Meta-analysis

Effects of preeclampsia and eclampsia on maternal metabolic and biochemical outcomes in later life: a systematic review and meta-analysis

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A B S T R A C T

Objective: To evaluate the association between preeclampsia (PE) and eclampsia (E) on subsequent metabolic and biochemical outcomes.

Methods: Systematic review and meta-analysis of observational studies. We searched five engines until November 2018 for studies evaluating the effects of PE/E on metabolic and biochemical outcomes after delivery. PE was defined as presence of hypertension and proteinuria at ≥20 weeks of pregnancy; controls did not have PE/E. Primary outcomes were blood pressure (BP), body mass index (BMI), metabolic syndrome (MetS), blood lipids and glucose levels. Random effects models were used for meta-analyses, and effects reported as risk difference (RD) or mean difference (MD) and their 95% confidence interval (CI). Subgroup analyses by time of follow up, publication year, and confounder adjustment were performed.

Results: We evaluated 41 cohorts including 3300 PE/E and 13,967 normotensive controls. Women were followed up from 3 months after delivery up to 32 years postpartum. In comparison to controls, PE/E significantly increased systolic BP (MD = 8.3 mmHg, 95%CI 6.8 to 9.7), diastolic BP (MD = 6.8 mmHg, 95%CI 5.6 to 8.0), BMI (MD = 2.0 kg/m²; 95%CI 1.6 to 2.4), waist (MD = 4.3 cm, 95%CI 3.1 to 5.5), waist-to-hip ratio (MD = 0.02, 95%CI 0.01 to 0.03), weight (MD = 5.1 kg, 95%CI 2.2 to 7.9), total cholesterol (MD = 4.6 mg/dL, CI 1.5 to 7.7), LDL (MD = 4.6 mg/dL; 95%CI 0.2 to 8.9), triglycerides (MD = 7.7 mg/dL, 95%CI 3.6 to 11.7), glucose (MD = 2.6 mg/dL, 95%CI 1.2 to 4.0), insulin (MD = 19.1 pmol/L, 95%CI 11.9 to 26.2), HOMA-IR index (MD = 0.7, 95%CI 0.2 to 1.2), C reactive protein (MD = 0.05 mg/dL, 95%CI 0.01 to 0.09), and the risks of hypertension (RD = 0.24, 95%CI 0.15 to 0.33) and MetS (RD = 0.11, 95%CI 0.08 to 0.15). Heterogeneity of effects was high for most outcomes. Risk of bias was moderate across studies. Subgroup analyses showed similar effects as main analyses.

Conclusion: Women who had PE/E have worse metabolic and biochemical profile than those without PE/E in an intermediate to long term follow up period.

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1. Introduction

Hypertensive disorders of pregnancy (HDP) are a heterogeneous group of syndromes affecting 3–10% of pregnancies, and include preeclampsia (PE), eclampsia (E), gestational hypertension, and pre-gestational hypertension [1,2]. PE and E have as a common definition the presence of new onset hypertension and proteinuria diagnosed during the second half (> 20 weeks) of pregnancy. E is associated with tonic-clonic seizures and general complications in a woman with or without preeclampsia. Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is a rare complication of PE/E which may be accompanied of fatigue, edema, headache, nausea, abdominal pain, visual alterations, hemorrhage, intravascular coagulation, kidney failure and placental abruption [1,2].

PE/E have negative consequences on maternal and fetal health during pregnancy, including increased perinatal mortality, pre-term births, small for gestational age infants, high rate of cesarean deliveries, and other adverse outcomes even at later postnatal periods [3–6]. PE/E are associated with elevated blood pressure, inflammation and endothelial dysfunction, and these findings may remain after delivery and contribute to future maternal cardiovascular risk [7–11]. Furthermore, two recent meta-analyses reported that PE was independently associated with higher risk of future diabetes and cardiovascular events [12,13]. In particular, PE increased the risk of future diabetes (risk ratio [RR] 2.37, 95% confidence interval [CI] 1.89, 2.97) appearing in women as early as during 1 year postpartum (RR 1.97, 95% CI 1.35, 2.87) and persisting the risk up to 10 years after delivery (RR 1.95, 95% CI 1.28, 2.97) [12]. PE was also independently associated with higher risk of future heart failure (RR 4.19, 95% CI 2.09–8.38), coronary heart disease (RR 2.50, 95% CI 1.43–4.37), cardiovascular disease death (RR 2.21, 95% CI 1.83–2.66), and stroke (RR 1.81, 95% CI 1.29–2.55) [13]. Risks persisted after different confounder adjustments.

We systematically evaluated the association between PE/E and metabolic and biochemical outcomes from observational studies with intermediate and long term of follow up.

2. Methods

This systematic review was reported according to the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) Group guidelines [14]. Formal institutional review board approval was not required as this manuscript only addresses data extracted from already published studies.

2.1. Study search

PubMed-Medline, Scopus, Web of Science, Cochrane Library, and EMBASE were searched from inception to November 2018 for observational studies evaluating the association between PE/E and metabolic and biochemical outcomes after delivery. Studies were included irrespective of age, parity, ethnicity, country of origin, publication date and language. A search strategy was developed for PubMed, and modified accordingly for other databases. Also, reference lists from selected studies were hand searched. Keywords were preeclampsia, eclampsia, HELLP, and each metabolic and biochemical outcome. The full Pubmed search strategy using Boolean operators AND or OR can be found in Appendix A, Supplementary Table 1.

PE, E and HELLP syndrome have a common definition: new onset hypertension and proteinuria appearing after 20 weeks of pregnancy according to different scientific societies such as the American College of Obstetrics and Gynecologists (ACOG) [2], the International Society for the study of Hypertension in Pregnancy (ISSHP) [15], the National High Blood Pressure Education Program Working Group (NHBPEPWG) [16], the World Health Organization International Classification of Diseases (ICD) [17], or the Australasian Society for the Study of Hypertension in Pregnancy Consensus
### Table 1: Characteristics of included studies.

