1 **Pre-eclampsia and future cardiovascular health: a systematic review and meta-analysis**

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3 Short title: Wu *et al.* Pre-eclampsia and future cardiovascular health.

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Abstract

Background - Pre-eclampsia is a pregnancy-specific disorder resulting in hypertension and multi-organ dysfunction. There is growing evidence that these effects persist after pregnancy. We aimed to systematically evaluate and quantify the evidence on the relationship between pre-eclampsia and the future risk of cardiovascular diseases.

Methods and Results - We studied the future risk of heart failure, coronary heart disease, composite cardiovascular disease, death due to coronary heart or cardiovascular disease, stroke and stroke death following pre-eclampsia. A systematic search of MEDLINE and EMBASE was performed to identify relevant studies. We used random effects meta-analysis to determine the risk. Twenty-two studies were identified with >6.4 million women including >258,000 women with pre-eclampsia. Meta-analysis of studies that adjusted for potential confounders demonstrated that pre-eclampsia was independently associated with an increased risk of future heart failure (RR 4.19, 95% CI 2.09, 8.38), coronary heart disease (RR 2.50, 95% CI 1.43, 4.37), cardiovascular disease death (RR 2.21, 95% CI 1.83, 2.66) and stroke (RR 1.81, 95% CI 1.29, 2.55). Sensitivity analyses showed that pre-eclampsia continued to be associated with an increased risk of future coronary heart disease, heart failure and stroke after adjusting for age (RR 3.89, 95% CI 1.83, 8.26), body mass index (RR 3.16, 95% CI 1.41, 7.07) and diabetes (4.19, 95% CI 2.09, 8.38).

Conclusions - Pre-eclampsia is associated with a four-fold increase in future incident heart failure and a two-fold increased risk in coronary heart disease, stroke and death due to coronary heart or cardiovascular disease. Our study highlights the importance of lifelong monitoring of cardiovascular risk factors in women with a history of pre-eclampsia.

Key words – preeclampsia/pregnancy, cardiovascular disease risk factors, pregnancy and postpartum

Introduction

Pre-eclampsia is a major cause of maternal mortality worldwide [1] and affects 2-8% of all pregnancies.[2, 3] It is confined to pregnancy and defined as onset of hypertension after 20 weeks of gestation with either proteinuria, organ dysfunction or uteroplacental dysfunction.[4] The pathogenesis of pre-eclampsia remains poorly understood and is thought to be due to the failure of spiral artery remodelling in the placenta causing placental hypo-perfusion and hypoxia. The resultant oxidative stress triggers an excessive systemic inflammatory response, which causes endothelial dysfunction and vasoconstriction leading to systemic hypertension and end organ hypo-perfusion.[2, 5] There is growing evidence that these effects on end organs persist after pregnancy.

Cardiovascular disease is a leading cause of mortality globally and also of maternal death in the UK and US.[6, 7] Several studies have examined the relationship between pre-eclampsia and future incident cardiovascular disease, though the literature has been inconsistent. Some studies reporting significantly higher risks of composite cardiovascular events or heart failure,[8, 9] while others have not demonstrated such relationships.[10, 11]

It is unclear whether pre-eclampsia is an independent risk factor for future cardiovascular disease or an early marker of women with high-risk profiles for future cardiovascular disease. Factors that predispose women to pre-eclampsia are also found in the risk profile for cardiovascular diseases. These include obesity,[12] metabolic abnormalities, dyslipdaemia, insulin resistance,[13] heightened inflammatory responses, hypercoagulable states and endothelial dysfunction.[14] Alternatively, the body may not fully recover from the damage to the vascular, endothelial and metabolic systems associated with pre-eclampsia and may manifest in later life with future cardiovascular events.[2] Lipid deposition in the spiral artery walls is more commonly seen in pre-eclamptic than healthy pregnancies, which mimic the early stages of atherosclerosis.[15]

1   Although the national guidance in the US [16, 17] and the UK [18] recommend that,

2   following a diagnosis of pre-eclampsia, women should be counselled and followed-up for

3   cardiovascular risk modification, no conclusive evidence exists for an effective risk reduction

4   strategy and such follow-up is probably not done in practice. In addition, more recent studies

5   have shown non-significant and conflicting data for the level of cardiovascular risk following

6   pre-eclampsia.[19, 20] There is a need to re-evaluate and quantify the risk of cardiovascular

7   events following pre-eclampsia to guide future management and risk modification, in order to

8   contribute to guidelines for clinicians. To this end, we conducted a systematic review and

9   meta-analysis of contemporary studies (published 2005-2015) to quantify the future risk of

10   cardiovascular events in women following pre-eclampsia.

11

12   **Methods**

13   *Eligibility criteria*

14   We selected studies investigating the long-term cardiovascular outcomes of women

15   with and without pre-eclampsia published in the English language between 2005 and August

16   2015. There was no restriction on the definition of pre-eclampsia. Primary cardiovascular

17   outcomes were heart failure, coronary heart disease, death due to coronary heart disease,

18   composite cardiovascular disease defined as a combination of cardiac, cerebrovascular and

19   peripheral vascular disease, death due to composite cardiovascular disease, stroke and stroke

20   death. The included studies had at least two groups (one with pre-eclampsia and one without

21   pre-eclampsia) and reported sufficient data to allow for accurate risk estimates to be

22   calculated. Studies assessing outcomes during antepartum or before 6 weeks' post-partum

23   were excluded. There was no restriction based on cohort type, study design or duration of

24   follow-up.

