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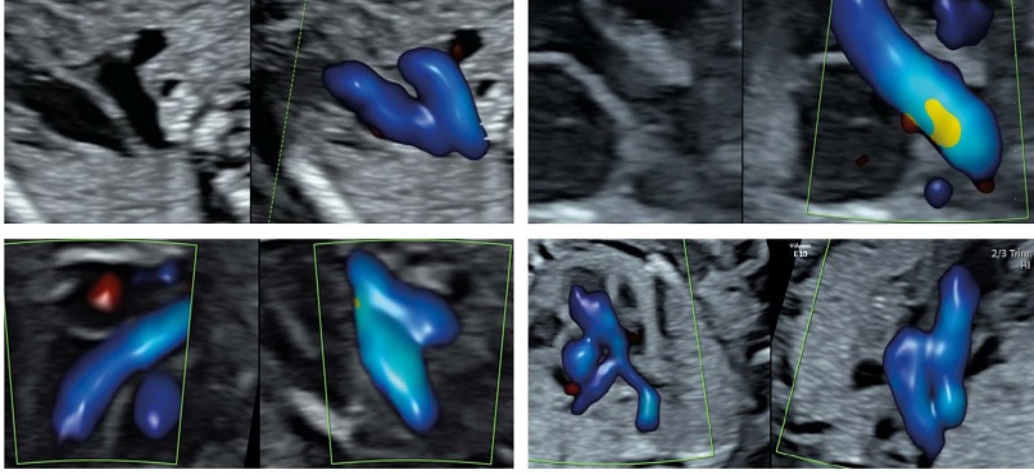

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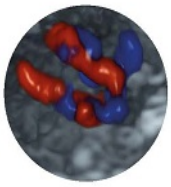

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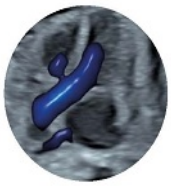

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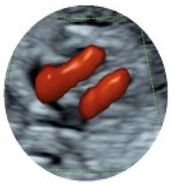

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Cardiovascular events following pregnancies complicated by preeclampsia with emphasis on the comparison between early and late onset forms: a systematic review and meta-analysis

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Running head: Cardiovascular health following preeclampsia.

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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

The Authors state no financial disclosures nor conflict of interest related to the content of this work.

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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

