[35] and an increased risk of developing CVD.[36] However, the reported risk in the one study that did adjust for antenatal smoking was comparable with the other studies.[16] Therefore, we assume that overestimation due to smoking is not substantial. Second, in the included cohorts the gestational age was mainly based on last menstrual period. Dating by ultrasonography in the first half of pregnancy results in a more accurate prediction of the delivery date than using menstrual data alone.[37] Inaccurate dating for some preterm deliveries, leading to possible inclusion of term births in the preterm group, would however lead to an underestimation of the observed risks. Third, heterogeneity in reported HR among studies was high for the CVD and IHD outcomes. This might be an effect of the small number of studies, different outcome measures, use of confounders and duration of follow-up which could lead to more between-study variation than would expected by chance.[26] We used a random-effects model and prediction intervals to incorporate and document the impact of between-study variation. When heterogeneity is substantial, a prediction interval rather than a CI provides insight in the uncertainty around the effect estimate.[28] All studies showed a positive effect on the relation between CVD and preterm delivery and the prediction intervals showed us that this effect is likely to vary between 1.09–3.51. Therefore, there appears to be a clear positive relation between CVD and spontaneous preterm delivery. Fourth, publication bias is a well-known limitation of meta-analysis. Since the number of studies is small, we choose not to use funnel plots for the assessment of publication bias. Moreover, most studies included in this meta-analysis were prospective cohort studies using nationally based registries. Therefore, all women living in a certain period in that country were included in these studies. Considering the magnitude of such cohorts, the reported results reflect the true risk of developing CVD after a pregnancy complicated by preterm delivery.

Finally, all studies were performed in north western European countries with predominantly white populations. Whether the relation between preterm delivery and CVD are consistent across other racial and ethnic groups cannot be concluded on the basis of our results.

Clinical implications

Spontaneous preterm delivery appears to be an almost equally strong risk factor for CVD compared to the 'classic' risk factors of elevated blood pressure, elevated lipid levels, overweight, smoking and diabetes mellitus with HRs between 2.0–2.5.[36] Pregnancy history is not mentioned in current cardiovascular risk charts that are used for the identification of high risk individuals.[38,39] However, recently published guidelines on primary prevention of CVD and stroke in women have included pregnancy complications such as preeclampsia, pregnancy-induced hypertension and gestational diabetes as risk factors for CVD.[40,41] These guidelines include the recommendation that women with a history of one of these pregnancy complications should be encouraged to optimise their lifestyle in order to prevent future CVD[41] and to evaluate and treat cardiovascular risk factors (hypertension, obesity, smoking and dyslipidaemia) in women with a history of preeclampsia.[40] A history of spontaneous preterm delivery may also identify women who are at an increased risk of CVD as well as the other pregnancy complications. However, before incorporating a history of spontaneous preterm delivery in the cardiovascular risk charts, future research is needed. This involves studies into the value of information of preterm delivery on top of the current risk chart information. It is not always clear-cut that increased RRs translate to added value in risk prediction,[42] in particular since the pathway of increased risk related to preterm delivery might go through elevation in lipids, blood pressure and weight. In conclusion, spontaneous preterm delivery is an independent risk factor for developing IHD, stroke and overall CVD.

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Conflict of interest

None declared.

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Appendix 1

Collaborators of the Dutch Multidisciplinary Guideline Development Group on Cardiovascular Risk Management after Reproductive Disorders

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Appendix 2

Search strategy

Medline (OVID)

1. Obstetric Labor, Premature/
2. ((preterm or premature) adj3 (birth* or deliver*)).ti,ab.
3. 1 or 2
4. exp Cardiovascular Diseases/
5. exp Renal Insufficiency/ or calcinosis/ or exp vascular calcification/ or Hypercholesterolemia/ or exp Obesity/ or exp Electrocardiography/ or exp Hypertension/ or exp Proteinuria/ or exp Diabetes Mellitus/ or Metabolic Syndrome X
6. (stroke or CVA or cerebrovascular or cardiovascul* or (myocard* adj2 infarct*) or atheroscleros* or 'vascular calcification*'' or ((renal or kidney) adj3 (insufficienc* or failure*)) or ''ischaemic attack*'' or TIA or ''angina pectoris'' or electrocardiogra* or ecg or hypercholesterolemia or obesity or hypertension or proteinuria or diabet* or ((endothelial or vascular) adj2 dysfunction*) or ((''left ventricular'' or myocardial) adj3 hypertroph*) or (metabol* adj2 syndrome*)).ti,ab.
7. 4 or 5 or 6
8. 3 and 7
13. limit 8 to english language
16. mothers/ or (maternal adj6 (cardiovascular or risk*)).ti,ab.
17. 13 and 16
22. (preterm and cardiovascular).ti.
23. 8 and 22
24. 17 or 23 (337) – 322 unique

Embase (Elsevier)

('cardiovascular disease'/exp/mj OR 'kidney failure'/exp/mj OR 'diabetes mellitus'/exp/mj OR 'electrocardiography'/exp/mj OR 'hypercholesterolemia'/exp/mj OR 'hypertension'/exp/mj OR 'obesity'/exp/mj OR 'proteinuria'/exp/mj OR 'blood vessel calcification'/exp/mj OR 'metabolic syndrome x'/exp/mj OR stroke:ab,ti OR cva:ab,ti OR cerebrovascular:ab,ti OR cardiovascul*:ab,ti OR (myocard* NEAR/2 infarct*):ab,ti OR atheroscleros*:ab,ti OR (vascular NEAR/2 calcification):ab,ti OR ((renal OR kidney) NEAR/3 (insufficienc* OR failure*)):ab,ti OR (ischaemic NEAR/2 attack*):ab,ti OR tia:ab,ti OR 'angina pectoris':ab,ti OR electrocardiogra*:ab,ti OR ecg:ab,ti OR hypercholesterolemia:ab,ti OR obesity:ab,ti OR hypertension:ab,ti OR proteinuria:ab,ti OR diabet*:ab,ti OR ((endothelial OR vascular) NEAR/2 dysfunction*):ab,ti OR (('left ventricular' OR myocardial) NEAR/3 hypertroph*):ab,ti OR (metabol* NEAR/2 syndrome*):ab,ti) AND ('premature labor'/exp/mj OR ((preterm OR premature) NEAR/3 (birth* OR deliver*)):ab,ti) AND ((maternal NEAR/6 (cardiovascular OR risk*)):ab,ti OR 'mother'/exp) AND [english]/lim AND [embase]/lim NOT 'conference abstract':it 402 references - 210 unique

"/" indicates MeSH-term or EMTREE-term, "exp" indicates inclusion of narrower MeSH- or EMTREE-terms in search strategy.