Cardiovascular events following pregnancies complicated by preeclampsia with emphasis on the comparison between early and late onset forms: a systematic review and meta-analysis

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Contribution

What are the novel findings of this work?

Based on the results of this meta-analysis both early-onset and late-onset PE represent risk factors for cardiovascular mortality and morbidity, however early-onset PE is associated with a higher risk of long-term adverse cardiovascular events compared to late-onset PE.

What are the clinical implications of this work?

Close surveillance of women with a history of PE is recommended, particularly of those who developed an early onset form which may act as an isolated major risk factor of cardiovascular events. In cases with previous late-onset PE lifestyle or medical interventions targeting the modifiable risk factors for adverse cardiovascular health are warranted.

ABSTRACT

Objective

To elucidate whether preeclampsia (PE) and the gestational age at onset of the disease (early-onset vs late-onset PE) has an impact on the risk of long-term cardiovascular complications.

Methods

MedLine and Scopus databases were searched until April 15, 2020 utilizing combinations of the relevant MeSH terms, key words, and word variants for "pre-eclampsia" "cardiovascular disease" and "outcome". Inclusion criteria were: (a) cohort or case-control design; (b) inclusion of women with a diagnosis of pre-eclampsia at the time of the first pregnancy; (c) enough data to compare each outcome in: (I) women with a diagnosis of pre-eclampsia versus women with normal pregnancies and/or (II) women with early-onset pre-eclampsia versus women with late-onset pre-eclampsia. The primary outcome was a composite score of cardiovascular morbidity including either maternal death, major cardiovascular and cerebrovascular events, hypertension need for anti-hypertensive therapy, type 2 diabetes mellitus dyslipidaemia, metabolic syndrome; secondary outcomes were the individual components of the primary outcome analysed separately. Data were combined using a random-effect generic inverse variance approach.

Results

MOOSE guidelines and PRISMA statement were followed. Seventy-three studies were included. Women with a prior history of PE had a higher risk of cardiovascular morbidity during life (OR: 2.05, 95% CI 1.9-2.3), death (OR: 2.18, 95% CI 1.73-1.93), major cardiovascular events (OR: 1.80, 95% CI 1.6-2.0), hypertension (OR: 3.93, 95% CI 3.1-50), need for anti-hypertensive medication (OR: 4.44, 95% CI 2.4-8.2), dyslipidaemia (OR: 1.32, 95% CI 1.3-1.4), diabetes (OR: 2.14, 95% CI 1.5-3.0), abnormal renal function (OR: 3.37, 95% CI 2.3-5.0) and metabolic syndrome (OR: 4.30, 95% CI 2.6-7.1) compared to those with no history of PE. More importantly, the strength of this association persisted when considering women who had PE ≤1, 1 to 10 and >10 years before the occurrence of these outcomes. When stratifying the analysis according to time at onset of PE, women with previous early-onset PE were at higher risk of composite adverse cardiovascular outcome (OR: 1.75, 95% CI 1.0-2.9), cardiovascular events (OR: 5.63, 95% CI 1.5-21.4) hypertension (OR: 1.48, 95% CI 1.3-1.7), dyslipidaemia (OR: 1.51, 95% CI 1.3-1.8), abnormal renal function (OR: 1.51. 95% CI 1.1-2.2) and metabolic syndrome (OR: 1.66, 95% CI 1.1-2.5) compared to women with late PE.

Conclusions

Preeclampsia as well as early-onset and late-onset PE all represent risk factors for adverse cardiovascular events later in life. Early-onset PE is associated with a higher burden of cardiovascular mortality and morbidity compared to late-onset PE.

INTRODUCTION

Preeclampsia (PE) is a leading cause of maternal and neonatal mortality and morbidity, complicating up to 5% of all pregnancies[1-3], and is defined as new onset hypertension after 20 weeks of gestation plus involvement of at least one organ system[4,5].

Despite decades of research the aetiology of PE still remains unknown[4]. The abnormal throphoblastic invasion of myometrial spiral arteries has been historically considered the primum movens for PE, however more recent studies have supported the concept that PE may result as a consequence of suboptimal cardiovascular adaptation to the pregnancy either due to a pre-existing predisposition or to additional risk factors for cardiovascular disease (CVD)[6,7].

Available knowledge has led to the distinction of two subtypes of PE which are conventionally distinguished based on the gestational age at onset: early-onset PE, commonly associated with fetal growth restriction (FGR) and abnormal placentation, and late-onset PE, characterized by appropriate fetal growth and associated with metabolic or inflammatory maternal factors[6,8,9]. These differences have led to the hypothesis that early-onset and late-onset PE actually represent two different clinical entities sharing the common clinical manifestations of hypertension and proteinuria[6,9].

Over the past decades, cohort studies as well as systematic review and meta-analyses have shown a significantly higher risk of cardiac, cerebrovascular and peripheral arterial disease and cardiovascular mortality in women with history of PE compared with women with uncomplicated pregnancies[10-19]. Of note, cohort studies have shown that such risk is higher among women who developed preeclampsia before 37 weeks of gestation[12,20,21]. If we assume that early-onset and late-onset PE represent different ends of the disease spectrum, it is reasonable to hypothesize a different long-term impact on the cardiovascular system, however, to our knowledge there is no systematic review specifically addressing the risk cardiovascular sequelae and risk factors for CVD according to the gestational age at diagnosis of the PE. The aim of this systematic review and meta-analysis is to explore the risk of cardiovascular mortality and morbidity in women with a history of PE based on evidence from recent literature and to elucidate whether the gestational age at onset of the disease (early-onset vs late-onset PE) is associated with a different risk of complications during life.

SOURCES

Bibliographic search, study selection criteria and quality assessment

MedLine, Embase and Scopus databases were initially searched to identify studies evaluating the incidence of: (1) composite adverse cardiovascular events (including cardio- and cerebrovascular diseases, cardiac death, hypertension, dyslipidemia, diabetes, metabolic syndrome, need for antihypertensive therapy); (2) cardiovascular and cerebrovascular diseases; (3) cardiac death; (4) diabetes; (5) hypertension; (6) dyslipidemia; (7) kidney disease (including either acute or chronic kidney disease and end-stage renal disease); (8) metabolic syndrome; (9) current antihypertensive therapy, in women with a prior PE diagnosis as compared to women with normal pregnancies. The bibliographic search was performed by three investigators (MEF, FDA and AD) up to April 15, 2020, and was adjusted for each database while maintaining a common overall architecture. We used various combinations of the following terms related to ten main domains: "pre-eclampsia OR preeclampsia OR EPH OR pregnancy toxemia OR edema-proteinuria-hypertension gestosis" (title/abstract) AND "cardiovascular disease*"(title/abstract) or "ischaemic heart disease OR ischemic heart disease OR coronary artery disease OR coronary heart disease OR myocardial infarction OR acute coronary syndrome"(title/abstract) or "stroke OR cerebrovascular disease OR cerebrovascular accident" (title/abstract) or "hypertension" (title/abstract) or "diabetes" (title/abstract) or "kidney disease OR renal impairment" (title/abstract) or "cholesterol* OR dyslipidemia" (title/abstract) or "metabolic syndrome*" (title/abstract) or "antihypertensive*" (title/abstract). The reference lists of reviews and retrieved articles were also searched for additional pertinent papers, and no language restrictions were used. Only full text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than 3 cases were excluded to avoid publication bias.

The study was registered with the PROSPERO database (Registration number: CRD42018107717).

Inclusion criteria were: (a) cohort or case-control design; (b) inclusion of women with a diagnosis of pre-eclampsia at the time of the first pregnancy (if possible), or ever formulated, and documented through clinical chart, or hospital discharge abstract databases, or nationwide/local registries of pathologies, or specific questionnaires; (c) enough data to compare each outcome in: (I) women with a PE diagnosis versus women with normal pregnancies and/or (II) women with early-onset PE versus women with late-onset PE. PE was defined as new onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) at or after 20 weeks' gestation in combination with the appearance of proteinuria (>0.3 grams/24 hours) after 20 weeks of gestation[22]. Early- and late-onset PE were defined as PE requiring delivery before or after 34 weeks of gestation, respectively.

The assessment of long-term outcomes at different time-points after an index date are typically performed through longitudinal studies, with large samples and follow-up even lasting decades. Thus, re-analyses of the same cohort including updated follow-up information, and multiple publications on the same subjects are common. To avoid duplication of data, we selected and extracted the relevant information using the following criteria in order of priority: (1) availability of data; (2) longer follow-up; (3) larger sample size; (4) higher level of statistical adjustment (i.e. the multivariate model including the highest number of potential confounders).

The primary outcome was to explore the risk of a composite score of cardiovascular morbidity including either any of the following events:

- Maternal death
- Major cardiovascular and cerebrovascular events including infarction, heart failure (any type), cerebral embolic, thrombotic, or hemorrhagic events lasting at least 30 min with or without persistent residual motor, sensory, or cognitive dysfunction and stroke
- Hypertension, as defined by blood pressure (BP) >140/90 mmHg on two consecutive measurements[23]
- Need for anti-hypertensive therapy
- Type 2 diabetes mellitus, as defined either by HbA1c ≥ 6.5 % (≥ 48 mmol/mol) or by random plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) or by fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl) or by OGTT 2-hour glucose in venous plasma ≥ 200 mg/dl (≥ 11.1 mmol/l)[24]
- Dyslipidaemia, defined as the occurrence of any alteration in plasma cholesterol, mainly related to high-density and low-density lipoprotein cholesterol and plasma triglycerides[25]
- Metabolic syndrome, as defined according to the criteria for the clinical diagnosis of metabolic syndrome proposed by the American Heart Association and including three out of five among elevated waist circumference, elevated triglycerides, reduced HDL-C, elevated blood pressure and elevated fasting glucose[26]

Secondary outcomes were the individual components of the primary outcome analysed separately.

Two authors (MEF, FDA) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained, and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author (AD). If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported

but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for observational studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability[27].

Data analysis

Data were combined using a random-effect generic inverse variance approach, which enables the inclusion of diverse estimates of Relative Risk (i.e. OR and HR) into the same meta-analysis. From each paper, we extracted the adjusted estimates of risk of each outcome, or, when these were not available, the unadjusted estimates. If a paper reported the results of different multivariate models, the most stringently controlled estimates (those from the model adjusting for more factors) were extracted. If different models controlled for the same number of covariates, the model containing the most relevant covariates was used for the analysis. When studies only reported separate estimates for early- and late-onset PE, the summary risk of each outcome was computed from the separate estimates available using a fixed-effect meta-analysis of the individual study data.

The units of the meta-analysis were single comparisons of the rate of each outcome in women with a history of PE versus women with normal pregnancies. Stratified analyses were also performed to explore the association between pre-eclampsia and three of the nine outcomes (composite adverse cardiovascular events, cardio-cerebrovascular diseases and death) among: (1) women with early-onset PE only and (2) women with late-onset PE only, both compared to women with normal pregnancies. Additional stratified analyses assessed the risk of the three outcomes separately by time between index pregnancy and outcomes occurrence (≤1 year; 1-10 years; >10 years). Moreover, to further explore the association between the exposure (PE) and cardiovascular morbidity, we compared each of the nine outcomes among women with a history of early-onset PE versus women with a history of late-onset PE.

When possible, sensitivity analyses were performed and all meta-analyses were re-run after the exclusion of studies with unadjusted estimates. Between-study heterogeneity was quantified using the I^2 statistic, and, for the analyses including ≥10 publications, potential publication bias was assessed through funnel plots (displaying ORs from individual studies versus their precision (1/standard error). The meta-analysis was designed following the MOOSE guidelines[28] and reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement[29]. All analyses were performed using RevMan software, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

General characteristics

Overall, 73 studies were included in the systematic review[12,20,21,30-99] (Table 1, Figure 1, Supplementary Table 1).

The results of the quality assessment of the included studies using NOS are presented in Supplementary Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, relatively small sample size and heterogeneity in the definition of the severity of PE.

Preeclampsia vs no preeclampsia

Fifty studies (including 10,966,043 women) explored the risk of composite cardiovascular morbidity in women who compared to those who did not experience PE during pregnancy (Table 2). Overall, women with a prior history of PE had a higher risk of cardiovascular morbidity during life, with an OR of 2.05, 95% CI (1.85-2.27) (Figure 2). When considering studies including adjusted models of cardiovascular disease, the risk of composite cardiovascular morbidity remained higher in women with PE compared to controls, with an OR of 1.99, 95% CI (1.79-2.22) (Figure 3). Furthermore, such relationship held true also when considering early-onset and late-onset PE vs controls (OR 3.79, 95%CI (2.70-5.31) and 1.89 (1.53-2.33), respectively) (Figure 4). Finally, the association between a history of PE and composite cardiovascular morbidity remained significant even when considering different time intervals between pregnancy and the occurrence of the outcome (≤1, 1 to 10 and >10 years) (Figure 5).

Looking at the risk of cardiovascular and cerebrovascular diseases following preeclampsia, which was evaluated in 31 studies (Table 2), preeclampsia in pregnancy was associated with an almost two-fold higher risk compared to uncomplicated controls (OR 1.80, 95%CI (1.62-2.00) and OR 1.79, 95%CI (1.61-2.01) for all studies and those including adjusted estimates only, respectively) (Figures 6 and 7, respectively). Such relationship was confirmed for early-onset PE (OR 1.75, 95%CI (1.20-2.55)) (Figure 8) and also when considering different time intervals between pregnancy and the occurrence of the outcome (≤1, 1 to 10 and >10 years) (Figure 9).

Women with a prior history of PE had a higher risk of death (12 studies, OR 2.18, 95%CI (1.73-1.93)) (Table 2, Figure 10) compared to those whose pregnancy was not complicated by preeclampsia.

More importantly, the strength of this association persisted when considering the time of onset of the preeclampsia (OR 5.12, 95%CI (3.22-8.12) and 1.65, 95%CI (1.46-1.86) for early-onset and late-onset PE, respectively) (Figure 11) as well as the timelag between preeclampsia and the occurrence of the outcome (Figure 12).

Ten (1,728,478 women) and twenty-one studies (2,711,443 women) explored the risk of developing diabetes and hypertension following PE (Table 2). Overall, PE carried an increased risk of both conditions during life with an OR of 2.14 (1.52-3.02) for diabetes (Figure 13) and 3.93 (95% CI 3.08-5.02) for hypertension (Figure 14); of note, women with history of PE had also a higher risk of requiring anti-hypertensive medication (OR 4.44, 95% CI 2.40-8.23) (Figure 15).

When exploring the risk of medical complications, women with history of PE showed a significantly higher risk of developing dyslipidaemia (OR: 1.32, 95% CI 1.27-1.37, kidney disease (OR: 3.37, 95% CI 2.28-5.00) as well as metabolic syndrome (OR: 4.30, 95% CI 2.61-7.08) compared to those with no history of PE (Figures 16-18).

All the results were substantially confirmed when the analyses were repeated excluding old studies which did not provide adjusted estimated (Table 2).

Early-onset vs late-onset preeclampsia

Four studies (including 2,979 women) explored the risk of composite cardiovascular morbidity in women who compared to those who did not experience PE during pregnancy (Table 3, Figures 19-24). Women with previous early-onset PE were at increased risk of composite adverse cardiovascular outcome (OR: 1.75, 95% CI 1.03-2.99), cardiovascular and cerebrovascular diseases (OR: 5.63, 95% CI 1.48-21.4), hypertension (OR: 1.48, 95% CI 1.26-1.72), dyslipidaemia (OR: 1.51, 95% CI 1.25-1.83), kidney disease (OR: 1.51. 95% CI 1.06-2.18) and metabolic syndrome (OR: 1.66, 95% CI 1.08-2.54) compared to women with late PE.

Again, all the results were confirmed following the exclusion of the studies without adjusted estimates.

DISCUSSION

Main findings

This systematic review with meta-analysis has confirmed that the risk of cardiovascular mortality and morbidity in women with history of PE is significantly higher compared with those women with past normotensive pregnancy. Based on our findings, the long-term risk of composite adverse cardiovascular outcome, major cardiovascular events and other complications including CV death, hypertension and metabolic syndrome was at least two-fold higher in women with previous PE compared to those with no history of PE. In women who had early- and late-onset PE the risk of composite adverse cardiovascular outcome and death was almost four- and two-fold higher, respectively, compared to women with no history of PE, however a higher burden on the cardiovascular health was demonstrated for early-onset PE compared to late-onset PE.