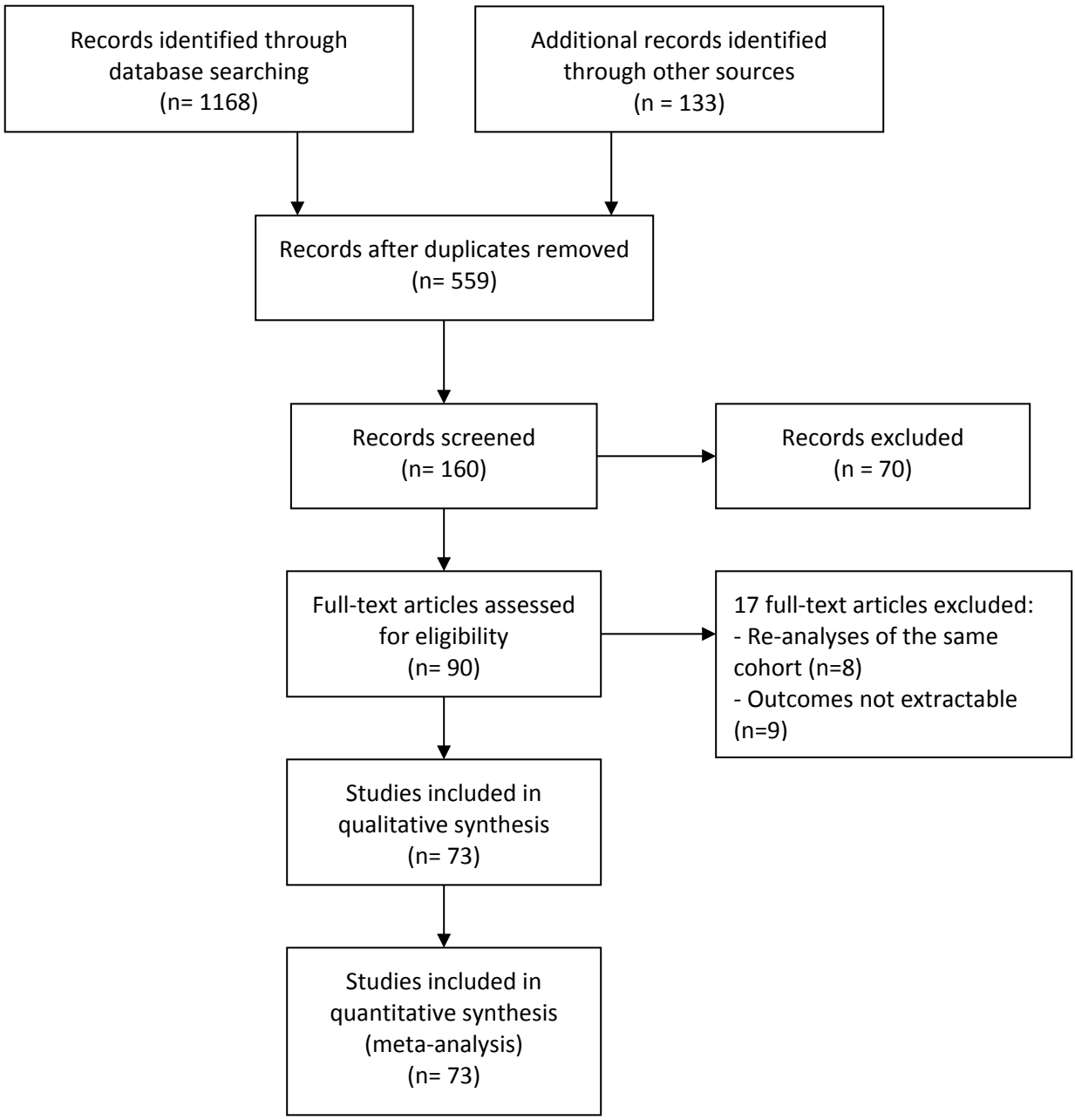


Figure 2. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

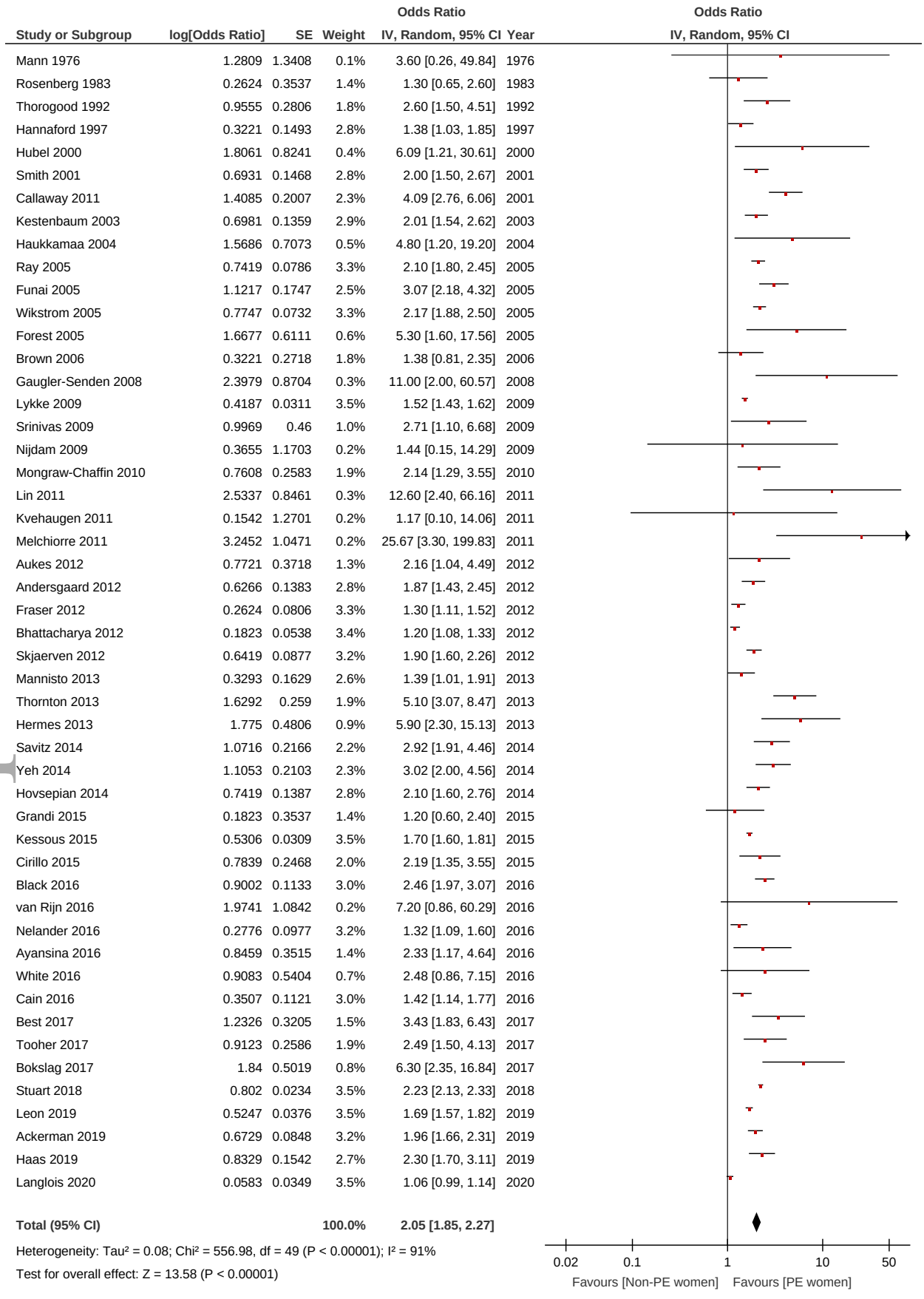


Figure 3. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

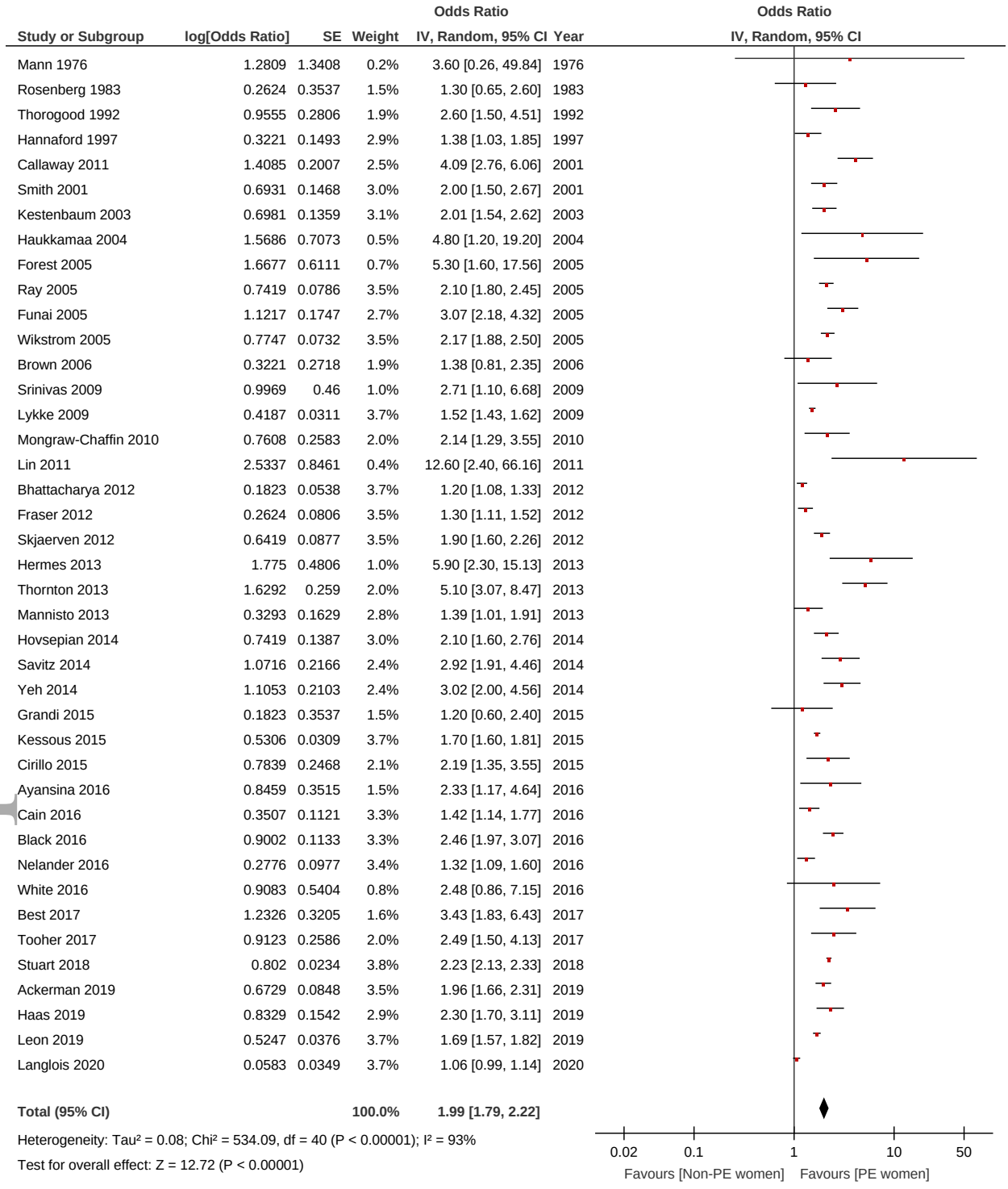
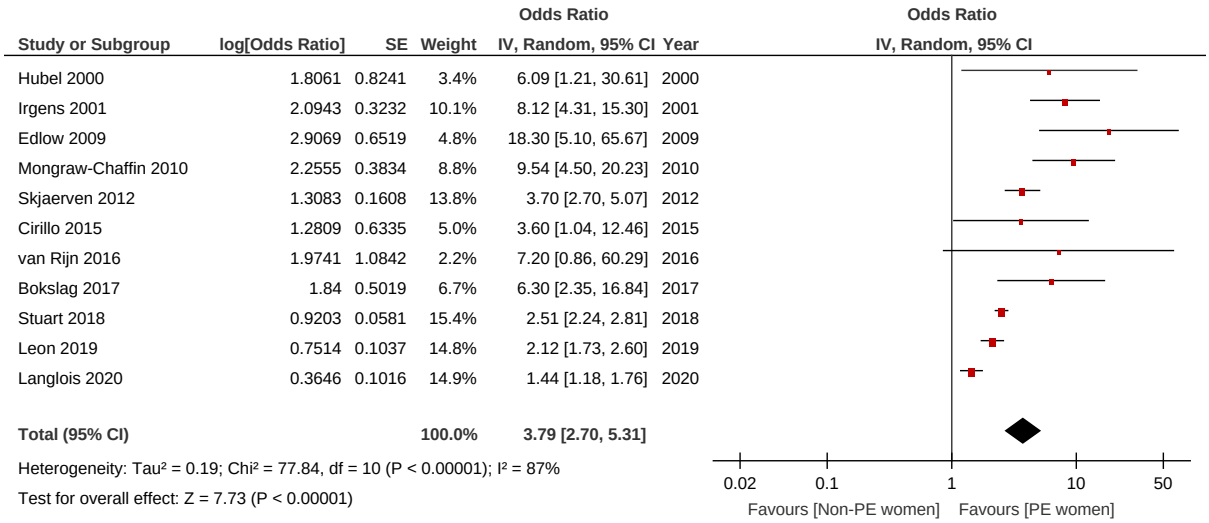


Figure 4. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status (a), and among women with a prior diagnosis of late-onset preeclampsia versus women with prior normal pregnancy status (b).

a)



b)