25

1   *Data sources and searches*

2   MEDLINE and EMBASE were searched using OVID SP for studies from January

3   2005 to August 2015. The detailed search strategy and search terms are outlined in Appendix

4   1. The relevant primary studies for inclusion on this study were extracted from a

5   comprehensive programme of evidence synthesis which explored the association between

6   pre-eclampsia and adverse cardiovascular or metabolic outcomes. A search for additional

7   articles was also conducted through manual searching of the bibliography of relevant review

8   articles and meta-analyses.

9

10   *Study selection and data extraction*

11   Four reviewers (PW, RH, RAK and AB) screened all titles that met the inclusion

12   criteria. This was followed by a screen of the remaining abstracts. The full articles were

13   screened by the same four reviewers and the final decision to include studies was made by

14   PW, RH and CSK. Independent double data extraction was done by four reviewers (PW, RH,

15   RAK and AB). Data was collected on study design, year, country, number of participants,

16   mean age, parity, cohort characteristics, definition and ascertainment of pre-eclampsia,

17   ascertainment of outcomes, timing of assessment, adequacy of follow-up and results. The

18   information was obtained from published data.

19

20   *Study quality assessment*

21   Study quality was assessed against the Newcastle-Ottawa Quality Assessment Scale

22   (PQAS) for cohort studies.[21] Our gold standard for each of the criteria were: selection of

23   exposed cohort from the general population of pregnant women; selection of non-exposed

24   cohort from the same population; reliable ascertainment of exposure such that the likelihood

25   of controls being misclassified as having pre-eclampsia when they did not or cases being

wrongly classified as not having pre-eclampsia was minimized; exclusion of women who had

cardiovascular outcome of interest prior to or during pregnancy; comparable cohort where

confounders, in particular age, smoking and other cardiovascular risk factors, were accounted

for; assessment of outcomes prospectively or through linkage of records and/or independent

blind assessment; follow-up duration for at least 1 year post-partum; and less than 10% of the

study participants in each cohort being lost to follow-up.

Data synthesis and analysis

We used RevMan Version 5.3.5 (Nordic Cochrane Centre) to conduct random effects

meta-analysis using the inverse variance method for pooling log risk ratios (RRs). We used

random effects because the studies were conducted in a wide range of settings in different

populations, hence the need to take heterogeneity into account for the pooled effect estimate.

Where possible, we chose to pool adjusted risk estimates from primary studies and when

these data were not available, raw data were used to calculate unadjusted risk estimates.

Analysis was performed considering adjusted and unadjusted group separately. Statistical

heterogeneity was assessed using the I^2 statistic where I^2 values of 30-60% represented

moderate level of heterogeneity.[22] Where there was greater than a moderate degree of

heterogeneity, we performed leave-one-out analysis to identify studies which contributed to

high degree of heterogeneity. In the case for an analysis where there is more than 10 studies

and little evidence of heterogeneity, we performed funnel plots to assess for publication bias.

Results

Description of studies included in analysis

The initial MEDLINE and EMBASE search produced 9,964 titles and abstracts,

following which 22 studies were included in the analysis (Figure 1). The studies examined

1   6,456,379 women in total (ranges from 137 to 2,066,230 women in each study). Studies

2   recruiting patients from the same population were paired to avoid duplication of participant

3   numbers.[8, 23-25]

4   Details of study design and demographics are shown in Supplemental Table 1. From

5   the 17 studies that reported the number of women in each group, there were 258,275 women

6   with pre-eclampsia and 4,006,431 controls. 4 studies recruited primiparous women only,[8, 19,

7   24, 26] while 17 studies included women of any parity.[9-11, 23, 25, 27-38] Studies reporting a mean or

8   median age at enrolment ranged from 23.4 to 32.3 years while follow-up ranged from 6

9   weeks' post-partum to 39.4 years.

10

11 *Quality assessment of included studies*

12   The study quality was evaluated using the Newcastle-Ottawa Quality Assessment

13 Scale (NOQAS) for cohort studies [21] as shown in Supplemental Tables 2 and 3. 19 studies

14 had reliable methods of ascertaining pre-eclampsia from databases,[8, 9, 19, 23-26, 30, 32, 35, 36]

15 medical records,[10, 11, 20, 28, 34] prospective measurements,[29, 33] or through completion of

16 questionnaire with trained staff.[30, 31] 19 studies used reliable methods of obtaining

17 cardiovascular outcomes either from databases,[8-10, 19, 23-26, 28, 32, 34-36] medical records,[11]

18 prospective measurements with echocardiography,[33, 38] or through completion of

19 questionnaire with trained staff.[29-31] There was adequate follow-up (>90%) in 17 studies.[8, 9, 11,

20 23-28, 30-36, 38] 18 studies used adjusted analyses.[8, 9, 19, 20, 23-26, 28-33, 35-38]

21

22 *Determining pre-eclampsia and results of studies*

23   Various methods were used to ascertain pre-eclampsia, with the most common being

24 the International Society of the Studies of Hypertension in Pregnancy (ISSHP) (2014)

25 definition.[4] Supplemental Table 4 shows the results of the studies.

1

2   *Pooled analysis of pre-eclampsia and cardiovascular outcomes*

3   The risk of heart failure with pre-eclampsia is shown in Figure 2. The pooled results

4   of 7 studies [8, 10, 23, 31, 33, 35, 38] suggest a 3.6-fold increased risk of heart failure with pre-

5   eclampsia (risk ratio (RR) 3.62, 95% CI 2.25, 5.85, I^2=83%, 2,764,824 participants). The risk

6   increases to over four-fold for the adjusted studies [10, 23, 35, 38] (adjusted risk ratio (aRR) 4.19,

7   95% CI 2.09, 8.38; I^2=71%, 1,986,285 participants). The factors that have been adjusted for

8   in the studies are shown in Supplemental Table 3. We performed leave out analyses to

9   explore the sources of heterogeneity (Supplemental Table 6). The heterogeneity was mainly

10   driven by the Mannisto 2013 study,[10] if this study was excluded, heterogeneity was reduced

11   to 46% in the adjusted analysis (aRR 5.57, 95% CI 3.14, 9.88).