Clinical significance of this study in respect of previous studies

A series of studies have consistently shown a higher risk of cardiac, cerebrovascular and peripheral arterial disease and cardiovascular mortality in women with history of PE compared to women with uncomplicated pregnancies[12,58,84,100]. A systematic review and meta-analysis including over 3 million cases and almost 200000 pregnancies complicated by PE demonstrated significantly increased risks of hypertension, major CV events and mortality following PE[10], and similar results were found in two other meta-analyses[11,13]. A recent cohort study which included over 1 million of women confirmed a higher risk of chronic hypertension in women who had a pregnancy complicated by preeclampsia compared to those with no history of PE[42]. Other cohort studies[12,20,21] showed an increased risk of ischemic heart disease, stroke and death from cardiovascular causes among women who had preeclampsia and a preterm delivery. Women experiencing preeclampsia and small-for-gestational age (SGA) offspring had increased risk of developing subsequent hypertension. The risk of developing congestive heart failure, ischemic heart disease and stroke was also increased when adding SGA and preterm delivery to a pregnancy complicated by preeclampsia[20,21]. The severity of preeclampsia also increased the risk of later ischaemic heart disease but not to the same extent as the gestation of onset. To our knowledge this present systematic review and meta-analysis first reports that preeclampsia leading to delivery before 34 weeks of gestation is associated with a higher burden of cardiovascular morbidity and mortality compared to preeclampsia associated with delivery beyond 34 weeks. Such finding supports previous hypothesis suggesting different subtypes of PE whose pathophysiology and long-term impact on cardiovascular health seems different[9]. The potential influence of genetic or epigenetic factors on the occurrence of either subtype of PE is currently under investigation[101,102].

Interpretation

The findings from our work confirm that early-onset PE represents a strong independent risk factor for the development of CVD later in life, being associated with a significantly higher risk of all the evaluated adverse outcomes. A higher risk for adverse cardiovascular events was also demonstrated for women with history of late onset PE although the magnitude of this increase seems greater for those with early onset form.

If we assume that the pathophysiology of the cardiovascular risk following PE is based on a permanent myocardial and vascular impairment – which in most cases may persist as subclinical following delivery – the results of our meta-analysis suggest that the extent of this impairment is more severe in those women developing early-onset disease.

A higher risk of composite adverse outcome and death was also found in women with history of late-onset PE compared to controls, albeit of a less extent compared to early-onset PE. We hypothesize this to be related to the fact that most of the women with late-onset PE present some modifiable risk factors which may be mitigated later in life such as obesity, dyslipidemia or insulin resistance[103-115].

On this ground, we recommend close surveillance of women with a history of preeclampsia and particularly of early-onset disease, while lifestyle or medical interventions on the acknowledged and modifiable risk factors remains warranted for the prevention of long-term cardiovascular complications.

Recent data on preconception cardiovascular function has shown that before pregnancy, women who are subsequently affected by PE and/or FGR have a subclinical impairment of the hemodynamic function compared with those with subsequent normal pregnancy outcome[7]. Therefore, it is still unclear whether PE initiates the damage to the mother's cardiovascular system which then leads to a higher risk of later-life CVD or whether PE and cardiovascular disorders share common risk factors preceding the pregnancy. Moreover, as recently suggested by the use of a competing risk approach, the presence of such risk factors among pregnant women seems to impact on the individual background risk and anticipate or delay the onset of preeclampsia[104,105].

Strengths and limitations

Thorough literature search and multitude of outcomes explored and stratification of the analysis according to early-onset and late-onset PE represent the major strengths of this work.

Differences among the included populations in management of PE, heterogeneity in the definition of early-onset and late-onset PE, time at follow-up and outcome measures as well as heterogeneity in post-natal medical assessment are the main limitations of the present systematic review. Additionally, a good amount of the included studies did not report subgroup analysis according to the onset time of the disease, and some of the explored outcomes were affected by the very small number of included studies and even smaller number of events, thus limiting the robustness of the results.

Another limitation is that the definitions of early-onset vs late-onset PE were most commonly based on the gestational age at delivery. Recent evidence has challenged this concept and suggested that the classification of the subtypes of PE should be based or on its association with fetal growth restriction or normally grown fetus)[116,118].

Additionally, we were unable to discriminate cases with recurrent PE, which may represent an indicator of a higher risk for future development of hypertension and CVD[119].

Conclusion

In summary, both early- and late-onset PE are associated with increased risk of adverse cardiovascular outcome compared to controls with no prior PE, however women with history of early-onset PE are at higher risk of cardiovascular mortality and morbidity compared to those with history of late-onset disease.

Disclosure of interest

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REFERENCES

1. World Health Organization (WHO). Make every mother and child count. World Health Report 2005. Geneva 2005
2. Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. Obstet Gynecol, 2008;112:359-72
3. Sibai BM. Prevention of preeclampsia: a big disappointment. Am J Obstet Gynecol, 1998;179:1275-8
4. Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B. Cardiac maladaptation in term pregnancies with preeclampsia. Pregnancy Hypertens. 2018 Jul;13:198-203
5. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet. 2016 Mar 5;387(10022):999-1011
6. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010 Aug 21;376(9741):631-44.
7. Foo FL, Mahendru AA, Masini G, Fraser A, Cacciatore S, MacIntyre DA, McEniery CM, Wilkinson IB, Bennett PR, Lees CC. Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction. Hypertension. 2018 Aug;72(2):442-450.
8. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H; TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet. 2015 May 30;385(9983):2162-72.
9. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008 Nov;52(5):873-80.
10. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ (Clinical research ed). 2007;335:974.
11. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol 2013;28:1–19.
12. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001;323:1213–7.
13. 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 Nov;156(5):918-30.
14. Ahmed R, Dunford J, Mehran R, Robson S, Kunadian V. Pre-eclampsia and future cardiovascular risk among women: a review. J Am Coll Cardiol. 2014;63(18):1815–1822. doi:10.1016/j.jacc.2014.02.529

15. Bello N, Rendon ISH, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. J Am Coll Cardiol. 2013;62(18):1715–1723. doi:10.1016/j.jacc.2013.08.717
16. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Nerenberg K, Platt RW. Cardiovascular Disease-Related Morbidity and Mortality in Women With a History of Pregnancy Complications [published correction appears in Circulation. 2019 Aug 27;140(9):e544]. Circulation. 2019;139(8):1069–1079. doi:10.1161/CIRCULATIONAHA.118.036748
17. Weissgerber TL, Milic NM, Milin-Lazovic JS, Garovic VD. Impaired Flow-Mediated Dilation Before, During, and After Preeclampsia: A Systematic Review and Meta-Analysis. Hypertension. 2016;67(2):415–423. doi:10.1161/HYPERTENSIONAHA.115.06554
18. Milic NM, Milin-Lazovic J, Weissgerber TL, Trajkovic G, White WM, Garovic VD. Preclinical atherosclerosis at the time of pre-eclamptic pregnancy and up to 10 years postpartum: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017;49(1):110–115. doi:10.1002/uog.17367
19. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, Zaman A, Fryer AA, Kadam U, Chew-Graham CA, Mamas MA. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2):e003497. doi:10.1161/CIRCOUTCOMES.116.003497
20. Riise HK, Sulo G, Tell GS, Igland J, Nygård O, Vollset SE, Iversen AC, Austgulen R, Daltveit AK. Incident Coronary Heart Disease After Preeclampsia: Role of Reduced Fetal Growth, Preterm Delivery, and Parity. J Am Heart Assoc. 2017 Mar 6;6(3).
21. 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 Jun;53(6):944-51.
22. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018 Jul;72(1):24-43.
23. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. Circulation. 2018 Jan 9;137(2):109-118.
24. Kerner W, Brückel J; German Diabetes Association. Definition, classification and diagnosis of diabetes mellitus. Exp Clin Endocrinol Diabetes. 2014 Jul;122(7):384-6.
25. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah

J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019 Jun 25;73(24):e285-e350.

26. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005 Oct 25;112(17):2735-52.
27. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [accessed 10 February 2018].
28. 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. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.
29. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. Published 2015 Jan 1. doi:10.1186/2046-4053-4-1 http://www.prisma-statement.org/ [accessed 20 December 2017].
30. 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(5):492 e491-497.
31. Callaway LK, David McIntyre H, Williams GM, Najman JM, Lawlor DA, Mamun A. Diagnosis and treatment of hypertension 21 years after a hypertensive disorder of pregnancy. Aust N Z J Obstet Gynaecol. 2011;51(5):437-440.
32. Thornton C, Dahlen H, Korda A, Hennessy A. The incidence of preeclampsia and eclampsia and associated maternal mortality in Australia from population-linked datasets: 2000-2008. Am J Obstet Gynecol. 2013;208(6):476 e471-475.
33. Tooher J, Thornton C, Makris A, Ogle R, Korda A, Hennessy A. All Hypertensive Disorders of Pregnancy Increase the Risk of Future Cardiovascular Disease. Hypertension. 2017;70(4):798-803.
34. Forest JC, Girouard J, Masse J, Moutquin JM, Kharfi A, Ness RB, Roberts JM, Giguere Y. Early occurrence of metabolic syndrome after hypertension in pregnancy. Obstet Gynecol. 2005;105(6):1373-1380.

35. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet. 2005;366(9499):1797-1803.
36. Smith GN, Pudwell J, Walker M, Wen SW. Risk estimation of metabolic syndrome at one and three years after a pregnancy complicated by preeclampsia. J Obstet Gynaecol Can. 2012;34(9):836-841.
37. Mehrabadi A, Liu S, Bartholomew S, Hutcheon JA, Magee LA, Kramer MS, Liston RM, Joseph KS, Canadian Perinatal Surveillance System Public Health Agency of Canada Hypertensive disorders of pregnancy and the recent increase in obstetric acute renal failure in Canada: population based retrospective cohort study. BMJ. 2014;349:g4731.
38. Grandi SM, Vallee-Pouliot K, Reynier P, Eberg M, Platt RW, Arel R, Basso O, Filion KB. Hypertensive Disorders in Pregnancy and the Risk of Subsequent Cardiovascular Disease. Paediatr Perinat Epidemiol. 2017;31(5):412-421.
39. Dai L, Chen Y, Sun W, Liu S. Association Between Hypertensive Disorders During Pregnancy and the Subsequent Risk of End-Stage Renal Disease: A Population-Based Follow-Up Study. J Obstet Gynaecol Can. 2018;40(9):1129-1138.
40. Langlois AWR, Park AL, Lentz EJM, Ray JG. Preeclampsia Brings the Risk of Premature Cardiovascular Disease in Women Closer to That of Men. Can J Cardiol. 2020;36(1):60-68.
41. 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(4):323-330.
42 Behrens I, Basit S, Melbye M, Lykke JA, Wohlfahrt J, Bundgaard H, Thilaganathan B, Boyd HA. Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. BMJ. 2017;358:j3078.
43. Kristensen JH, Basit S, Wohlfahrt J, Damholt MB, Boyd HA. Pre-eclampsia and risk of later kidney disease: nationwide cohort study. BMJ. 2019;365:l1516.
44. 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(6):805-808.
45 Mannisto T, Mendola P, Vaarasmaki M, Järvelin MR, Hartikainen AL, Pouta A, Suvanto E. Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation. 2013;127(6):681-690.
46 Hubel CA, Snaedal S, Ness RB, Weissfeld LA, Geirsson RT, Roberts JM, Arngrimsson R. Dyslipoproteinaemia in postmenopausal women with a history of eclampsia. BJOG. 2000;107(6):776-784.
47. Funai EF, Friedlander Y, Paltiel O, Tiram E, Xue X, Deutsch L, Harlap S. Long-term mortality after preeclampsia. Epidemiology. 2005;16(2):206-215.
48. Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Sheiner E. Long-term maternal atherosclerotic morbidity in women with pre-eclampsia. Heart. 2015;101(6):442-446.

49. 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(6):1345-1351.
50. Gaugler-Senden IP, Berends AL, de Groot CJ, Steegers EA. Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health. Eur J Obstet Gynecol Reprod Biol. 2008;140(2):171-177.
51. 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.
52. Stekkinger E, Zandstra M, Peeters LL, Spaanderman ME. Early-onset preeclampsia and the prevalence of postpartum metabolic syndrome. Obstet Gynecol. 2009;114(5):1076-1084.
53. Aukes AM, De Groot JC, Wiegman MJ, Aarnoudse JG, Sanwikarja GS, Zeeman GG. Long-term cerebral imaging after pre-eclampsia. BJOG. 2012;119(9):1117-1122.
54. Hermes W, Franx A, van Pampus MG, Bloemenkamp KWM, Bots ML, van der Post JA, Porath M, Ponjee GAE, Tamsma JT, Mol BWJ, de Groot CJM. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. Am J Obstet Gynecol. 2013;208(6):474 e471-478.
55. Scholten RR, Hopman MT, Sweep FC, Van de Vlugt MJ, Van Dijk AP, Oyen VJ, Lotgering FK, Spaanderman MEA. Co-occurrence of cardiovascular and prothrombotic risk factors in women with a history of preeclampsia. Obstet Gynecol. 2013;121(1):97-105.
56. Veerbeek JH, Hermes W, Breimer AY, van Rijn BB, Koenen SV, Mol BW, Franx A, de Groot CJM, Koster MPH. Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension. Hypertension. 2015;65(3):600-606.
57. van Rijn BB, Bruinse HW, Veerbeek JH, Uiterweer EDP, Koenen SV, van der Bom JG, Rijkers GT, Roest M, Franx A. Postpartum Circulating Markers of Inflammation and the Systemic Acute-Phase Response After Early-Onset Preeclampsia. Hypertension. 2016;67(2):404-414.
58. Bokslag A, Teunissen PW, Franssen C, van Kesteren F, Kamp O, Ganzevoort W, Paulus WJ, de Groot CJM. Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life. Am J Obstet Gynecol. 2017;216(5):523 e521-523 e527.
59. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. N Engl J Med. 2008;359(8):800-809.
60. Kvehaugen AS, Dechend R, Ramstad HB, Troisi R, Fugelseth D, Staff AC. Endothelial function and circulating biomarkers are disturbed in women and children after preeclampsia. Hypertension. 2011;58(1):63-69.
61. Andersgaard AB, Acharya G, Mathiesen EB, Johnsen SH, Straume B, Oian P. Recurrence and long-term maternal health risks of hypertensive disorders of pregnancy: a population-based study. Am J Obstet Gynecol. 2012;206(2):143 e141-148.

62. Skjaerven R, Wilcox AJ, Klungsoyr K, Irgens LM, Vikse BE, Vatten LJ, Terje Lie R. Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study. BMJ. 2012;345:e7677.
63. Egeland GM, Skurtveit S, Staff AC, Eide GE, Daltveit AK, Klungsøyr K, Trogstad L, Magnus PM, Brantsæter AL, Haugen M. Pregnancy-Related Risk Factors Are Associated With a Significant Burden of Treated Hypertension Within 10 Years of Delivery: Findings From a Population-Based Norwegian Cohort. J Am Heart Assoc. 2018;7(10).
64. Wikstrom AK, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. BJOG. 2005;112(11):1486-1491.
65. Nelander M, Cnattingius S, Akerud H, Wikstrom J, Pedersen NL, Wikstrom AK. Pregnancy hypertensive disease and risk of dementia and cardiovascular disease in women aged 65 years or older: a cohort study. BMJ Open. 2016;6(1):e009880.
66. Khashan AS, Evans M, Kublickas M, McCarthy FP, Kenny LC, Stenvinkel P, Fitzgerald T, Kublickiene K. Preeclampsia and risk of end stage kidney disease: A Swedish nationwide cohort study. PLoS Med. 2019;16(7):e1002875.
67. 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(4):1162-1168.
68. Lin YS, Tang CH, Yang CY, 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(2):325-330.
69. Wu CC, Chen SH, Ho CH, Liang FW, Chu CC, Wang HY, Lu YH. End-stage renal disease after hypertensive disorders in pregnancy. Am J Obstet Gynecol. 2014;210(2):147 e141-148.
70. Yeh JS, Cheng HM, Hsu PF, Sung SH, Liu WL, Fang HL, Chuang SY. Synergistic effect of gestational hypertension and postpartum incident hypertension on cardiovascular health: a nationwide population study. J Am Heart Assoc. 2014;3(6):e001008.
71. Kuo YL, Chan TF, Wu CY, Ker CR, Tu HP. Preeclampsia-eclampsia and future cardiovascular risk among women in Taiwan. Taiwan J Obstet Gynecol. 2018;57(3):364-369.
72. Hannaford P, Ferry S, Hirsch S. Cardiovascular sequelae of toxaemia of pregnancy. Heart. 1997;77(2):154-158.
73. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. Hypertension. 2011;58(4):709-715.
74. Bhattacharya S, Prescott GJ, Iversen L, Campbell DM, Smith WC, Hannaford PC. Hypertensive disorders of pregnancy and future health and mortality: A record linkage study. Pregnancy Hypertens. 2012;2(1):1-7.

75. Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D, Casas JP, Chappell L. Preeclampsia and Cardiovascular Disease in a Large UK Pregnancy Cohort of Linked Electronic Health Records: A CALIBER Study. Circulation. 2019;140(13):1050-1060.
76. 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(1):35-45.
77. 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(2):94-100.
78. Fraser A, Nelson SM, Macdonald-Wallis C, Cherry C, Butler E, Sattar N, Lawlor DA. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation. 2012;125(11):1367-1380.
79. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet. 2001;357(9273):2002-2006.
80. 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(7394):845.
81. Libby G, Murphy DJ, McEwan NF, Greene SA, Forsyth JS, Chien PW, Morris AD, DARTS/MEMO Collaboration. 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(3):523-530.
82. Ayansina D, Black C, Hall SJ, Marks A, Millar C, Prescott GJ, Wilde K, Bhattacharya S. Long term effects of gestational hypertension and pre-eclampsia on kidney function: Record linkage study. Pregnancy Hypertens. 2016;6(4):344-349.
83. 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(20):2801-2806.
84. 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(5):982-989.
85. 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(4):1055-1059.
86. Edlow AG, Srinivas SK, Elovitz MA. Investigating the risk of hypertension shortly after pregnancies complicated by preeclampsia. Am J Obstet Gynecol. 2009;200(5):e60-62.
87. 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(6):501-509.

88. 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(1):166-171.
89. Hovsepian DA, Sriram N, Kamel H, Fink ME, Navi BB. Acute cerebrovascular disease occurring after hospital discharge for labor and delivery. Stroke. 2014;45(7):1947-1950.
90. Savitz DA, Danilack VA, Elston B, Lipkind HS. Pregnancy-induced hypertension and diabetes and the risk of cardiovascular disease, stroke, and diabetes hospitalization in the year following delivery. Am J Epidemiol. 2014;180(1):41-44.
91. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the Child Health and Development Studies pregnancy cohort. Circulation. 2015;132(13):1234-1242.
92. Black MH, Zhou H, Sacks DA, Dublin S, Lawrence JM, Harrison TN, Reynolds N. Hypertensive disorders first identified in pregnancy increase risk for incident prehypertension and hypertension in the year after delivery. J Hypertens. 2016;34(4):728-735.
93. Cain MA, Salemi JL, Tanner JP, Kirby RS, Salihu HM, Louis JM. Pregnancy as a window to future health: maternal placental syndromes and short-term cardiovascular outcomes. Am J Obstet Gynecol. 2016;215(4):484 e481-484 e414.
94. White WM, Mielke MM, Araoz PA, Lahr BD, Bailey KR, Jayachandran M, Miller VM, Garovic VD. A history of preeclampsia is associated with a risk for coronary artery calcification 3 decades later. Am J Obstet Gynecol. 2016;214(4):519 e511-519 e518.
95. Best LG, Lunday L, Webster E, Falcon GR, Beal JR. Pre-eclampsia and risk of subsequent hypertension: in an American Indian population. Hypertens Pregnancy. 2017;36(2):131-137.
96. Kattah AG, Scantlebury DC, Agarwal S, Mielke MM, Rocca WA, Weaver AL, Vaughan LE, Miller VM, Weissgerber TL, White W, Garovic VD. Preeclampsia and ESRD: The Role of Shared Risk Factors. Am J Kidney Dis. 2017;69(4):498-505.
97. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, Rich-Edwards JM. Hypertensive Disorders of Pregnancy and Maternal Cardiovascular Disease Risk Factor Development: An Observational Cohort Study. Ann Intern Med. 2018;169(4):224-232.
98. Ackerman CM, Platner MH, Spatz ES, Illuzzi JL, Xu X, Campbell KH, Smith GN, Paidas MJ, Lipkind HS. Severe cardiovascular morbidity in women with hypertensive diseases during delivery hospitalization. Am J Obstet Gynecol. 2019;220(6):582 e581-582 e511.
99. Haas DM, Parker CB, Marsh DJ, Grobman WA, Ehrenthal DB, Greenland P, Bairey Merz CN, Pemberton VL, Silver RM, Barnes S, McNeil RB, Cleary K, Reddy UM, Chung JH, Parry S, Theilen LH, Blumenthal EA, Levine LD, Mercer BM, Simhan H, Polito LA, Wapner RJ, Catov J, Chen I, Saade GR, NHLBI nuMoM2b Heart Health Study. Association of Adverse Pregnancy Outcomes With Hypertension 2 to 7 Years Postpartum. J Am Heart Assoc. 2019;8(19):e013092.

100. Haukkamaa L, Moilanen L, Kattainen A, Luoto R, Kahonen M, Leinonen M, Jula A, Kesäniemi YA, Kaaja R. Pre-eclampsia is a risk factor of carotid artery atherosclerosis. Cerebrovasc Dis. 2009;27(6):599-607.

101. Buurma AJ, Turner RJ, Driessen JH, Mooyaart AL, Schoones JW, Bruijn JA, Bloemenkamp KWM, Dekkers OM, Baelde HJ. Genetic variants in pre-eclampsia: a meta-analysis. Hum Reprod Update. 2013;19(3):289–303. doi:10.1093/humupd/dms060

102. Kazmi N, Sharp GC, Reese SE, Vehmeijer FO, Lahti J, Page CM, Zhang W, Rifas-Shiman SL, Rezwan FI, Simpkin AJ, Burrows K, Richardson TG, Santos Ferreira DL, Fraser A, Harmon QE, Zhao S, Jaddoe VWV, Czamara D, Binder EB, Magnus MC, Håberg SE, Nystad W, Nohr EA, Starling AP, Kechris KJ, Yang IV, DeMeo DL, Litonjua AA, Baccarelli A, Oken E, Holloway JW, Karmaus W, Arshad SH, Dabelea D, Sørensen TIA, Laivuori H, Raikkonen K, Felix JF, London SJ, Hivert MF, Gaunt TR, Lawlor DA, Relton CL. Hypertensive Disorders of Pregnancy and DNA Methylation in Newborns. Hypertension. 2019;74(2):375–383. doi:10.1161/HYPERTENSIONAHA.119.12634

103. Lazdam M, de la Horra A, Diesch J, Kenworthy Y, Davis E, Lewandowski AJ, Szmigielski C, Shore A, Mackillop L, Kharbanda R, Alp N, Redman C, Kelly B, Leeson P. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. Hypertension. 2012 Nov;60(5):1338-45.

104. Wright D, Wright A, Nicolaides KH. THE COMPETING RISK APPROACH FOR PREDICTION OF PREECLAMPSIA [published online ahead of print, 2019 Nov 13]. Am J Obstet Gynecol. 2019;S0002-9378(19)32618-3. doi:10.1016/j.ajog.2019.11.1247

105. Wright D, Tan MY, O'Gorman N, Poon LC, Syngelaki A, Wright A, Nicolaides KH. Predictive performance of the competing risk model in screening for preeclampsia [published correction appears in Am J Obstet Gynecol. 2019 Apr 24;:]. Am J Obstet Gynecol. 2019;220(2):199.e1–199.e13. doi:10.1016/j.ajog.2018.11.1087.

106. Chen CW, Jaffe IZ, Karumanchi SA. Pre-eclampsia and cardiovascular disease. Cardiovasc Res 2014;101:579–86.

107. Rodie VA, Freeman DJ, Sattar N, Greer IA. Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? Atherosclerosis 2004;175:189–202.

108. van Rijn BB, Nijdam ME, Bruinse HW, Roest M, Uiterwaal CS, Grobbee DE, Bots ML, Franx A. Cardiovascular disease risk factors in women with a history of early-onset preeclampsia. Obstet Gynecol 2013;121:1040–8.

109. Walsh SW. Obesity: a risk factor for preeclampsia. Trends Endocrinol Metab 2007;18:365–70.

110. Ford CA, Nonnemaker JM, Wirth KE. The influence of adolescent body mass index, physical activity, and tobacco use on blood pressure and cholesterol in young adulthood. J Adolesc Health 2008;43:576–583.

111. Shroff R, Kerchner A, Maifeld M, Van Beek EJ, Jagasia D, Dokras A. Young obese women with polycystic ovary syndrome have evidence of early coronary atherosclerosis. J Clin Endocrinol Metab 2007;92: 4609–4614.
112. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology 2003;14:368–374.
113. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics; 2010 update. A report from the American Heart Association. Circulation 2010;121:e46–e215.
114. Wu P, Kwok CS, Haththotuwa R, Kotronias RA, Babu A, Fryer AA, Myint PK, Chew-Graham CA, Mamas MA. Pre-eclampsia is associated with a twofold increase in diabetes: a systematic review and meta-analysis. Diabetologia. 2016;59(12):2518–2526. doi:10.1007/s00125-016-4098-x
115. Visser S, Hermes W, Ket JC, Otten RHJ, van Pampus MG, Bloemenkamp KWM, Franx A, Mol BW, de Groot CJM. Systematic review and metaanalysis on nonclassic cardiovascular biomarkers after hypertensive pregnancy disorders. Am J Obstet Gynecol. 2014;211(4):373.e1–373.e3739. doi:10.1016/j.ajog.2014.03.032
116. Ferrazzi E, Zullino S, Stampalija T, Vener C, Cavoretto P, Gervasi MT, Vergani P, Mecacci F, Marozio L, Oggè G, Algeri P, Ruffatti A, Milani S, Todros T. Bedside diagnosis of two major clinical phenotypes of hypertensive disorders of pregnancy. Ultrasound Obstet Gynecol. 2016 Aug;48(2):224-31.
117. Ferrazzi E, Stampalija T, Monasta L, Di Martino D, Vonck S, Gyselaers W. Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy. Am J Obstet Gynecol. 2018 Jan;218(1):124.e1-124.e11.
118. Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB, Lees CC. Early and late pre-eclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study. Am J Obstet Gynecol. 2018 May;218(5):517.e1-517.e12.
119. Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, Vogelvang TE, Lely AT, Franx A, van Rijn BB. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. BJOG. 2018 Dec;125(13):1642-1654.

Figure legends

Figure 1. PRISMA flow diagram

Figure 2. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

Figure 3. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

Figure 4. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status (a), and among women with a prior diagnosis of late-onset preeclampsia versus women with prior normal pregnancy status (b).

Figure 5. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

Figure 6. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

Figure 7. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

Figure 8. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status.

Figure 9. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

Figure 10. Pooled risk of death among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

Figure 11. Pooled risk of death among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status (a), and among women with a prior diagnosis of late-onset preeclampsia versus women with prior normal pregnancy status (b).

Figure 12. Pooled risk of death among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

Figure 13. a) Pooled risk of diabetes among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of diabetes among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

Figure 14. a) Pooled risk of hypertension among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of hypertension among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

Figure 15. a) Pooled risk of anti-hypertensive therapy among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of antihypertensive therapy among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

Figure 16. a) Pooled risk of dyslipidemia among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of dyslipidemia among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

Figure 17. a) Pooled risk of kidney disease among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of kidney disease among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

Figure 18. a) Pooled risk of metabolic syndrome among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of metabolic syndrome among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

Figure 19. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

Figure 20. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

Figure 21. Pooled risk of hypertension among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

Figure 22. Pooled risk of dyslipidemia among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

Figure 23. Pooled risk of kidney disease among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

Figure 24. Pooled risk of metabolic syndrome among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

Table 1. Characteristics of the included studies.

n	First author	Year	Journal	Country	Study design	Sample	Time between index pregnancy and outcomes	Extracted outcomes	Sub-analyses by time of PE onset
1	Callaway[30]	2007	Am J Obstet Gynecol	Australia	Cohort	3639	21 years	Diabetes	NR
2	Callaway[31]	2011	Austr NZ J Obstet Gynecol	Australia	Cohort	2112	21 years	Composite AE; Hypertension	NR
3	Thornton[32]	2013	Am J Obstet Gynecol	Australia	Cohort	691,738	1 year	Composite AE; CV mortality	NR
4	Tooher[33]	2017	Hypertension	Australia	Cohort	31,656	20 years	Composite AE; CV events; Hypertension; Abnormal renal function	NR
5	Forest[34]	2005	Obstet Gynecol	Canada	Cohort	336	8 years	Composite AE; Metabolic syndrome	NR
6	Ray[35]	2005	Lancet	Canada	Cohort	1,026,265	9 years	Composite AE; CV events	NR
7	Smith[36]	2012	J Obstet Gynecol Can	Canada	Cohort	120	3 years	Metabolic syndrome	NR
8	Mehrabadi[37]	2014	BMJ	Canada	Cohort	2,193,425	Acute (no other details)	Abnormal renal function	NR
9	Grandi[38]	2017	Circulation	Canada	Cohort	156,967	NR	Composite AE; CV events; Hypertension	NR
10	Dai[39]	2018	J Obstet Gynecol Can	Canada	Cohort	1,598,043	12 years (median)	Abnormal renal function	NR
11	Langlois[40]	2020	Can J Cardiol	Canada	Cohort	165,558	16 years (median)	Composite AE; CV events	Early PE vs controls

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12	Lykke[21]	2009	Hypertension	Denmark	Cohort	782,287	14.6 years (mean)	Composite AE; CV events; Diabetes	NR
13	Lykke[41]	2010	Pediatr Perinat Epidemiol	Denmark	Cohort	782,287	14.6 years (mean)	Death	NR
14	Behrens[42]	2017	BMJ	Denmark	Cohort	1,025,118	10 to 14 years	Hypertension	NR
15	Kristensen[43]	2019	BMJ	Denmark	Cohort	1,772,330	18.6 years (mean)	Abnormal renal function	Early PE vs controls; late PE vs controls
16	Haukkamaa[44]	2004	Am J Cardiol	Finland	Case-control	352	>20 years	Composite AE; CV events	NR
17	Mannisto[45]	2013	Circulation	Finland	Cohort	10,314	39.4years (mean)	Composite AE; CV events; Death; Diabetes; Hypertension	NR
18	Hubel[46]	2000	BJOG	Iceland	Case-control	60	30 years	Composite AE; Anti-hypertensive medication	Early PE vs controls
19	Funai[47]	2005	Epidemiology	Israel	Cohort	37,061	24-36 years	Composite AE; Death	NR
20	Kessous[48]	2015	Heart	Israel	Cohort	96,280	11 years (mean)	Composite AE; CV events; Abnormal renal function	NR
21	Blaauw[49]	2006	Obstet Gynecol	Netherland	Cohort	44	3 to 13 months	Abnormal renal function	NR
22	Gaugler-Senden[50]	2008	Eur J Obstet Gynecol Repr Biol	Netherland	Case-control	40	5.5 years	Composite AE; Hypertension	NR
23	Nijdam[51]	2009	BMC Fam Pract	Netherland	Cohort	185	3 years	Composite AE; CV events; Hypertension; Dyslipidemia	NR
24	Stekkinger[52]	2009	Obstet Gynecol	Netherland	Cohort	849	≥6 months	Composite AE; Hypertension; Dyslipidemia; Metabolic syndrome; Abnormal renal function	Early vs late PE

25	Aukes[53]	2012	BJOG	Netherland	Cohort	148	5 years	Composite AE; CV events	Early vs late PE
26	Hermes[54]	2013	Am J Obstet Gynecol	Netherland	Cohort	405	2.5 years	Composite AE; Hypertension; Metabolic syndrome	NR
27	Scholten[55]	2013	Obstet Gynecol	Netherland	Cohort	1234	6 to 12 months	Hypertension; Dyslipidemia; Metabolic syndrome	Early vs late PE
28	Veerbek[56]	2015	Hypertension	Netherland	Cohort	748	3 months to 5 years	Composite AE; Hypertension; Metabolic syndrome; Anti-hypertensive medications	Early vs late PE
29	van Rijn[57]	2016	Hypertension	Netherland	Cohort	73	1.5 to 3.5 years	Composite AE; Diabetes; Hypertension; Abnormal renal function	Early PE vs controls
30	Bokslag[58]	2017	Am J Obstet Gynecol	Netherland	Cohort	187	9 to 16 years	Composite AE; Hypertension; Use of anti-hyper medication; Metabolic syndrome	Early PE vs controls
31	Irgens [Ψ 12]	2001	BMJ	Norway	Cohort	626,272	13 years	Composite AE (Death Included only in sub-analyses: same cohort of Vikse 2008 and Skjaerven 2012)	Early PE vs controls; late PE vs controls
32	Vikse[59]	2008	NEJM	Norway	Cohort	570,433	26.5 years (mean)	Abnormal renal function (end-stage renal disease)	NR
33	Kvehaugen[60]	2011	Hypertension	Norway	Cohort	43	5 to 8 years	Composite AE; Medication	NR
34	Andersgaard[61]	2012	Am J Obstet Gynecol	Norway	Cohort	9974	≥20 years	Composite AE; CV events; Hypertension; Diabetes	NR
35	Skjaerven[62]	2012	BMJ	Norway	Cohort	836,147	25 years (median)	Composite AE; Death	Early PE vs controls; late PE vs controls
36	Riise[20]	2017	J Am Heart Assoc	Norway	Cohort	506,350	≥7 years	CV events	NR
37	Egeland[63]	2018	Circulation	Norway	Cohort	60,027	≤10 years	Hypertension; Anti-hypertensive medications	NR