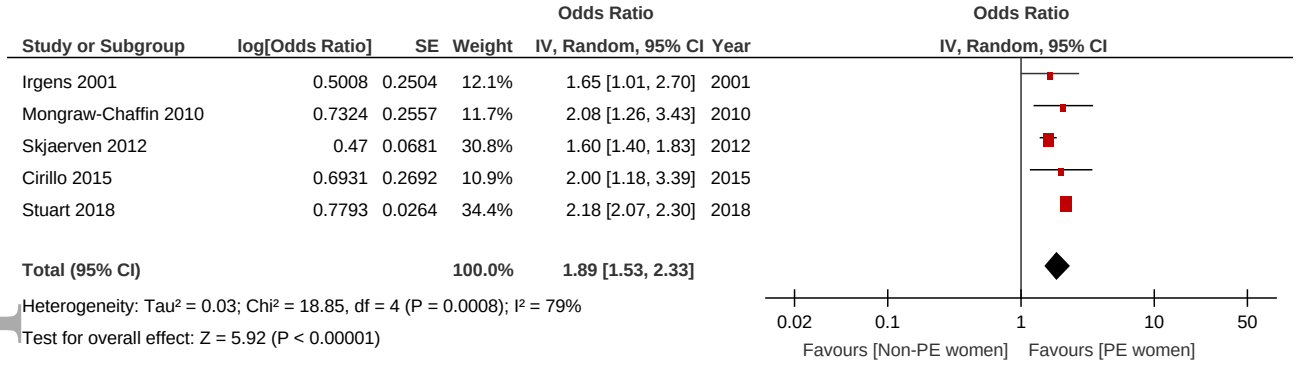


Figure 5. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

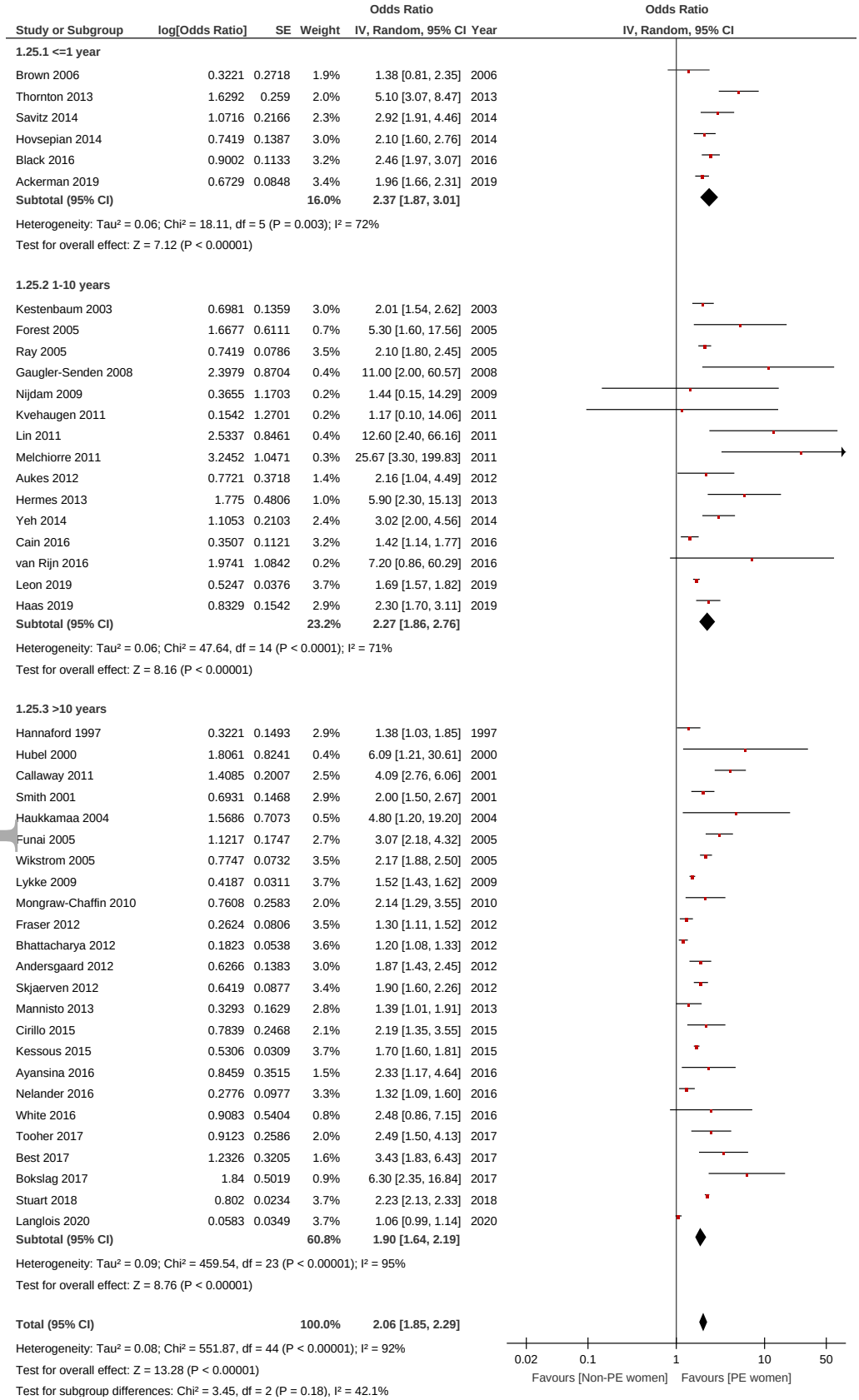


Figure 6. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

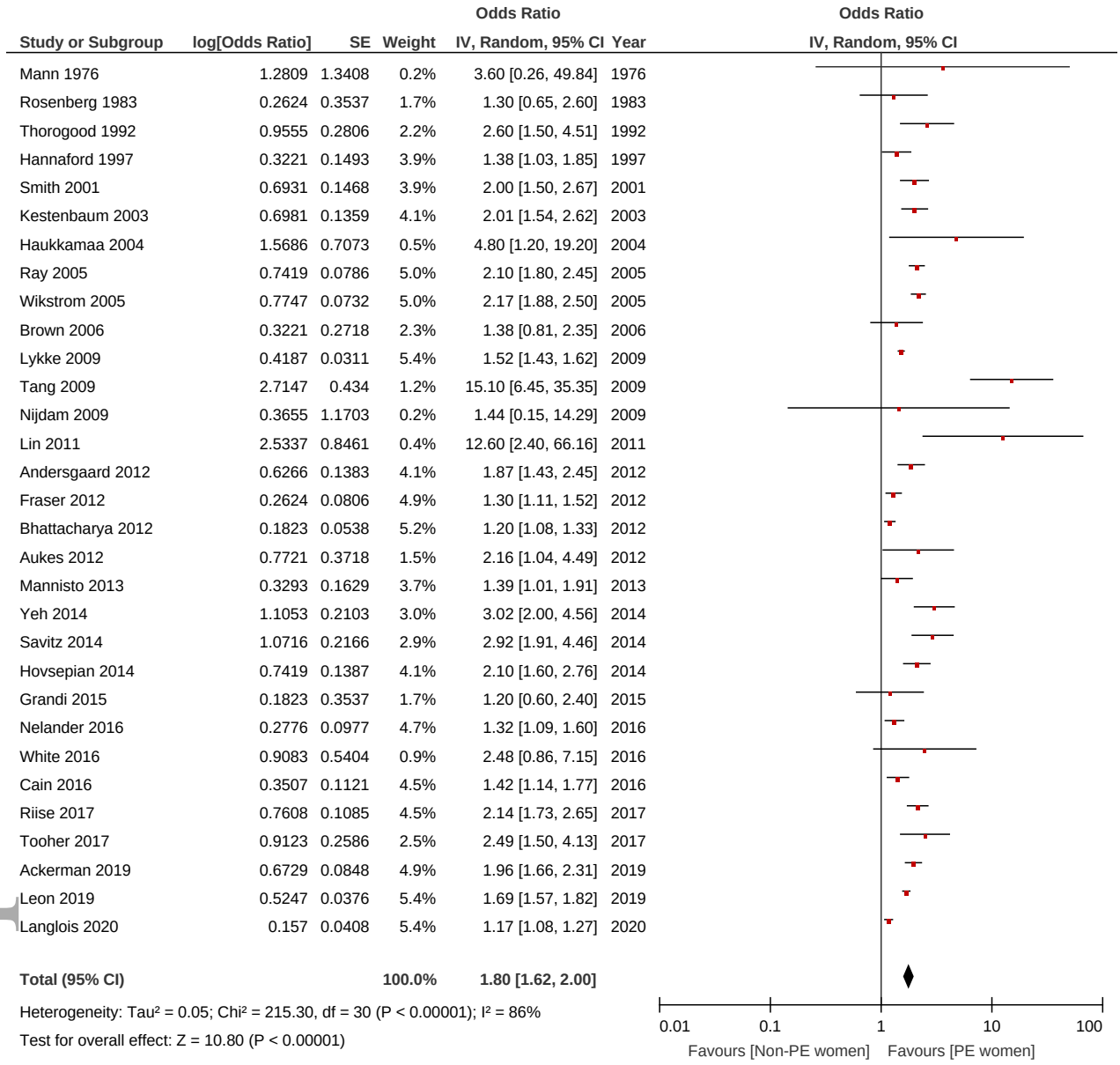


Figure 7. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

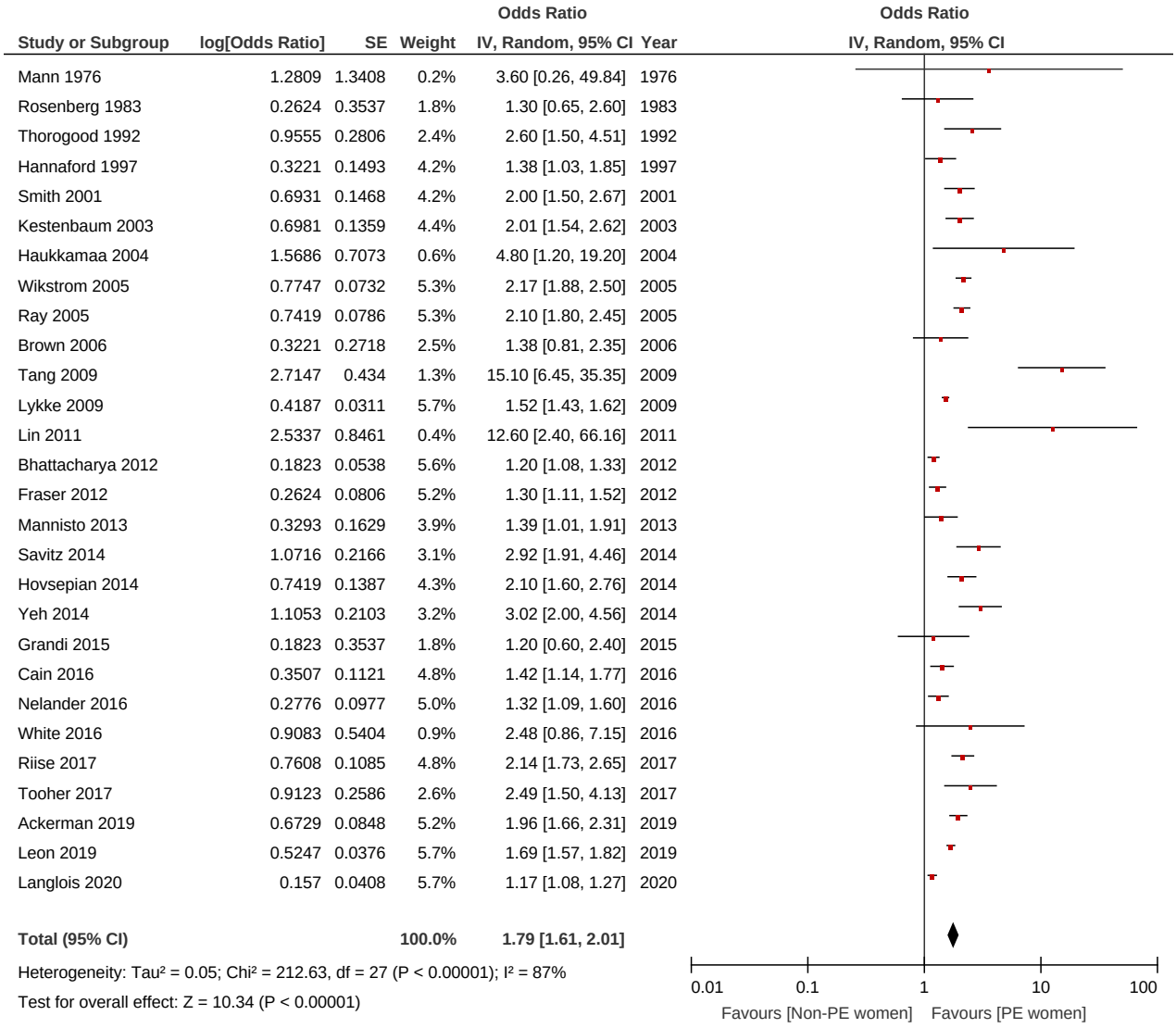


Figure 8. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status.

