Eur J Epidemiol (2013) 28:1–19
DOI 10.1007/s10654-013-9762-6

REVIEW

Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis

Morven Caroline Brown · Kate Elizabeth Best · Mark Stephen Pearce · Jason Waugh · Stephen Courtenay Robson · Ruth Bell

Received: 15 May 2012 / Accepted: 7 January 2013 / Published online: 9 February 2013

Abstract There is increasing evidence that pre-eclampsia, a principal cause of maternal morbidity, may also be a risk factor for future cardiovascular and cerebrovascular events. This review aimed to assess the current evidence and quantify the risks of cardiovascular disease (CVD), cerebrovascular events and hypertension associated with prior diagnosis of pre-eclampsia. Medline and Embase were searched with no language restrictions, as were core journals and reference lists from reviews up until January 2012. Case–control and cohort studies which reported cardiovascular and cerebrovascular diseases or hypertension diagnosed more than 6 weeks postpartum, in women who had a history of pre-eclampsia relative to women who had unaffected pregnancies, were included. Fifty articles were included in the systematic review and 43 in the meta-analysis. Women with a history of pre-eclampsia or eclampsia were at significantly increased odds of fatal or diagnosed CVD [odds ratio (OR) = 2.28, 95 % confidence interval (CI): 1.87, 2.78], cerebrovascular disease (OR = 1.76, 95 % CI 1.43, 2.21) and hypertension [relative risk (RR) = 3.13, 95 % CI 2.51, 3.89]. Among pre-eclamptic women, pre-term delivery was not associated with an increased risk of a future cardiovascular event (RR = 1.32, 95 % CI 0.79, 2.22). Women diagnosed with pre-eclampsia are at increased risk of future cardiovascular or cerebrovascular events, with an estimated doubling of odds compared to unaffected women. This has implications for the follow-up of all women who experience pre-eclampsia, not just those who deliver preterm. This association may reflect shared common risk factors for both pre-eclampsia and cardiovascular and cerebrovascular disease.

Keywords Pre-eclampsia · Cardiovascular disease · Cerebrovascular disease · Hypertension

M. C. Brown · M. S. Pearce
Institute of Health & Society, Newcastle University, Sir James Spence Institute of Child Health, Royal Victoria Infirmary, Newcastle upon Tyne, England NE1 4LP, UK

K. E. Best · R. Bell (✉)
Institute of Health & Society, Newcastle University, Baddiley-Clark Building, Newcastle upon Tyne, England NE2 4AX, UK
e-mail: ruth.bell@ncl.ac.uk

J. Waugh
Directorate of Women's Services, Newcastle upon Tyne NHS Foundation Trust, Newcastle upon Tyne, UK

S. C. Robson
Institute of Cellular Medicine, Newcastle University, William Leech Building, The Medical School, Newcastle upon Tyne NE2 4HH, UK

Introduction

Pre-eclampsia is a pregnancy specific syndrome and a principal cause of maternal morbidity, occurring in 2–8 % of pregnancies and accounting for up to 15 % of maternal deaths [1]. There is increasing evidence that the harmful effects of pre-eclampsia on a woman's health may not be restricted to the pregnancy period, but that this hypertensive disorder of pregnancy could represent an important risk factor for future cardiovascular and cerebrovascular events [2, 3]. It is important to further investigate this association as cardiovascular disease (CVD) is globally the most common cause of death in women [4].

Potential explanations for the association between pre-eclampsia and CVD are debated. It has been proposed that persisting endothelial damage caused by pre-eclampsia may result in an increased risk of CVD [5]. Alternatively, an unfavourable cardiovascular risk profile characterised

by higher levels of glucose, cholesterol, hypertension and abdominal obesity may contribute to both the development of pre-eclampsia and CVD in later life [6, 7].

Although a lack of agreement has existed surrounding its classification [8], since 2001 the International Society for the Study of Hypertension in Pregnancy (ISSHP) has advocated that pre-eclampsia be defined as new onset hypertension (≥140/90 mmHg) in combination with the appearance of proteinuria (>0.3 g/24 h) after 20 weeks gestation [9]. However, with almost a third of women with pre-existing hypertension developing superimposed pre-eclampsia during pregnancy [10], accurate classification may not be possible until several weeks after the birth [11].

National guidance in England recommends that women who experience pre-eclampsia, and their primary care physicians, be informed of the increased risk of developing high blood pressure and its related complications [12], and in the US, the American Heart Association (AHA) advise that women with a history of hypertensive disorders of pregnancy be referred for assessment and modification of cardiovascular risk factors [13]. There is a need for quantifiable risk information to enable effective management and accurate risk information to be passed on to women with a history of pre-eclampsia and the physicians involved in their care [8].

Previous meta-analyses have reported that after pre-eclampsia, women are at approximately double the risk of developing cardiovascular or cerebrovascular diseases and more than three times the risk of developing hypertension [2, 3]. Severity, as defined both by onset before 37 weeks gestation [2], and pre-eclampsia in combination with further complications (eclampsia/pre-term delivery/poor fetal growth/fetal death), may be associated with an even greater risk of CVD later in life [2, 3]. We conducted a systematic review and meta-analysis of observational studies to assess the current evidence, to quantify the risks of cardiovascular and cerebrovascular events that may follow a diagnosis of pre-eclampsia and to investigate the effect of pre-eclampsia severity on risk.

Methods

Search strategy and study selection

The systematic review was conducted according to published guidelines for meta-analysis of observational studies in epidemiology (MOOSE) [14]. Medline and Embase were searched from January 2006 to January 2012 inclusive. A search strategy was compiled using keywords for the exposure (e.g. pre-eclampsia, pregnancy induced hypertension), the outcome (e.g. cardiovascular, cardiac, coronary, heart, myocardial infarction, death, mortality, stroke) and exploded subject headings (pregnancy-induced hypertension, pregnancy toxaemia, cardiovascular diseases) for each database. A detailed list of terms is available from the authors. There were no language restrictions to the search. Studies prior to 2006 were identified from previously published meta-analyses [2, 3], supplemented by an additional search using exploded subject headings. Manual searching of core journals and citation lists of relevant articles and reviews was also carried out from 2006 onwards.

Case–control and cohort studies were included. Articles were included if they reported cardiovascular outcomes in women of any age or parity who had a history of pre-eclampsia and were compared to women who had uncomplicated/normotensive pregnancies. Articles were included if they stated they were investigating women with pre-eclampsia, regardless of the explicit definition of pre-eclampsia. Primary outcomes were: fatal and diagnosed/reported cardiovascular events (ischaemic heart disease including myocardial infarction, angina pectoris, coronary failure and insufficiency and atherosclerosis); fatal and diagnosed/reported cerebrovascular disease (ischaemic and haemorrhagic stroke); and hypertension. Only studies reporting these outcomes beyond 6 weeks postpartum were included.

Data extraction and quality assessment

A data extraction form was piloted before continuing to extract study characteristics and quality assessment variables for each of the included studies. Data extraction was completed by two reviewers (M. B. and K. B.). Where required, authors were contacted for additional information.

Studies for all outcomes were classed as higher quality if they satisfied all of the following criteria: pre-eclampsia was explicitly defined as hypertension (BP ≥ 140/90 mmHg) in combination with proteinuria (0.3 g/24 h) after 20 weeks gestation [9]; pre-eclampsia diagnoses were taken from medical records as opposed to patient self-report; and CVD and cerebrovascular disease diagnoses were identified from physical examination, medical records or death certificates as opposed to patient self report, while hypertension (BP ≥ 140/90 mmHg) at follow-up was identified in studies which used either physical examination alone, or studies which detected hypertension through physical examination and/or current use of anti-hypertensives or a previous diagnosis from medical records.

Meta-analysis

Separate meta-analyses were performed for the three outcomes. All three models used random effects and were generated using the inverse variance method to better

account for heterogeneity between studies [15]. Raw numbers were extracted from each paper and unadjusted odds ratios (ORs) were calculated and pooled in the meta-analyses. Where cohort studies alone were included, a pooled relative risk (RR) was similarly estimated. Where multiple studies had analysed the same set or subset of study participants for matching outcomes, only the original study was incorporated into the meta-analysis unless the most recent paper included additional participants. Where both outcomes were reported, the number of diagnoses as opposed to the number of fatalities was used in the meta-analysis. Studies that reported composite figures of cardiovascular or cerebrovascular events were not included in the meta-analyses.

Separate analysis was carried out on articles that reported the number of pre-term deliveries (<37 weeks gestation), as an indicator of more severe pre-eclampsia. A pooled RR was calculated to determine the risk of future cardiovascular events occurring in women with pre-eclampsia and pre-term delivery compared to pre-eclampsia alone.

Heterogeneity and publication bias

Heterogeneity between all studies was tested using Cochran's Q test and further quantified using the I^2 statistic, where $I^2 > 50$ % indicated significant heterogeneity [16]. To further identify origins of heterogeneity, separate estimates for case–control and cohort studies were also calculated, as were individual estimates for fatalities and diagnoses. Publication bias was investigated by examining funnel plots and by performing Egger's test.

Sensitivity analysis

A further sub-group analysis was performed to compare higher quality studies (as defined previously) with those that did not meet these criteria.

Statistical analyses were performed using the statistical software package Stata, version 11 (StataCorp, College Station, TX, USA) and $p < 0.05$ was considered statistically significant.

Results

Systematic review

A total of 244 potentially relevant articles were identified (Fig. 1). After screening abstracts and full texts according to the inclusion criteria, 31 papers since 2006 were identified; eight with CVD, five with cerebrovascular disease and 18 with hypertension as an outcome. A further 26 articles were identified from previous systematic reviews and no additional papers pre-2006 were identified from the supplementary search. Two papers included in previous reviews were excluded from the current meta-analysis: one reported pre-eclampsia as part of a composite group of maternal placental syndromes [17]; another did not provide data for women with uncomplicated, normotensive pregnancies [18]. Therefore, 55 articles which reported on 46 studies, the majority of which were conducted in the US or Northern Europe were included. Five papers reported duplicate data [19–23]. Here the original paper was used unless the most recent reported a larger sample. Two papers reported different data from the Royal College of General Practitioners' (RCGP) Oral Contraception Study [24, 25], and Lykke et al. [26, 27] used the same Danish population data to report CVD morbidity and CVD mortality.