12   The relationship between pre-eclampsia and future risk of coronary heart disease and

13   coronary heart disease death is shown in Figure 3 and 4. For coronary heart disease there was

14   a two-fold increase risk of events with pre-eclampsia (RR 2.11, 95% CI 1.60, 2.77, I^2=87%,

15   3,239,797 participants). The risk was even greater in the adjusted studies [10, 19, 23, 25, 31, 35, 37]

16   (aRR 2.50, 95% CI 1.43, 4.37, I^2=89%, 2,068,673 participants). The heterogeneity was

17   mainly driven by the Lin 2011 study,[23] if this study was excluded, heterogeneity was reduced

18   to 66% in the adjusted analysis (aRR 1.67, 95% CI 1.19, 2.33. Supplemental Table 6). The 4

19   adjusted studies [10, 19, 34, 36] reporting coronary heart disease death also show a two-fold

20   increased risk with pre-eclampsia (aRR 2.10, 95% CI 1.25, 3.51, I^2=64%, 677,378

21   participants). The heterogeneity was mainly driven by the Bhattacharya 2012 study,[19] if this

22   study was excluded, heterogeneity was reduced to 2% in the adjusted analysis (aRR 2.63,

23   95% CI 1.74, 3.98. Supplemental Table 6).

24   The risk of composite cardiovascular disease and cardiovascular disease death with

25   pre-eclampsia is shown in Supplemental Figure 1 and Figure 5. The pooled results from 6

studies [10, 11, 20, 23, 27, 32] with 1,398,119 participants suggest a significantly increased risk of cardiovascular disease (RR 1.65, 95% CI 1.36, 2.01, I^2=42%). However, the results were not statistically significant for the 3 studies [10, 20, 23] that adjusted for baseline confounders prior to pregnancy (aRR 1.85, 95% CI 0.80, 4.29, I^2=72%). For cardiovascular disease death, the pooled results of 4 studies [23-25, 28, 36] with 2,614,180 participants suggest a two-fold increase in cardiovascular disease death with pre-eclampsia (aRR 2.21, 95% CI 1.83, 2.66, I^2=54%). All 4 studies adjusted for potential confounders.

Figure 6 and Supplemental Figure 2 show the results for pooled analysis for studies on pre-eclampsia and stroke and stroke death. For stroke, there was a two-fold increased risk of events with pre-eclampsia (RR 1.71, 95% CI 1.38, 2.11, I^2=69%, 4,906,182 participants). This increase in risk persisted in studies which adjusted for confounders (aRR 1.81, 95% CI 1.29, 2.55, I^2=74%, 4,131,344 participants).[9, 10, 19, 25, 35, 37] The heterogeneity was mainly driven by the Bhattacharya 2012 study,[19] if this study was excluded, heterogeneity was reduced to 24% in the adjusted analysis (aRR 2.04, 95% CI 1.60, 2.60. Supplemental Table 6). 2 studies reported stroke death showed a two-fold increased risk with pre-eclampsia, however the result was not statistically significant (aRR 1.97, 95% CI 0.80, 4.88, I^2=86%).

Sensitivity analysis for follow-up time

We conducted sensitivity analyses to consider the effect of follow-up time for cardiovascular outcomes that were significant in the adjusted studies (Table 1). The risk of heart failure was the highest 1-10 years (aRR 8.42, 95% CI 4.39, 16.17) after the pre-eclamptic pregnancy compared with <1 year (aRR 4.10, 95% CI 2.90, 5.80) or >10 years (aRR 1.60, 95% CI 0.73, 3.50) post-partum. For coronary heart disease (aRR 3.10, 95% CI 1.56, 6.16) and stroke (aRR 2.22, 95% CI 1.73, 2.85), the increase in risk was significant within the first year following delivery compared to other time points. In cardiovascular

1   disease death, the increase in risk were similar at 1-10 years (aRR 2.30, 95% CI 1.65, 3.20)

2   and >10 years (aRR 2.21, 95% CI 1.73, 2.81) post-delivery. All studies on coronary heart

3   disease death had a follow-up of >10 years, therefore we could not conduct further sensitivity

4   analysis on duration of follow-up.

5

6   *Sensitivity analysis considering studies that adjusted for or had exclusions based on baseline*

7   *age, body mass index (BMI) or weight, diabetes or gestational diabetes (GDM), smoking and*

8   *hypertension between pre-eclampsia and control groups*

9   Sensitivity analyses were performed to consider age as a confounding factors in the 5

10   cardiovascular outcomes that were significant in adjusted studies (Table 2). These showed

11   that the risk remained significant in all outcomes: heart failure (aRR 3.89, 95% CI 1.83, 8.26),

12   coronary heart disease (aRR 3.13, 95% CI 1.45, 6.75), coronary heart disease death (aRR

13   2.63, 95% CI 1.74, 3.98), cardiovascular disease death (aRR 2.21, 95% CI 1.83, 2.66), and

14   stroke (aRR 2.04, 95% CI 1.60, 2.60).