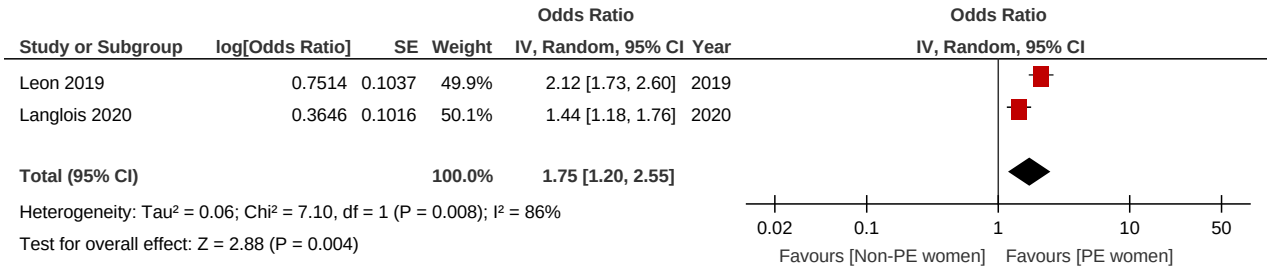


Figure 9. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

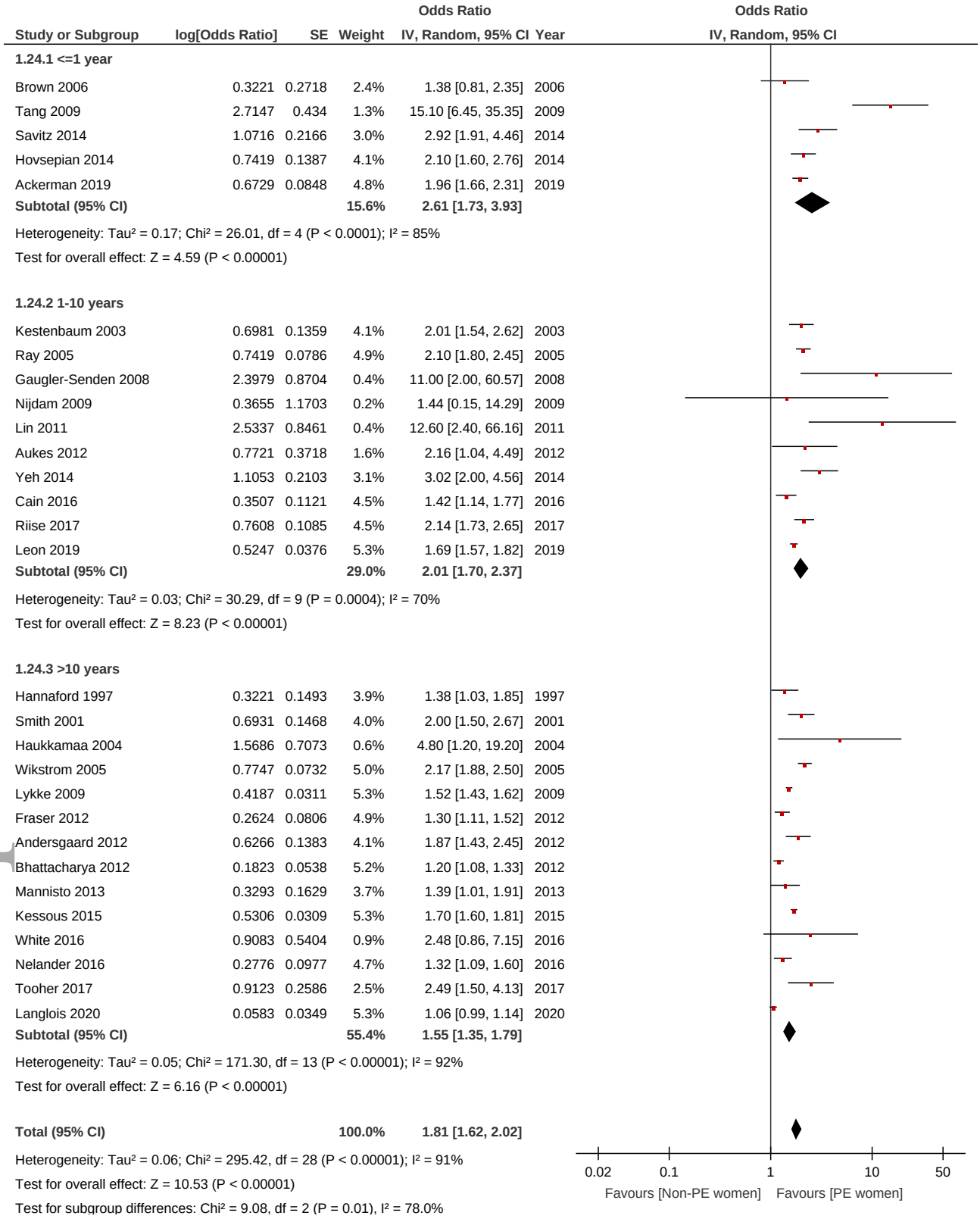


Figure 10. Pooled risk of death among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies.

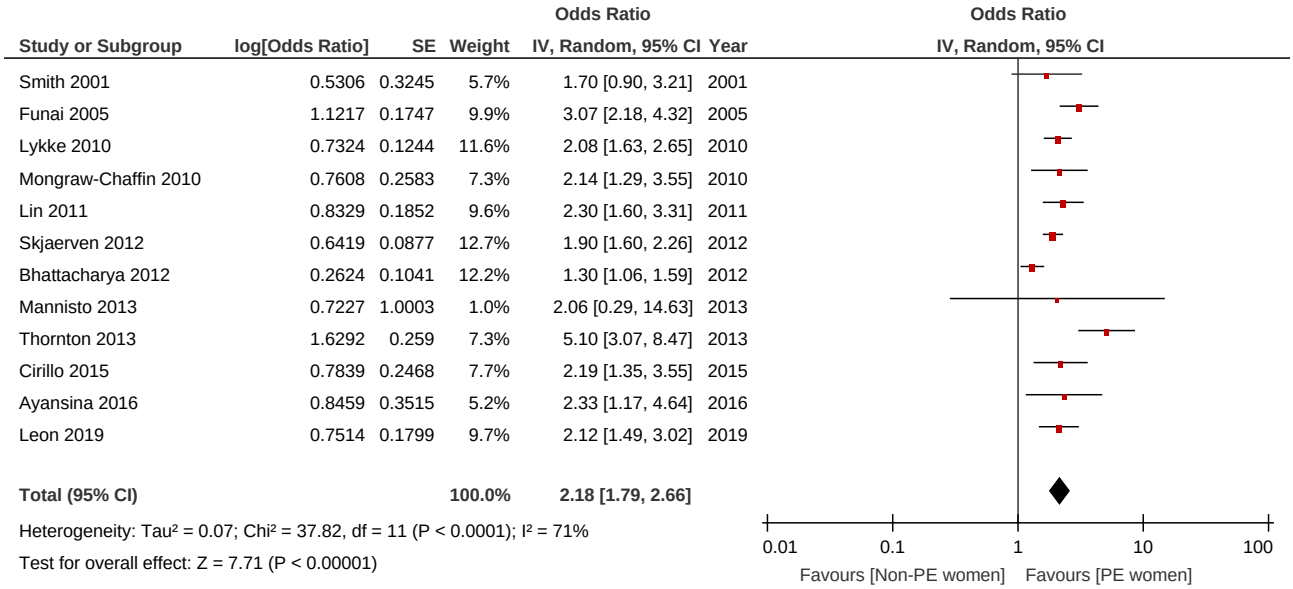
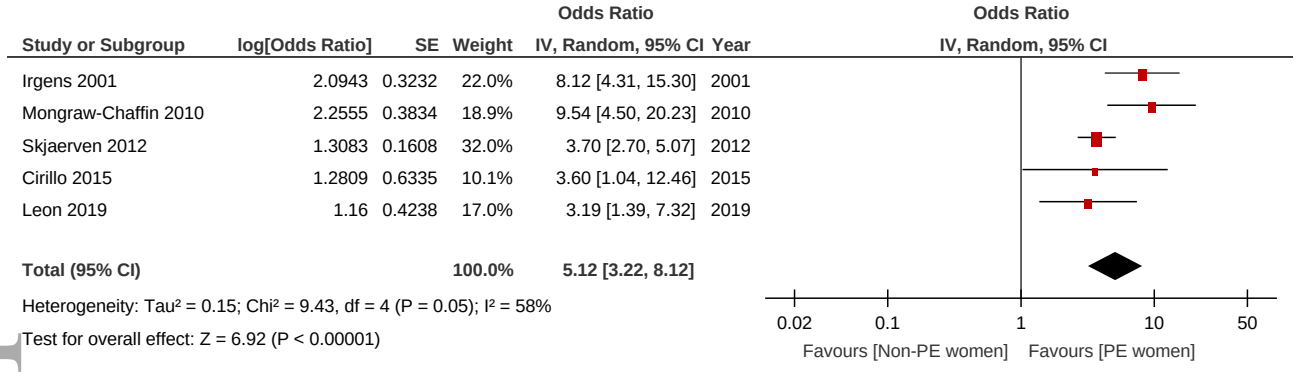