38	Wikstrom[64]	2005	Br J Obstet Gynecol	Sweden	Cohort	403,550	15 years	Composite AE; CV events	NR
39	Nelander[65]	2016	BMJ Open	Sweden	Cohort	3232	12 years	Composite AE; CV events	NR
40	Khashan[66]	2019	Plos Med	Sweden	Cohort	1,366,441	16.4 years (median)	Abnormal renal function	Early PE vs controls; late PE vs controls
41	Tang[67]	2009	Stroke	Taiwan	Cohort	1,132,019	3 months to 1 year	CV events	NR
42	Lin[68]	2011	Am J Cardiol	Taiwan	Cohort	1,132,064	3 years	Composite AE; Death; CV events	NR
43	Wu[69]	2014	Am J Obstet Gynecol	Taiwan	Cohort	944,474	9 years (median)	Abnormal renal function	NR
44	Yeh[70]	2014	J Am Heart Assoc	Taiwan	Cohort	6300	6 years	Composite AE; CV events; Hypertension	NR
45	Kuo[71]	2018	Taiwan J Obstet Gynecol	Taiwan	Cohort	6475	9.8 years (mean)	Diabetes	NR
46	Hannaford[72]	1997	Heart	UK	Cohort	8244	≈30 years	Composite AE; CV events	NR
47	Melchiorre[73]	2011	Hypertension	UK	Case-control	112	2 years	Composite AE; Hypertension	NR
48	Bhattacharya[74]	2012	Pregnancy Hypert	UK	Cohort	34,854	≤50 years	Composite AE; CV events; Death; Hypertension; Abnormal renal function	NR
49	Leon[75]	2019	Circulation	UK	Cohort	1,303,365	9.3 years (median)	Composite AE; CV events; Death; Hypertension	Early PE vs controls
50	Thorogood[76]	1992	Am J Epidemiol	UK (Engl, Wales)	Case-control	841	NR	Composite AE; CV events	NR

51	Mann[77]	1976	Br J Prev Obst Med	UK (England)	Case-control	270	NR	Composite AE; CV events	NR
52	Fraser[78]	2012	Circulation	UK (England)	Cohort	4376	16 to 20 years	Composite AE; CV events	NR
53	Smith[79]	2001	Lancet	UK (Scotland)	Cohort	129,920	15 to 19 years	Composite AE; Death; CV events	NR
54	Wilson[80]	2003	BMJ	UK (Scotland)	Cohort	3593	20 years	Anti-hypertensive medications	NR
55	Libby[81]	2007	Diabetologia	UK (Scotland)	Cohort	7187	>30 years	Diabetes	NR
56	Ayansina[82]	2016	Pregn Hypert	UK (Scotland)	Cohort	77,941	≈30 years	Composite AE; Death; Abnormal renal function	NR
57	Rosenberg[83]	1983	JAMA	USA	Case-control	1057	NR	Composite AE; CV events	NR
58	Kestenbaum[84]	2003	Am J Kidney Dis	USA	Cohort	124,141	7.8 years	Composite AE; CV events	NR
59	Brown[85]	2006	Stroke	USA	Case-control	682	≥42 days	CV events	NR
60	Edlow[86]	2009	Am J Obstet Gynecol	USA	Case-control	219	6-13 months	Hypertension; Diabetes; Dysplipidemia	Early PE vs controls
61	Srinivas[87]	2009	J Mat Fet Neonatal Med	USA	Case-control	368	NR	Composite AE; Metabolic syndrome	NR
62	Mongraw-Chaffin[88]	2010	Hypertension	USA	Cohort	14,403	37 years (median)	Composite AE; Death	Early PE vs controls
63	Hovsepian[89]	2014	Stroke	USA	Cohort	2,066,230	6 weeks	Composite AE; CV events	NR

64	Savitz[90]	2014	Am J Epidemiol	USA	Cohort	849,639	1 year	Composite AE; CV events; Diabetes	NR
65	Cirillo[91]	2015	Circulation	USA	Cohort	14,062	≈50 years	Composite AE; Death	Early PE vs controls; late PE vs controls
66	Black[92]	2016	J Hypert	USA	Cohort	5960	≤1 year	Composite AE; Hypertension	NR
67	Cain[93]	2016	Am J Obstet Gynecol	USA	Cohort	302,689	5 years	Composite AE; CV events	NR
68	White[94]	2016	Am J Obstet Gynecol	USA	Cohort	80	30 years	Composite AE; CV events	NR
69	Best[95]	2017	Hypert Pregn	USA	Case-control	420	13 years (mean)	Composite AE; Hypertension	NR
70	Kattah[96]	2017	Am J Kidney Dis	USA	Case-control	132	18 years (median)	Abnormal renal function	NR
71	Stuart[97]	2018	Ann Intern Med	USA	Cohort	58,671	25 to 32 years	Composite AE; Hypertension; Diabetes; Dylipidemia	Early PE vs controls; late PE vs controls
72	Ackerman[98]	2019	Am J Obstet Gynecol	USA	Cohort	569,900	Immediately post-partum	Composite AE; CV events	NR
73	Haas[99]	2019	J Am Heart Assoc	USA	Cohort	4484	3.2 years (mean)	Composite AE; Hypertension	NR

PE: Pre-eclampsia; Composite AE: composite adverse cardiovascular events (including cardio- and cerebrovascular disease, cardiac death, hypertension, metabolic syndrome, need for anti-hypertensive therapy); CV events: cardio- and cerebrovascular events; Abnormal renal function: including either acute or chronic kidney disease and end-stage renal disease; NR: Not reported.

ΨAs the cohort of Irgens 2001 was partially overlapping with Vikse 2008 and Skjaevern 2012, the study was included only in the sub-analyses by time of PE onset.

Table 2. Pooled risk of each outcome among women with a prior diagnosis of pre-eclampsia versus women with prior normal pregnancy status (see Figures 2-24 for the references to the included studies).

Outcomes	N. of studies (sample)	n / N *	Crude proportion, %	Pooled OR (95% CI)	I^2, %
Composite adverse cardiovascular events [A]	50 (10,966,043)	8795 / 473,770 vs 77,529 / 8,816,146	1.85 vs 0.87	2.05 (1.85-2.27)	91
Adjusted estimates only	41 (10,955,248)	7051 / 274,730 vs 59,955 / 6,157,885	2.57 vs 0.97	1.99 (1.79-2.22)	93
Stratified by time of pre-eclampsia onset:					
- Early onset	11 (3,019,017)	4770 / 148,124 vs 41,300 / 2,868,663	3.22 vs 1.44	3.79 (2.70-5.31)	87
- Late onset	5 (1,549,555)	2533 / 67,100 vs 22,322 / 1,480,225	3.77 vs 1.51	1.89 (1.53-2.33)	79
Stratified by time between index pregnancy and outcome:					
- ≤1 year	6 (2,117,919)	360 / 203,008 vs 3024 / 1,914,911	0.18 vs 0.15	2.37 (1.87-3.01)	72
- 1 to 10 years	15 (2,900,650)	1655 / 72,859 vs 22,530 / 2,636,683	2.27 vs 0.85	2.27 (1.86-2.76)	71
- >10 years	24 (2,721,741)	6210 / 167,288 vs 46,301 / 2,314,978	3.71 vs 2.00	1.90 (1.64-2.19)	95
Cardiovascular and cerebrovascular diseases	31 (10,763,599)	6440 / 510,316 vs 59,158 / 10,053,273	1.26 vs 0.59	1.80 (1.62-2.00)	86
Adjusted estimates only	28 (10,753,319)	6097 / 509,307 vs 57,813 / 10,244,012	1.19 vs 0.56	1.79 (1.61-2.01)	93
Stratified by time of pre-eclampsia onset:					
- Early onset	2 (1,468,923)	2113 / 80,740 vs 18,956 / 1,388,183	2.62 vs 1.36	1.75 (1.20-2.55)	86
- Late onset	0	--		--	--
Stratified by time between index pregnancy and outcome:					
- ≤1 year	5 (3,768,831)	283 / 189,167 vs 2285 / 3,556,157	0.15 vs 0.08	2.61 (1.73-3.93)	85
- 1 to 10 years	10 (4,401,547)	1704 / 101,995 vs 23,807 / 3,108,454	1.67 vs 0.77	2.01 (1.70-2.37)	70
- >10 years	14 (1,680,677)	3624 / 121,832 vs 26,037 / 1,380,306	2.97 vs 1.89	1.55 (1.35-1.79)	92
Death [B]	12 (5,064,156)	2861 / 119,570 vs 40,480 / 3,607,506	2.39 vs 1.12	2.18 (1.79-2.66)	71
Stratified by time of pre-eclampsia onset:					
- Early onset	5 (2,794,249)	1472 / 83,082 vs 24,851 / 2,711,167	1.77 vs 0.92	5.12 (3.22-8.12)	58
- Late onset	4 (1,490,884)	611 / 57,528 vs 7088 / 1,433,356	1.06 vs 0.49	1.65 (1.46-1.86)	0
Stratified by time between index pregnancy and outcome:					
- ≤1 year	1 (691,738)	17 / 22,298 vs 80 / 669,440	0.08 vs 0.01	5.10 (3.07-8.47)	--
- 1 to 10 years	2 (2,435,429)	861 / 25,554 vs 17,763 / 1,277,811	3.37 vs 1.39	2.21 (1.71-2.84)	0
- >10 years	9 (1,936,989)			1.98 (1.62-2.43)	64
Diabetes	10 (1,728,478)	1946 / 47,022 vs 9640 / 824,062	4.14 vs 1.17	2.14 (1.52-3.02)	95
Adjusted estimates only	8 (1,718,431)	1636 / 46,077 vs 9640 / 816,846	3.55 vs 1.18	2.28 (1.58-3.28)	96

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Hypertension	21 (2,711,443)	7296 / 78,982 vs 86,531 / 2,571,050	9.24 vs 3.37	3.93 (3.08-5.02)	99
Adjusted estimates only	15 (2,695,024)	6873 / 77,787 vs 85,193 / 2,563,530	8.84 vs 3.32	3.74 (2.87-4.87)	99
Dyslipidemia	3 (59,075)	6396 / 9686 vs 26,882 / 49,389	66.0 vs 54.4	1.32 (1.27-1.37)	0
Adjusted estimates only	2 (58,890)	6396 / 9651 vs 26,881 / 49,239	66.3 vs 54.6	2.54 (0.81-2.95)	36
Kidney disease [C]	14 (8,696,440)	779 / 203,916 vs 9278 / 6,186,679	0.38 vs 0.15	3.37 (2.28-5.00)	94
Adjusted estimates only	12 (8,696,323)	775 / 203,850 vs 9278 / 6,186,628	0.38 vs 0.15	3.35 (2.25-5.00)	95
Metabolic syndrome	5 (1416)	184 / 674 vs 38 / 742	27.3 vs 5.1	4.30 (2.61-7.08)	0
Adjusted estimates only	4 (1229)	112 / 543 vs 29 / 686	20.6 vs 4.2	4.05 (2.42-6.77)	8
Anti-hypertensive therapy	5 (63,910)	501 / 2898 vs 1207 / 61,012	17.3 vs 1.97	4.44 (2.40-8.23)	66
Adjusted estimates only	2 (63,620)	417 / 2711 vs 1195 / 60,909	15.4 vs 1.96	4.22 (1.98-2.97)	89

OR = Odds ratio; CI = Confidence Interval.
* Number of women with the outcome / Total number of pre-eclamptic women vs Number of women with the outcome / Total number of healthy women. Some studies did not report raw data separately by exposure group, thus the sum of the total number of women in either group may be lower than the overall sample.
[A] Including: cardio- and cerebrovascular disease, cardiac death, hypertension, metabolic syndrome, need for anti-hypertensive therapy. [B] All adjusted estimates. [C] Including either acute or chronic kidney disease and end-stage renal disease.

Table 3. Pooled risk of selected outcomes among women with a prior diagnosis of early pre-eclampsia versus women with a prior diagnosis of late pre-eclampsia (see Figures 19-24 for the references to the included studies).

Outcomes	**N. of studies (sample)**	**Pooled OR (95% CI)**	**I^2, %**
Composite adverse cardiovascular events [A]	4 (2979)	1.75 (1.03-2.99)	81
Cardiovascular and cerebrovascular diseases	1 (148)	5.63 (1.48-21.4)	--
Hypertension	2 (2083)	1.48 (1.26-1.72)	0
Dyslipidemia	3 (2831)	1.51 (1.25-1.83)	0
Kidney disease [B]	1 (849)	1.52 (1.06-2.18)	--
Metabolic syndrome	3 (2831)	1.66 (1.08-2.54)	67

OR = Odds ratio; CI = Confidence Interval.
[A] Including: cardio- and cerebrovascular disease, cardiac death, hypertension, metabolic syndrome, need for anti-hypertensive therapy. [B] Including either acute or chronic kidney disease and end-stage renal disease.