15   The effect of pregestational BMI or weight and pregestational diabetes or GDM was

16   examined for the heart failure, coronary heart disease and stroke outcomes. The risk for all 3

17   outcomes remained significantly increased despite adjustment for BMI or weight (heart

18   failure: aRR 2.74, 95% CI 1.10, 6.83; coronary heart disease: aRR 1.84, 95% CI 1.23, 2.74;

19   stroke: aRR 1.94, 95% CI 1.42, 2.65) and diabetes or GDM (heart failure: aRR 3.89, 95% CI

20   1.83, 8.26; coronary heart disease: aRR 2.16, 95% CI 1.03, 4.52; stroke: aRR 2.46, 95% CI

21   1.11, 5.43).

22   We considered the effect of pregestational smoking for coronary heart disease and

23   stroke outcomes and found that the increased risk remained significant (coronary heart

24   disease: aRR 1.56, 95% CI 1.11, 2.20; stroke: aRR 1.64, 95% CI 1.12, 2.40). However, when

25   we examined the effect of pregestational hypertension for the coronary heart disease outcome,

1 the increase in risk was non-significant. We could not examine other important confounding

2 factors, such as family history of cardiovascular disease or hypercholesterolaemia, due to the

3 lack of studies presenting this data.

4 The full cardiovascular risk factor profile of the pre-eclampsia and the control

5 population is shown in Supplemental Table 5. There were significant differences in age, BMI,

6 diabetes, smoking and blood pressure between the pre-eclampsia and control groups at

7 baseline in 1,[32] 3,[10, 19, 32] 1,[32] 2,[10, 19] and 1 studies,[11] respectively, which only contributed to

8 2% of total participant women. However, the cardiovascular risk factor profiles were not

9 available in the majority of the studies included in this systematic review and meta-analysis.

10 Only 3 studies had adjusted their results to account for the risk factor profile differences in

11 age,[32] BMI,[10] diabetes,[32] and smoking.[10, 19]

12

13 **Discussion**

14 In this systematic review and meta-analysis, 22 studies with over 6.4 million women

15 were included. We showed an association of pre-eclampsia with future incident coronary

16 heart disease, composite cardiovascular disease, heart failure, stroke and deaths due to

17 coronary heart disease. The adjusted risk ranged between 1.8-2.5 fold compared to those

18 without a history of pre-eclampsia in all cardiac outcomes, except in heart failure where a

19 four-fold increase in risk was found. For coronary heart disease, heart failure and stroke, the

20 increase in risk remained significant after adjusting for age, BMI and diabetes. Pre-eclampsia

21 is a well-recognised risk factor for future hypertension. Our study confirms pre-eclampsia to

22 be a risk factor for future cardiac disease although we are unable to determine whether this

23 relationship is confounded by an adverse cardiovascular risk factor profile in patients with

24 pre-eclampsia at baseline or whether pre-eclampsia is an independent risk factor.

1   Our meta-analysis supports previous literature in terms of a two-fold increased risk of

2   cardiovascular disease death [39, 40] and stroke,[41] but unique to this study, we conducted

3   sensitivity analyses to consider the effects of potential confounding factors such as age, BMI,

4   diabetes, hypertension and smoking, as well as examining the cardiovascular risk factors

5   profiles at baseline. Compared with previous meta-analyses, we considered heart failure as a

6   separate entity and showed a much higher risk than previously reported in composite cardiac

7   outcomes.

8   Due to the gaps in the current literature, it is difficult to ascertain whether

9   confounding factors have contributed towards the associations we identified. After

10   considering the effects of hypertension in the future coronary heart disease outcome, we

11   found that the link between pre-eclampsia and future coronary heart disease was no longer

12   statistically significant. This suggests that the association may be confounded by

13   hypertension. We were unable to fully evaluate the effects of all confounding factors and

14   undertake further sensitivity analysis due to the absence of such data in the included studies.

15   The increased risk in future cardiovascular diseases may be driven by unmeasured

16   confounders as none of the included studies have adjusted for all of the established

17   cardiovascular risk factors such as age, BMI, diabetes, family history of cardiovascular

18   disease, hypercholesterolaemia, hypertension and smoking. For instance, only 2 of the 4

19   studies that examined heart failure had adjusted for pre-existing cardiovascular disease prior

20   to delivery.[23, 35] Pre-eclampsia and cardiovascular diseases are known to share risk factors.

21   According to the American College of Obstetricians and Gynaecologists, the recognised risk

22   factors for pre-eclampsia are: obesity, chronic hypertension, diabetes, chronic renal disease,

23   previous pre-eclampsia, systemic lupus erythematosus, age over 40 years, primiparity,

24   multiple pregnancy, *in vitro* fertilization and family history of pre-eclampsia.[42] Apart from

25   the pregnancy specific factors and age, all other risk factors overlap with those recognized by

American Heart Association [17] and American Stroke Association.[16] These factors may be in the same causal pathways for cardiovascular diseases and it is difficult to establish whether pre-eclampsia is a predictor of cardiovascular events through distinct pathways or through inherent adverse cardiovascular profiles, such as obesity and hypertension, in women who develop pre-eclampsia.

There is also a potential of confounding by pregnancy induced hypertension in 2 of the studies (Kessous 2015 [32] and Hovsepian 2014 [9]) as women with pregnancy induced hypertension could have been included in the pre-eclampsia group. Historically it was thought that pregnancy induced hypertension is a milder form of pre-eclampsia, however it is increasing speculated that pre-eclampsia and pregnancy induced hypertension have separate underlying pathophysiological mechanisms with distinct cardiovascular consequences for the women and their offspring. Therefore, we have conducted additional sensitivity analyses in the stroke and cardiovascular disease outcomes where these 2 studies were excluded and showed that the increased risk persisted (Stroke: aRR 1.75, 95% CI 1.15, 2.65. Cardiovascular disease: RR 1.79, 95% CI 1.40, 2.31).