Figure 11. Pooled risk of death among women with a prior diagnosis of early-onset preeclampsia versus women with prior normal pregnancy status (a), and among women with a prior diagnosis of late-onset preeclampsia versus women with prior normal pregnancy status (b).

a)



b)

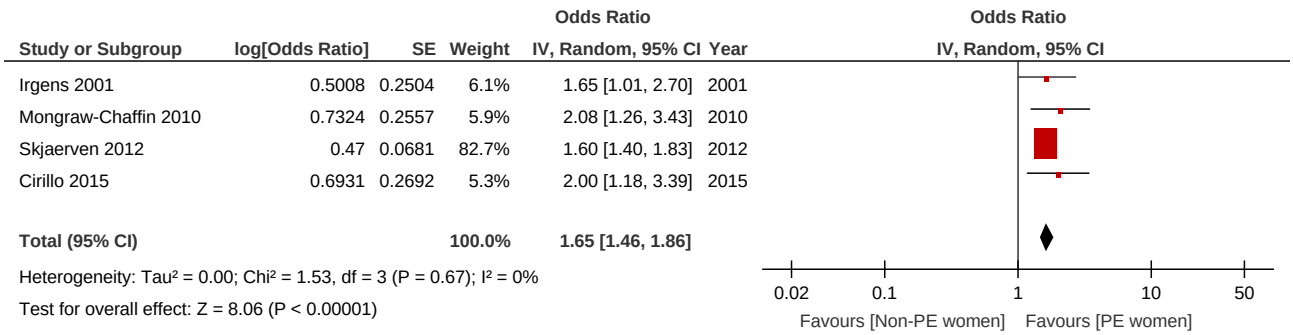


Figure 12. Pooled risk of death among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - By timelag between index pregnancy and outcome.

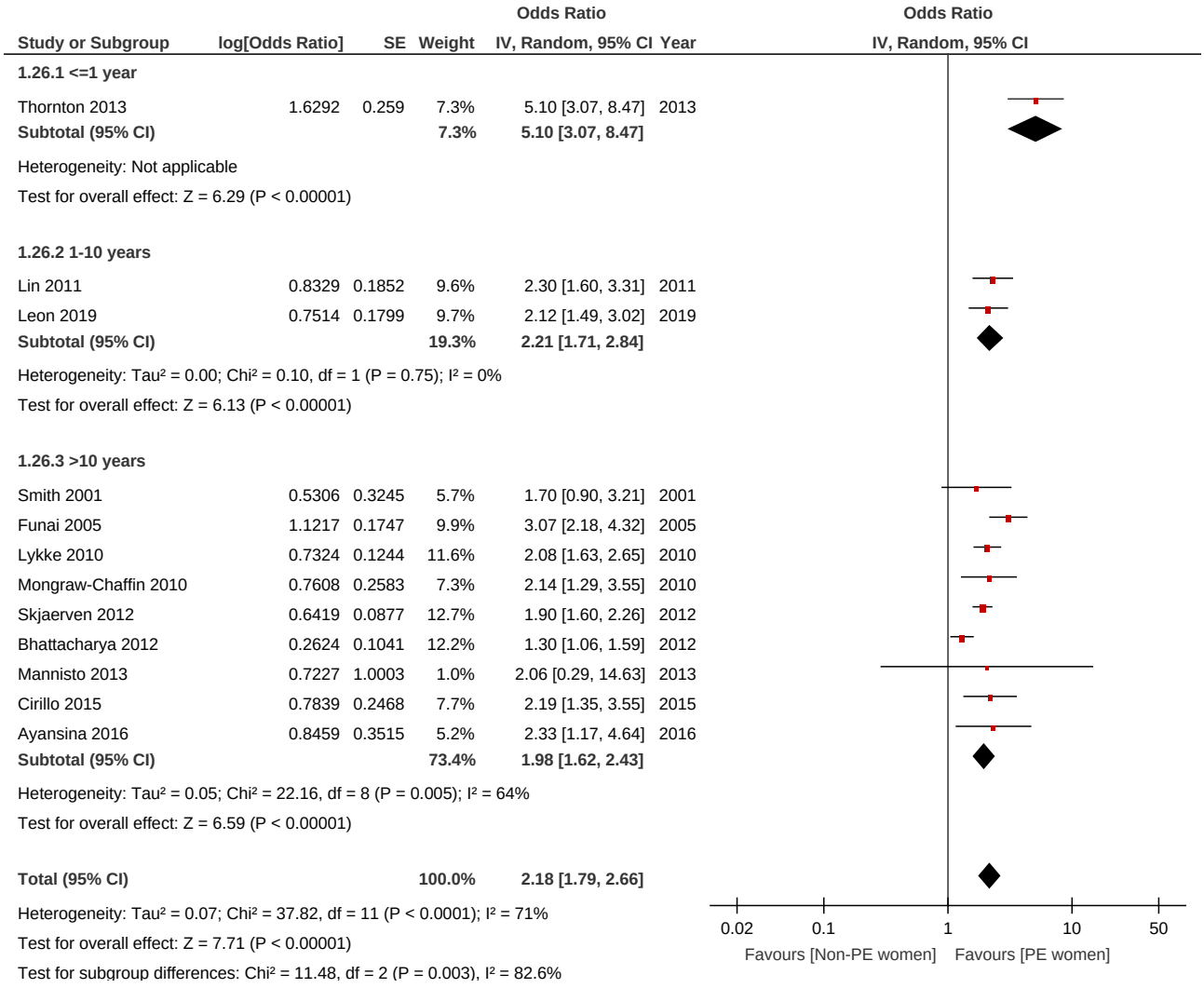
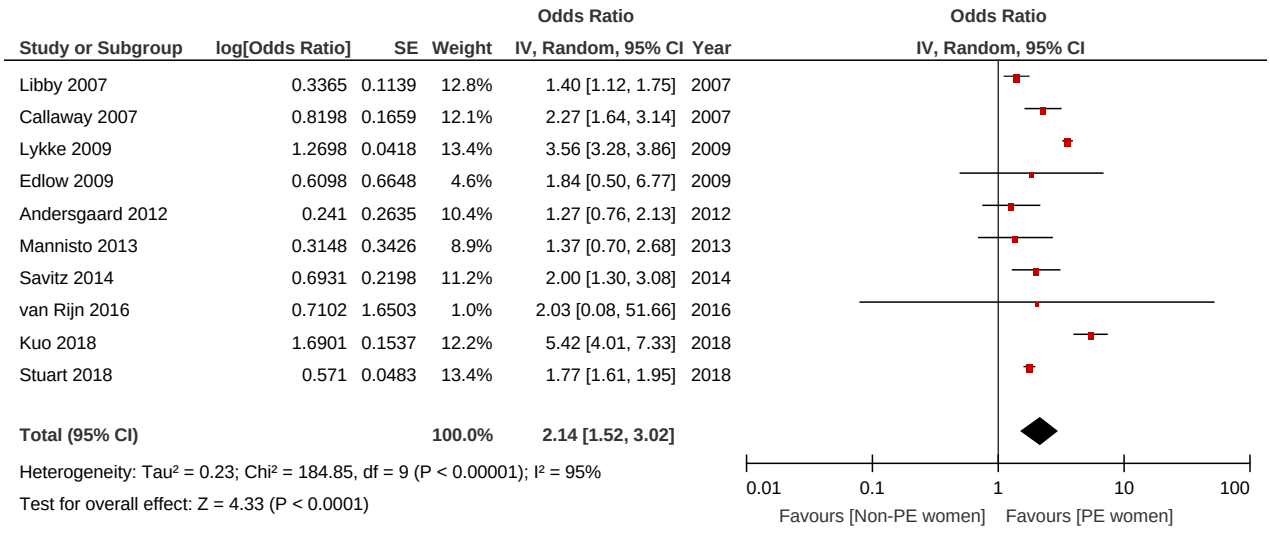


Figure 13. a) Pooled risk of diabetes among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of diabetes among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates only.

a)



b)