| Author, year [reference] | Country; study design | Exclusion reasons | Data during the index pregnancy: preeclampsia (PE) | Data during the index pregnancy: control (CG) | Time of follow up and/or age | Matching variables for controls |
|--------------------------|-----------------------|-------------------|--------------------------------------------------|-----------------------------------------------|----------------------------|---------------------------------|
| Akhter T, 2013 [23]      | Sweden; Prospective cohort study | Chronic hypertension, renal disease, or pregestational or gestational DM or if they were pregnant with <1 fetus | PE according to the ACOG; n = 48 women; Age 30 [26, 34] years | Primiparous = 39 (71%); GAD 37 [34, 38] weeks | One year postpartum | Gestational duration |
| Andersgaard AB, 2012 [24] | Norway; Retrospective cohort study | Women with normo- or normo/microalbuminuria, hypertension with or without normoalbuminuria | PE: hypertension + proteinuria, N = 901 women; Age: 25.4 (24.4-26.4) years before the study of outcomes | Women reporting ≥1 child birth; GAD: not reported | Women reporting ≥1 child birth; GAD: not reported | Age 48.8 (25-87) years (PE group), and 47.4 (25-94) years (control group) |
| Aykas F, 2015 [25]       | Turkey; Retrospective cohort study | None of the patients and controls had a history of hypertension | PE according to the ACOG; N = 25 women; Age: 27.44 ± 6.68 years | Pregnanacies 1 (1-2); GAD: not reported | Pregnancies 2 (1-2); GAD: not reported | Follow-up period of PE group (6.12 ± 3.59 years and 6.05 ± 4.06 years in the CG) |
| Bar J, 1999 [26]         | Israel; Prospective cohort study | None of the women had a previous definitive diagnosis of hypertension or renal disease | PE according to the ACOG; n = 48 women according to the ACOG; Age: 36 ± 5 years | Parity not reported; Preterm delivery 30 (62.5%); IUGR: 27 (56%) | Parity not reported; Preterm delivery 2 (4%); IUGR 1 (2.2%) | Examination of the study and control groups was performed 3-5 years after delivery |
| Barden AE, 1999 [27]     | Australia; Retrospective cohort study | Known history of hypertension or renal disease | PE according to the ACOG; N = 62 women; Age: 27.5 ± 0.8 years | 27 primiparous and 35 multiparous | 30 primiparous and 54 multiparous | Not matched |
| Berends AL, 2008 [28]    | The Netherlands; Retrospective cohort study | Multiple pregnancies | PE according to the ACOG; N = 36 women; Age = 36.2 ± 5.8 years | Parity not reported; GAD: 37 ± 34 weeks | Parity not reported; GAD: 39.6 ± 1.4 weeks | Not matched |
| Bokslag A, 2017 [29]     | The Netherlands; Prospective cohort study | Multiple pregnancy; congenital abnormalities; chronic hypertension, use of antihypertensive medication; DM or gestational diabetes; CVDs, including renal diseases; Raynaud’s disease, or the use of cardiovascular related medication before index pregnancy | PE according to the ISSHP; N = 131, including severe PE and one or more of the following conditions: (i) proteinuria ≥ 24 h (n = 59; 45.0%); (ii) HELLP syndrome (n = 43; 32.8%); (iii) eclampsia seizure (n = 10; 7.6%) or (iv) pulmonary edema (n = 6; 4.6%); Age: 30.9 ± 5.0 years | Primiparous: 101 (71.1%); GAD: 305.4 ± 21.1 | Primiparous: 29 (51.8%); GAD: 400.0 ± 1.4 weeks | Maternal age (range: 5 years) and date of delivery (range: 1 year) |
| Breitveld NM, 2015 [30]  | The Netherlands; Retrospective cohort study | DM, auto-immune diseases and pre-existent hypertension prior to index-pregnancy. Participants who did not wish to be informed about the outcome of the screening | PE according to the ISSHP, developing before 34 weeks’ gestation. N = 115 patients; Age 39 ± 4.0 | Primiparous: 41/115 (36%); GAD 33.3 ± 4.3 weeks | Primiparous: 5/50 (10%); GAD 39.6 ± 2.3 weeks | Not matched |
| Carleton H, 1988 [31]    | United States; Prospective cohort study | Not reported | PE according to the ACOG, N = 23 women; Age: -26. years | 23 Primiparous; GAD: not reported | 23 matched controls (parity, ethnicity, age, weight) without PE. | Year delivered, age, race, and weight ± 1/3 |
| Chambers JC, 2001 [32]   | United Kingdom; Retrospective cohort study | Exclusion criteria: atherosclerosis, malignancy, major organ failure, vasculitis, systemic infection, recent major surgery or trauma, and known diabetes | PE hypertension + proteinuria, N = 113 Single episode PE: 78 women; recurrent PE: 35 women; Age: Single episode: 34 ± 5; Recurrent episodes: 37 ± 5 years | Parity not reported; GAD: not reported | Parity not reported; GAD: not reported | Not matched |