A mechanistic link to explain the association between pre-eclampsia and future heart failure remains elusive. Pre-eclampsia has been found to be associated with a three-fold risk of future hypertension [40] and a doubling in risk of future diabetes.[43] Therefore, heart failure in this group of women may be due to aetiologies other than ischaemic cardiomyopathy, for example hypertensive heart disease or diabetic cardiomyopathy. It has been suggested that the left ventricular (LV) remodelling and hypertrophy seen during pre-eclamptic pregnancies continues after the pregnancy.[33] On the other hand, women with pre-existing LV dysfunction and placental insufficiency are more likely to develop pre-eclampsia than those with normal LV function, suggesting a correlation rather than causation.[44] Furthermore, in peri-partum cardiomyopathy where a significant proportion of women continue to have LV dysfunction

1 years following delivery, the prevalence of pre-eclampsia is four times more common than in

2 healthy pregnancies.[45]

3   Risk stratification enables early identification of women at high risk of cardiovascular

4 disease and allows optimization of targeted care towards prevention. There are several

5 cardiovascular risk scores in use, though most were developed with an under-representation

6 of women. The Reynolds risk score is gender-specific [46] and has been shown to perform

7 better than the Framingham risk score in predicting cardiovascular events in women.[47]

8 However, currently there are no risk calculators incorporating pregnancy complications. The

9 American Heart Association has included pre-eclampsia and gestational hypertension as a

10 risk factor for coronary artery disease and advocates active follow-up of risk factors.[17] They

11 suggest that pre-eclampsia manifesting in pregnancy is akin to a failed stress test of future

12 vascular or metabolic disease. Using the Framingham prediction score, pre-eclampsia has

13 been found to be independently associated with an increased 10-year cardiovascular risk

14 score both at 3-8 years [48] and 18 years [49] follow-up intervals.

15   The strength of our study is the large sample size from contemporary studies with a

16 total of 45,938,256 patient-years follow-up. As a part of a larger programme of evidence

17 synthesis, we used a comprehensive search strategy to examine the long-term cardiovascular

18 outcomes in pre-eclampsia. The inclusion of more recent studies means that there is a greater

19 likelihood of their findings being relevant and more generalizable to current practice. In our

20 study, we used independent reviewers for performing double data extractions and for data

21 analysis. The majority of the studies were designed to examine future cardiovascular diseases

22 as their main outcome (*n*=21), and contribute to 99% of the women in our meta-analysis.

23   The main limitation of our study is that significant unmeasured confounders may have

24 contributed to our reported association between pre-eclampsia and future cardiovascular risk.

25 Although most of the studies (*n*=20) have attempted to adjust for some potential confounding

factors, none of the studies included here have adequately adjusted for all relevant risk factors. In the few studies (2.6% of total participants) that reported baseline cardiovascular risk factor profiles, a majority of the cohort (2% of total participants) had significant baseline risk factor profile differences between the pre-eclamptic and the non-pre-eclamptic populations at index pregnancy. Other limitations include an inherent limitation from publication bias, where studies with positive findings are more likely to be published than those with negative or neutral results. As the majority were from retrospective studies, we had limited control over the quality of data collected. There could have been incomplete, inaccurate or inconsistent historical data on exposure as well as recall bias, which could have affected whether the case and control groups were ascribed correctly. In particular, four studies used questionnaire data to assess the cardiovascular outcomes.[27, 30, 31, 37] Furthermore, we limited the studies to those in English, and may have missed important research data from non-English publications.

Potential reasons for heterogeneity may be due to differences in the study population, research methodology and inherent differences between studies. As shown in Supplemental Table 1, 3 studies were conducted in ethnically diverse populations to the other studies, as they were conducted on the continent of Asia (Funai 2005,[28] Kessous 2015,[32] Lin 2011 & Tang 2009 [23, 25]), while the remainder were in Europe or North America. Two studies examined primiparous women only (Bhattacharya 2012,[19] Wikstrom 2005 [26]), while the others studied women of any parity. Specific populations were analysed in two studies, which were Gordin 2007 [29] (women with type 1 diabetes) and Stuart 2013 [37] (nurses).

In terms of methodology, Supplemental Table 3 shows that there were differences between methods of data collection and the actual type of data collected. Most of the data were collected through medical records or databases, where codes were employed to identify the outcomes. However, 5 studies utilised questionnaires or interviews (Andersgaard 2012,[27] Gordin 2007,[29] Haukkamaa 2009,[30] Kaaja 2005,[31] Stuart 2013 [37]) and 2 studies performed

1   echocardiography (Ghossein-Doha 2014,[38] Melchiorre 2011 [33]). Although codes are more

2   objective, the research team is relying on historical accounts in the records from the clinician.

3   On the other hand, though questionnaires, interviews or echocardiograms ensure direct

4   patient contact with reliable outcome data collection, these methods are prone to selection

5   bias from the research team.

6   The leave out analyses for the main outcomes (Supplemental Table 6), demonstrates

7   that there are underlying differences in the study cohorts that may also have contributed to

8   the heterogeneity we observed. In the heart failure outcome, the heterogeneity was mainly

9   driven by Mannisto 2013 within the adjusted studies.[10] Compared with the other 3 studies,

10 Mannisto et al. was the only study with a prospective design. For the coronary heart disease

11 outcome, the heterogeneity was mainly from Lin 2011, which is the only research conducted

12 in Asia within this group of studies.[23] For both the coronary heart disease death and stroke

13 outcomes, the heterogeneity was mainly driven by Bhattacharya 2012.[19] In this study, the

14 participants were younger in their index pregnancy with pre-eclampsia (out of the studies that

15 included data on age during index pregnancy) compared with participants in the other studies.