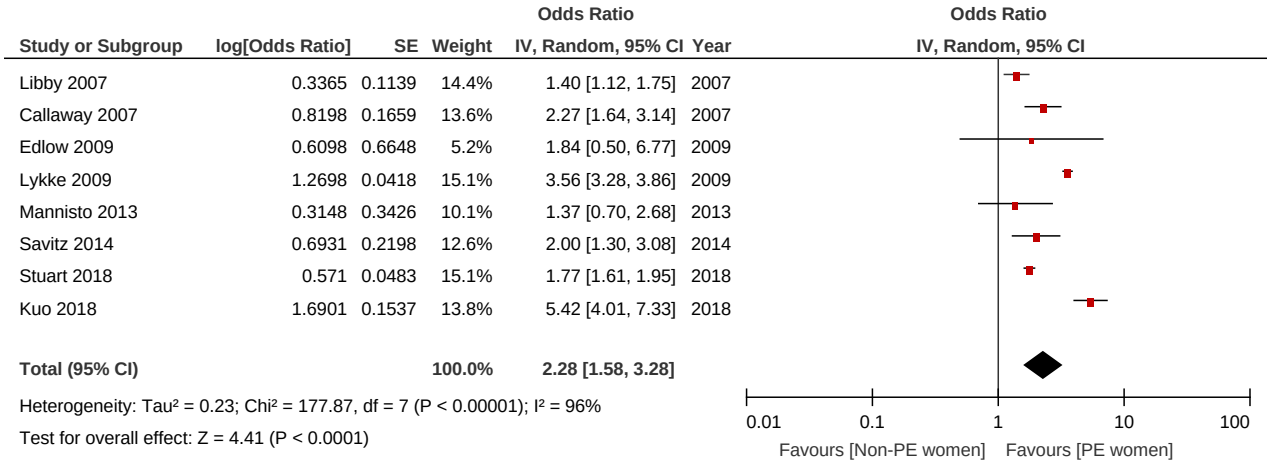
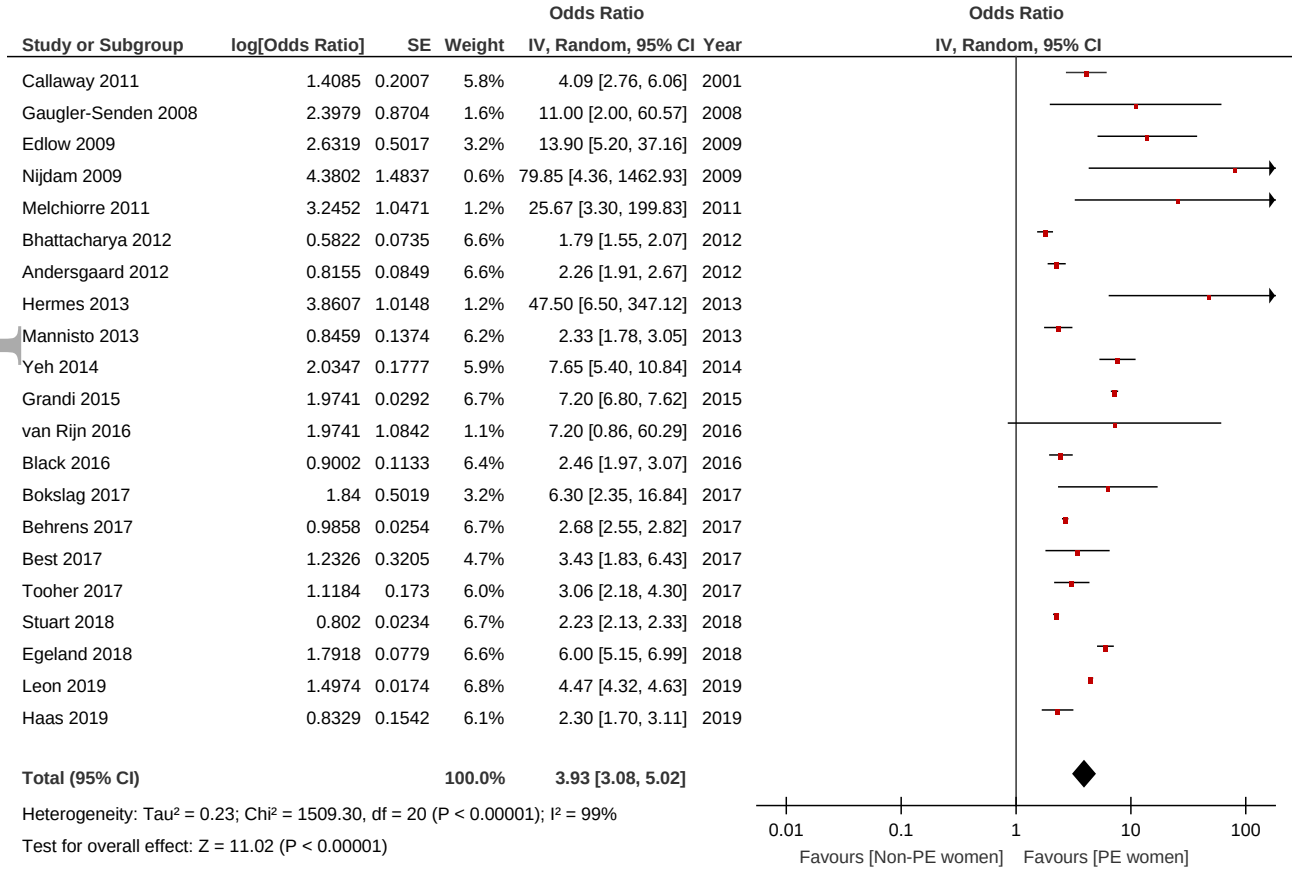


Figure 14. a) Pooled risk of hypertension among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of hypertension among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates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

a)



b)

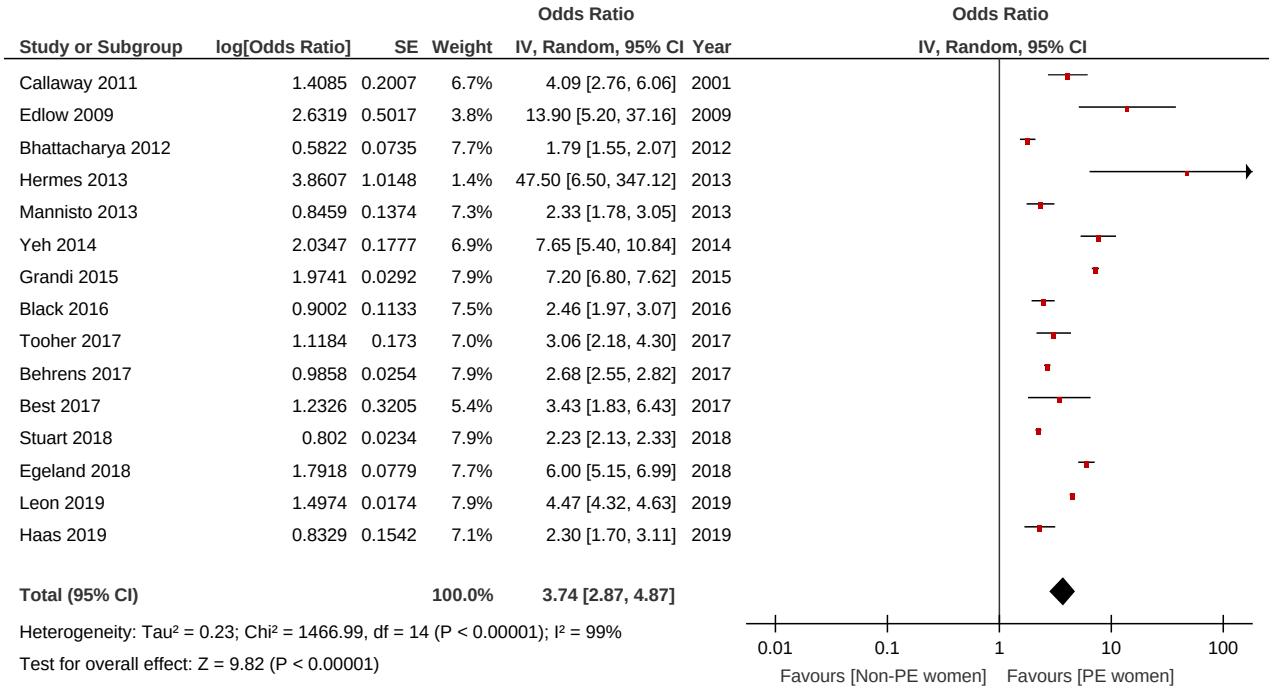
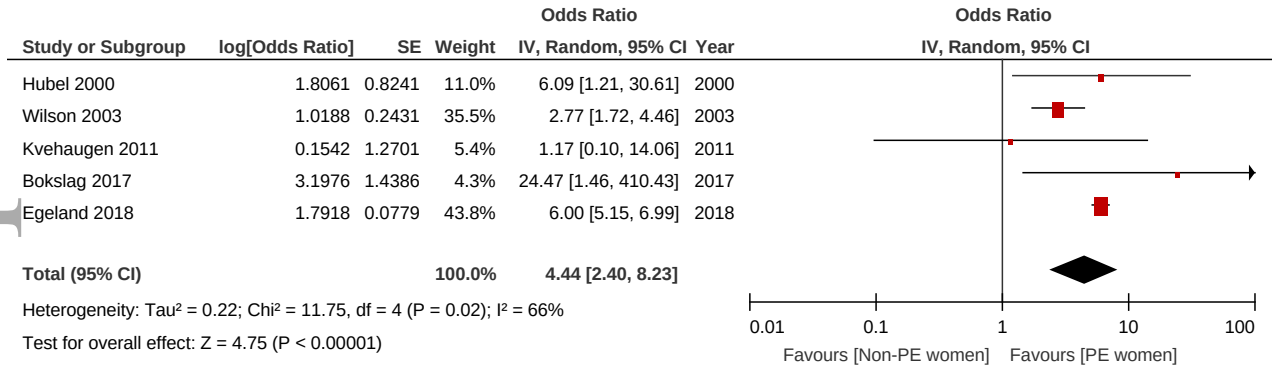