(continued on next page)
| Author, year [reference] | Country; study design | Exclusion reasons | Data during the index pregnancy: preeclampsia (PE) | Data during the index pregnancy: control (CG) | Time of follow up and/or age | Matching variables for controls |
|--------------------------|-----------------------|------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------|-------------------------------|
| Christensen M., 2016 [33] | Denmark; Retrospective cohort study | Unexposed women who experienced hypertensive disorder of pregnancy before or after 2001–2004 were excluded. Five cases and four controls were excluded because of current pregnancy or breastfeeding. One case was excluded because of a history of breast cancer with chemotherapy. | PE according to the ACOG; N = 21 patients with PE in 2001–2004; Age: time since delivery, years: 10.28 ± 0.70 years; Parity: Median 1.0; GAD: 39.1 ±3 weeks | Primiparous n = 16 (76%); GAD: 262 ± 19 days | Ten year after delivery; Age: exposed women 40.75 ± 2.7 years; non-exposed women 40.67 ± 2.3 years | Study 4 years after index delivery, Not matched |
| Coffeng SM, 2011 [34] | The Netherlands; Prospective cohort study | | Severe early-onset PE according to the ISSHP; N = 16 severe early-onset PE; Age: 29.7 ± 4.8 years | Parity and GAD not reported | | |
| Dantas EMM, 2013 [35] | Brazil; Prospective cohort study | Not reported | PE according to the diagnostic criteria of the NHBPEPWG; N = 10 women (one women developed HELLP syndrome); Age: 27.0 ± 6.7 years | Normotensive pregnancies. N = 17 women; Age: 260 ± 2.5 years | Study at 5 years follow-up. | Age and parity |
| Drost JT, 2012 [36] | The Netherlands; Prospective cohort study | Pregnant or lactating women | PE < 32 weeks. N = 339 women with PE according to the ISSHP; Age: 29.8 ± 3.8 years | Pregnant women without PE; N = 332 women without PE; Age: 28.6 ± 4.1 years | | |
| Forest JC, 2005 [37] | Canada; Retrospective cohort study | Pregnant women and women who had delivered within 6 months of the scheduled visit | PE according to the ACOG; N = 63 PE; Age: 27.4 ± 3.9 years | Number of pregnancies: 2.7 ± 1.4; GAD: not reported | | |
| Freeman DJ, 2004 [38] | United Kingdom; Retrospective cohort study | Other hypertensive disorders of pregnancy | PE according to the ISSHP, N = 40 pregnancies between 1975 and 1985; Age: 24.9 ± 5.2 years; PE: 40 women with preeclampsia according to the ICD 9 codes, who delivered between 1976 and 1982; Age: 24.2 ± 3.7 | Primiparous and multiparous women; GAD: 35.3 ± 3.8 weeks | | |
| Garovic VD, 2017 [39] | United States; Retrospective cohort study | Women with previous CVD events, such as myocardial infarction, congestive heart failure, stroke, and dysrhythmias | PE: 63 women according to the diagnostic criteria of the NHBPEPWG; Age: 27.4 ± 3.9 years | 40 age- and parity-matched normotensive pregnancies; Age: 247 ± 3.9 years | | |
| Giroud D J, 2007 [40] | Canada; Retrospective cohort study | Multiparous women and women with known renal diseases, diabetes mellitus, or CVD | PE: 63 women according to the diagnostic criteria of the NHBPEPWG; Age: 27.4 ± 3.9 years | Women without PE, N = 38 pregnancies; Age: 247 ± 3.9 years | | |
| Hamad RR, 2007 [41] | Sweden; Retrospective cohort study | No hormonal therapy for 6 months before the study or other drug treatment; breast-feeding terminated. No DM, gestational DM, coagulation disorders, renal diseases, and chronic hypertension | Severe PE according to the ISSHP, N = 18 women; Age: 30 ± 4 years | Women without adverse outcomes; GAD: 39.1 ± 2.8 years | | |
| He S, 1999 [42] | Sweden; Retrospective cohort study | Negative history of hematological, cardiovascular, hepatic or renal disorder before index pregnancy | PE 25 women (11 mild PE, and 14 severe PE); Age: 33 ± 6 years | N = 24 women; Age: Matched by age, parity and index of pregnancy 34 ± 6 years | | |