Thus 50 papers were included in the systematic review, including eight case–control studies and 42 cohort studies. Of these, 43 were included in the meta-analyses (seven case–control studies, 36 cohorts) (Fig. 1). Two papers were excluded due to the reporting of a composite outcome of CVD and cerebrovascular disease [28, 29], one paper with no reported hypertensive outcomes in any patients [30], three where the numbers could not be confirmed [31–33], and one presenting death data on the same cohort for which diagnosis data was previously available[27]. The paper by Wilson et al. [34] reported both diagnoses and fatalities for cardiovascular and cerebrovascular outcomes so the diagnoses figures were used. Freibert et al. [35] presented self-reported data for a number of CVD outcomes and as a combined category could not be provided, only the data for heart attacks was used.

Of those studies that reported a mean/median age of participants, these ranged from 25 to 60 years old. Mean/median follow-up in cohorts ranged from 225 days to 37 years.

Appraisal of study quality

Cardiovascular disease Eighteen articles (five case–control, 13 cohort) reported CVD outcomes (Table 1). These articles reported myocardial infarction diagnosis [35–37], coronary artery disease diagnosis [33, 38–40], coronary heart disease diagnosis [31], first diagnosis of ischaemic heart disease [25, 26], both deaths and diagnosis of ischaemic heart disease [34, 41, 42], and cardiovascular death [27, 43–45].

Cardiovascular outcomes were most commonly identified through International Classification of Diseases (ICD) codes on discharge or death registries. Eight of 18 studies identified pre-eclamptic women through antenatal medical records [26, 27, 34, 41–45]. Five of the 18 studies defined pre-eclampsia in line with the ISSHP definition [31, 34, 38, 39, 45], but two of these proceeded to identify women with

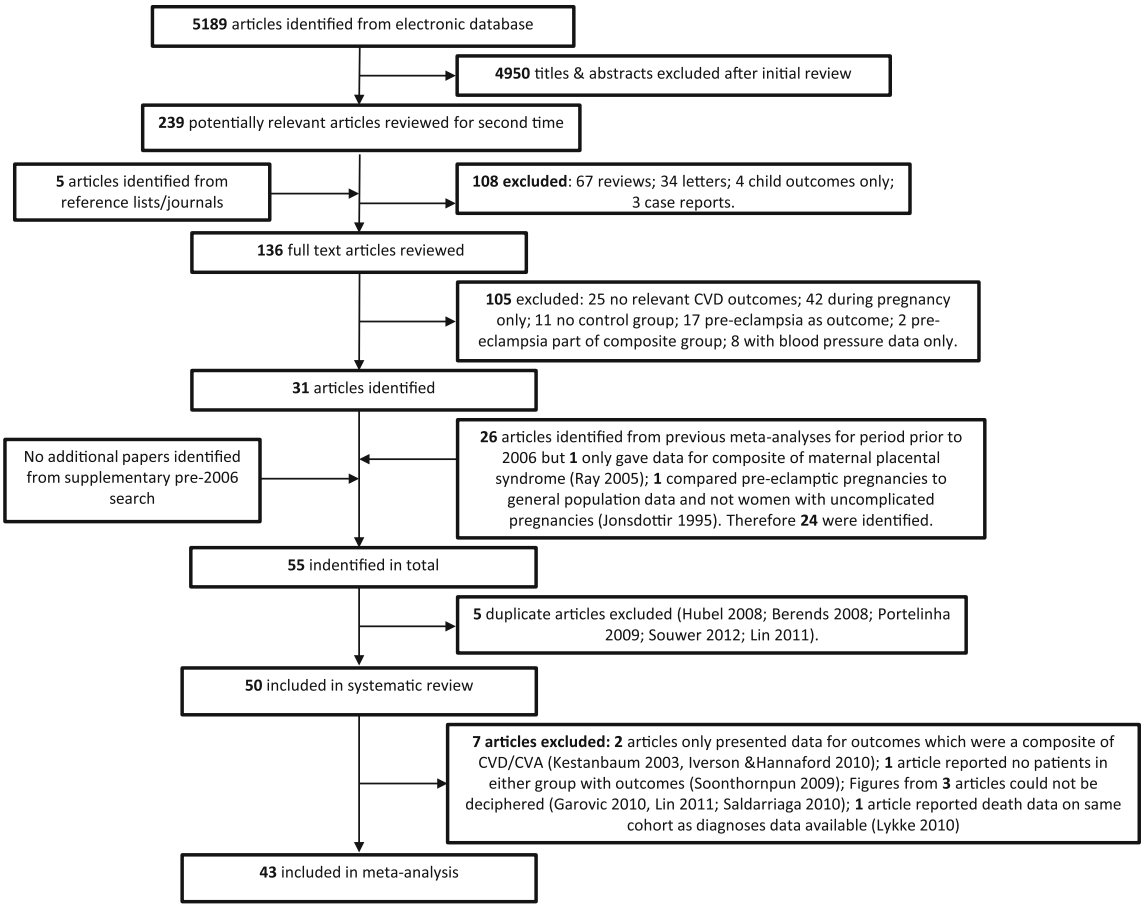


Fig. 1 Process of study selection

pre-eclampsia using a patient survey only [31, 38]. Overall two of the 18 studies satisfied all of the quality criteria [34, 45], meaning it was not possible to conduct a sub-group analysis using all of these quality criteria. Therefore, for the cardiovascular outcome, we also included studies that defined pre-clampsia as both hypertension (BP $\geq$ 140/90 mmHg) and significant proteinuria. Of the 16 remaining studies, seven met these less stringent quality criteria [26, 34, 41–45], and were included in the sub-group analysis.

Cerebrovascular disease Cerebrovascular outcomes were reported in nine articles: three case–control studies [46–48], and six cohort studies (Table 2) [25, 26, 31, 32, 34, 44]. Disease diagnoses were reported by four studies and this included diagnosis of stroke [26, 31], diagnosis of atherothrombotic occlusive vascular disease [47], and first cerebral infarction [46]. Cerebrovascular disease death was reported by two studies [44, 48], and three provided data for both deaths and diagnoses [25, 32, 34].

To identify cerebrovascular outcomes, the majority of papers reviewed medical records or death registries for the relevant ICD codes [26, 32, 34, 44, 46–48]. Five studies confirmed a history of pre-eclampsia by reviewing medical records [26, 32, 34, 44, 47]. Only two papers used the ISSHP criteria to identify women with pre-eclampsia [34, 47]. We therefore also included papers that defined pre-eclampsia as both hypertension (BP $\geq$ 140/90 mmHg) and significant proteinuria. Using these new criteria, four studies with cerebrovascular outcomes were included in the sub group meta-analysis [26, 34, 44, 47].

Hypertension Hypertension was reported by 32 papers, all of which were cohort studies (Table 3). Hypertension was often not the main outcome of the study. To diagnose hypertension at follow-up, just over half of the studies measured blood pressure during a physical examination [6, 34, 49–64]. Patient recall (either current medication and/or previous diagnoses) was also a common method.

On the whole, patients were identified or recruited prospectively from hospital/maternity records. Although eighteen of the papers defined pre-eclampsia as BP $\geq$ 140/90 mmHg and proteinuria >0.3 g/24 h after 20 weeks gestation [19, 20, 31, 34, 39, 52–55, 57, 58, 60–66], only 12 met the quality criteria including ISSHP definition [34, 52–55, 57, 58, 60, 62–64, 66].

Table 1 Characteristics of studies in systematic review for risk of cardiovascular disease outcomes after pre-eclampsia

Author	Outcomes reported	Recruitment	Pre-eclampsia definition; source of data	Outcome definition; source of data	Duration of follow-up	Mean age at follow-up (years)
Case-control						
Mann et al. [36] UK—England	Non-fatal myocardial infarction (MI)	Hospital-based case control study	None specified; patient interviews/ questionnaires	Hospital admission for MI	N/A	<45 at admission
Rosenberg et al. [37] USA	First non-fatal MI	Hospital-based case control study	None specified; patient interviews	Diagnosis met WHO criteria for MI; hospital admission	N/A	Range 25–49. Median cases 44; controls 42
Croft and Hannaford [24] UK—England	First MI	Cases experienced first acute MI while on RCGP Oral Contraception Study	ICD 8th revision codes, but GP not given specific definition; GP medical record	ICD codes 8th revision codes. No specific criteria given to GP; GP medical records	N/A	50 women <44 and 108 >45
Haukkamma et al. [38] Finland	Coronary artery disease (CAD)	Cases diagnosed at a university hospital. Controls attended private gynaecological clinic	BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation; patient questionnaire	Diagnosis of CAD if angiography showed stenosis of >50 % in 1–3 coronary arteries; physical examination	N/A	<66. Median cases 55; 52 controls
Saldarriaga [33] Columbia	Coronary Heart Disease (CHD)	Women who had undergone coronary angiograph at a cardiovascular clinic. Cases were those with CHD. Controls were those who had cardiac catheterisation but no significant lesions on angiography	None specified; patient interviews and review of medical records	CHD determined by presence of significant lesions on angiography; physical examination	N/A	<55. Mean cases 49.5; 46.5 controls
Cohort						
Hannaford et al. [25] UK—England	Total Ischaemic heart disease (IHD)	Women from the RCGP Oral Contraception Study	None specified; GP medical record	No specific classification given to GP; GP medical records	Up to 26 years	Mean 29 at recruitment
Irgens et al. [44] Norway	Cardiovascular death	Data from medical birth register of all births in Norway since 1967	Pre-eclampsia (not defined) and all pregnancies in which both hypertension induced by pregnancy and proteinuria were recorded; medical birth registry	ICD 8th/9th Revision codes; cause of death register	Median 13 years; range 0–25	N/A
Smith et al. [41] UK—Scotland	IHD death	All singleton first births in Scotland between 1981 and 1985	Non pre-existing hypertension with albuminuria, oedema or both; The Scottish Morbidity Records—maternity	ICD 9th/10th revision codes; general registrars office database	Range 15–19 years	Median 38.5
Wilson et al. [34] UK—Scotland	Total IHD	All preeclamptics/ eclamptics during first singleton birth from 1951 to 1970	BP $\geq$ –, 90, protein 0.3 g after 20 weeks gestation; maternity databank	ICD 9th/10th revision codes; death registry, hospital discharge registry	N/A	Mean 60