Figure 15. a) Pooled risk of anti-hypertensive therapy among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of anti-hypertensive therapy among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy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

a)



b)

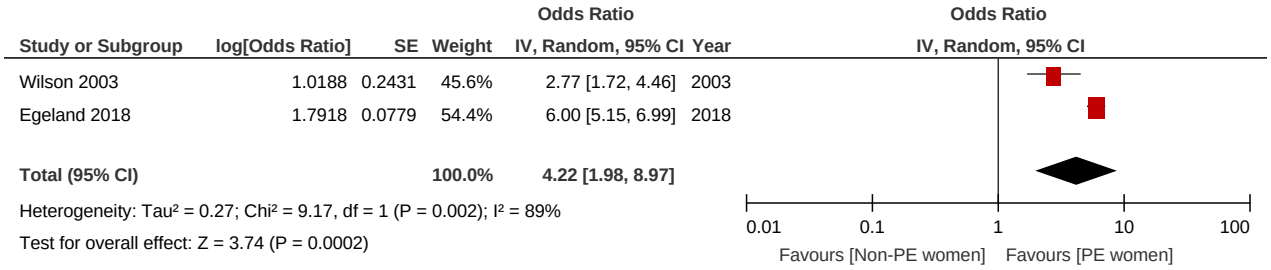
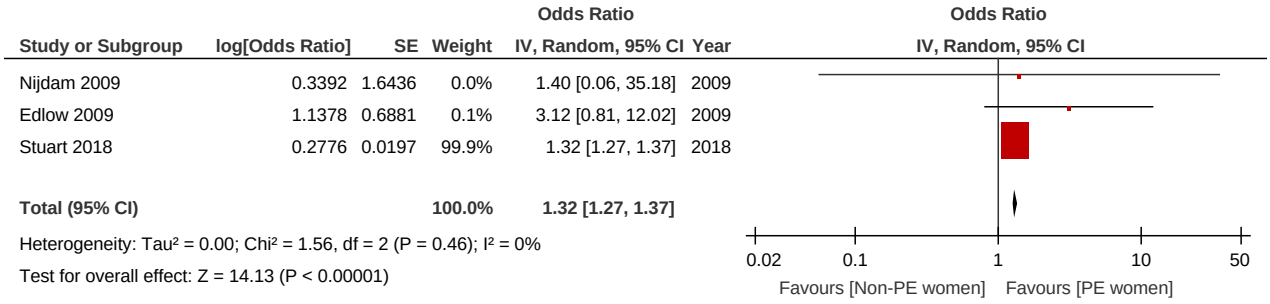


Figure 16. a) Pooled risk of dyslipidemia among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of dyslipidemia among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted estimates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

a)



b)

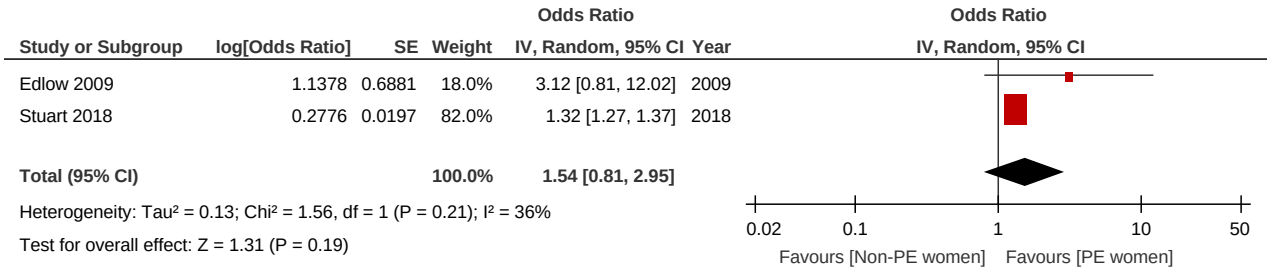
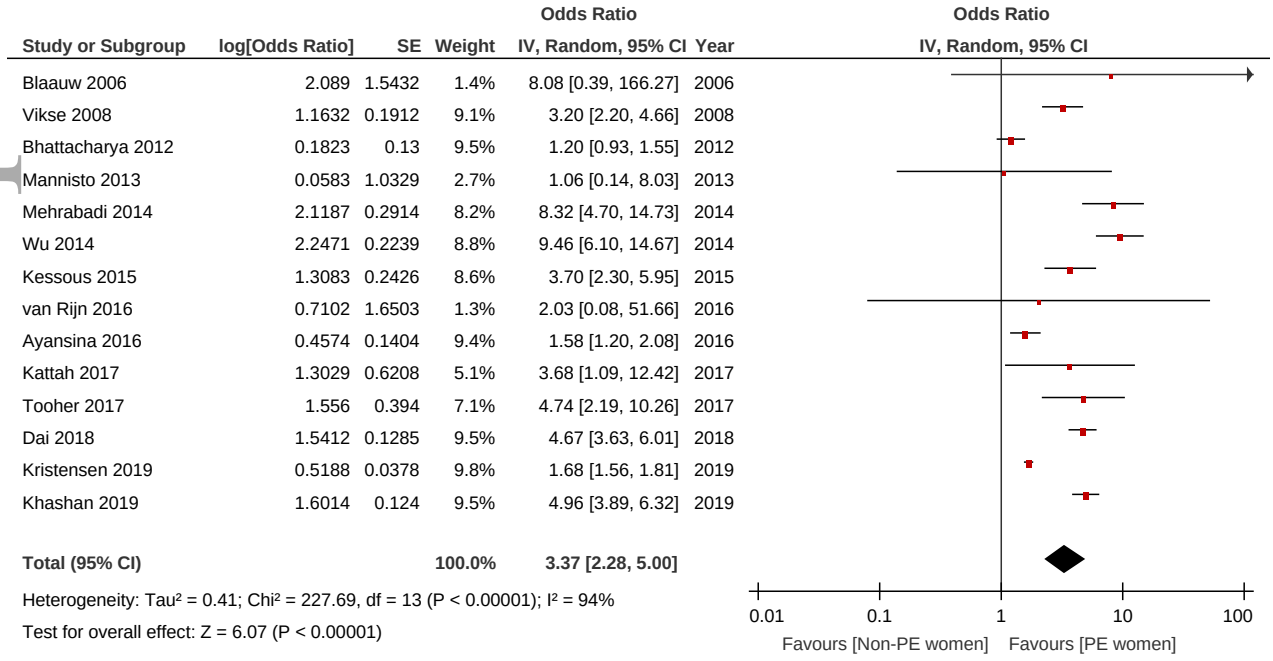


Figure 17. a) Pooled risk of kidney disease among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of kidney disease among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status - Adjusted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

a)



b)

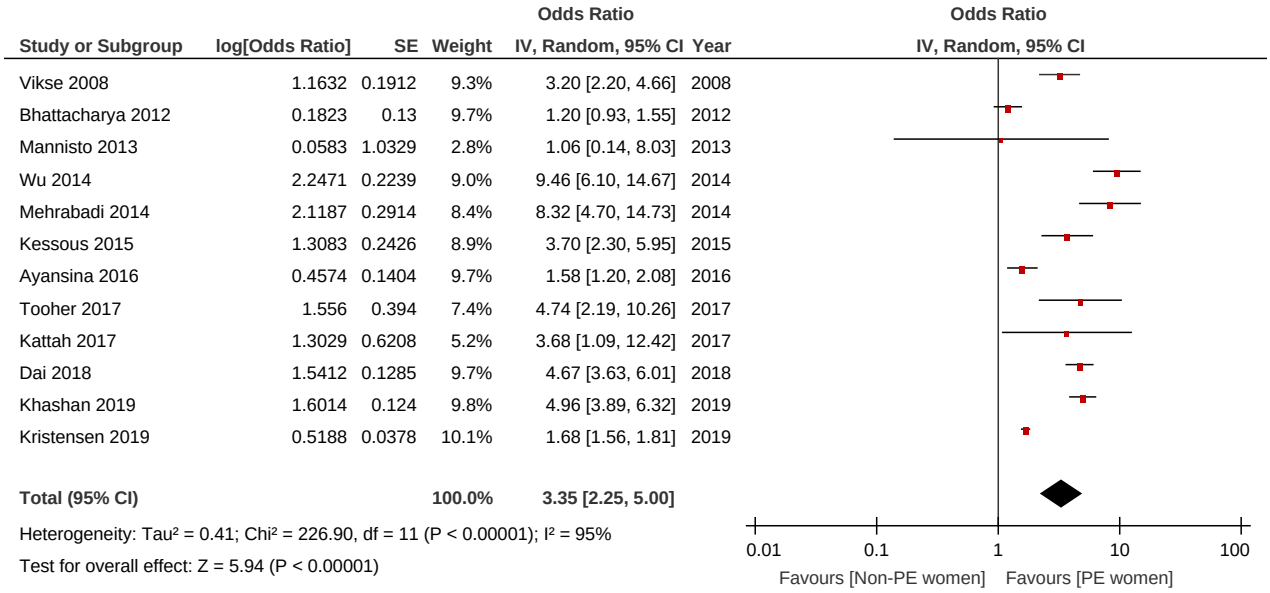
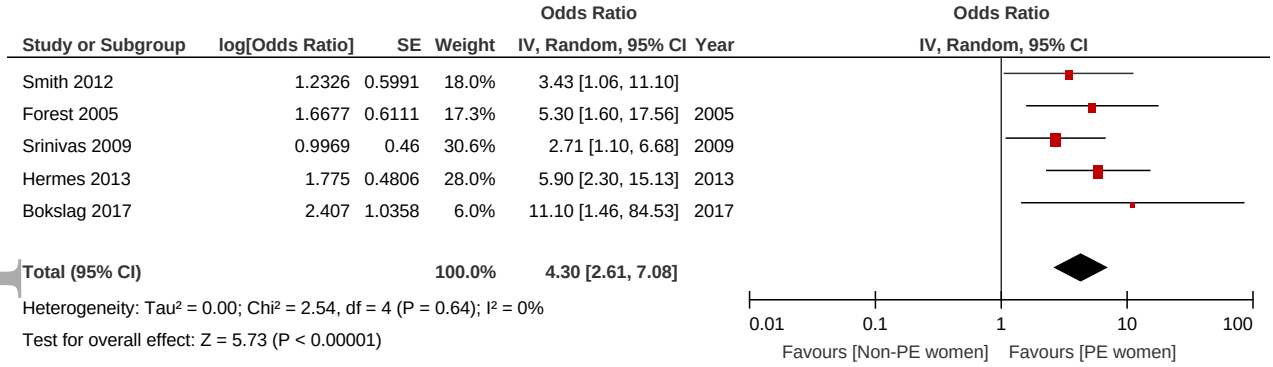