16   In the sensitivity analysis regarding duration of follow-up, the increased risk for heart

17 failure was greater at 1-10 years compared with <1 year post-partum in the adjusted studies,

18 however at >10 years postnatally, the risk was lower than that at 1-10 years and no longer

19 significant. This may be due to a higher absolute risk in the control group during longer

20 follow-up periods (i.e. >10 years). Therefore, the reduction in the relative risk may be a

21 product of the higher baseline risk. Furthermore, the effect is exacerbated by the small

22 sample size and number of events in the control group reported.[10]

23   Further research is required to determine whether women with pre-eclampsia have an

24 adverse cardiovascular risk factor profile at baseline which contributes to their increased risk

25 of cardiovascular diseases in later life. The development of effective strategies towards

reducing these unfavourable risk profiles are required in order to plan the logistics for follow-up of these women at high risk, such as where, when and how they should be followed-up and the type of intervention needed to rescue the progression of adverse events. The perinatal period is an opportune time for health screening, education, intervention and monitoring in at-risk women. In a focus group study, women with previous pre-eclampsia were found to be generally unaware of their increased risk of future cardiovascular diseases, but were motivated to undertake lifestyle modifications to reduce risk.[50] In view of the burden and impact of cardiovascular disease on women in our society, we recommend a detailed cost-benefit analysis to determine the postnatal timing for a screening programme in this high risk population.

Conclusions

Over 258,000 women with pre-eclampsia were examined in this meta-analysis of 22 studies. We found that pre-eclampsia is linked with a four-fold increase in future heart failure. Significant unmeasured confounders may have contributed to the association we identified. In keeping with current recommendations, the findings from our study highlight the importance of patient education about risk and life style modifications to reduce risk, as well as regular monitoring of cardiovascular risk factors in women with a history of pre-eclampsia.

Disclosures

1	None.

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Legends

Table 1. Sensitivity analysis with regards to duration of follow-up.

Table 2. Sensitivity analysis with regards to age, pregestational body mass index or weight, pregestational smoking, pregestational diabetes or gestational diabetes and pregestational hypertension.

Figure 1. Flow diagram of study inclusion.

Figure 2. Risk of heart failure with pre-eclampsia.

Figure 3. Risk of coronary heart disease with pre-eclampsia.

Figure 4. Risk of coronary heart disease death with pre-eclampsia.

Figure 5. Risk of cardiovascular disease death with pre-eclampsia.

Figure 6. Risk of stroke with pre-eclampsia.

Table 1. Sensitivity analysis with regards to duration of follow-up.

Outcomes		<1 year	1-10 years	>10 years
Cardiovascular disease death	Adjusted	-	RR 2.30 (1.65-3.20), n=1	RR 2.21 (1.73-2.81), n=3
Coronary heart disease	Adjusted	RR 3.10 (1.56-6.15), n=1	RR 3.78 (0.43-77.30), n=2	RR 1.46 (0.95-2.25), n=3
	Unadjusted	-	-	RR 2.09 (1.64-2.66), n=3
Coronary heart disease death	Adjusted	-	-	RR 2.10 (1.25-3.51), n=4
Heart failure	Adjusted	RR 4.10 (2.90-5.80), n=1	RR 8.42 (4.39-16.17), n=2	RR 1.60 (0.73-3.50), n=1
	Unadjusted	-	RR 4.27 (2.09-8.71), n=1	RR 2.73 (1.30-5.74), n=2
Stroke	Adjusted	RR 2.22 (1.73-2.85), n=2	RR 3.56 (0.52-24.28), n=2	RR 1.18 (0.95-1.46), n=2
	Unadjusted	-	-	RR 1.60 (1.47-1.74), n=1

Table 2. Sensitivity analysis with regards to age, pregestational body mass index or weight, pregestational smoking, pregestational diabetes or gestational diabetes and pregestational hypertension.

Outcomes	Age	BMI / Weight	Diabetes / GDM	Smoking	Hypertension
Cardiovascular mortality	RR 2.21 (1.83-2.66), n=4	-	-	-	-
Coronary heart disease	RR 3.13 (1.45-6.75), n=5	RR 1.84 (1.23-2.74), n=3	RR 2.16 (1.03-4.52), n=2	RR 1.56 (1.11-2.20), n=4	RR 3.84 (0.81-18.16), n=3
Coronary heart disease death	RR 2.63 (1.74-3.98), n=3	-	-	-	-
Heart failure	RR 3.89 (1.83-8.26), n=3	RR 2.74 (1.10-6.83), n=2	RR 3.89 (1.83-8.26), n=3	-	-
Stroke	RR 2.04 (1.60-2.60),	RR 1.94 (1.42-2.65), n=3	RR 2.46 (1.11-5.43), n=3	RR 1.64 (1.12-2.40), n=4	-

	n=5				

BMI - Body Mass Index; GDM – Gestational Diabetes

Figure 1. Flow diagram of study inclusion.

PRISMA 2009 Flow Diagram

Identification	Records identified through EMBASE and MEDLINE database searching between 2005 to August 2015 (N = 9,964).

Screening	Title and abstract screened for potential inclusion (N = 9,964).	Records excluded which did not meet the inclusion criteria on reviewing the titles and abstracts (N = 9,888).