Table 1 continued

Author	Outcomes reported	Recruitment	Pre-eclampsia definition; source of data	Outcome definition; source of data	Duration of follow-up	Mean age at follow-up (years)
Funai et al. [43] Israel	CVD death	Surveillance of labour ward logbooks for pregnancy complications in obstetric units from 1964 to 1976	BP $\geq$ 140/90, +1 protein. Pre-existing hypertension excluded; labour ward logbooks	ICD 9th revision codes; population death registry	Median 30 years range; 24.5–36.5	Median 53
Kaaja et al. [40] Finland	CAD	Data from cross-sectional population survey (FINRISK)	BP $\geq$ 140/90, Protein not specified; patient questionnaire	Patient self-report in last 12 months; patient questionnaire	28	Mean pre-eclampsia (PE) group 48; control group 46; range 25–64
Wikstrom et al. [42] Sweden	Fatal and non-fatal IHD	First singleton births from birth register of all births in Sweden for 1973–1986.	Mild: BP $\geq$ 140/90, protein 0.3 g; severe – / 110, 0.5 g. Excluded women with essential hypertension; medical birth register	ICD 9th/10th revision codes; hospital discharge registry, cause of death registry	Mean 15 years	Median 48; range 33–75
Haukkamaa [39] Finland	CAD	Data from population cross-sectional survey (health 2000 survey)	BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation; patient survey	Patient self-report; patient interview	N/A	Mean 57; range 45–74
Lykke et al. [26] Denmark	First diagnosis of IHD and congestive heart failure	All singleton deliveries in Denmark from 1 January 1978 to 1 October 2007	ICD 8th/10th revision codes: severe pre-eclampsia and mild pre-eclampsia (pregnancy-induced hypertension with significant proteinuria); discharge diagnoses in national patient registry	ICD 8th/10th revision codes national patient registry and cause of death registry	Median 14.6 years; range 0.25–30.20	Mean 41.6
Garovic et al. [31] USA	CHD	Women who were part of the Family Blood Pressure Programme study (FBPP)	BP $\geq$ 140/90 and proteinuria after 20 weeks gestation; patient questionnaire	Patient self-report; patient interview	N/A	Estimated at 70 years
Lykke et al. [27] Denmark	CVD death	As above	ICD 8th/10th revision codes as above; discharge diagnoses in national patient registry	ICD 8th/10th revision codes; as above	Median 14.8 years; range 0.25–30.20	Mean 41.6
Mongraw-Chaffin et al. [45] USA	CVD death	Women enrolled in the Child Health and Development Studies (CHDS) cohort with singleton pregnancy between 1959 and 1967	BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation; medical records from cohort study	ICD 7th/10th revision codes; California Vital Status	Median 37 years	Median 56
Freibert et al. [35] USA	CVD diagnoses	Data from the 2006 to 2008 Kentucky Women's Health Registry	High blood pressure during pregnancy; patient questionnaire	Patient self-report of angina, heart attack, heart failure, arrhythmia; patient questionnaire	N/A	>50 Mean PE group 58; mean control group 60

Table 2 Characteristics of studies in systematic review for risk of cerebrovascular disease outcomes after pre-eclampsia

Author	Outcomes reported	Recruitment	Pre-eclamspia definition; source of data	Outcome definition; source of data	Duration of follow-up	Mean age at follow-up (years)
Case–control						
Thorogood et al. [48] UK—England and Wales	Cerebrovascular disease deaths	All cerebrovascular deaths between Jan 1986 and Dec 1988. Controls randomly selected from same GP practitioners	Any history of raised BP during pregnancy; GP interview—confirmed through clinical notes	ICD codes 9th revision; death registry—diagnosis confirmed through clinical notes/ postmortem reports	N/A	Range 16–39
Brown et al. [46] USA	First cerebral infarction	Data from a large population based case control study. Women hospitalised with first cerebral infarction. Controls recruited by random digit dialling	BP $\geq$ 140/90, protein 0.3 g during gestation; patient interview	ICD codes 9th revision; hospital admission	Range 42 days–3 years	Range 15–44
Ben-Ami et al. [47] Israel	Atherothrombotic occlusive vascular disease (AOVD)	Cases attended a medical centre due to documented AOVD. Controls recruited from gynecology clinics	BP $\geq$ 140/90 and proteinuria after 20 weeks gestation; questionnaire—then confirmed against hospital records	ICD codes 9th revision hospital; admission for AOVD	N/A	Cases 43; controls 42
Cohort						
Hannaford et al. [25] UK—England	Total cerebrovascular disease	Women from the RCGP Oral Contraception Study	No specific classification given to GP; medical checklist completed by GP	No specific classification given to GP; medical record completed by GP	Up to 26 years	Mean 29 at recruitment
Irgens et al. [44] Norway	Stroke death	Data from medical birth register of all births in Norway since 1967	Pre-eclampsia (not defined) and all pregnancies in which both hypertension induced by pregnancy and proteinuria were recorded; medical birth registry	ICD codes 8th/9th revision; cause of death register	Median 13 years; range 0–25	N/A
Wilson et al. [34] UK—Scotland	Total cerebrovascular disease—deaths and hospital admissions	All preeclamptics/ eclamptics during first singleton birth from 1951 to 1970 at maternity hospital in Aberdeen	BP $\geq$ –,90, protein 0.3 g after 20 weeks gestation; maternity databank	ICD codes 9th/10th revision; death registry and hospital discharge registry	N/A	Mean 60 years
Lykke et al. [26] Denmark	First diagnosis of stroke	All singleton deliveries in Denmark from 1 January 1978 to 1 October 2007	ICD 8th/10 th revision codes: severe pre-eclampsia and mild pre-eclampsia (pregnancy induced hypertension with significant proteinuria); discharge diagnoses in national patient registry	ICD codes 8th/10th revision; national patient registry and cause of death register	Median 14.6 years; range 0.25–30.20	Mean 41.6

Table 2 continued

Author	Outcomes reported	Recruitment	Pre-eclamspia definition; source of data	Outcome definition; source of data	Duration of follow-up	Mean age at follow-up (years)
Tang et al. [32] Taiwan	Total stroke	A population-based study cohort of 1,136,477 birth records for years 1990–2003	ICD 9th revision codes 642.4 and 642.7 (which includes pre-eclampsia superimposed on existing hypertension); discharge diagnoses of delivery	ICD 9th revision codes for : haemorraghic stroke 430–432; ischaemic stroke 433.437; national health insurance claims dataset	Range 6 weeks–12 months	Range 15–50
Garovic et al. [31] USA	Diagnosis of stroke	Women who were part of the Family Blood Pressure Programme study (FBPP)	BP $\geq$ 140/90 and proteinuria after 20 weeks gestation; patient report in pregnancy questionnaire	Patient self report of stroke or cerebral haemorrhage; patient interview	N/A	Estimated at 70

Meta-analysis

Cardiovascular disease

Women who experienced pre-eclampsia were at more than twofold increased odds of CVD later in life (OR = 2.28, 95 % CI 1.87, 2.77) (Fig. 2). There was a high degree of heterogeneity between the 14 studies (I^2 = 78.9 %, $p < 0.001$) but there was no evidence of bias ($p = 0.166$). The 11 cohort and four case–control articles had similar ORs (OR = 2.24, 95 % CI 1.80, 2.80 and OR = 2.57, 95 % CI 1.49, 4.45, respectively) but cohort studies accounted for more heterogeneity than case–control studies (I^2 = 82.5 vs 66.8 %). The odds of a fatal outcome [41, 43–45] were greater than the odds of a diagnosis [24–26, 34, 36–40, 42] (OR = 2.89, 95 % CI 1.71, 4.89 and OR = 2.01, 95 % CI 1.68, 2.41; respectively) and fatal outcomes had greater heterogeneity between studies than diagnosed outcomes (I^2 = 83.0 vs 64.9 %).

Cerebrovascular disease

Women who previously experienced pre-eclampsia were at increased odds of a cerebrovascular event (OR = 1.77, 95 % CI 1.43, 2.21) (Fig. 3). While there was no strong evidence of bias ($p = 0.209$) or heterogeneity (I^2 = 48.2 %; $p = 0.072$) between studies, the pooled effect size of the three case–control studies (OR = 2.46, 95 % CI 1.35, 4.49) was slightly greater than that of the four cohort studies (OR = 1.60, 95 % CI 1.48, 1.74). The two studies investigating fatal cerebrovascular disease [44, 48], and the five analysing cerebrovascular disease diagnosis [25, 26, 34, 46, 47], had very similar pooled effect sizes (OR = 1.75, 95 % CI 1.37, 2.24 and OR = 1.73 95 % CI 0.88, 3.40, respectively).

Hypertension

Women who previously experienced pre-eclampsia were at increased risk of developing hypertension (RR = 3.13, 95 % CI 2.51, 3.89) (Fig. 4). There was a high degree of heterogeneity between studies (I^2 = 88.6 %; $p < 0.001$) but there was no evidence of publication bias ($p = 0.854$).

Pre-term delivery

Three articles reported CVD outcomes for women who had pre-eclampsia and delivered pre-term relative to those who had pre-eclampsia only [26, 41, 42]. Among women with pre-eclampsia, there was no evidence that women who delivered pre-term had greater odds of CVD (RR = 1.32, 95 % CI 0.79, 2.22) (Fig. 5). There was significant heterogeneity between the three studies (I^2 = 75.5 %; $p = 0.017$) but there was no evidence of bias ($p = 0.881$). There were not enough studies to analyse the added effect of pre-term delivery in the other outcomes.

Sensitivity analysis

Cardiovascular disease

There remained a twofold increased odds of CVD when the higher quality studies (OR = 2.26, 95 % CI 1.71, 3.00) and the lower quality studies were considered separately (OR = 2.27, 95 % CI 1.71, 2.99). However there was greater heterogeneity between the higher quality studies (I^2 = 89.0 vs 40.5 %).