Table 1 (continued)
| Authors and Year | Location | Study Type | Criteria | Age, race/ethnicity, current age, and age at delivery | Number of Participants | Pregnancy Outcome | Follow-up Details |
|------------------|----------|------------|----------|-------------------------------------------------|-----------------------|-----------------|-----------------|
| Hubel CA, 2008   | Iceland | Retrospective cohort study | Women with hypertension before week 20 of gestation or reported history of hypertension were excluded. None of the women had a history of gestational DM | Age, pregnancy, and parity | 28 non-obese women with previous severe PE-eclampsia group: 41.8 ± 0.9 years; Control group: 41.8 ± 0.9 years | Control 28 women with uncomplicated pregnancy; Age not reported | Delivery between 1931 and 1998. Women were 50 to 67 years old at reexamination (32 years after delivery) |
| Innes KE, 2005   | United States | Retrospective cohort study | Cancer, hypertension, renal disease, or diabetes. None were currently breast-feeding. A history of infertility, multi-fetal gestation, or gestational DM currently on medications known to alter hormone or lipid levels | Age, pregnancy, and parity | 36.0 [33.0, 39.0]; Controls: 40.5 [39.0, 44.0] | Parity: 2.0 [2.0, 3.0], GAD: Median 32.3 weeks | Cases on race/ethnicity, current age, and age at delivery |
| Kvehaugen AS, 2010 | Norway | Retrospective cohort study | Women with current pregnancy or lactation were excluded. None of the women had CVD and none were diagnosed with de novo DM2 after index pregnancy | Age, pregnancy, and parity | PE: 23 women; preeclampsia: Age; 30.0 [27.0, 32.0] | Parity: 2.0 [1.0, 2.0], Multiparous 60%; GAD: Median 32.0 weeks | Age at the study: PE women 36.0 [33.0, 39.0]; Controls: 40.5 [39.0, 44.0] |
| Laivuori H, 1996 | Finland | Retrospective cohort study | Women with concomitant disease, such as DM or a history of gestational DM, chronic hypertension, and kidney disease or coagulation disorders were excluded | Age, pregnancy, and parity | PE or eclampsia in 22 women; Age: 24.8 ± 2.0 years | Parity: First pregnancy; GAD: 36.2 ± 0.5 years | All subjects were menstruating regularly at the time of the study. Follow up interval ranged from 1 to 10 years and averaged 3.69 ± 0.47 years |
| Lampinen KH, 2008 | Finland | Retrospective cohort study | Women with concomitant disease, such as DM or a history of gestational DM, chronic hypertension, and kidney disease or coagulation disorders were excluded | Age, pregnancy, and parity | Severe PE: 28 non-obese women with previous severe preeclampsia or eclampsia; Age: 33.7 ± 5 years | Primiparity: 14/28 (50%); GAD: 33 [29, 36] weeks | Women were studied 5 to 6 years after the index pregnancy. |
| Mangos GJ, 2012 | Australia | Retrospective cohort study | Pregnant women were excluded who had DM, prior essential hypertension in pregnancy or renal disease | Age, pregnancy, and parity | PE: 39 women according to the ASHPC statement criteria for the diagnosis preeclampsia; Age: 37 ± 6 years | Multiparous: 26 (67%); GAD: not reported | BMI (28.7–7.0) |
| Manten GTR, 2007 | The Netherlands | Retrospective cohort study | Women with fasting glucose levels ≥ 7.0 mmol/L | Age, pregnancy, and parity | PE: 256 women with preeclampsia according to the ACOG criteria, HELLP syndrome n = 163 (64%); Age: 31 ± 4 | Primiparous 203 (79%); GAD: 217 ± 28 days | Women were studied at least 3 months after delivery, and after ending lactation |
| McDonald SD, 2013 | Canada | Retrospective cohort study | Women with prior chronic hypertension in pregnancy; gestational hypertension; known CVD; chronic medical conditions such as liver disease, untreated hyper or hypothyroidism, renal disease, or malignancy | Age, pregnancy, and parity | PE: 109 women with preeclampsia according to the NHBPEPW group; Age of oldest child median 19 [15, 25] years; Age at index pregnancy: not reported | Parity not reported; GAD: not reported | Study performed two decades after delivery; Age: PE group 49 (IQR 44–55) years; Control group: 49 [IQR 45–56] years |
| Nisell H, 1999 | Sweden | Retrospective cohort study | History of CVD, renal or endocrine disease. None had a diagnosis of gestational DM. None were taking any drugs or any form of hormonal contraception. Breast feeding was completed in all cases | Age, pregnancy, and parity | PE: 21 women with preeclampsia according to the ACOG criteria; Age: 30 SEM 1 | Parity: Primiparous 14; GAD: 37.1 SEM 0.8 | Women were followed up to 25–119 weeks after delivery |
| Nohira T, 2013 | Japan | Retrospective | Patients who had CVD prior to pregnancy were excluded. None of the patients were taking any drugs or any form of hormonal contraception. Breast feeding was completed in all cases | Age, parity, and follow-up | PE: 58 women with severe | Parity: 0.896 ± | Elapse time from delivery to the next pregnancy: 0.874 ± | (continued on next page)
| Author, year [reference] | Country; study design | Exclusion reasons | Data during the index pregnancy: preeclampsia (PE) | Data during the index pregnancy: control (CG) |
|--------------------------|-----------------------|------------------|-----------------------------------------------|-----------------------------------------------|
|                          |                       |                  | Inclusion criteria; n (women); age at pregnancy | Inclusion criteria; n (women); age at pregnancy |
|                          |                       |                  | Parity index pregnancy; GAD, weeks             | Parity index pregnancy; GAD, weeks             |
| Östlund E, 2013 [53]     | Sweden; Prospective cohort study | No smoking and none used oral contraceptives | PE: 15 women with severe preeclampsia; Age 11 years after delivery: 39.4 ± 3.6 years | Control: 16 non-complicated pregnant women; Age: 11 years after delivery 41.2 ± 3.2 years |
|                          |                       |                  | Parity: 1.8 ± 0.9; GAD: 245 ± 6 days           | Parity: 2.5 ± 0.7; GAD: 281 ± 6 days           |
|                          |                       |                  | 48 women without medical complications associated to pregnancy; Age: 28 [25, 33] | Data at recall: women with PE: Age 34 [30, 39]; control group: 34 [31, 39] years. Years since delivery: PE: 6 [4, 8] years; Control group: 6 [4, 8] |
| Portelinha A, 2008 [54]  | Portugal; Retrospective cohort study | Prior history of hypertension, heart disease, DM, renal disease, infections, recent surgery and current pregnancy. None women were postmenopausal | PE: 58 women according to the ISSHP; Age: 27 [24, 3] | Parity: not reported; GAD: 39 [36, 40]; Cesarean rate: 28.6% |
|                          |                       |                  | Parity: not reported. GAD: 34 [33, 37] weeks; Cesarean rate: 74.1% | Data at recall: women with PE: Age 34 [31, 39] years; control group 34 [31, 40] years |
|                          |                       |                  | Control group 60 women; Age: 28 [25, 33] | Parity: not reported; GAD: 39.0 [38.1, 40.0] |
| Portelinha A, 2010 [55]  | Portugal; Retrospective cohort study | Prior history of hypertension, CVD, DM, renal disease, infections, recent surgery and current pregnancy. None women were postmenopausal | PE: 90 women according to the ISSHP; Age: 28 [24, 32] | Parity: not reported; GAD: 35 [32.5, 37.0] |
|                          |                       |                  | Parity: not reported | Control group 60 women; Age: 28 [25, 33] |
| Pouta A; 2004 [56]       | Finland; Retrospective cohort study | Not found/not reported | PE: 49 pregnant women according to the ISSHP; Age: Average 25 years | Parity: Primigravida; GAD: not reported |
|                          |                       |                  | Parity: Primiparous; GAD: not reported | 1369 control pregnant women; Age: average 25 years |
|                          |                       |                  | Control group: 2964 normotensive pregnant women; Age: not reported | Parity: Primiparous; GAD: not reported |
| Romundstad PR; 2010 [57] | Norway; Retrospective cohort study | Pregnant women with missing information on essential measurements | PE: 168 women with preeclampsia according to the ACOG criteria; Age: not reported | Parity: not reported; GAD: not reported |
|                          |                       |                  | Parity: not reported; GAD: not reported | Control group: 2964 normotensive pregnant women; Age: not reported |
| Sattar N, 2003 [58]      | United Kingdom; Retrospective cohort | No subject had any clinical disease at the time of sampling | PE: 40 primigravid women with preeclampsia according | Parity: Primiparous women; GAD: 40 |
|                          |                       |                  | Parity: Primiparous women; GAD: 36 | Control: 40 uncomplicated pregnant women matched as a |

Matching variables for controls:
- prepregnancy BMI, smoking habits and family history of DM, CVD and preeclampsia
- Age, parity and date of delivery
- Age, BMI, time since pregnancy, smoking, contraceptive intake, alcohol consumption
- Not matched
- The median interval from first delivery to examination at 31 years was 6 years in all groups [IQR: 5 months to 11 years]. Recall for study 21 years after delivery.
- Not matched
- Age

Time of follow up and/or age:
- Delivery: PE group: 12.3 ± 3.17 (Age: 38.26 ± 12.63); Control group: 12.7 ± 3.33 years (Age: 39.54 ± 10.26)
- Study performed 11.2 ± 0.6 years following the index pregnancy
- Age, parity and date of delivery
- Age, parity and date of delivery
- Age
- Not matched
study or had a recent infection within the last 10 days.