Eligibility	Full-text articles assessed for eligibility (N = 76).	Full-text articles excluded (N = 58). • Did not evaluate CVD as an outcome (N = 52). • Studied maternal placental syndrome/ hypertensive disorders in pregnancy rather than pre-eclampsia (N = 4). • Never pregnant control group (N = 1). • Case-control study of CVD vs no CVD (N = 1).

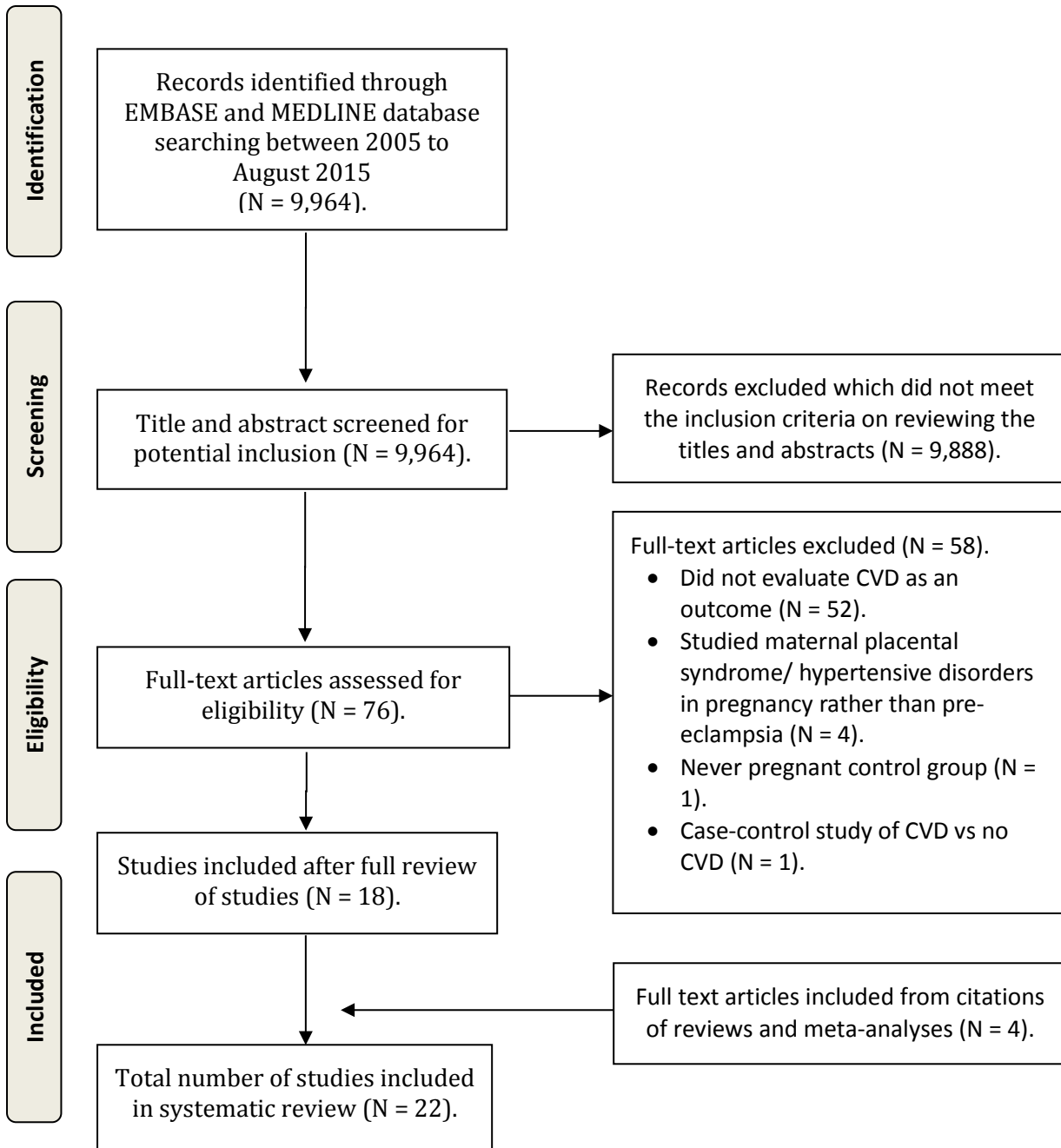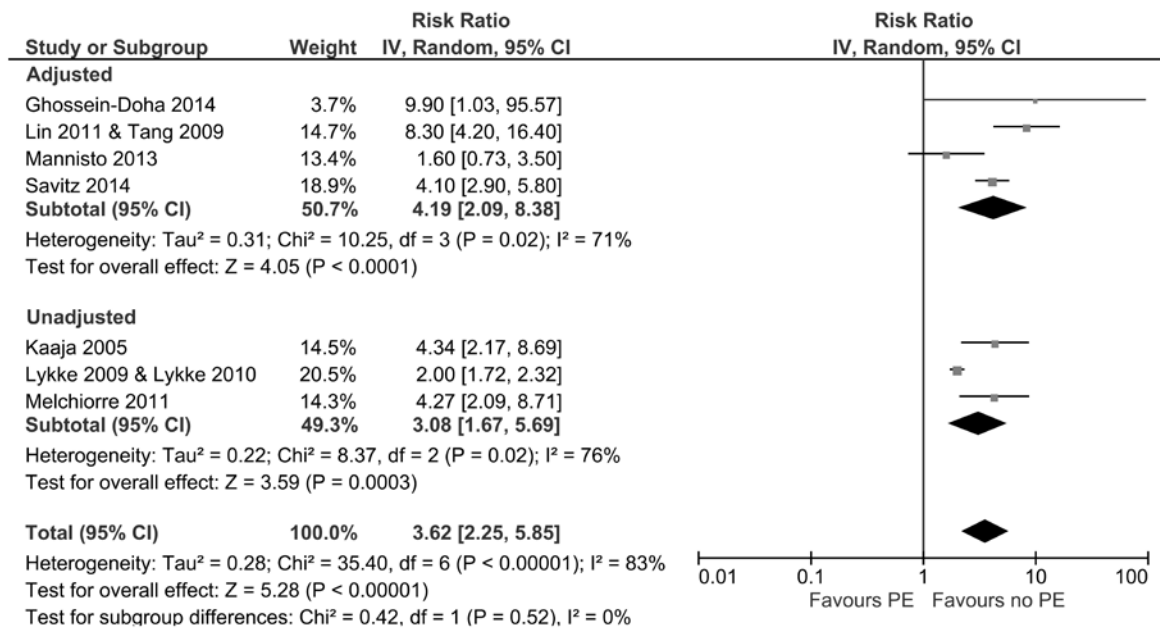|		
Included	Studies included after full review of studies (N = 18).	Full text articles included from citations of reviews and meta-analyses (N = 4).
	Total number of studies included in systematic review (N = 22).	