Identification

Screening

Eligibility

Included

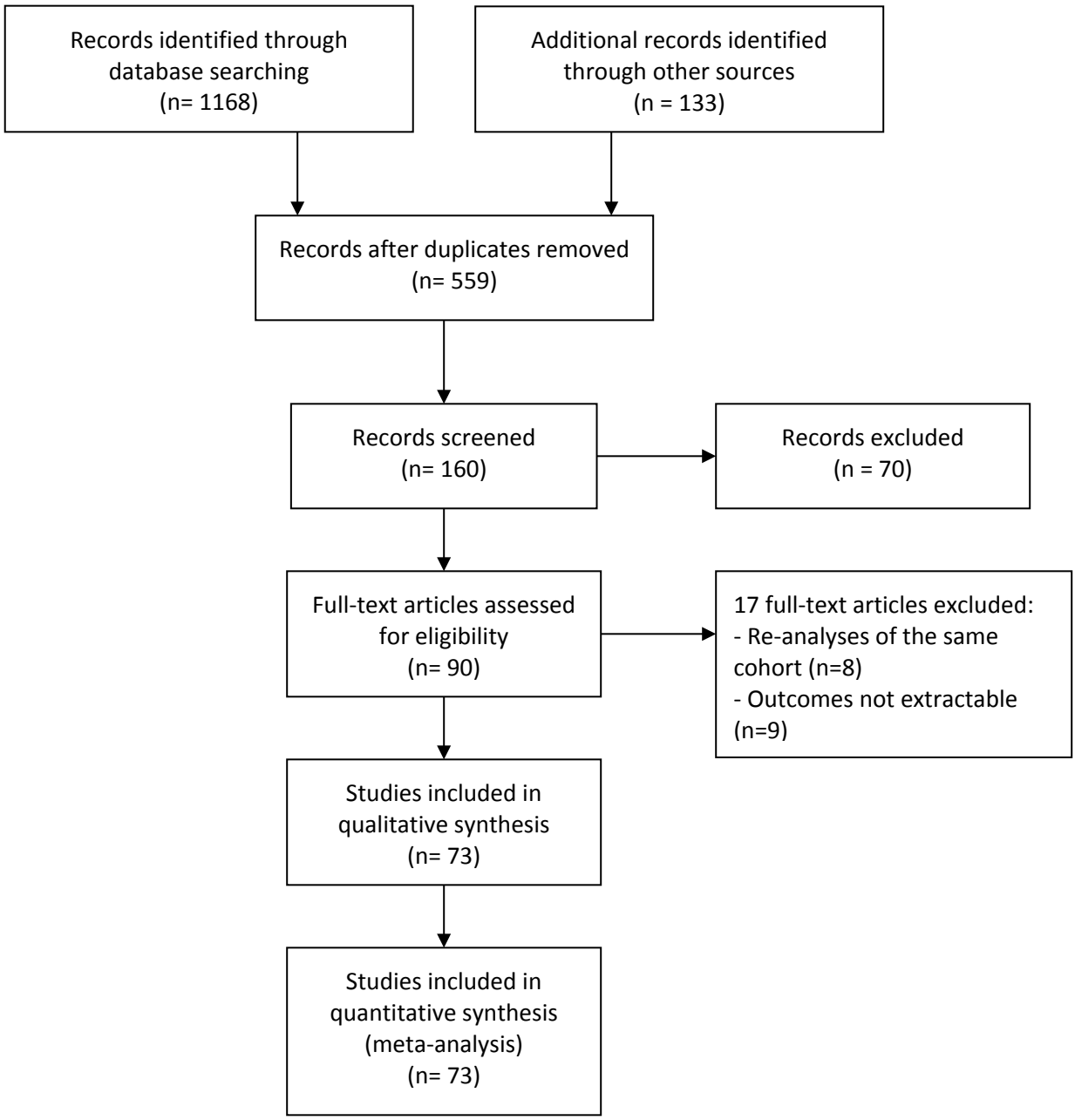


Figure 2. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

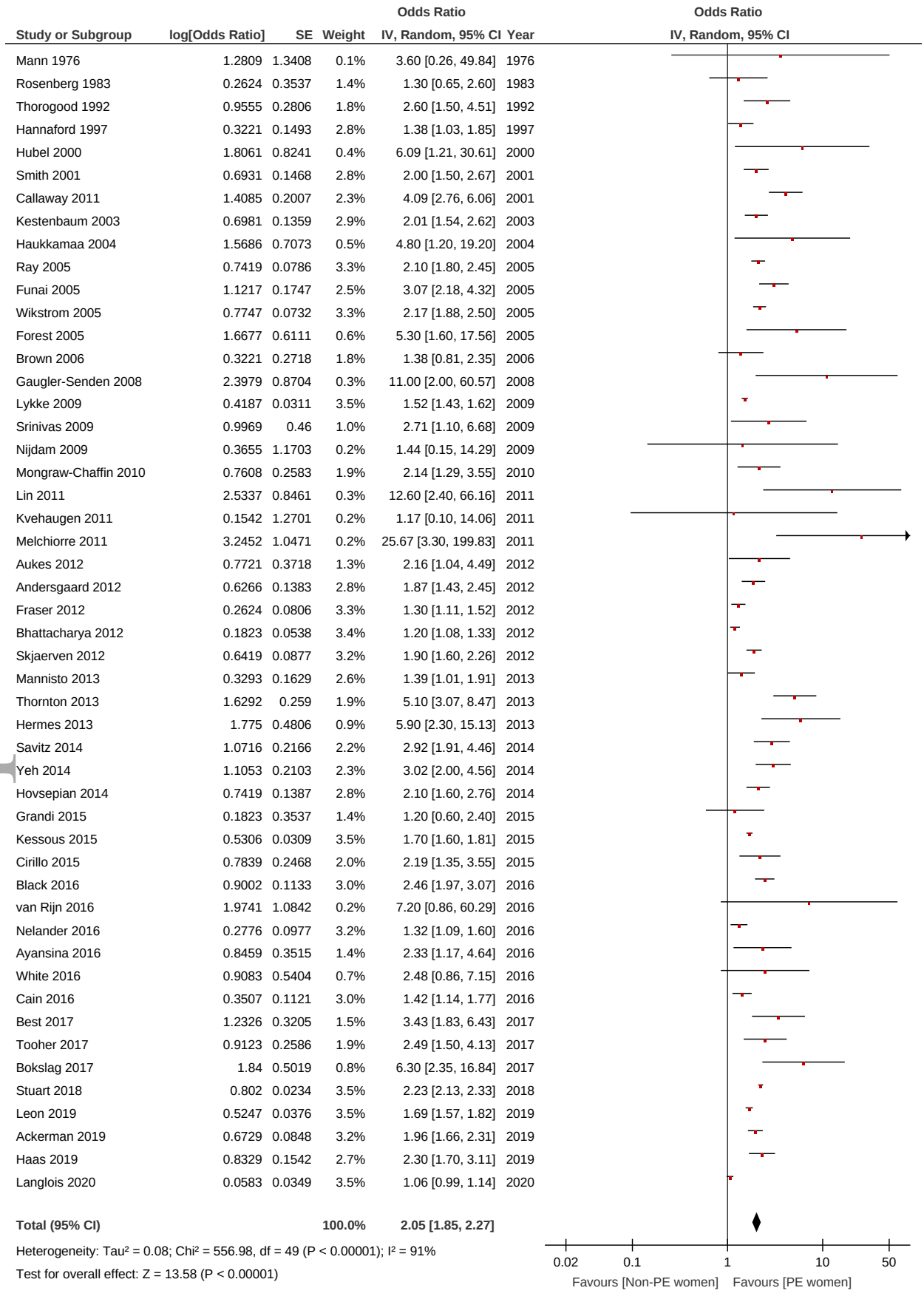


Figure 3. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

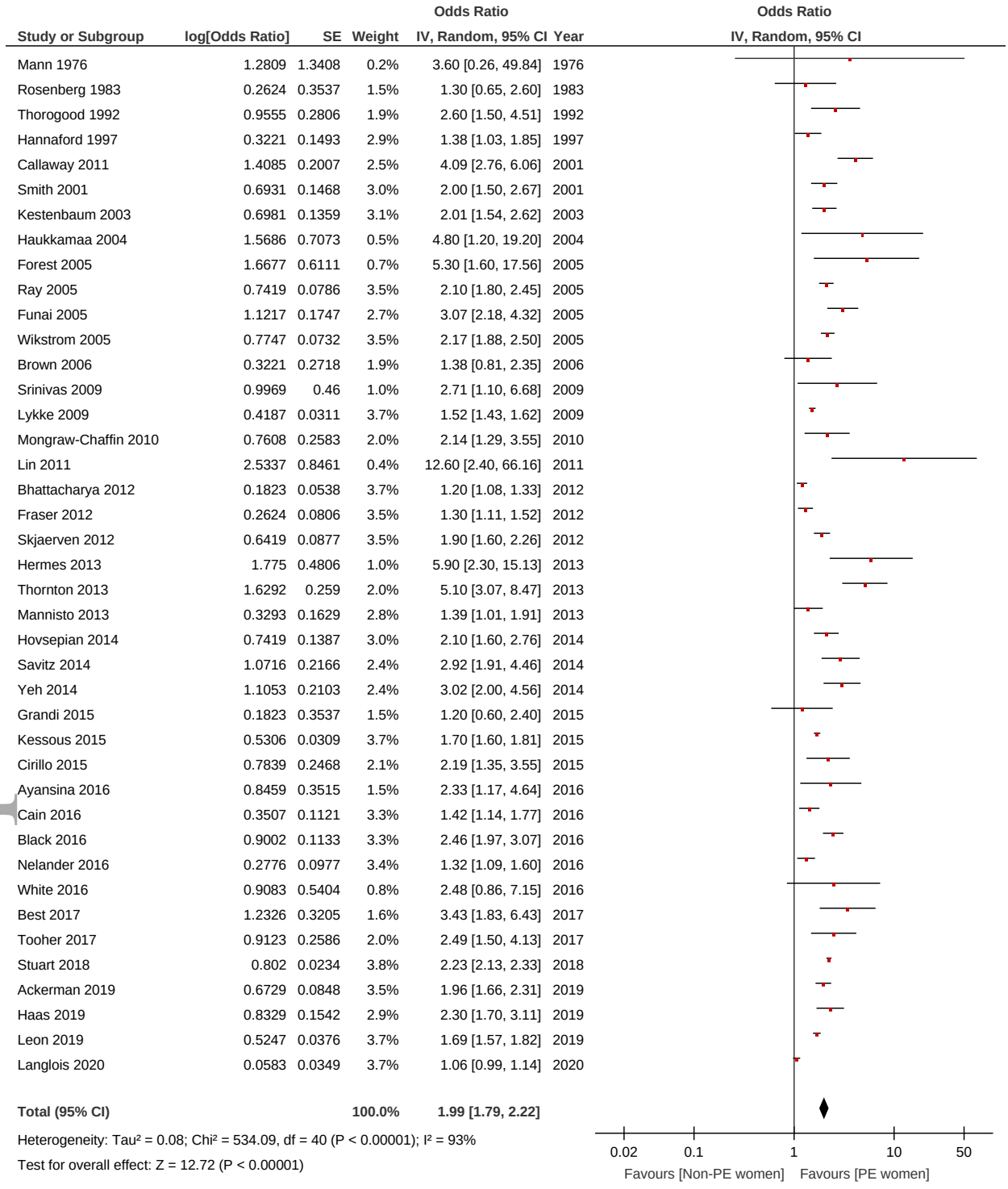
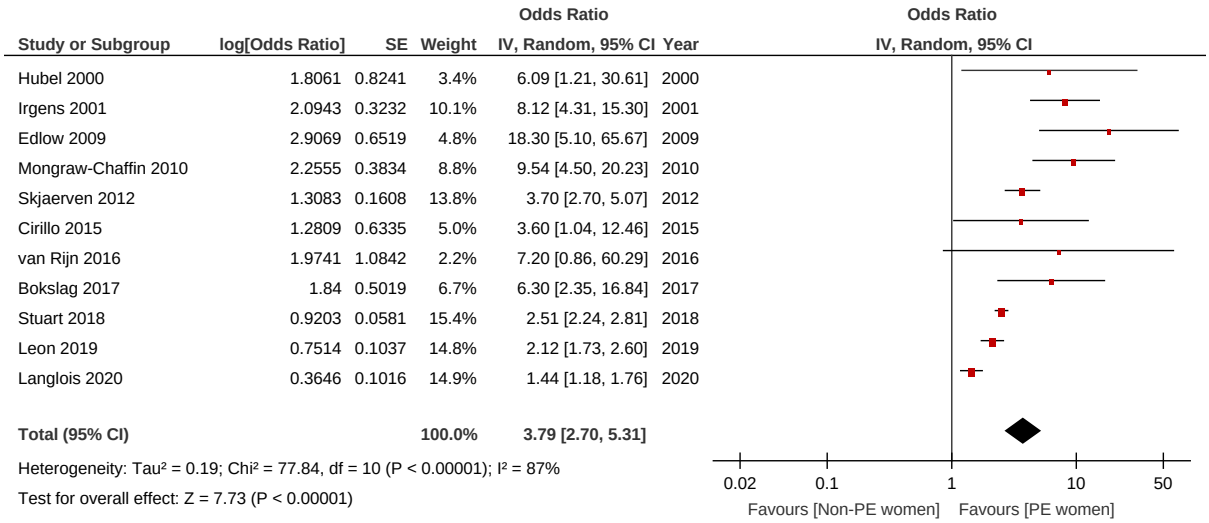


Figure 4. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status (a), and among women with a prior diagnosis of late-onset preeclampsia versus women with prior normal pregnancy status (b).

a)



b)