Smith GN, 2009 Canada; Prospective cohort study
Women with a history of hypertension, diabetes (including development of gestational diabetes in any pregnancy), renal disease, or CVD were excluded
PE: 70 women with PE according to the ACOG criteria; Age: 30.5 ± 5.7 years
Parity (%): Primiparous 43 ± 61.4; Previous pregnancy with PE 11 (15.9%); GAD: 35.6 ± 3.8 weeks
Control group: 70 normotensive pregnancies; Age: 30.3 ± 4.1 years
Parity: not reported; GAD: not reported

Sspan J, 2010 Maastricht. The Netherlands; Retrospective cohort study
None of the participants were using cholesterol-lowering medication
PE: according to the diagnostic criteria of the NHBPEPWG, N = 22 women; Age: 23 (20–28) years
Parity: parous women; GAD 34.6/7 (27–43) weeks
Control: 29 women with uneventful pregnancies; cases and controls 23 (20–28) years
Parity: parous women; GAD: 40/4/7 (38–42) weeks

Suzuki H, 2008 Japan; Retrospective cohort study
None of the women had a history of gestational DM
PE: 48 women according to the ACOG criteria; Age at first pregnancy: 34 ± 8 years
Parity: not reported; GAD: not reported
Control: 201 normotensive pregnant women; Age at first pregnancy 28 ± 1 years
Parity: not reported; GAD: not reported

White WM, 2016 United States; Retrospective cohort study
Myocardial infarction, congestive heart failure, stroke, dementia, any cancer, autoimmune disease and neurological conditions
PE: 40 women with PE according to the ICD 9, who delivered between 1976 and 1982; Age: mean age 24 years
Parity: matched; GAD: not reported
40 age- and parity-matched women without histories of preeclampsia, who delivered between 1976 and 1982
Parity: matched; GAD: not reported
Mean age of the study participants at the time of imaging was 59.5 ± 4.6 years
Parity and age at index birth: Mean age at delivery: 24 years

Zoet GA, 2018 The Netherlands; Retrospective cohort study
Women aged < 45 or ≥ 55 years
PE: 164 women with hypertension + proteinuria; Age: not reported
Parity: not reported; GAD: not reported
387 women of similar age and ethnicity from the Multi-Ethnic Study of Atherosclerosis; Age: not reported
Age and Parity: not reported
Asymptomatic women, aged 45 to 55 years, with a history of PE 10 to 20 years earlier
Age and ethnicity

Continuous variables described as mean ± standard deviation (SD) or median [interquartile range (IQR)]. *P < 0.001; ACOG: American College of Obstetrics and Gynecology; ASSHP: Australasian Society for the Study of Hypertension in Pregnancy Consensus; BMI: Body mass index; BP: Blood pressure; CG: Control group; E: Eclampsia; CVD: Cardiovascular disease; DM: Diabetes mellitus; DM2: Type 2 diabetes mellitus; GAD: Gestational age at delivery; HDP: Hypertensive disorders of pregnancy; HELLPs: hemolysis, elevated liver enzymes, and low platelets; ICD: International Classification of Diseases; IQR: interquartile range; ISSHP: International Society for the Study of Hypertension in Pregnancy; IUGR: Intrauterine growth restriction; NHBPEPWG: National High Blood Pressure Education Program Working Group; PE: Preeclampsia (Hypertension gestational + proteinuria) after 20 weeks of pregnancy; SEM: Standard error of the mean.
Definitions of PE severity, E and HELLP syndrome were equivalent for all these different scientific organizations: occurrence of hypertension (systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg) and proteinuria urinary albumin excretion >300 mg/24 h or equivalent during the second half of pregnancy in gravid women.

### Table 2
Meta-analyses of study outcomes.

| Outcomes                                      | Number of studies (total sample) | Mean difference (MD) or risk difference (RD) and 95%CI | P for effect | I² |
|-----------------------------------------------|----------------------------------|---------------------------------------------------------|--------------|----|
| Systolic blood pressure                       | 38 (17,267)                      | MD = 8.3 mmHg (6.8 to 9.7)                              | < 0.0001     | 78%|
| Diastolic blood pressure                      | 37 (17,232)                      | MD = 6.8 mmHg (5.6 to 8.0)                              | < 0.0001     | 83%|
| Hypertension                                  | 12 (2261)                        | RD = 0.24% (0.15 to 0.33)                               | < 0.0001     | 89%|
| Body mass index                               | 34 (17,039)                      | MD = 2.0 kg/m² (1.6 to 2.4)                             | < 0.0001     | 56%|
| Waist circumference                           | 13 (11,371)                      | MD = 4.3 cm (3.1 to 5.5)                                | < 0.0001     | 31%|
| Waist-to-hip ratio                            | 10 (2364)                        | MD = 0.02 (0.01 to 0.03)                                | 0.004        | 59%|
| Weight                                        | 5 (422)                          | MD = 5.1 kg (2.2 to 7.9)                                | 0.005        | 0% |
| Lipoprotein (a)                               | 4 (445)                          | MD = 19.5 mg/L (−0.8 to 4.7)                            | 0.17         | 7% |
| Total cholesterol                             | 29 (13,477)                      | MD = 46 mg/dL (15.7 to 75)                              | 0.003        | 56%|
| HDL-cholesterol                               | 29 (13,367)                      | MD = −2.1 mg/dL (−3.5 to −0.8)                          | 0.001        | 57%|
| VLDL-cholesterol                              | 3 (162)                          | MD = 0.3 mg/dL (−1.9 to 2.5)                            | 0.77         | 15%|
| Triglycerides                                 | 28 (13,336)                      | MD = 7.7 mg/dL (3.6 to 11.7)                            | 0.0002       | 46%|
| Glucose                                       | 25 (4936)                        | MD = 2.6 mg/dL (2.2 to 4.0)                             | 0.0003       | 78%|
| Glycosylated hemoglobin                       | 10 (9608)                        | MD = 0.15% (−0.2 to 0.5)                                | 0.36         | 98%|
| Insulin                                       | 14 (2337)                        | MD = 19.1 pmol/L (11.9 to 26.2)                         | < 0.0001     | 71%|
| HOMA-IR                                       | 14 (1812)                        | MD = 0.7 (0.2 to 1.2)                                   | 0.008        | 97%|
| IGF-1                                         | 3 (104)                          | MD = −15.1 ng/mL (−40.0 to 9.8)                         | 0.23         | 0% |
| C reactive protein                            | 11 (1476)                        | MD = 0.05 mg/dL (0.01 to 0.09)                           | 0.01         | 51%|
| Microalbuminuria                              | 2 (420)                          | RD = 0.22% (−0.15 to 0.59)                              | 0.24         | 96%|
| Albuminuria                                   | 3 (589)                          | MD = 0.5 g/mol creatinine (−0.2 to 1.2)                 | 0.20         | 92%|
| Metabolic syndrome                            | 5 (265)                          | RD = 0.11% (0.08 to 0.15)                               | < 0.00001    | 0% |

CI: Confidence interval; HDL-cholesterol: high-density lipoprotein cholesterol; IGF-1: Insulin growth factor 1; LDL-cholesterol: low-density lipoprotein cholesterol; VLDL-cholesterol: very low-density lipoprotein cholesterol.