Cerebrovascular disease

The pooled ORs were similar for the higher quality studies (OR = 1.81, 95 % CI 1.19, 2.76 vs OR = 1.88, 95 % CI

Table 3 Characteristics for studies in systematic review for risk of hypertensive outcomes after pre-eclampsia

Author	Outcomes reported	Recruitment	Pre-eclampsia definition and source of data	Outcome definition and source of data	Duration of follow-up	Mean age at follow-up (years)
Adams and MacGillivray [49] UK	Hypertension	Aberdeen Maternity Hospital records from 1938 to 1943 reviewed for primiparae under the age of 30 who still resided in Aberdeen in 1958–59	BP ≥ –, 90, protein 0.25 g with blood pressure falling to normal in the puerperium; maternity records	BP ≥ –, 90 mmHg; physical examination	Range 15–21 years	Range 35–50
Epstein [50] USA	Hypertension	White women who delivered with diagnosis of toxaemia of pregnancy. Controls delivered at same hospital	Hypertension, proteinuria and oedema in last trimester (pre-existing hypertension excluded); maternity records	BP ≥ 150/90 mmHg; physical examination	Range 12–17 years. Mean 15	Mean 45
Sibai et al. [66] USA	Hypertension	Women who delivered with a diagnosis of severe pre-eclampsia or eclampsia during first pregnancy, followed by normal blood pressure within 8 weeks of delivery and with at least one subsequent pregnancy beyond 20 wks gestation	BP ≥ 160/110, protein 3+ after 20 weeks gestation; maternity records	Documented hypertension and receiving medication; patient records from hospital/medical providers	Range 2–24. Mean cases 7 years; controls 8 years	N/A
Carleton et al. [51] USA	Hypertension	Women who had diagnosis of pre-eclampsia and enrolled in the Kaiser health plan in 1982. Matched controls randomly selected from log of deliveries	BP ≥ –, 85, protein 0.1 g; maternity records	BP ≥ –, 90 mmHg; physical examination	Average of 10 years	<25 at recruitment
Nisell et al. [52] Sweden	Hypertension	All women who had preeclamptic deliveries at a hospital in 1986. Controls were women who had experienced normal pregnancy during same year	Mild: BP ≥ 140/90, protein 0.3–3 g; severe: >160/110 and/or protein >0.3 g/24 after 20 weeks of pregnancy; medical records	BP ≥ –, 90 mmHg and/or on antihypertensive medication; physical examination	7 years	Mean PE group 29; controls 30 at delivery
North et al. [53] New Zealand	Hypertension	Samoan primiparous preeclamptics for years 1980–93. Controls randomly selected from same database. Additional controls selected from Samoan communities	BP ≥ 140/90, protein 0.3 g after 20 weeks gestation; hospital records	BP ≥ 140, 90 mmHg; physical examination	Mean 5 years	Mean 30
Laivuori et al. [54] Finland	Hypertension	Preeclamptic women who had delivered first child at a hospital between 1976 and 1978. Controls from same period on same database	BP ≥ 160/110, protein 0.3 g after 29 weeks in previously healthy women; hospital records	BP ≥ 150, 100 mmHg; physical examination	Mean 17 years	Mean 42
Hannaford et al. [25] UK—England	Hypertension	Women from the RCGP Oral Contraception Study	None specified; medical checklist completed by GP	No specific classification given to GP; medical record completed by GP	Up to 26 years	Mean 29 at recruitment
Hubel et al. [89] Iceland	Hypertension	All maternity records reviewed for period 1931–1996 for eclamptic women, who were postmenopausal at time of study. Normotensive controls from same study population.	BP ≥ 140/90, protein info not available; maternity records	Use of anti-hypertensive medication; patient questionnaire	Mean PE group 32.6; controls 32.7 years	Range of 50–67. Mean age PE group 57; controls 56
Marin et al. [55] Spain	Hypertension	Cases taken from follow-up of larger original study group of pregnant women with hypertension from 1973 to 1996. Control group from birth register	BP ≥ 140/90, protein 0.3 g after 20 weeks gestation; medical records	BP ≥ 140,90 mmHg or had been previously diagnosed; physical examination	Range 6–24 years; mean PE group 13.6; controls 16.2 years	Mean PE group 43; controls 42

Table 3 continued

Author	Outcomes reported	Recruitment	Pre-eclampsia definition and source of data	Outcome definition and source of data	Duration of follow-up	Mean age at follow-up (years)
Shammas et al. [56] Jordan	Hypertension	Women who delivered during 1988 at medical centre with pre-eclampsia. Controls were women with uncomplicated delivery	None specified; medical records	BP ≥ –, 90 mmHg; physical examination	10 years since birth	
Sattar et al. [90] UK—Scotland	Hypertension	Review of medical records for women who delivered between 1975 and 1985 with pre-eclampsia. Controls from same records	BP ≥ –, 90, protein 0.1 g; maternity records	Use of anti-hypertensive medication; patient questionnaire	Median 20; range 15–25 years	Median PE group 43; control 44
Wilson et al. [34] UK—Scotland	Hypertension	Cohort identified from maternity hospital database. All preeclamptics/eclamptics during first singleton birth from 1951 to 1970	BP ≥ –,90, protein 0.3 g from 20 weeks gestation; maternity databank	WHO criteria; ICD codes 9th/10th revision; questionnaire and physical exam for hypertension	N/A	Mean 60
Kaaja et al. et al. [40] Finland	Hypertension (last 12 months)	Data from cross-sectional population survey (FINRISK)	BP ≥ 140/90, protein not specified; patient survey	Patient self-report of hypertension in last 12 months; Patient questionnaire	N/A	Mean PE group: 48; control 46; range 25–64
Blaauw et al. [57] The Netherlands	Hypertension	Women hospitalised for early onset pre-eclampsia. Control group from same hospital. Also advertised in paper for a nulliparous group	BP ≥ 160/110, protein 0.3 g after 20 weeks gestation; hospital records	May have been diagnosed differently in groups: PE group ≥ 125/80. Controls ≥ 140/90; physical examination	Range 3–13 months	Mean 31
Kharazmi et al. [59] Finland	Hypertension	Data from large cross-sectional survey (Health 2000 survey). This supplemental study included all women aged 30–99	None specified; patient response at home health interview	BP ≥ 140, 90 mmHg; physical examination		Range 30–99
Manten et al. [65] The Netherlands	Hypertension	Women with history of pre-eclampsia who delivered at a medical centre before 34 weeks. Controls were from same medical centre.	BP ≥ –, 90, protein 0.3 g after 20 weeks gestation but also included women who were chronic hypertensives and developed de novo protienuria; recruited prospectively in hospital	Use of anti-hypertensive medication and/or prior diagnosis; patient questionnaire	Mean PE group 9.8 months; controls 5.8 months	Mean PE group 31; controls 33
Berends et al. [6] The Netherlands	Hypertension	Data from a large cohort study, genetic research in isolated populations. Cases with a history of pre-eclampsia in singleton pregnancies	BP ≥ 140/90, protein 0.3 g after 20 weeks gestation or super-imposed pre-eclampsia (new onset proteinuria in chronic hypertensives); national birth registration records	Use of anti-hypertensive medication and/or BP ≥ 140/ 90 mmHg; physical examination	Mean PE group 7 years; control 13 years	Mean PE group 36; controls 39 at time of study
Diehl et al. [69] USA	Hypertension	Women diagnosed with either preeclampsia, eclampsia or toxaemia between 1960 and 1979 at a medical centre were randomly selected. Controls from same centre	BP ≥ 140/90, protein 0.3 g; hospital diagnostic index	Use of anti-hypertensive medication; patient questionnaire	Median: PE group 24.5; controls 27.3 years	Mean: PE group 54; controls 56
Gaugler-Senden et al. [61] The Netherlands	Hypertension	All consecutive women who were admitted to medical centre between 1993 and 2003 with severe, early onset pre-eclampsia before 24 weeks gestation. Controls were selected from same hospital	BP ≥ –/110 or 140/90, protein 0.3 g in combination with eclampsia or HELLP after 20 weeks gestation and also super-imposed pre-eclampsia; medical records	BP ≥ –, 90 mmHg and/or on antihypertensive medication; physical examination	Mean 5.5 years; range 4–10 years	Median PE group 39; controls 38