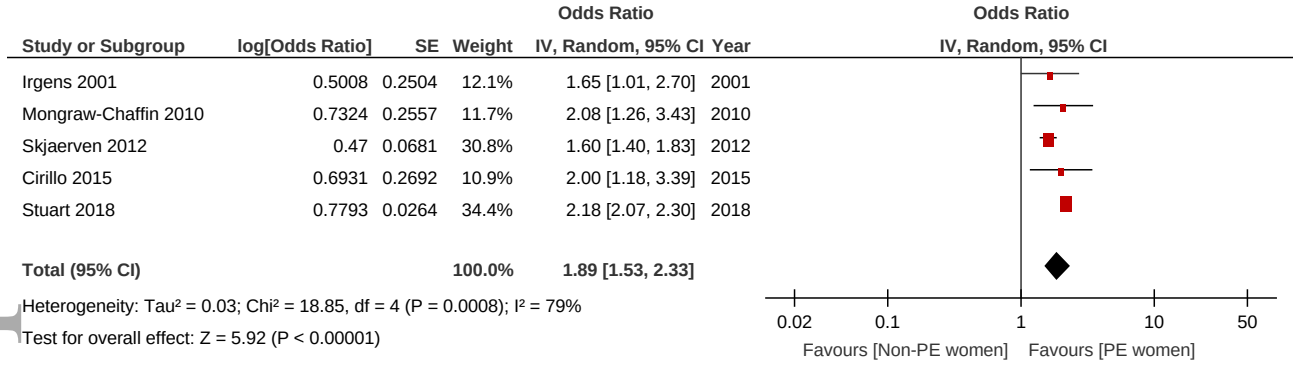


Figure 5. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

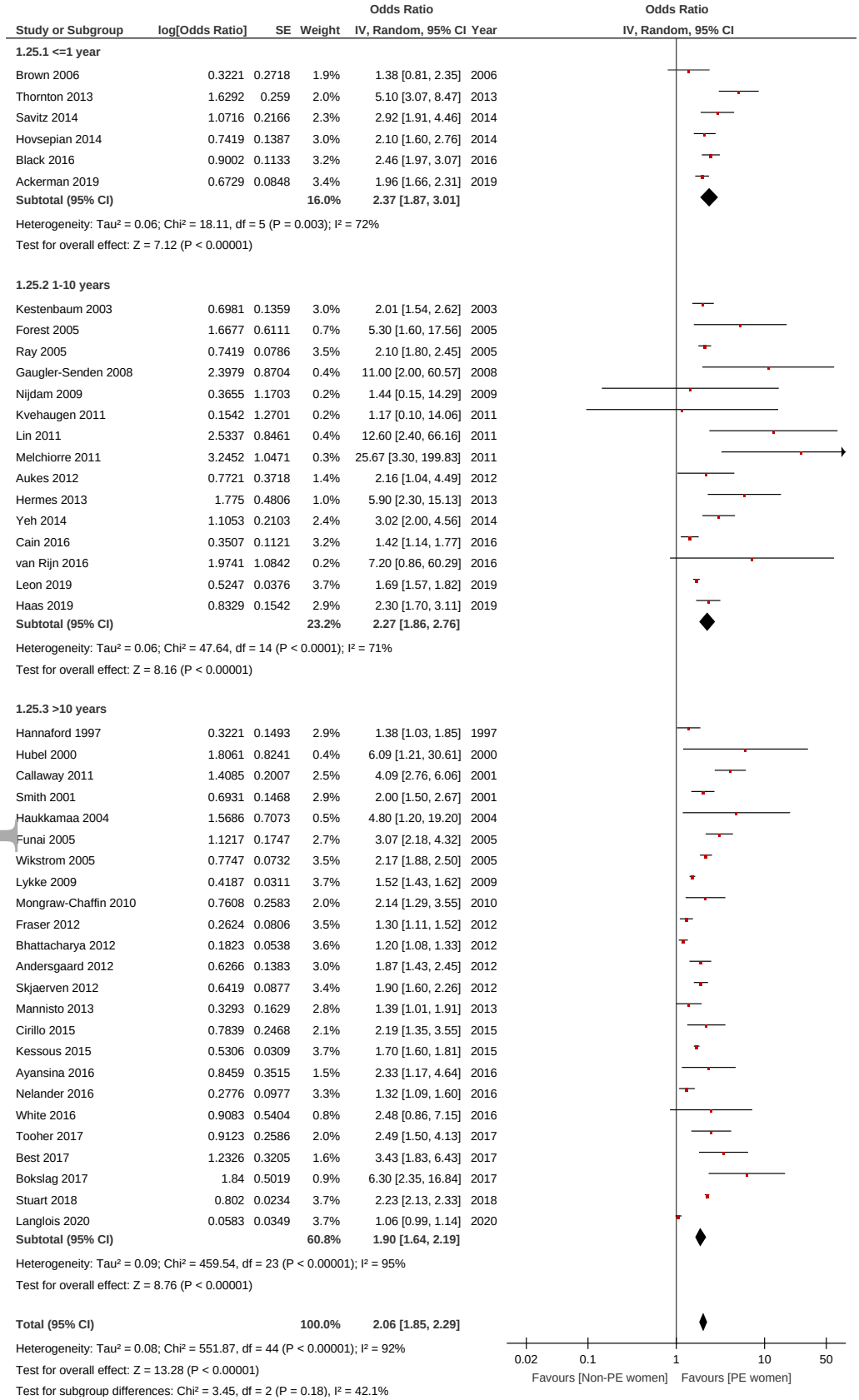


Figure 6. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

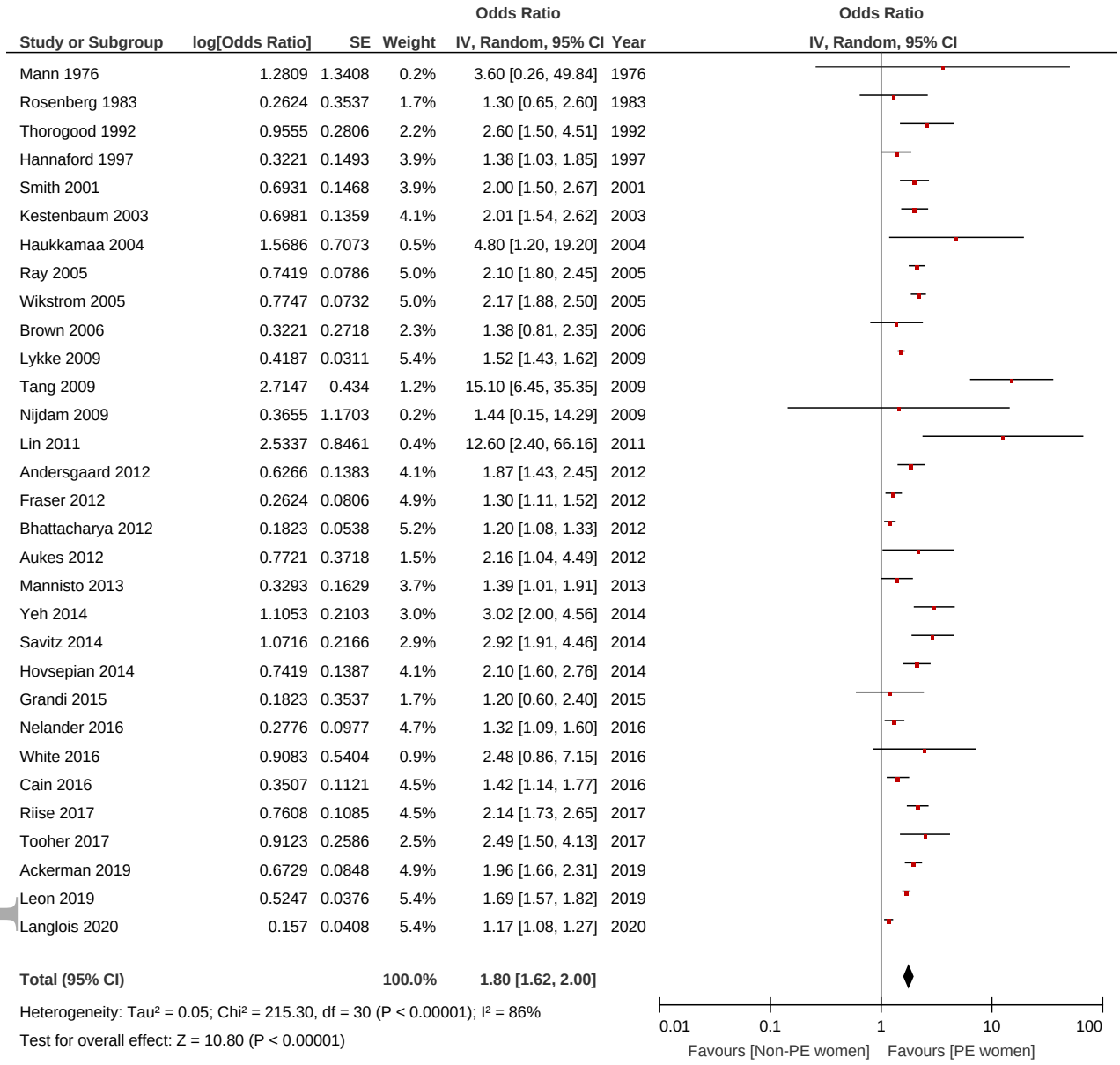


Figure 7. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

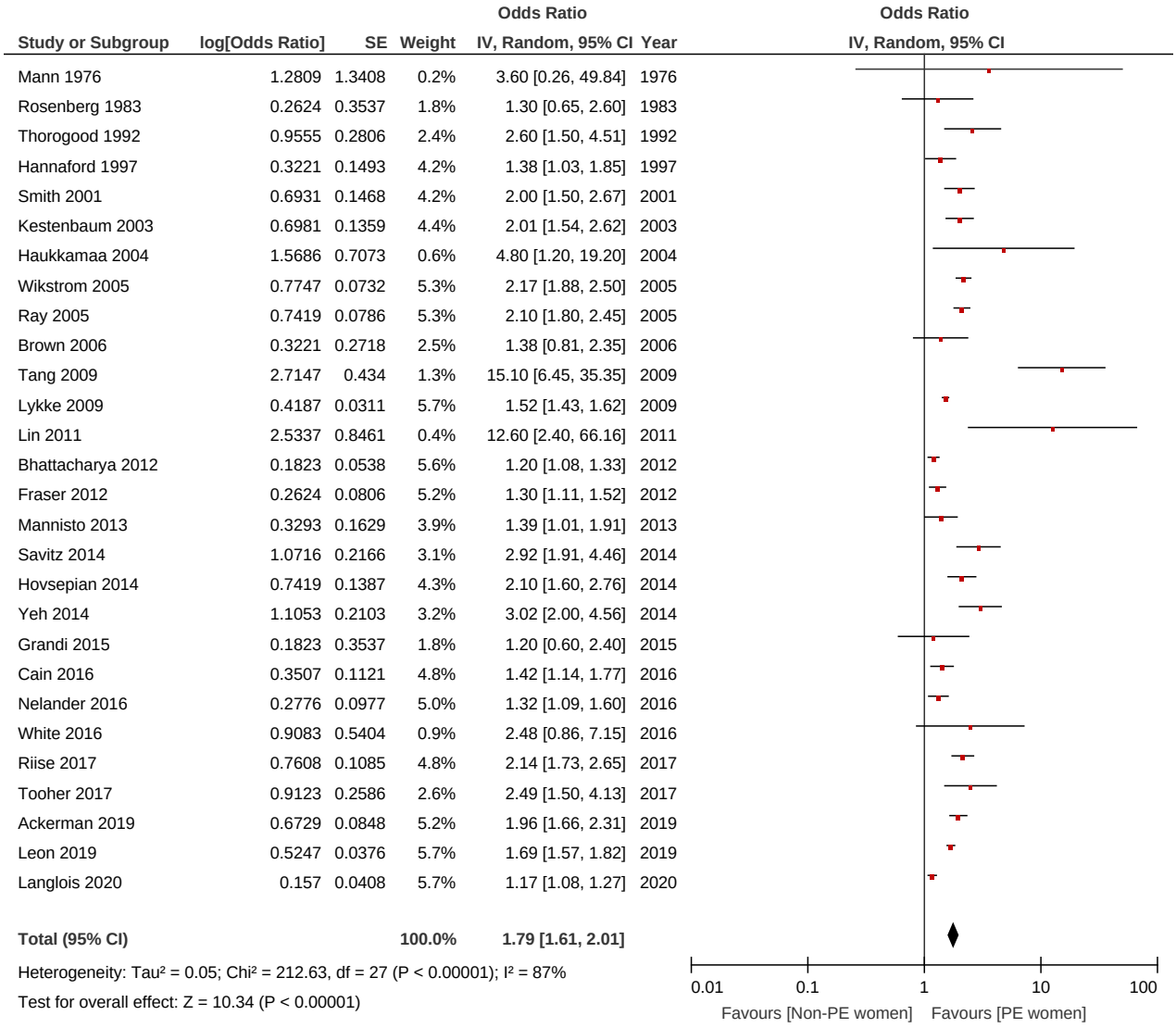


Figure 8. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status.

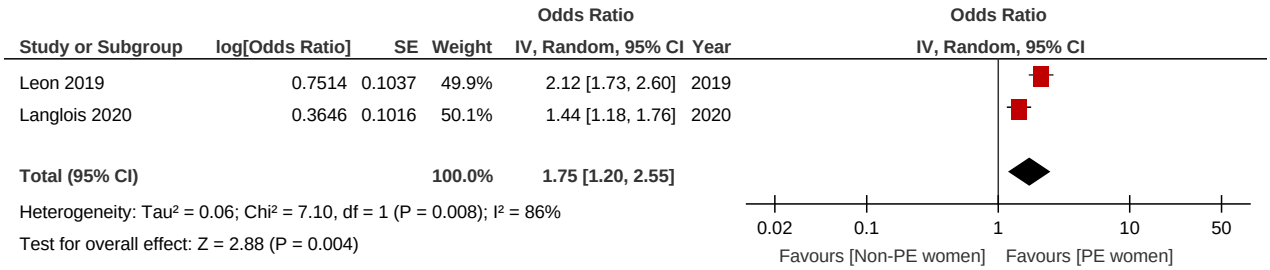


Figure 9. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

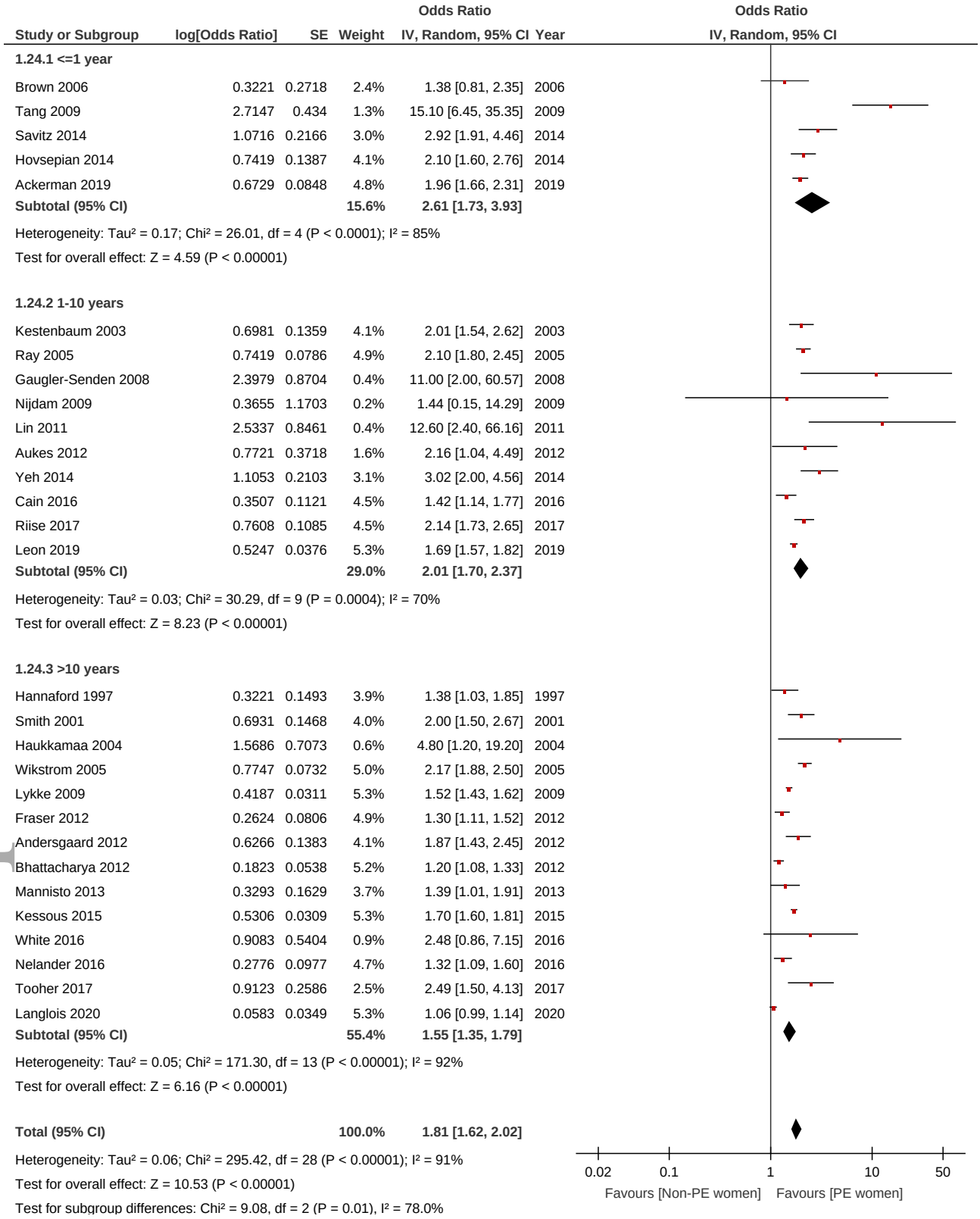


Figure 10. Pooled risk of death among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

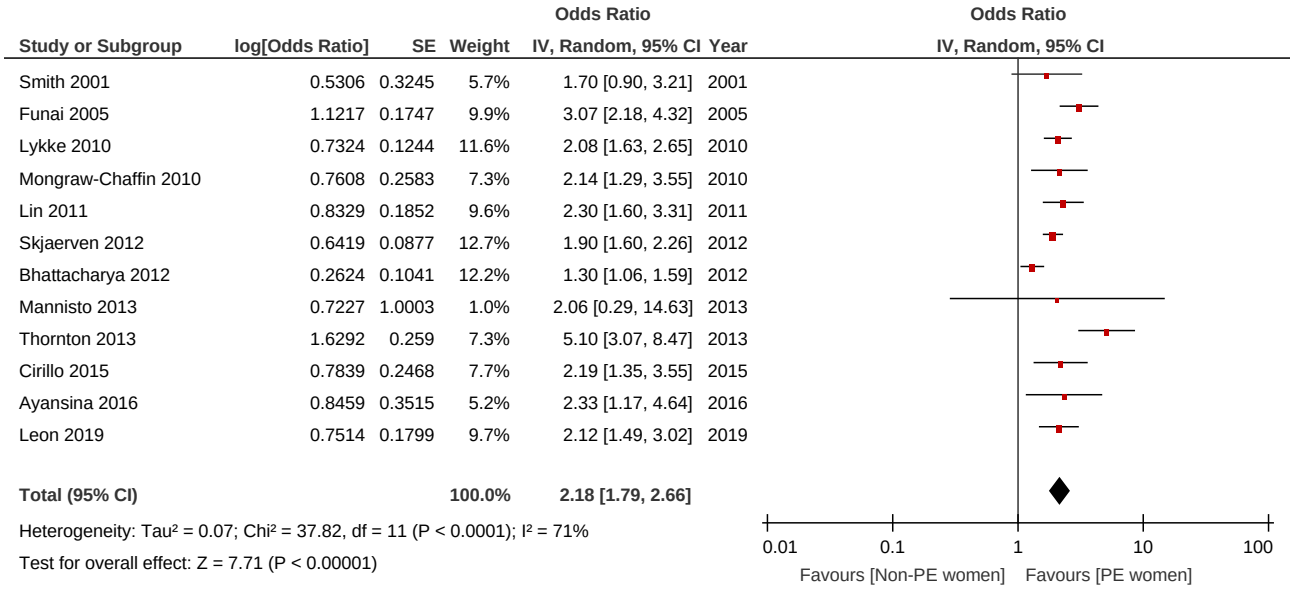
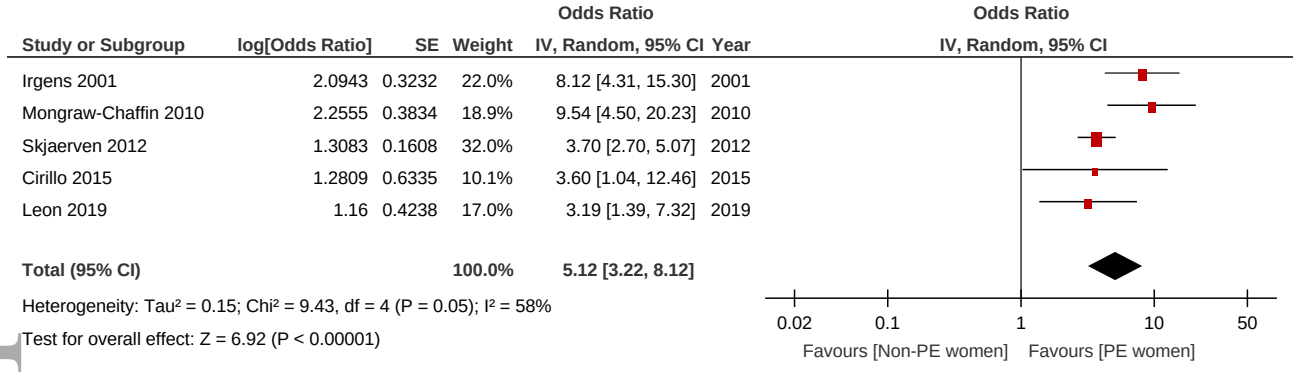


Figure 11. Pooled risk of death among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status (a), and among women with a prior diagnosis of late-onset preeclampsia versus women with prior normal pregnancy status (b).

a)



b)

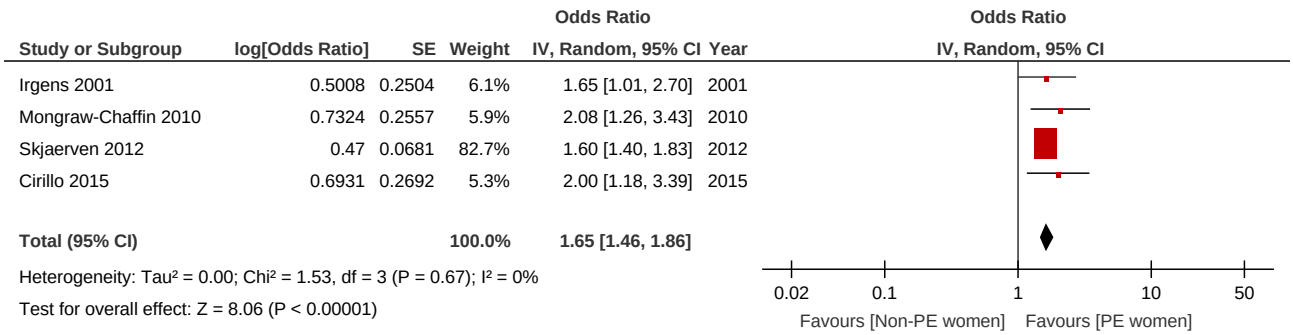


Figure 12. Pooled risk of death among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