Fig. 2. Meta-analyses of blood pressure-related outcomes: Mean differences of systolic blood pressure (SBP) and proteinuria urinary albumin excretion >300 mg/24 h or equivalent during the second half of pregnancy in gravid women.
without previous hypertension or kidney disease. Proteinuria may be visually assessed by dipstick or by an automated device and confirmed by a 24 h urine collection.

2.2. Outcomes of interest

Outcomes of interest were metabolic and cardiovascular biomarkers measured at least three months after delivery, such as SBP, DBP, hypertension, body mass index (BMI), waist, waist-to-hip ratio (WHR), weight, lipoprotein (a) [Lp(a)], total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (VLDL), triglycerides, glucose, glycosilated hemoglobin (HbA1c), insulin, homeostatic model assessment insulin resistance (HOMA-IR), insulin growth factor 1 (IGF-1), C-reactive protein (CRP), microalbuminuria, albuminuria, and metabolic syndrome (MetS). We extracted MetS definitions as provided by study authors, which may or not be based on published guidelines or consensus.

2.3. Study selection and data extraction

We included prospective or retrospective observational studies evaluating singleton PE and/or E and without previous kidney diseases.
Normotensive uncomplicated pregnancies reported in the respective publication were considered as control groups. Published studies were eligible for inclusion if they reported metabolic or biochemical outcomes of interest three months after delivery or later. Exclusion criteria were: (a) PE data was not available or could not be extracted from the study groups; (b) no appropriate control group; (c) other hypertensive disorders different from PE, E and HELLP syndrome; (d) chronic pregestational diseases; and (e) metabolic or biochemical outcomes of interest measured within three months after delivery. Three of the authors (VAV, FRPL, YL) independently evaluated full-text articles for compliance with inclusion and exclusion criteria. Disagreements were managed through discussion with the other authors (FRPL, AVH) to reach a consensus. Authors were contacted if supplementary information or clarification was required in order to analyze study eligibility.

Extracted data included year of publication, country(ies) of study conduction, sample size for preeclampsia and control groups, time of follow up, baseline patient characteristics, outcomes per group, and variables used for confounder adjustment. Data extraction was also independently performed by 2 authors (VAV, YL) and disagreements were solved by discussion with all authors.

**Fig. 3.** Meta-analyses of anthropometric outcomes: Mean differences of body mass index (BMI) (Fig. 3A), waist circumference (Fig. 3B), waist-to-hip ratio (WHR), (Fig. 3C), and weight (Fig. 3D). A. BMI, n=34 studies (I²=56%). B. Waist circumference, n=13 studies (I²=31%). C. Waist-to-hip ratio, n=10 studies (I²=59%). D. Weight, n=5 studies (I²=0%).
2.4. Risk of bias assessment

The risk of bias of selected studies was assessed independently by two authors (VP. and AVH) using the Newcastle-Ottawa scale (NOS) for cohort studies [19]. The NOS consists of three parameters of quality: selection, comparability and outcome assessment. The NOS assigns a maximum of four points for selection, two points for comparability and three points for exposure or outcome. NOS scores of ≥7 were considered as high-quality studies and NOS scores of 5–6 were considered moderate quality. Any discrepancies were addressed by a re-evaluation of the original article to reach consensus.

2.5. Statistical analyses

Inverse variance random-effects models were used for meta-analyses. Effects were reported as risk difference (RD) for dichotomous outcomes or mean differences (MD) for continuous outcomes and their 95% CIs. Continuous outcomes were adjusted for baseline values per exposure arm. For studies reporting medians (m) and interquartile ranges (IQR), means were estimated by \( x = (a + 2m + b)/4 \), where \( m \) is median and \( a \) and \( b \) are P25 and P75, respectively [20]. SDs were estimated using \( SD = IQR/1.35 \). When median and ranges were provided, the mean was estimated by \( x = (a + 2m + b)/4 \) using the values of the median \( m \), the smallest and largest value \( a \) and \( b \), respectively; SD was estimated by \( SD = range/4 \) if sample size was \( >70 \) and \( SD = range/6 \) if sample size was \( >70 \) [20].

A \( p < 0.1 \) for the Chi-square test was defined as an indicator of heterogeneity; a \( Tau^2 \) of 1 was defined as the presence of substantial statistical heterogeneity. An \( I^2 \) value of 0–30% was used to define low heterogeneity, 30–60% moderate heterogeneity, and >60% substantial heterogeneity [21]. Potential publication bias was estimated by the Begg’s funnel plot and the Egger’s linear regression test [22].

We predefined subgroup analyses by (i) time of follow up, (ii) year of publication, and (iii) presence of adjustment for confounders. Statistical analyses were conducted using Review Manager (RevMan 5.3; Cochrane Collaboration, Oxford, UK) and the Comprehensive Meta-analysis (Version 2; Biostat, Englewood, NJ).

3. Results

3.1. Selection of studies

A total of 2671 abstracts were identified through search engine and 14 additional full-papers were identified by manual search. After removal of duplicates, 2022 items were evaluated, of which 1966 did not fulfill inclusion criteria. Hence, 56 full texts were assessed for eligibility. Nine papers did not report separated information of PE/E patients, five reported duplicate information, and one was a cross-sectional study (Fig. 1). Finally, a total of 41 full papers [23–63] were evaluated for qualitative and quantitative assessment.

3.2. Characteristics of included studies

The 41 cohort studies included 3300 women who previously suffered PE/E and 13,967 controls. Six publications reported complementary information from three pairs of studies (first pair [37,40], second pair [39,62], and third pair [54,55]) (Table 1). PE/E sample sizes across studies ranged from 10 [35] to 901 [24]. Included studies described 207 women with HELLP syndrome in three studies, as compared with normotensive pregnant women [29,35,49]. Women were followed up from three months post-delivery [32,49] to 20 years after delivery [24,38,39,43,50,57,60,62]. Publications included women from Europe [23–25,28–30,32–34,36,38,41–43,45–47,49,51,53–58,60,63], North America [31,37,39,40,44,50,59,62], and from other world regions [26,27,35,48,52,61]. There were no differences in baseline demographics and clinical characteristics between arms within each study (Table 1).

Diagnoses of PE and E were based on definitions from different scientific organizations such as ACOG (n = 14 studies), ISSHP (n = 9 studies), NHBPEWG (n = 4 studies), ICD (n = 2 studies), and ASSHPC (n = 1 study), and standard clinical diagnosis of PE/E (n = 10 studies) (Table 1). Other publications defined PE without referring to scientific...
societies and as an association of conventional hypertension and proteinuria developing after 20 weeks of pregnancy (n = 10 studies) which remitted within a few days after delivery. All included studies had similar PE/E definitions: new onset hypertension and proteinuria after 20 weeks of gestation and in the case of E also included coma and/or seizures in previously normotensive women without renal pathology.