Table 3 continued

Author	Outcomes reported	Recruitment	Pre-eclampsia definition and source of data	Outcome definition and source of data	Duration of follow-up	Mean age at follow-up (years)
Aukes et al. [62] The Netherlands	Hypertension	Preeclamptic women who were referred to a centre for high-risk pregnancies from 1988 to 2005 due to developing seizures (eclampsia). Controls from same hospital or recruited through hospital employees and family members	Eclampsia—seizures in women with pre-eclampsia, BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation. Also up to 1 week postpartum; medical records	BP $\geq$ 140, 90 mmHg; physical examination	Mean: PE group 5.3 years; controls 7.1	Mean 38
Edlow [91] USA	Hypertension	Participants originally recruited in a previous prospective study. All women admitted with pre-eclampsia at a hospital between 2005 and 2007 were invited to take part	BP $\geq$ 140/90 with protein, but also included women with just BP $\geq$ 140/90; recruited prospectively in hospital	Use of anti-hypertensive medication/ has someone told you that your BP is high; telephone interview with patient	Mean PE group 225 days; controls 230 days. Range 6–13 months	Mean PE group 26; controls 28
Haukkamaa et al. [39] Finland	Hypertension	Data from population cross-sectional survey (Health 2000 survey)	BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation; identified in survey and then confirmed against hospital discharge data	Currently on blood pressure medication; patient interview	N/A	Range 45–74. mean 57
Lykke et al. [26] Denmark	First diagnosis of hypertension	All singleton deliveries in Denmark from 1 January 1978 to 1 October 2007 extracted from national patient registry	ICD 8th/10th revision codes: severe pre-eclampsia and mild pre-eclampsia (pregnancy induced hypertension with significant proteinuria); discharge diagnoses in national patient registry	ICD 8th/10th revision codes; national patient registry and cause of death register	Range: 0.25–30.20 years median 14.6	Mean 41.6
Magnussen et al. [92] Norway	Hypertension	Participants of population study (HUNT). All women linked to medical birth registry to obtain information on first singleton births between 1967 until time of study (1995–1997)	None specified; diagnosis from medical birth registry	Use of anti-hypertensive medication; patient questionnaire	Mean of 16 years (for whole hypertensive group not just PE)	Mean 40 (for whole hypertensive group)
Soonthornpun et al. [30] Thailand	Hypertension	Women who had been diagnosed with severe pre-eclampsia at a hospital. Controls from same hospital	BP $\geq$ 160/110, protein 0.5 g; hospital records	Physical examination	Mean: PE group 2.6 years ($\pm$1.6); controls 4.5 years ($\pm$2.8)	Mean PE group 31; controls 32
Spaan et al. [60] The Netherlands	Hypertension	Women who had pre-eclamptic pregnancy in period 1979–1987 at a hospital. Controls from same hospital	BP $\geq$ 140/90, protein 0.3 g, after 20 weeks gestation; medical records	BP $\geq$ 140, 90 mmHg and/or use of anti-hypertensive medication; physical examination	Mean 23 years; range 20–28	Mean 49
Canti et al. [58] Brazil	Hypertension	Women who had previously presented in hospital with pre-eclampsia. Controls were women who delivered on same day at same hospital.	BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation; medical records	BP $\geq$ 140, 100 mmHg; physical examination	>10 years. Mean cases 15.9; controls 14.6	Mean: PE group 39; controls 37
Garovic et al. [31] USA	Hypertension	Women who were part of the Family Blood Pressure Programme (FBPP)	BP $\geq$ 140/90 and proteinuria after 20 weeks gestation; patient questionnaire	Previous diagnosis of hypertension; use of anti-hypertensive medication or BP $\geq$ 140/90; patient interview and physical examination	N/A	Estimated at 70 years

Table 3 continued

Author	Outcomes reported	Recruitment	Pre-eclampsia definition and source of data	Outcome definition and source of data	Duration of follow-up	Mean age at follow-up (years)
Portelinha et al. [20] Portugal	Hypertension	Women with a history of pre-eclampsia and normotensive pregnancy controls identified from medical records at 3 hospitals in Portugal	BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation; medical records	Use of anti-hypertensive medication; interview/ questionnaire	Mean 6 years; range 4–9 years	Mean 34
Shahbazian et al. [63] Iran	Hypertension	Primiparous women diagnosed with pre-eclampsia or eclampsia at two hospitals in Iran. Controls were volunteers who had an uncomplicated pregnancy at hospitals during same period	BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation; medical records	BP $\geq$ 140, 90 mmHg and/or use of anti-hypertensive medication; physical examination	Mean 5.7 years; range 5.2–7.3 years	Mean PE group 25; controls 25.8
Melchiorre et al. [64] UK	Hypertension	Women recruited at pregnancy. Cases with pre-eclampsia. Controls were normotensive women with singleton pregnancy	BP $\geq$ 140/90, protein 0.3 g after 20 weeks gestation; Medical records	BP $\geq$ 140, 90 mmHg; physical examination	2 years	Mean PE group 33; controls 34

1.45, 2.44). The degree of heterogeneity found between the high quality studies was much higher than that between the lower quality studies (I^2 = 62.9–7.2 %).

Hypertension

The RRs for the higher quality studies were slightly higher than those of the lower quality studies (RR = 3.18, 95 % CI 2.07, 4.88 compared to RR = 3.11, 95 % CI 2.42, 3.99) and the I^2 values for heterogeneity were lower (I^2 = 50.2 vs 91.5 %).

Discussion

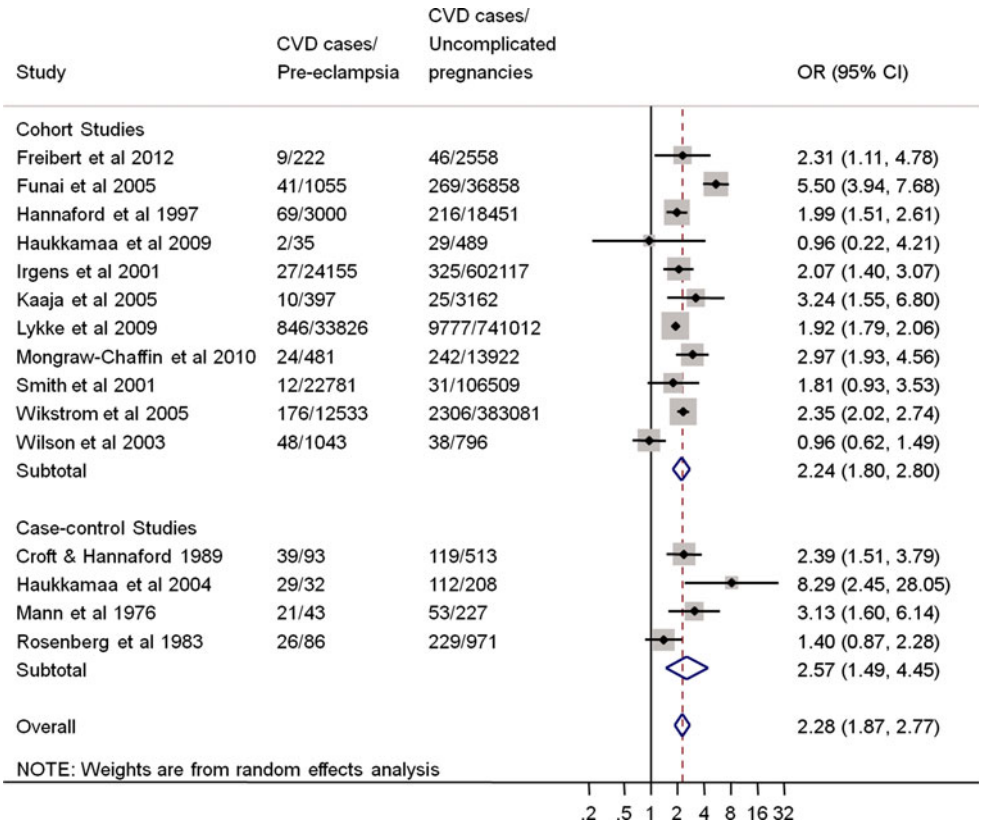
Summary of findings

This systematic review and meta-analysis found increased odds of future cardiovascular and cerebrovascular events and an increased risk of hypertension following a diagnosis of pre-eclampsia. Hypertension had the strongest association with pre-eclampsia. The odds of CVD did not appear to be further increased if pre-eclampsia was complicated by a pre-term delivery. There was substantial heterogeneity between studies investigating hypertension, which was to some extent explained by differences in study quality. We identified heterogeneity between studies with CVD outcomes, which was partially explained by a stronger effect of fatal compared to diagnosed outcomes.

Strengths and limitations

We used a comprehensive search procedure and followed validated systematic review methods, complying with the MOOSE guidelines [14]. Studies from a wide range of countries were included, the search was not restricted to English language articles and an additional 31 articles were found since 2006. Authors were contacted where additional information was required to maximise the number of articles included. We also used sensitivity analyses to explore the effect of varying definitions of exposure and outcome, including use of the ISSHP diagnostic criteria for pre-eclampsia in the hypertension outcomes. Bias and heterogeneity were examined using several techniques to ensure our results were robust. For example, we investigated variation between case–control and cohort studies (for cardiovascular and cerebrovascular outcomes). By finding a lower heterogeneity within sub-groups than between all studies combined, we identified a potential source of heterogeneity. Furthermore, the effects of study quality on the overall results were examined. However, while we tested for bias and in most cases found non-significant results, publication bias cannot be fully eliminated as there will be studies with no significant results that may not have been published.

However, this systematic review has some limitations. The validity of the review's conclusions is directly related to the quality of the studies it examines. Both the ISSHP and the Royal College of Obstetricians and Gynaecologists advise that while clinically the diagnosis of pre-eclampsia should be inclusive, specificity of diagnosis in research is vital and the definition of new onset hypertension (BP $\geq$ 140/90 mmHg) after 20 weeks gestation in combination with the appearance of proteinuria (>0.3 g/24 h) should be adopted where necessary [9, 67]. However, many authors often fail to explain in sufficient detail their diagnostic



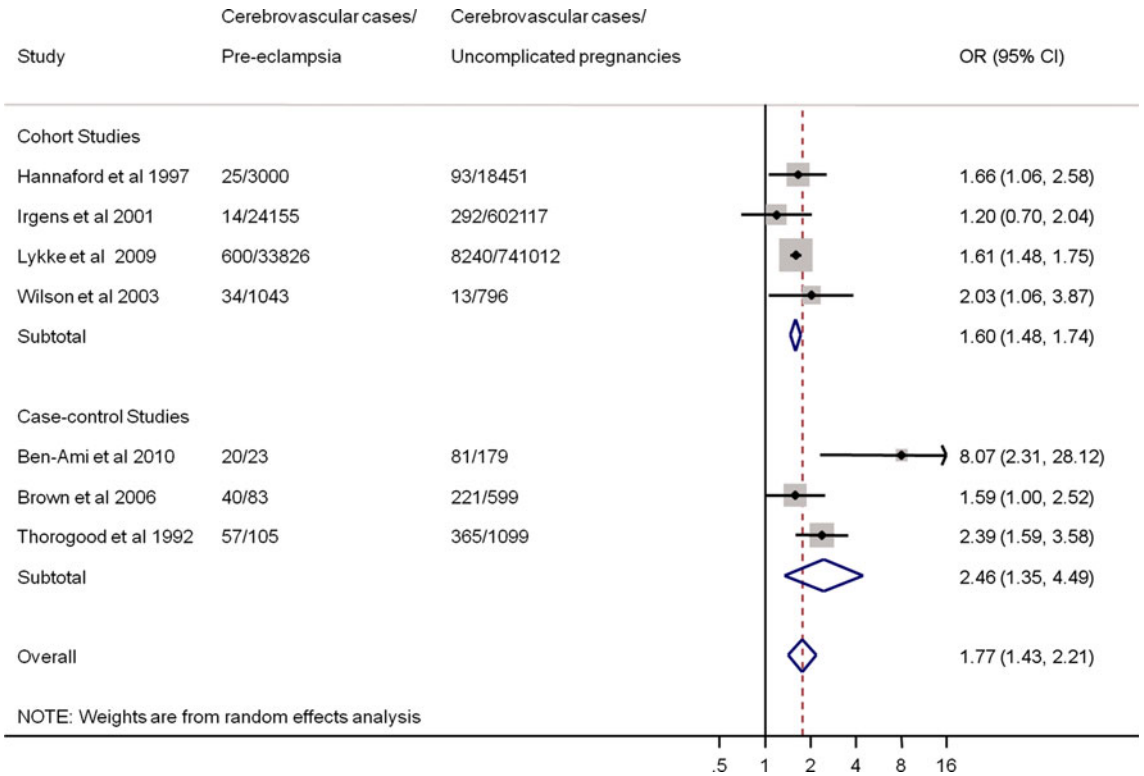


Fig. 2 Forest plot showing the odds of future cardiovascular disease following pre-eclampsia