Figure 2. Risk of heart failure with pre-eclampsia.

Figure 3. Risk of coronary heart disease with pre-eclampsia.

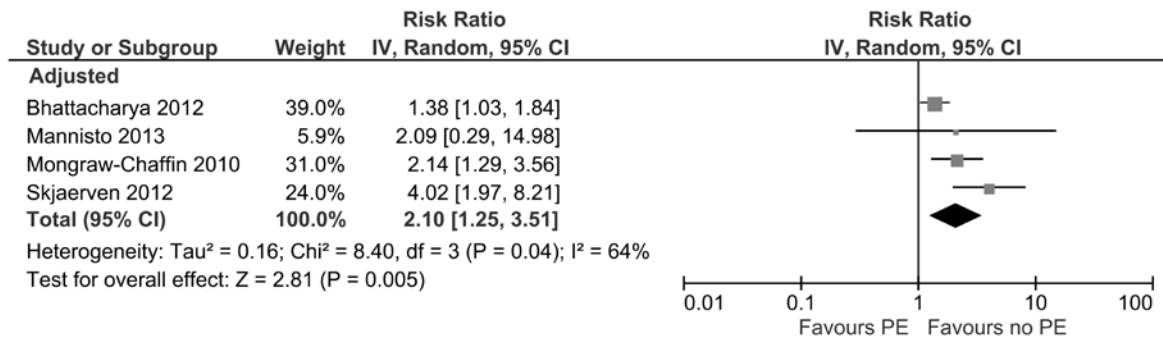**Figure 4.** Risk of coronary heart disease death with pre-eclampsia.

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI
Adjusted		
Bhattacharya 2012	39.0%	1.38 [1.03, 1.84]
Mannisto 2013	5.9%	2.09 [0.29, 14.98]
Mongraw-Chaffin 2010	31.0%	2.14 [1.29, 3.56]
Skjaerven 2012	24.0%	4.02 [1.97, 8.21]
Total (95% CI)	**100.0%**	**2.10 [1.25, 3.51]**

Heterogeneity: Tau² = 0.16; Chi² = 8.40, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 2.81 (P = 0.005)

Figure 5. Risk of cardiovascular disease death with pre-eclampsia.

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI
Adjusted		
Funai 2005	18.4%	3.07 [2.18, 4.33]
Lin 2011 & Tang 2009	19.3%	2.30 [1.65, 3.20]
Lykke 2009 & Lykke 2010	26.8%	2.08 [1.63, 2.65]
Skjaerven 2012	35.6%	1.90 [1.62, 2.23]
Subtotal (95% CI)	**100.0%**	**2.21 [1.83, 2.66]**

Heterogeneity: Tau² = 0.02; Chi² = 6.49, df = 3 (P = 0.09); I² = 54%
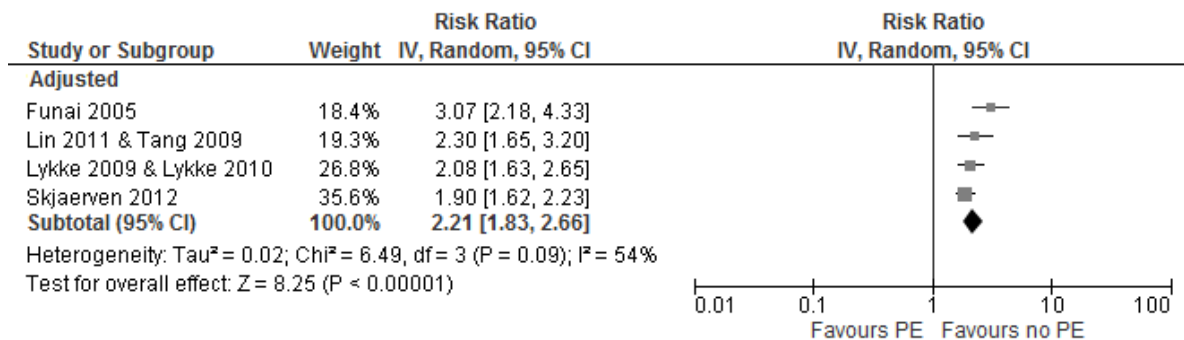Test for overall effect: Z = 8.25 (P < 0.00001)

Figure 6. Risk of stroke with pre-eclampsia.