3.3. Risk of bias assessment

Using the NOS scale, all but one study [25] were identified as high quality (Appendix A, eSupplementary Table 1). All studies clearly identified the study population; patients were representative of average PE/E cases and controls were derived from the same population as cases. In all studies, secure patient records were used for ascertainment of PE/E and assessment of outcomes. All studies had adequate follow-up time. Overall 23 studies identified important confounders or prognostic factors and were used for adjustment of the association between PE/E and cardiovascular risk. There was considerable variation in the selection of confounding variables for adjustment (Appendix A, eSupplementary Table 1). The most common confounder that was adjusted for was age.

3.4. Meta-analyses of outcomes

3.4.1. Blood pressure

In 38 studies (n = 17,267), SBP was significantly higher in women with previous diagnoses of PE/E as compared to normotensive women (Table 2, Fig. 2A). In 37 studies (n = 17,232) DBP was significantly higher in women with previous diagnosis of PE/E (Table 2; Fig. 2B). In 12 studies (n = 2263), hypertension risk was significantly higher in women with PE/E (Table 2; Fig. 2C). There was high heterogeneity of effects on SBP and DBP across studies.

3.4.2. Anthropometric outcomes

In 34 studies (n = 17,039) BMI was significantly higher in women with previous diagnosis of PE/E (Table 2, Fig. 3A). In 13 studies (n = 11,371) waist circumference was significantly higher in women with previous diagnosis of PE/E (Table 2, Fig. 3B). In 10 studies (n = 2364) the WHR was significantly higher in women with previous diagnosis of PE/E (Table 2, Fig. 3C). In five studies (n = 422) weight was significantly higher in women with previous diagnosis of PE/E (Table 2; Fig. 3D). There was low to

![Fig. 4. Meta-analyses of lipid-related outcomes: Mean differences of serum lipoprotein (a) [Lp(a)] (Fig. 4A), total cholesterol (Fig. 4B), HDL-cholesterol (Fig. 4C), LDL-cholesterol (Fig. 4D), VLDL-cholesterol (Fig. 4E) and triglycerides (Fig. 4F). A. Lipoprotein (a), n=4 studies (I²=7%). B. Total cholesterol, n=29 studies (I²=56%). C. HDL-cholesterol, n=29 studies (I²=57%). D. LDL-cholesterol, n=24 studies (I²=81%). E. VLDL-cholesterol, n=3 studies (I²=15%). F. Triglycerides, n=28 studies (I²=46%).](image-url)
moderate heterogeneity of effects on anthropometric outcomes across studies.

3.4.3. Lipid-related outcomes

In 4 studies (n = 445) there was no significant difference in Lp(a) levels between women with and without PE/E (Table 2; Fig. 4A). In 29 studies (n = 13,477) TC was significantly higher in women with previous PE/E (Table 2; Fig. 4B). In 29 studies (n = 13,367) HDL was significantly lower in those with previous PE/E (Table 2; Fig. 4C). In 24 studies (n = 5220) LDL was significantly higher in women with previous PE/E (Table 2; Fig. 4D). In three studies (n = 162) there was no difference in VLDL in women with previous PE/E (Table 2; Fig. 4E). There was low to high heterogeneity of effects on lipid outcomes across studies.

3.4.4. Glucose- and insulin-related outcomes

In 25 studies (n = 4936) serum glucose was significantly higher in women with PE/E (Table 2, Fig. 5A). In 10 studies (n = 9608) there was no effect on HbA1c (Table 2; Fig. 5B). In 14 studies (n = 2327) HbA1c was significantly lower in women with PE/E (Table 2; Fig. 5C). In 28 studies (n = 13,336) triglycerides were higher in women with previous PE/E (Table 2; Fig. 4F). There was low to high heterogeneity of effects on lipid outcomes across studies.

3.4.5. Triglyceride-related outcomes

In 22 studies (n = 10,520) triglycerides were significantly lower in women with PE/E (Table 2; Fig. 4D). In 28 studies (n = 13,336) triglycerides were higher in women with previous PE/E (Table 2; Fig. 4E). There was low to high heterogeneity of effects on lipid outcomes across studies.

3.4.6. Insulin-related outcomes

In 25 studies (n = 4936) serum glucose was significantly higher in women with PE/E (Table 2, Fig. 5A). In 10 studies (n = 9608) there was no effect on HbA1c (Table 2; Fig. 5B). In 14 studies (n = 2327) HbA1c was significantly lower in women with PE/E (Table 2; Fig. 5C). In 28 studies (n = 13,336) triglycerides were higher in women with previous PE/E (Table 2; Fig. 4F). There was low to high heterogeneity of effects on lipid outcomes across studies.

3.4.7. Fasting insulin-related outcomes

In 22 studies (n = 10,520) fasting insulin was significantly lower in women with PE/E (Table 2; Fig. 4D). In 28 studies (n = 13,336) fasting insulin was higher in women with previous PE/E (Table 2; Fig. 4E). There was low to high heterogeneity of effects on lipid outcomes across studies.
serum insulin was significantly higher in women with PE/E (Table 2; Fig. 5C). In 14 studies (n = 1812) the HOMA-IR index was significantly higher in women with PE/E (Table 2; Fig. 5D). In three studies (n = 104) there was no effect on IGF-1 in women with PE/E (Table 2; Fig. 5E). There was high heterogeneity of effects on glucose-related outcomes across studies.

3.4.5. Other outcomes

In 11 studies (n = 1376) CRP levels were significantly higher in women with PE/E (Table 2; Fig. 6a). In two studies (n = 428), there was no significant difference in microalbuminuria risk between women with and without PE/E (Table 2; Fig. 6b). In three studies (n = 589), there was no significant difference in albuminuria levels between women with and without PE/E (Table 2; Fig. 6c). In five studies (n = 1688), the risk of MetS was significantly higher in women with PE/eclampsia (Table 2; Fig. 6d). There was low to high heterogeneity of effects across studies.

3.5. Subgroup analyses

Evaluation of subgroup effects by year of publication, time of follow up and adjustment of effects for confounders provided similar results as main analyses (Appendix A, eSupplementary eFigures 1 to 8).