Fig. 3 Forest plot showing the odds of future cerebrovascular disease following pre-eclampsia

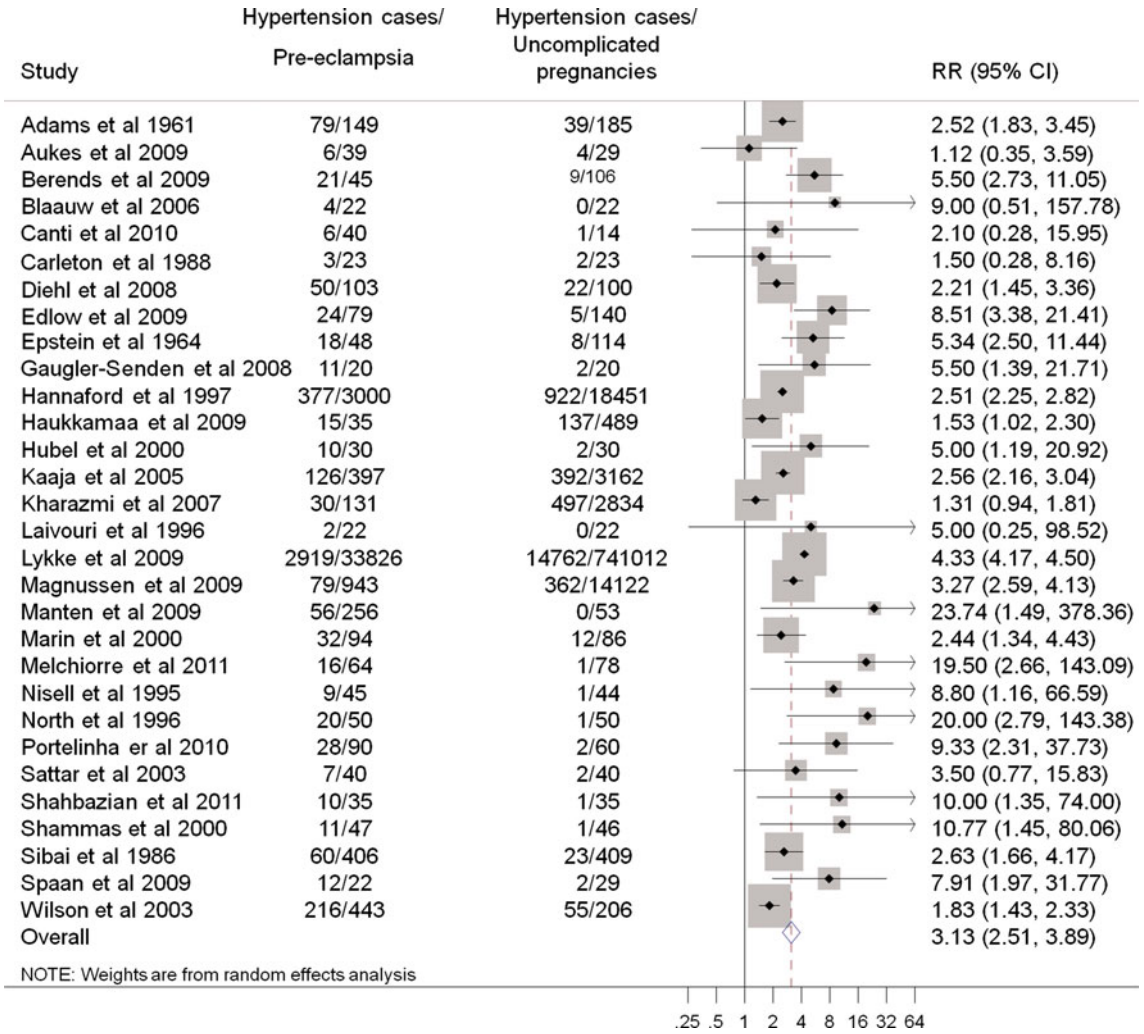


Fig. 4 Forest plot showing the risk of future hypertension following pre-eclampsia

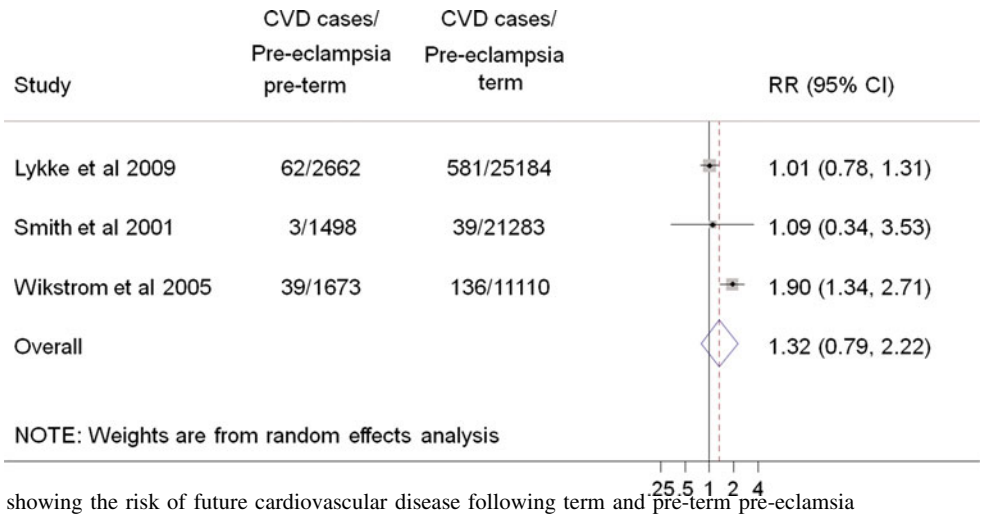


Fig. 5 Forest *plot* showing the risk of future cardiovascular disease following term and pre-term pre-eclamsia

criteria and some stated the ISSHP definition but proceeded to include women who had new onset proteinuria superimposed on chronic hypertension or identified women with pre-eclampsia through a patient questionnaire. Therefore, while we aimed to perform a sub-group analysis on those papers using the ISSHP definition there were not enough of these articles reporting CVD and cerebrovascular outcomes, and so a less stringent definition of pre-eclampsia had to be used. In addition, although some papers explicitly stated that they had excluded women with pre-existing hypertension, others did not. Therefore, where the 'after 20 weeks gestation' cut-off was cited, it had to be presumed that this would be the case. Length of follow-up was variable and while we included papers which reported outcomes past 6 weeks postpartum, we acknowledge that literature regarding the time which pre-eclampsia takes to resolve is unclear. However, 3 months has been cited by guidelines as a point where normalisation of blood pressure after pre-eclampsia would be expected [68] and only one of our studies, which had a long range of follow-up, reported outcomes prior to this point [44]. These factors could be a cause of heterogeneity in our meta-analyses which dilutes or exaggerates the effects, therefore making the estimates of risk after pre-eclampsia misleading.

Patient self-report may result in an under-reporting of disease. Hypertension may be present but as yet undetected, and recall bias is also an important consideration. Diehl et al. [69] found that some 24.5 years after the index pregnancy, 82 of 103 women correctly verified their history of pre-eclampsia. However, Coolman et al. [70] found that although 76 of 87 patients at 2 months postpartum correctly identified their recent pre-eclampsia, a positive response was also given by a further 43 women with pregnancy-induced hypertension and 28 women who had no hypertensive complications in pregnancy. If women also incorrectly self-report hypertension, or indeed a history of pre-eclampsia, this may explain why we identified increased heterogeneity in studies with self-reported outcomes compared to those where hypertension and pre-eclampsia were diagnosed by physical exam/medical records (using our quality criteria sub-analysis). However the RRs in the higher quality studies (which excluded self-reported hypertension and pre-eclampsia and used studies which defined pre-eclampsia in line with the ISSHP criteria) and the lower quality studies were very similar. The agreement of patient self-report with medical records for CVDs has also been found to be variable [71, 72]. However, in addressing these issues in the quality criteria, and by using a sensitivity analyses, the results suggested that there was little difference in the pooled estimates of the studies of this design.

The reliability of ICD coding of pre-eclampsia has been found to vary greatly [73], and coding of pre-eclampsia when compared to the criteria given by the American College of Obstetrics and Gynecology was accurate in only 54 % of cases. It has also been found that chronic hypertension, as well as milder forms of pregnancy-induced hypertension, are under-reported in hospital discharge and birth records and, therefore, studies may overestimate the proportion of more severe forms and ultimately overstate the risk which pre-eclampsia imparts on future CVD risk [74].

All types of cardiovascular and cerebrovascular events were combined in each meta-analysis, which may have been a cause of heterogeneity. Eleven studies reported outcomes specifically for myocardial infarctions or ischaemic heart disease, or coronary artery disease but four papers had composite groups of cardiovascular death [27, 43–45]. Therefore, we could not investigate whether certain types of cardiovascular or cerebrovascular disease were more strongly associated with pre-eclampsia. However, we were able to compare fatal CVD outcomes with CVD diagnoses, finding a stronger association with a fatal cardiovascular event after pre-eclampsia. This may be partially due to an over-reporting of more serious cases of pre-eclampsia which could lead to higher estimates of fatal disease or alternatively, pre-eclampsia itself could be a marker for more extreme cases of CVD.