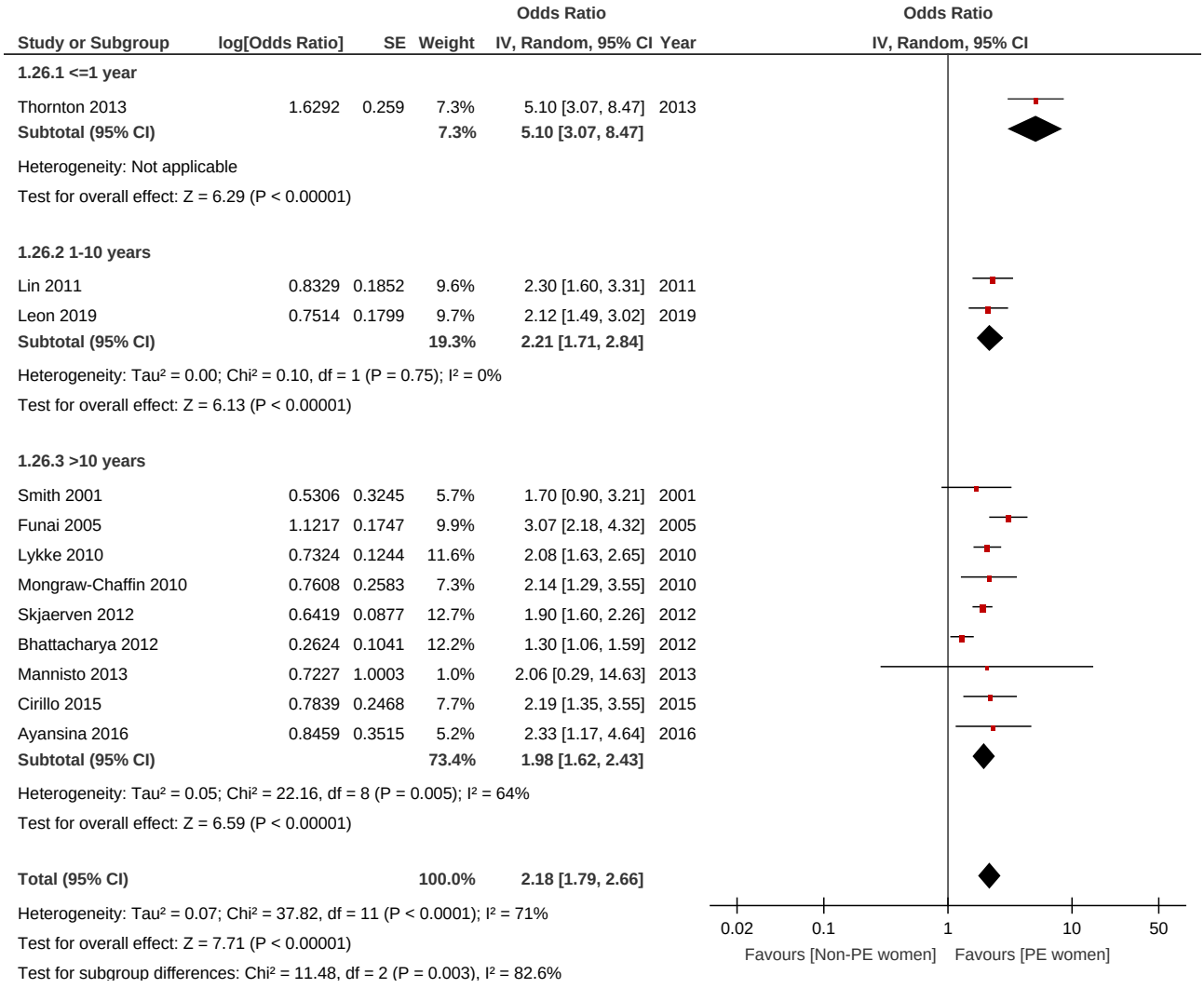
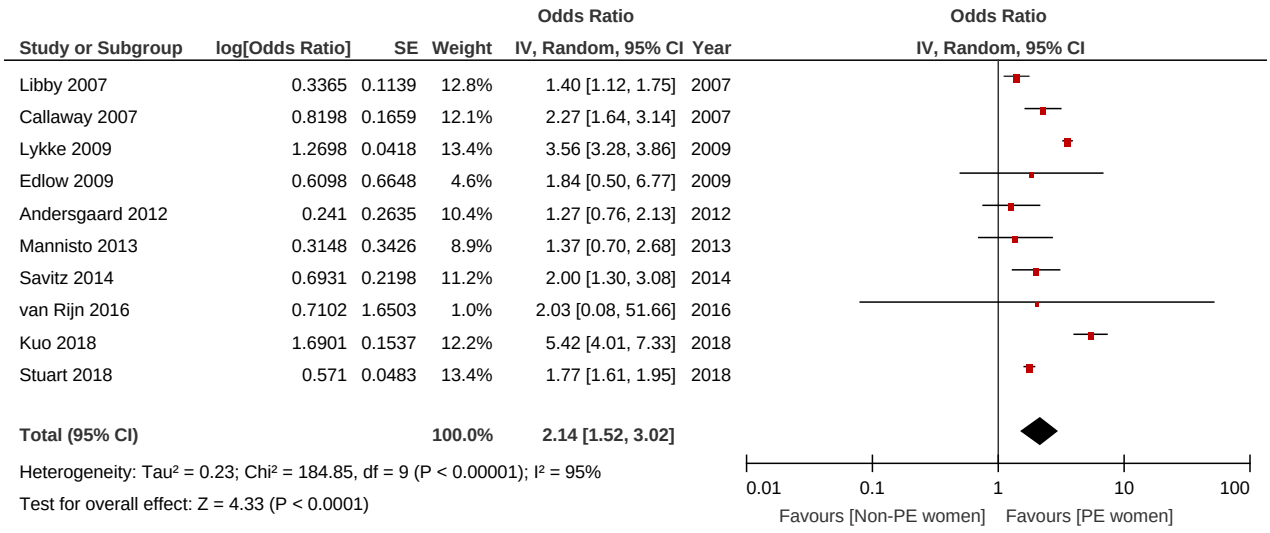


Figure 13. a) Pooled risk of diabetes among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of diabetes among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

a)



b)

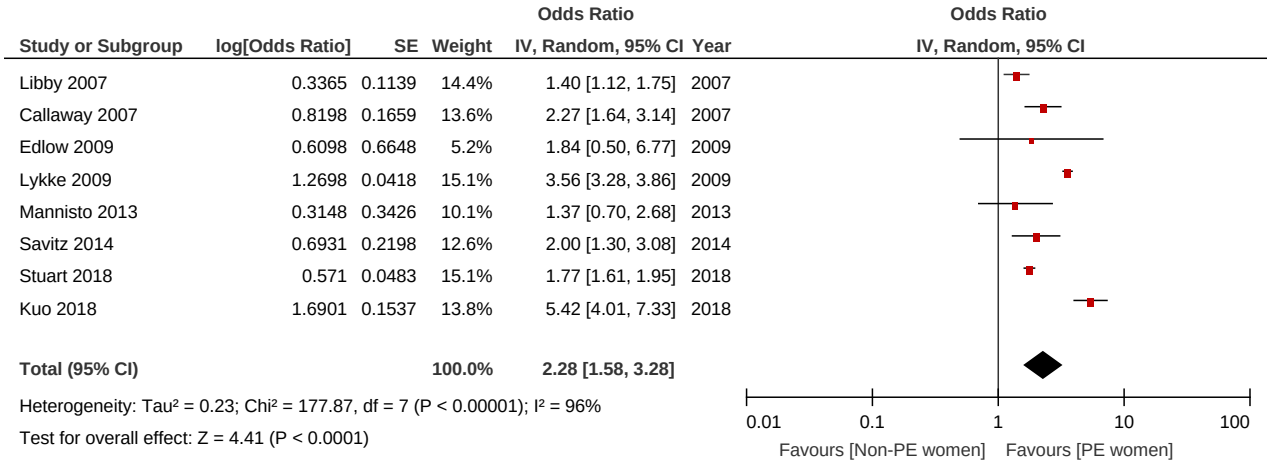
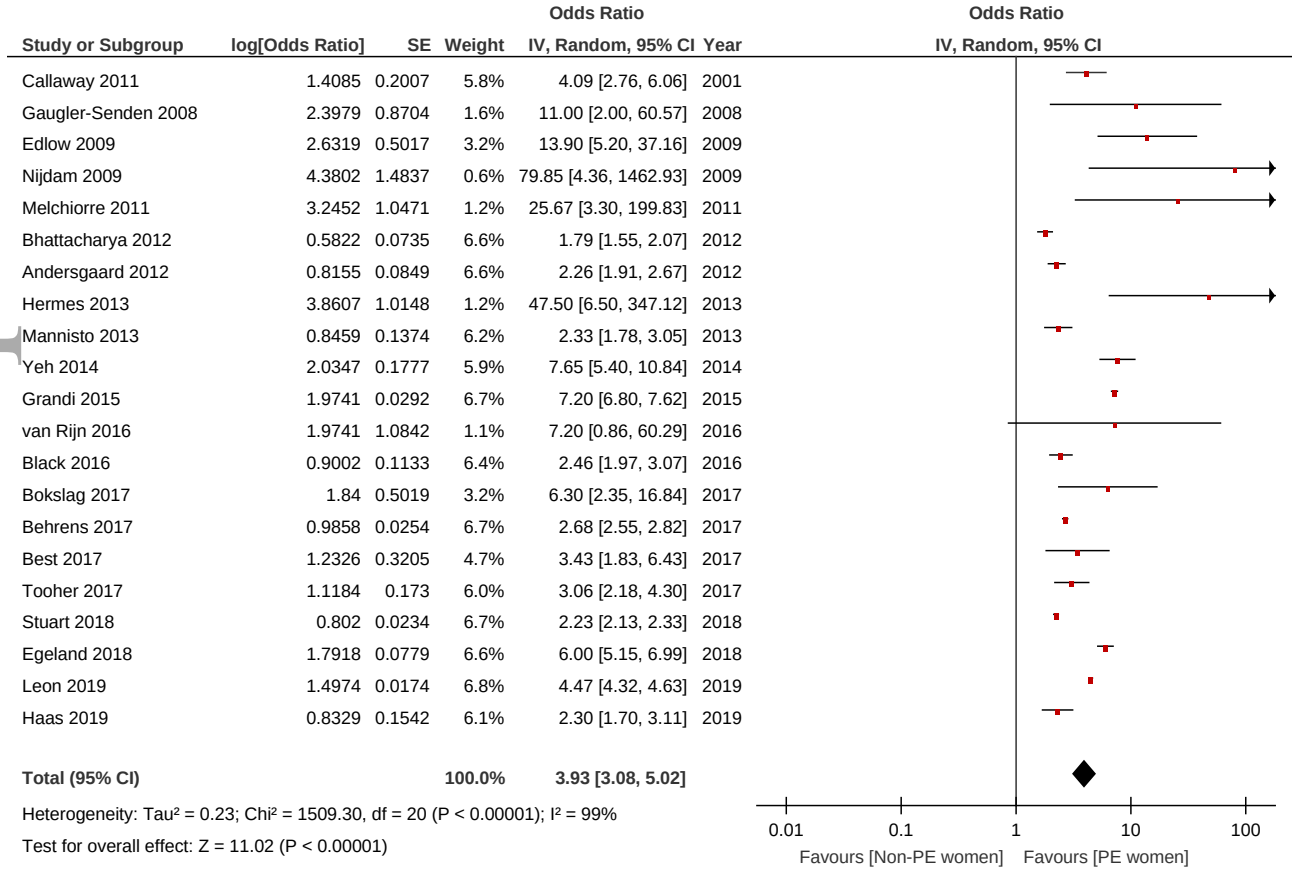


Figure 14. a) Pooled risk of hypertension among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of hypertension among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

a)



b)

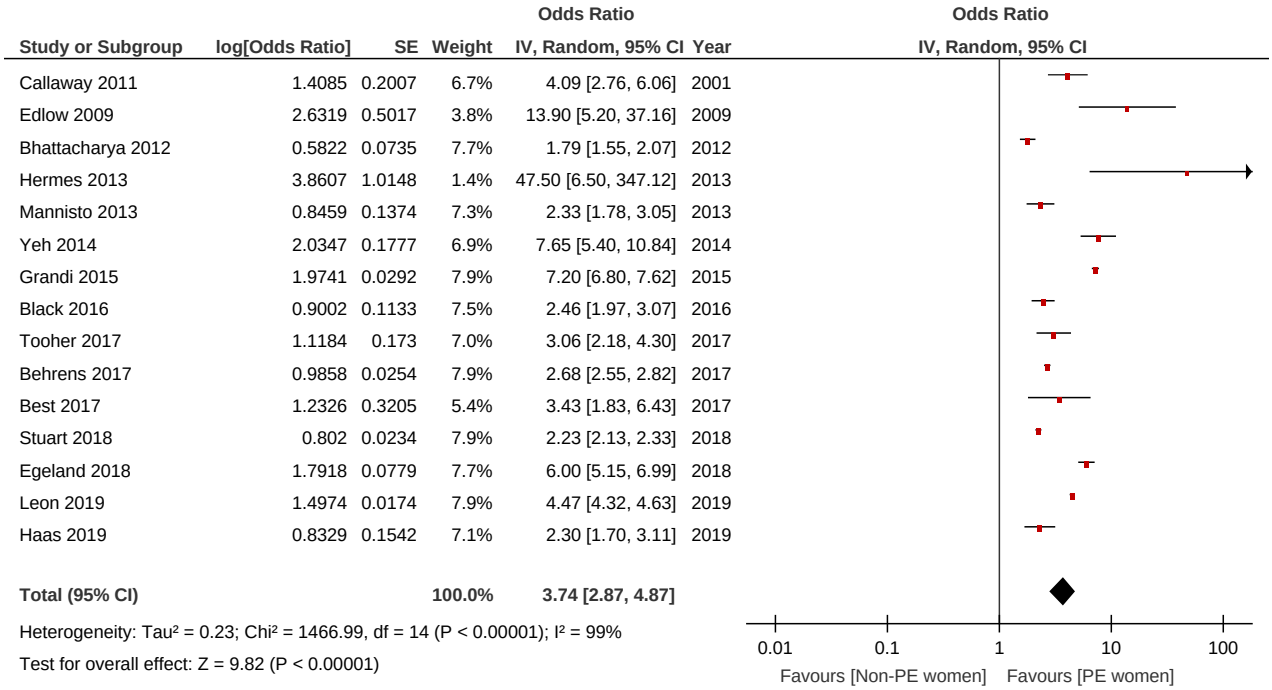
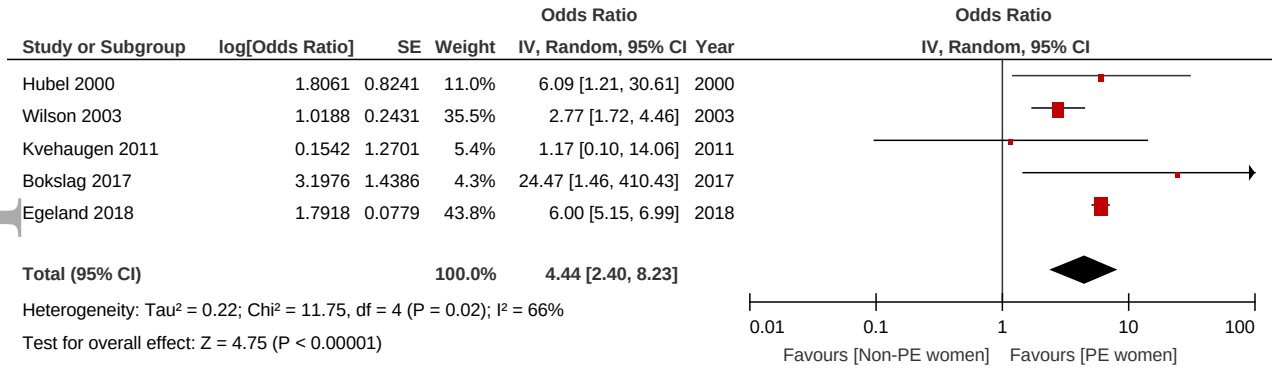


Figure 15. a) Pooled risk of anti-hypertensive therapy among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of anti-hypertensive therapy among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

a)



b)