Figure 18. a) Pooled risk of metabolic syndrome among women with a prior diagnosis of pre-eclampsia versus women with prior normal pregnancy status - All studies. b) Pooled risk of metabolic syndrome among women with a prior diagnosis of preeclampsia versus women with prior normal pregnancy status -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

a)



b)

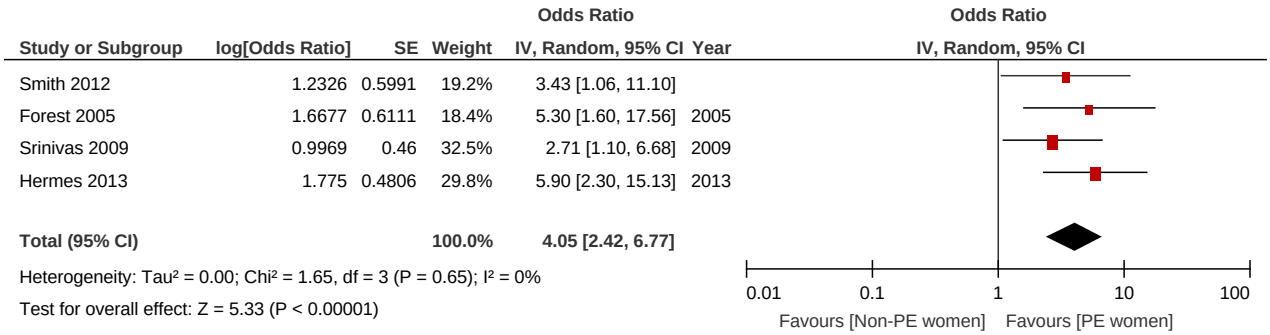


Figure 19. Pooled risk of composite adverse cardiovascular events among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

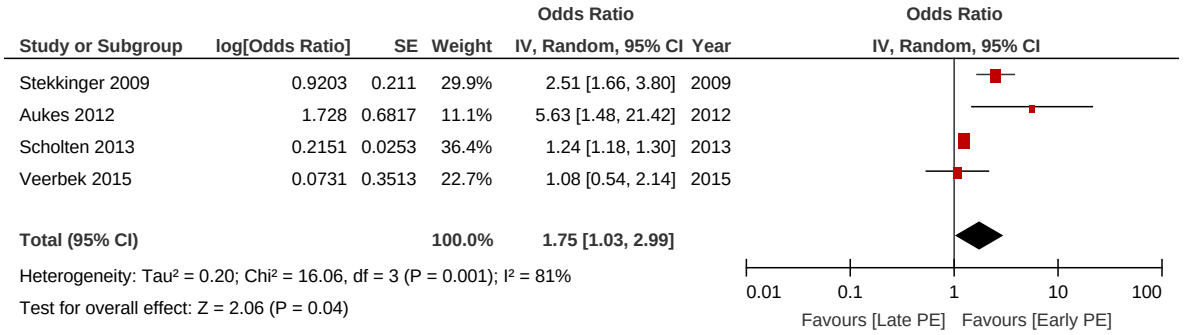


Figure 20. Pooled risk of cardiovascular and cerebrovascular diseases among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

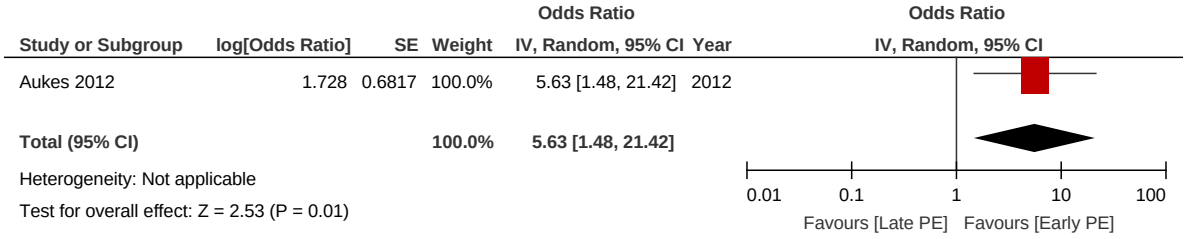


Figure 21. Pooled risk of hypertension among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

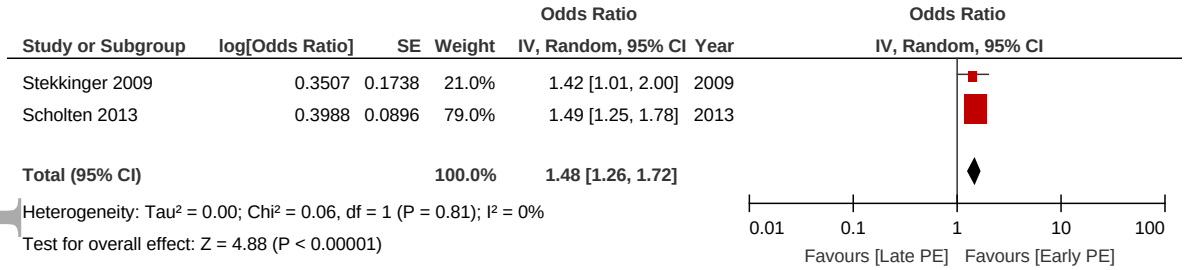


Figure 22. Pooled risk of dyslipidemia among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

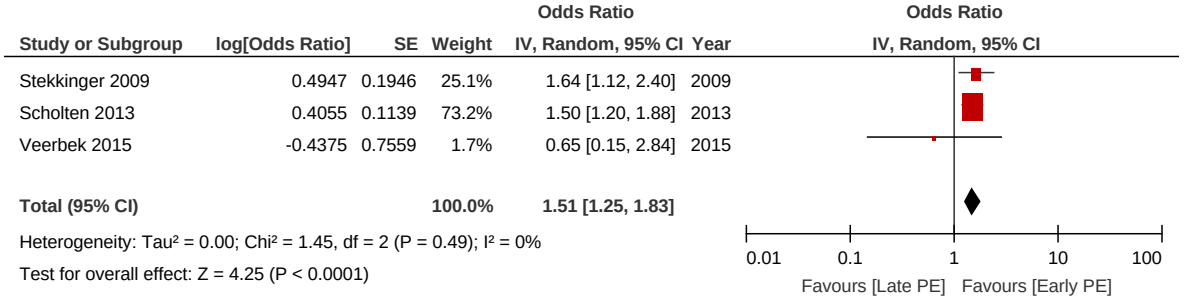


Figure 23. Pooled risk of kidney disease among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.

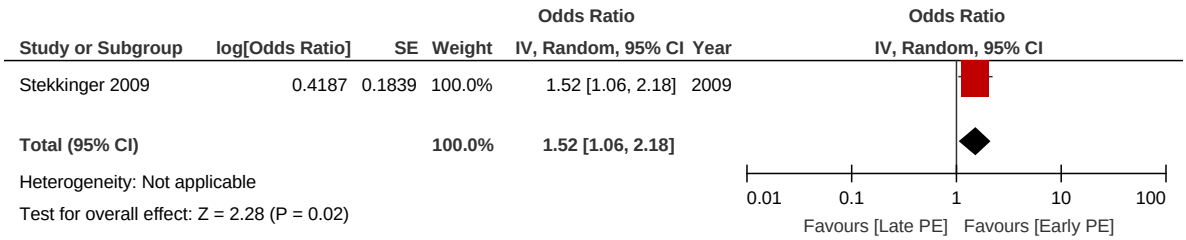


Figure 24. Pooled risk of metabolic syndrome among women with a prior diagnosis of early-onset preeclampsia versus women with a prior diagnosis of late-onset preeclampsia - All studies.