Comparison with previous studies

We found an additional 31 articles published since the most recent reviews. Our findings for the risk of cardiovascular, cerebrovascular and hypertensive outcomes after pre-eclampsia were similar to those of Bellamy et al. and McDonald et al. [2, 3]. We used unadjusted, crude ORs while the earlier reviews used the ratios reported in each article, which may have contributed to a slight difference. Using unadjusted ORs may have contributed to the heterogeneity between studies examining hypertension particularly if the study population varied substantially between studies.

A previous review reported that pre-eclampsia resulting in delivery before 37 weeks gestation was more strongly associated with future CVD than those cases with more severe hypertension or proteinuria [2]. This was based on pre-term data from only one study [44]. We compared outcomes for pre-eclampsia both with and without pre-term birth. In doing so, we found that the risk of CVD did not appear to be increased if pre-eclampsia was further complicated by a pre-term delivery. However, these data were only available for three studies [27, 41, 42]. Early onset and late onset pre-eclampsia may be different phenotypes with different aetiologies [75], however, current classifications of pre-eclampsia do not stratify by gestational age at onset [76]. In addition, management of pre-eclampsia is variable and while induction of labour is advised by some

protocols, others favour expectant monitoring [75, 77]. Therefore, some mothers who experience onset prior to 37 weeks may not deliver until after this point. Thus, we acknowledge that use of gestation at delivery as a proxy for severity, as opposed to gestation at onset, may result in bias.

Potential mechanisms

Although pre-eclampsia has been reported to have a detrimental effect on future cardiovascular health, the relationship between the two is not clear. It is not known whether pre-eclampsia represents an independent causal factor due to vascular changes induced by systemic endothelial damage which manifest in later life as CVD [5], or if the two simply share common underlying risk factors, with pre-eclampsia representing an earlier stage on the path to cardiovascular problems. Pre-eclampsia has been associated with higher rates of metabolic syndrome and its components such as larger waist circumferences and BMI [6, 19], higher glucose levels [6, 78], and diabetes after delivery [79–81]. Further, Magnussen et al. [7] reported a higher incidence of some of these factors during pregnancies complicated by pre-eclampsia. However, it is not yet clear whether these cardiovascular risk markers are present before pregnancy and perhaps exacerbated by the pregnancy, or whether they develop in the period after delivery, but the case for pre-pregnancy interventions to prevent both pre-eclampsia and CVD has been presented [8]. Longitudinal studies which recruit women prior to pregnancy are required.

Implications

Although the absolute increase in cardiovascular risk associated with pre-eclampsia may be small, it could have major implications for women's health due to the significance of CVD within women. CVD is responsible for 22 % of premature deaths in British females [82], and 55,000 more women than men under the age of 75 years die of stroke each year in the US [13]. The identification and management of women who present with risk factors could prevent future cardiovascular morbidity and mortality [83]. Although it has not been established whether pre-eclampsia represents an independent risk factor, the current lifetime risk for all women is high at approximately 40 % [84].

More than 90 % of myocardial infarctions in women have been attributed to modifiable risk factors [85], and recent AHA guidelines for the prevention of CVD in women call for a renewed emphasis on lifestyle modification and the use of anti-hypertensive and cholesterol lowering medications to reduce risk [13]. However, few women are currently offered risk reduction interventions following pregnancy complicated by pre-eclampsia [10], and GP follow-up of formerly pre-eclamptic women has been found to be inadequate in regions of Canada [86] and the Netherlands [87]. A recent study of primary health care providers at a hospital in the US found that high numbers of physicians remain unaware of the link between pre-eclampsia and future disease, and very few provide cardiovascular risk reduction counselling to these patients [88]. Further research is needed to clarify whether pre-eclampsia is an independent risk factor for CVD and whether there is value in adding a history of pre-eclampsia to current risk prediction formulas used in cardiovascular risk reduction programmes.

Conclusion

Pre-eclampsia is associated with an approximate twofold increase in odds of CVD and cerebrovascular disease, and a threefold increased risk of hypertension. We found no evidence that the risks of CVD increase when pre-eclampsia is associated with pre-term delivery, although acknowledge there are limitations to our methodology. Women who experience pre-eclampsia should be aware of their increased risk and may benefit from formal postnatal screening for accepted risk factors for CVD.

Acknowledgments This research is funded by Newcastle upon Tyne Hospitals NHS Foundation Trust.

Conflict of interest None to declare.

References

1. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33:130–7.
2. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335:974.
3. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156:918–30.
4. World Health Organization. Women's health. 2009. http://www.who.int/mediacentre/factsheets/fs334/en/index.html. Accessed 03 Jul 2011.
5. Magee L, Newstead J, Ng J, Ct A, Von Dadelszen P. Pre-eclampsia as a marker of cardiovascular disease. Fetal Matern Med Rev. 2008;19:271–92.
6. Berends AL, de Groot CJM, Sijbrands EJ, Sie MPS, Benneheij SH, Pal R, Heydanus R, Oostra BA, van Duijn CM, Steegers EAP. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. Hypertension. 2008;51:1034–41.
7. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ. 2007;335:978.
8. Rodie VA, Freeman DJ, Sattar N, Greer IA. Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? Atherosclerosis. 2004;175:189–202.

9. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20:IX–XIV.
10. Garovic VD, Hayman SR. Hypertension in pregnancy: an emerging risk factor for cardiovascular disease. Nat Clin Pract Nephrol. 2007;3:613–22.
11. Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? Ther Adv Cardiovasc Dis. 2008;2:249–59.
12. National Institute for Health and Clinical Excellence. Hypertension in pregnancy the management of hypertensive disorders during pregnancy, vol. CG107. London: Royal College of Obstetricians and Gynaecologists; 2010.
13. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VRL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. Circulation. 2011;123:1243–62.
14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283:2008.
15. Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. London: BMJ Books; 2001.
16. Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557.
17. Ray J, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet. 2005;366:1797–803.
18. Jónsdóttir LS, Arngrimsson R, Geirsson RT, Slgvaldason H, Slgfússon N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. Acta Obstet Gynecol Scand. 1995;74:772–6.
19. Berends AL, Zillikens MC, De Groot CJM, Rivadeneira F, Oostra BA, Van Duijn CM, Steegers EAP. Body composition by dual-energy X-ray absorptiometry in women with previous pre-eclampsia or small-for-gestational-age offspring. BJOG. 2009;116:442–50.
20. Portelinha A, Belo L, Cerdeira AS, Braga J, Tejera E, Pinto F, Pinto A, Areias MJ, Patricio B, Rebelo I. Lipid levels including oxidized LDL in women with history of preeclampsia. Hypertens Pregnancy. 2010;29:93–100.
21. Hubel CA, Powers RW, Snaedal S, Gammill HS, Ness RB, Roberts JM, Arngrimsson R. C-reactive protein is elevated 30 years after eclamptic pregnancy. Hypertension. 2008;51:1499–505.
22. Souwer ETD, Blaauw J, Coffeng SM, Smit AJ, Van Doormaal JJ, Faas MM, Van Pampus MG. Decreased arterial elasticity in formerly early-onset preeclamptic women. Acta Obstet Gynecol Scand. 2011;90:797–801.
23. Lin YS, Tang CH, Yang CYC, Wu LS, Hung ST, Hwa HL, Chu PH. Effect of pre-eclampsia-eclampsia on major cardiovascular events among peripartum women in Taiwan. Am J Cardiol. 2011;107:325–30.
24. Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. BMJ. 1989;298:165–8.
25. Hannaford P, Ferry S, Hirsch S. Cardiovascular sequelae of toxaemia of pregnancy. Heart. 1997;77:154–8.
26. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension. 2009;53:944–51.
27. Lykke JA, Langhoff-Roos J, Lockwood CJ, Triche EW, Paidas MJ. Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery. Paediatr Perinat Epidemiol. 2010;24:323–30.
28. Kestenbaum B, Seliger SL, Easterling TR, Gillen DL, Critchlow CW, Stehman-Breen CO, Schwartz SM. Cardiovascular and thromboembolic events following hypertensive pregnancy. Am J Kidney Dis. 2003;42:982–9.
29. Iversen L, Hannaford PC. Toxaemia of pregnancy and risk of mortality in later life: evidence from the royal college of general practitioners' oral contraception study. Hypertens Pregnancy. 2010;29:180–97.
30. Soonthornpun K, Soonthornpun S, Wannaro P, Setasuban W, Thamprasit A. Insulin resistance in women with a history of severe pre-eclampsia. J Obstet Gynaecol Res. 2009;35:55–9.
31. Garovic VD, Bailey KR, Boerwinkle E, Hunt SC, Weder AB, Curb D, Mosley TH Jr, Wiste HJ, Turner ST. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. J Hypertens. 2010;28:826–33.
32. Tang CH, Wu CS, Lee TH, Hung ST, Yang CYC, Lee CH, Chu PH. Preeclampsia–eclampsia and the risk of stroke among peripartum in Taiwan. Stroke. 2009;40:1162–8.
33. Saldarriaga CI, Franco G, Garzon AM, Garcia I, Mejia N, Restrepo A. Factores de riesgo para la enfermedad coronaria temprana en mujeres [Risk factors for premature coronary disease in women]. Biomedica. 2010;30:559–66.
34. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WCS. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ. 2003;326:845.
35. Freibert SM, Mannino DM, Bush H, Crofford LJ. The association of adverse pregnancy events and cardiovascular disease in women 50 years of age and older. J Womens Health (Larchmt). 2011;20:287–93.
36. Mann JI, Doll R, Thorogood M, Vessey MP, Waters WE. Risk factors for myocardial infarction in young women. Br J Prev Soc Med. 1976;30:94–100.
37. Rosenberg L, Miller DR, Kaufman DW, Helmrich SP, Van de Carr S, Stolley PD, Shapiro S. Myocardial infarction in women under 50 years of age. JAMA. 1983;250:2801–6.
38. Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R. Risk for subsequent coronary artery disease after preeclampsia. Am J Cardiol. 2004;93:805–8.
39. Haukkamaa L, Moilanen L, Kattainen A, Luoto R, Kahonen M, Leinonen M, Jula A, Kesaniemi YA, Kaaja R. Pre-eclampsia is a risk factor of carotid artery atherosclerosis. Cerebrovasc Dis. 2009;27:599–607.
40. Kaaja R, Kinnunen T, Luoto R. Regional differences in the prevalence of pre-eclampsia in relation to the risk factors for coronary artery disease in women in Finland. Eur Heart J. 2005;26:44–50.
41. Smith GCS, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet. 2001;357:2002–6.
42. Wikström A-K, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. BJOG. 2005;112:1486–91.
43. Funai EF, Friedlander Y, Paltiel O, Tiram E, Xue X, Deutsch L, Harlap S. Long-term mortality after preeclampsia. Epidemiology. 2005;16:206–15.
44. Irgens HU, Reisaeter L, Irgens LM, Lie RT, Roberts JM. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study/pre-eclampsia and cardiovascular disease later in life: who is at risk? BMJ. 2001;323:1213–7.

45. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. Hypertension. 2010;56: 166–71.
46. Brown DW, Dueker N, Jamieson DJ, Cole JW, Wozniak MA, Stern BJ, Giles WH, Kittner SJ. Preeclampsia and the risk of ischemic stroke among young women: results from the stroke prevention in young women study. Stroke. 2006;37:1055–9.
47. Ben-Ami S, Oron G, Ben-Haroush A, Blickstein D, Hod M, Bar J. Primary atherothrombotic occlusive vascular events in premenopausal women with history of adverse pregnancy outcome. Thromb Res. 2010;125:124–7.
48. Thorogood M, Mann J, Murphy M, Vessey M. Fatal stroke and use of oral contraceptives: findings from a case–control study. Am J Epidemiol. 1992;136:35–45.
49. Adams E, MacGillivray I. Long-term effect of pre-eclampsia on blood-pressure. Lancet. 1961;278:1373–5.
50. Epstein FH. Late vascular effects of toxemia of pregnancy. N Engl J Med. 1964;271:391–5.
51. Carleton H, Forsythe A, Flores R. Remote prognosis of pre-eclampsia in women 25 years old and younger. Am J Obstet Gynecol. 1988;159:156–60.
52. Nisell H, Lintu H, Lunell NO, Möllerström G, Pettersson E. Blood pressure and renal function seven years after pregnancy complicated by hypertension. BJOG. 1995;102:876–81.
53. North RA, Simmons D, Bamfather D, Upjohn M. What happens to women with preeclampsia? Microalbuminuria and hypertension following preeclampsia. Aust N Z J Obstet Gynaecol. 1996; 36:233–8.
54. Laivuori H, Tikkanen MJ, Ylikorkala O. Hyperinsulinemia 17 years after preeclamptic first pregnancy. J Clin Endocrinol Metab. 1996;81:2908–11.
55. Marin R, Gorostidi M, Portal CG, Sanchez M, Sanchez E, Alvarez J. Long-term prognosis of hypertension in pregnancy. Hypertens Pregnancy. 2000;19:199–209.
56. Shammas AM, Maayah JF. JF. Hypertension and its relation to renal function 10 years after pregnancy complicated by pre-eclampsia and pregnancy induced hypertension. Saudi Med J. 2000;21:190–2.
57. Blaauw J, van Pampus MG, Van Doormaal JJ, Fokkema MR, Fidler V, Smit AJ, Aarnoudse JG. Increased intima–media thickness after early-onset preeclampsia. Obstet Gynecol. 2006;107:1345–51.
58. Canti IC, Komlos M, Martins-Costa SH, Geraldo Lopes Ramos J, Capp E, Corleta HE. Risk factors for cardiovascular disease ten years after preeclampsia [Fatores de risco para doenca cardiovascular dez anos apos pre-eclampsia]. Sao Paulo Med J. 2010; 128:10–3.
59. Kharazmi E, Kaaja R, Fallah M, Luoto R. Pregnancy-related factors and the risk of isolated systolic hypertension. Blood Press. 2007;16:50–5.
60. Spaan JJ, Ekhart T, Spaanderman MEA, Peeters LLH. Remote hemodynamics and renal function in formerly preeclamptic women. Obstet Gynecol. 2009;113:853–9.
61. Gaugler-Senden IPM, Berends AL, de Groot CJM, Steegers EAP. Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health. Eur J Obstet Gynecol Reprod Biol. 2008;140:171–7.
62. Aukes AM, de Groot JC, Aarnoudse JG, Zeeman GG. Brain lesions several years after eclampsia. Am J Obstet Gynecol. 2009; 200:504.e1–5.
63. Shahbazian N, Shahbazian H, Ehsanpour A, Aref A, Gharibzadeh S. Hypertension and microalbuminuria 5 years after pregnancies complicated by pre-eclampsia. Iran J Kidney Dis. 2011;5:324–7.
64. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. Hypertension. 2011;58:709–15.
65. Manten GTR, Sikkema MJ, Voorbij HAM, Visser GHA, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Hypertens Pregnancy. 2007;26: 39–50.
66. Sibai B, el Nazer A, Gonzalez-Ruiz A. Severe preeclampsia-eclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis. Am J Obstet Gynecol. 1986;155: 1011.
67. Royal College of Obstetricians and Gynaecologists. Pre-eclampsia-study group consensus statement. 2003. http://www.rcog.org.uk/womens-health/clinical-guidance/pre-eclampsia-study-group-consensus-statement. Accessed 25 Sep 2011.
68. Brown M, Haugue WM, Higgins J, Lowe S, McCowan L, Oats J, Peek MJ, Rowan JA, Walthers BNJ. The detection, investigation, and management of hypertension in pregnancy: executive summary. Aust N Z J Obstet Gynacol. 2000;40:133–8.
69. Diehl CL, Brost BC, Hogan MC, Elesber AA, Offord KP, Turner ST, Garovic VD. Preeclampsia as a risk factor for cardiovascular disease later in life: validation of a preeclampsia questionnaire. Am J Obstet Gynecol. 2008;198:e11–3.
70. Coolman M, de Groot CJM, Jaddoe VW, Hofman A, Raat H, Steegers EAP. Medical record validation of maternally reported history of preeclampsia. J Clin Epidemiol. 2010;63:932–7.
71. Malik AS, Giamouzis G, Georgiopoulou VV, Fike LV, Kalogeropoulos AP, Norton CR, Sorescu D, Azim S, Laskar SR, Smith AL, Dunbar SB, Butler J. Patient perception versus medical record entry of health-related conditions among patients with heart failure. Am J Cardiol. 2010;107:569–72.
72. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol. 2004;57:1096–103.
73. Geller SE, Ahmed S, Brown ML, Cox SM, Rosenberg D, Kilpatrick SJ. International classification of diseases-9th revision coding for preeclampsia: how accurate is it? Am J Obstet Gynecol. 2004;190:1629–33.
74. Roberts CL, Bell JC, Ford JB, Hadfield RM, Algert CS, Morris JM. The accuracy of reporting of the hypertensive disorders of pregnancy in population health data. Hypertens Pregnancy. 2008; 27:285–97.
75. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376:631–44.
76. Von Dadelszen P, Magee L, Roberts JM. Sub-classification of preeclampsia. Hypertens Pregnancy. 2003;22:143–8.
77. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet. 2009;374:979–88.
78. Srinivas SK, Sammel MD, Bastek J, Ofori E, Andrela CM, Wolfe ML, Reilly M, Elovitz MA. Evaluating the association between all components of the metabolic syndrome and pre-eclampsia. J Matern Fetal Neonatal Med. 2009;22:501–9.
79. Callaway LK, Lawlor DA, O'Callaghan M, Williams GM, Najman JM, McIntyre HD. Diabetes mellitus in the 21 years after a pregnancy that was complicated by hypertension: findings from a prospective cohort study. Am J Obstet Gynecol. 2007;197: 492.e1–7.
80. Carr DB, Newton KM, Utzschneider KM, Tong J, Gerchman F, Kahn SE, Easterling TR, Heckbert SR. Preeclampsia and risk of developing subsequent diabetes. Hypertens Pregnancy. 2009;28: 435–47.
81. Libby G, Murphy DJ, McEwan NF, Greene SA, Forsyth JS, Chien PW, Morris AD, for the DMC. Pre-eclampsia and the later

development of type 2 diabetes in mothers and their children: an intergenerational study from the Walker cohort. Diabetologia. 2007;50:523–30.
82. British Heart Foundation. Coronary heart disease statistics. 2010. http://www.bhf.org.uk/research/statistics.aspx. Accessed 8 Jan 2012.
83. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H, White RR, Roddy M, Hladunewich M. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol. 2009;200:58.e1–8.
84. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PWF, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113:791–8.
85. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, Investigators IS. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet. 2004;364:937–52.
86. MacDonald SE, Walker M, Ramshaw H, Godwin M, Chen X-K, Smith G. Hypertensive disorders of pregnancy and long-term risk of hypertension: what do Ontario prenatal care providers know, and what do they communicate? JOGC. 2007;29:705–10.
87. Nijdam ME, Timmerman MR, Franx A, Bruinse HW, Numans ME, Grobbee DE, Bots ML. Cardiovascular risk factor assessment after pre-eclampsia in primary care. BMC Fam Pract. 2009; 10:77.
88. Young B, Hacker MR, Rana S. Physicians' knowledge of future vascular disease in women with preeclampsia. Hypertens Pregnancy. 2012;31:50–8.
89. Hubel CA, Snaedal S, Ness RB, Weissfeld LA, Geirsson RT, Roberts JM, Arngrímsson R. Dyslipoproteinaemia in postmenopausal women with a history of eclampsia. BJOG. 2000;107:776–84.
90. Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension. 2003;42:39–42.
91. Edlow AG, Srinivas SK, Elovitz MA. Investigating the risk of hypertension shortly after pregnancies complicated by preeclampsia. Am J Obstet Gynecol. 2009;200:e60–2.
92. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol. 2009;114:961–70.