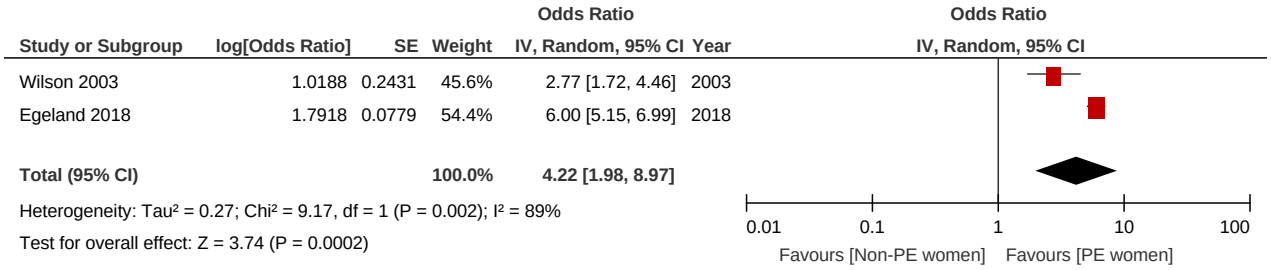
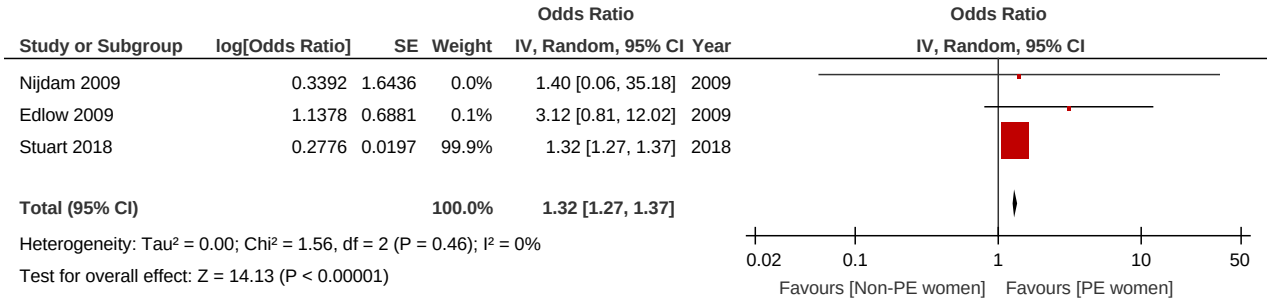


Figure 16. a) Pooled risk of dyslipidemia among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of dyslipidemia among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

a)



b)

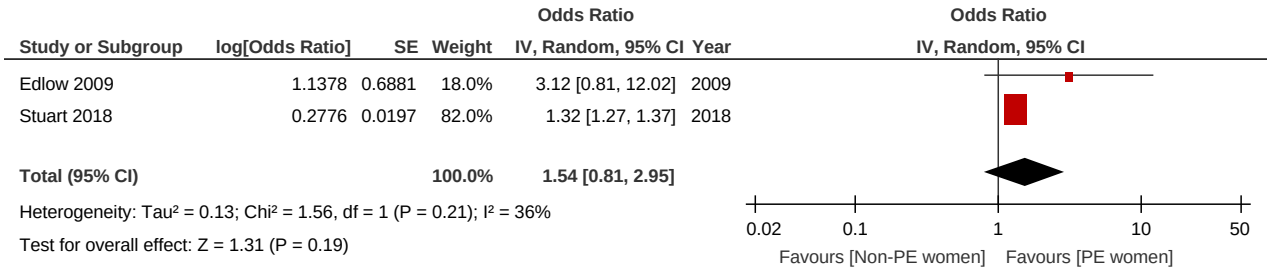
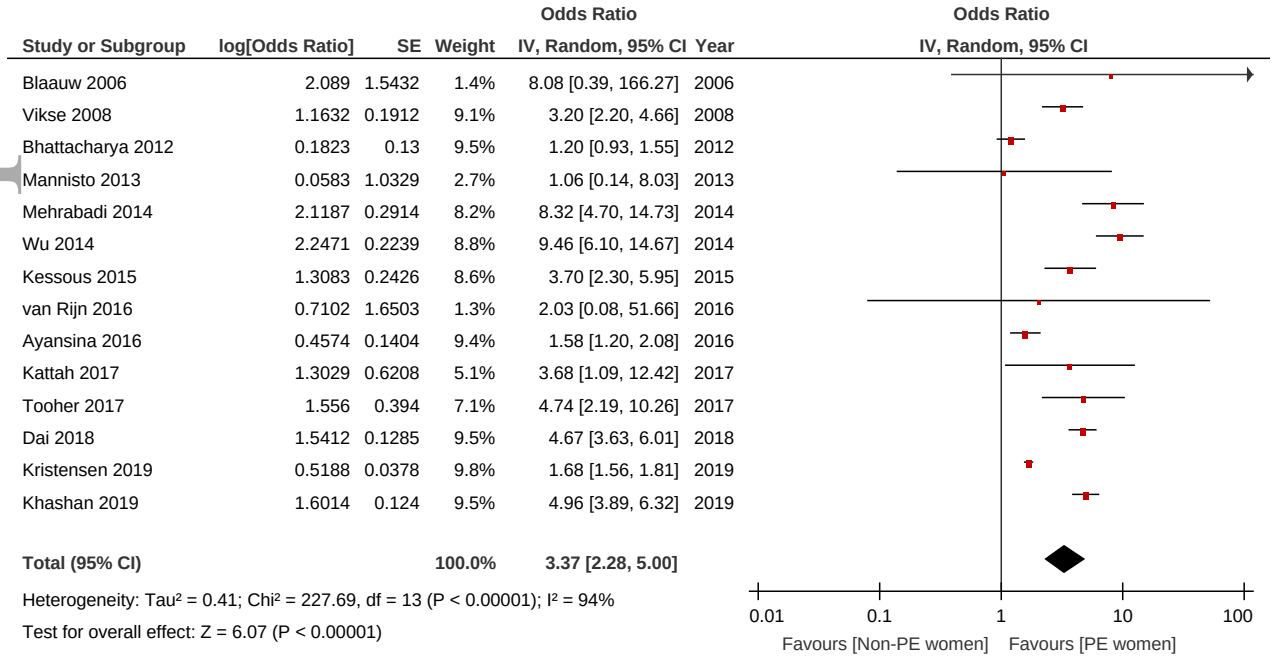


Figure 17. a) Pooled risk of kidney disease among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of kidney disease among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

a)



b)

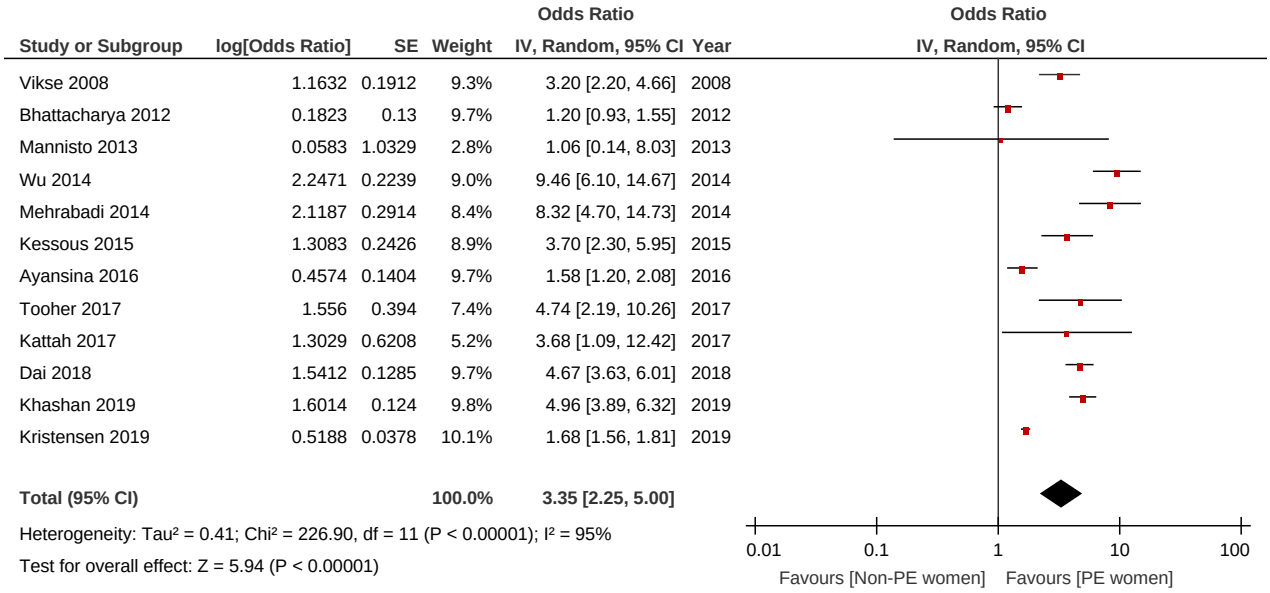
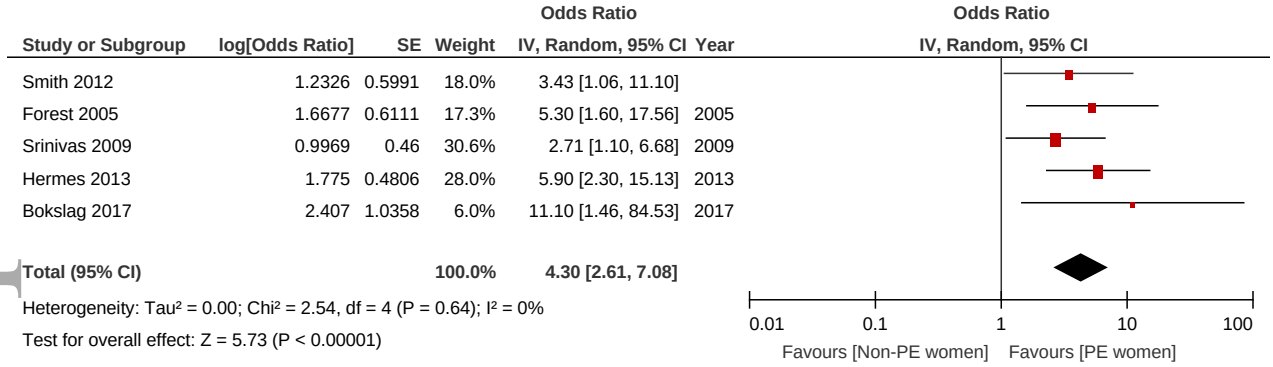


Figure 18. a) Pooled risk of metabolic syndrome among women with a prior diagnosis of pre-eclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of metabolic syndrome among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

a)



b)

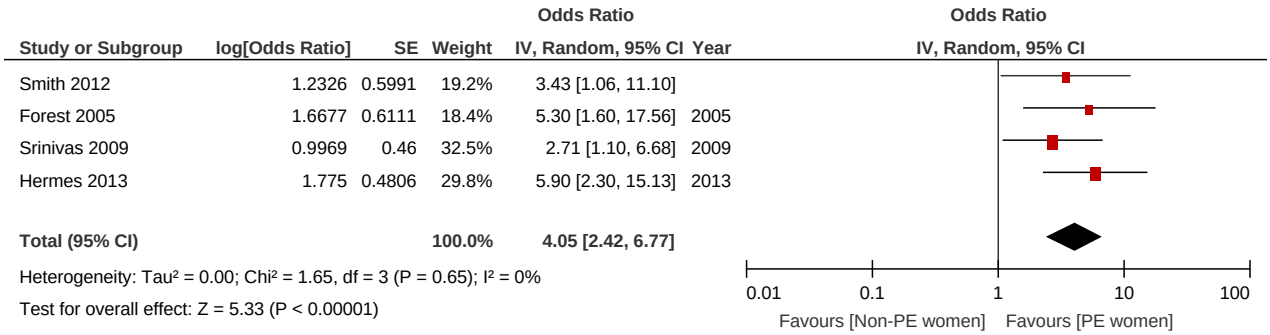


Figure 19. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

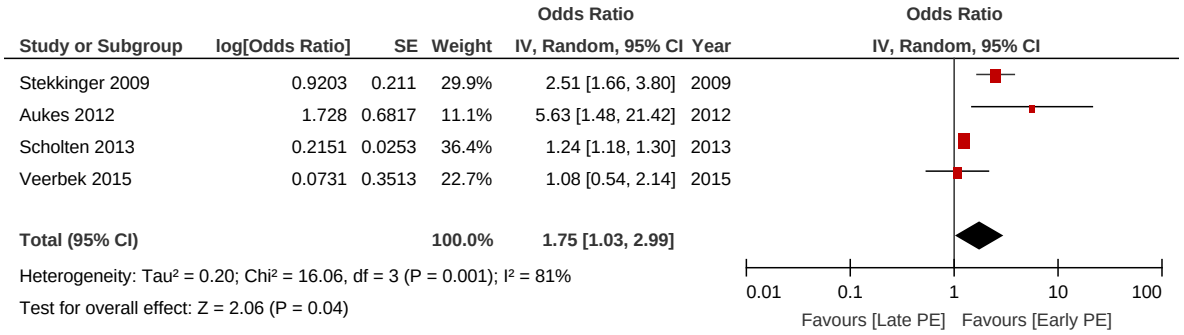


Figure 20. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

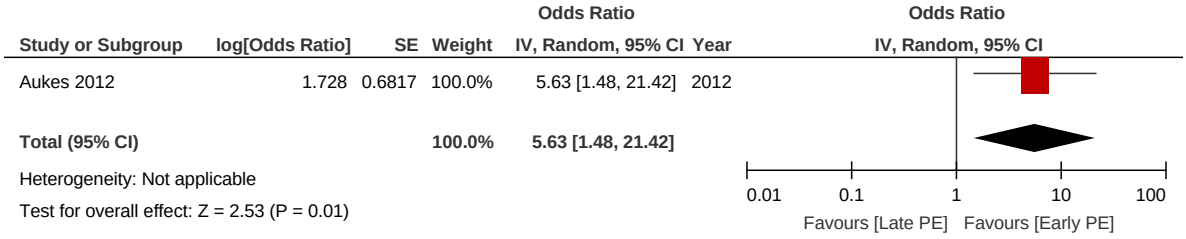


Figure 21. Pooled risk of hypertension among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

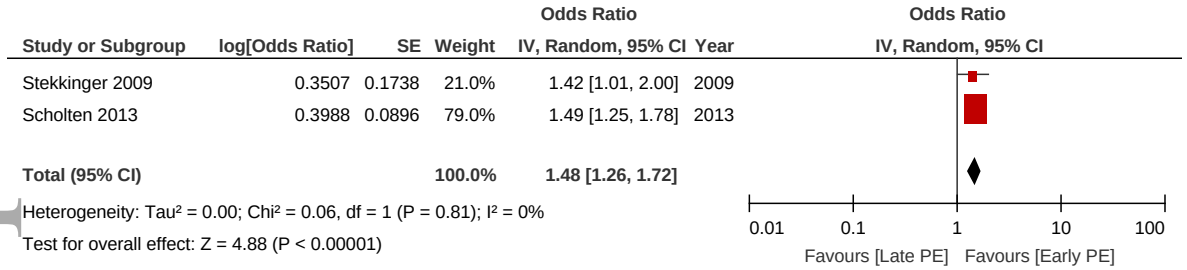


Figure 22. Pooled risk of dyslipidemia among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

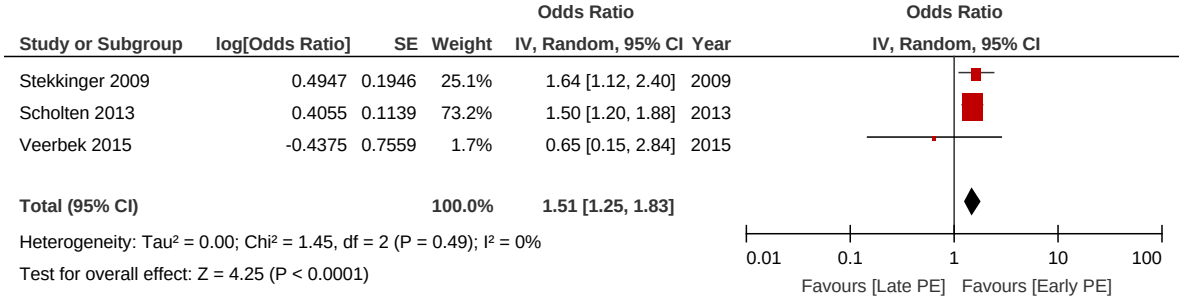


Figure 23. Pooled risk of kidney disease among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

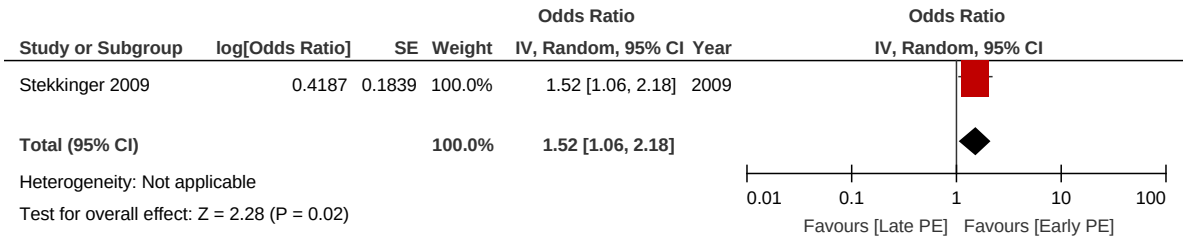


Figure 24. Pooled risk of metabolic syndrome among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.