3.6. Publication bias

Funnel plots of outcomes available in >10 studies showed that there was no asymmetry of points, except for triglycerides and glucose where small studies (i.e. those with larger SEs) were absent.

4. Discussion

4.1. Main findings

We found that women with PE/E or HELLP syndrome in comparison to women with normotensive pregnancies had later in life (i) higher hypertension risk and BP levels; (ii) higher BMI, waist circumference, waist-to-hip ratio, and weight, (iii) higher levels of total cholesterol, LDL, and triglycerides and lower levels of HDL; (iv) higher levels of serum glucose, insulin, the HOMA-IR index, C reactive protein, and (v) higher risk of MetS. These results were based in cohort studies with low risk of bias (only one publication has high risk of bias), although heterogeneity of studies was high for several outcomes. In this study, we only included women with PE/E and/or HELLP syndrome as defined by medical and scientific organizations, since other hypertensive disorders of pregnancy may have a different pathophysiology, are heterogeneous in their clinical characteristics and managements, or
have different specific therapies during early pregnancy or before pregnancy.

4.2. What is known in the literature about the research question

PE/E is a heterogeneous multisystem disorder appearing during the second half of pregnancy in women without previous hypertension and proteinuria or renal disease, and is characterized by new onset hypertension and proteinuria after 20 weeks of pregnancy; PE/E is associated with high risks of preterm birth, intrauterine growth restriction, abruptio placentae, perinatal mortality and maternal morbidity and mortality. The degree of hypertension and proteinuria and the existence of other accompanying findings are variable [1,6,64–66]. PE/E risk factors include nulliparity, multifetal pregnancy, family history of PE, prior pregnancy complicated with placental insufficiency, excessive pre-pregnancy BMI, advanced maternal age, and use of assisted reproductive techniques [1,6].

The Cardiovascular Risk in Young Finns Study linked data from primiparous women with pre-conceptional lipid metabolism, blood pressure and insulin and glucose metabolism, showing that high levels of triglycerides were associated with increased risk of PE and gestational diabetes [67]. Therefore, some pre-gestational metabolic alterations may in part contribute to the risk of PE and may persist after pregnancy. Also, women with PE have higher risk of developing later diabetes, hypertension and cardiovascular risk factors, especially when the hypertensive disorder occurred in late pregnancy or when there were two PE episodes (i.e. in two different pregnancies) [68]. Women with PE/E have increased prevalence of subsequent hypertension, dyslipidemia, diabetes, congestive heart failure, stroke, renal and other subclinical alterations [8,12,13,69–71].

Our systematic review and meta-analyses identified hypertension, altered metabolic, and endocrine changes in women with PE/E as compared to women with normotensive pregnancies, before severe clinical complications are diagnosed. Risks of metabolic, anthropometric, glucose- and insulin-related outcomes, and hypertension and MetS reported in our study are intermediate risk factors of cardiovascular disease and type 2 diabetes mellitus. Lipid differences reported here suggest that women at risk of PE/E have a trend for abnormal...
adjustment during pregnancy. Recent evidence from a population-based prospective cohort suggested that women with high blood pressure during pregnancy and postpartum have altered maternal lipid profile during early pregnancy [72].

PE is currently considered as a form of type 5 cardiorenal syndrome, an under-recognized entity in women’s cardiovascular health [73,74], which is associated with maternal endothelium alterations [75,76]. It seems that women at risk of PE have impaired utero-placental blood flow that may be associated with relatively hypoxic trophoblast that alters placental villous angiogenesis and produces abnormal vascular reactivity during gestation and metabolic changes [77–79]. From our results, it seems that some alterations persist for long period of time, even decades, after PE since hypertension, lipid metabolic alterations, altered body composition, hyperglycemia, and hyperinsulinemia were found in this systematic review.

Women with PE/E should be monitored and treated after delivery, including excessive body weight, metabolic alterations, hypertension and glucose and insulin disorders. It remains to be determined if postpartum and long term strict metabolic control intervention can reduce alterations found in this study in women with PE/E in comparison to those without PE/E. Preventive clinical management should include screening and management of modifiable risk factors/outcomes and give healthy recommendation to neutralize negative changes demonstrated in this systematic review in women with PE/E. However, it remains to be determined if the alterations reported here are due to or are initiated by the PE/E phenomenon, or if the pregnancy findings are the result of a common cause in young women that is still present in older women.

4.3. Strengths and limitations

Our systematic review has several strengths: it was centered in PE/E, including women who suffered HELLP syndrome, without considering other hypertensive disorders of pregnancy which may have different
pathophysiology, organic causes and require different management to PE/E. We also evaluated several sources of heterogeneity of effects on outcomes across studies. Although strict diagnostic criteria were used in the conduct of the review, included studies were heterogeneous about intervals between pregnancy and later in life assessment and about information on lifestyle, nutrition and physical activity during the interval between pregnancy and later in life assessment. However, we could assume that these factors are similar in the normotensive pregnant women included as controls.

Subgroup analyses showed that effects were similar for studies with different intervals of time elapsed from pregnancies. Also, adjustment for confounding factors of the association between PE/E and outcomes, such as age and parity, was present in several studies; subgroup analyses by adjustment for confounders gave similar effects than studies without such adjustments. Finally, our study had other strengths including (i) exhaustive searches with low chances of selection bias; (ii) extractions were independent and double checked for accuracy with low risk of information bias; (iii) the majority of studies were of low risk of bias; and (iv) there was low publication bias.

Some limitations are worth to comment. Authors did not provide outcome data per PE and E separately, and PE/E treatment details were not described in most of studies. Also, MetS definitions were heterogeneous across studies, and may or not be based on published guidelines or consensus.

Fig. 6. Meta-analyses of other outcomes: Mean difference (MD) of serum CRP (Fig. 6a), risk difference (RD) of microalbuminuria (Fig. 6b), MD of albuminuria levels (Fig. 6c), and RD of metabolic syndrome (MetS) (Fig. 6d). a. C-reactive protein, n=11 studies (I²=51%). b. Microalbuminuria, n=2 studies (I²=96%). c. Albuminuria levels, n=3 studies (I²=92%). d. MetS, n=5 studies (I²=8%).
4.4. Interpretation

PE and E are severe complications for both the mother and the fetus that sometimes should be controlled by termination of pregnancy [1,5,6,7]. The causes and triggers may be related abnormal maternal hepatic, vascular and kidney mechanisms or due to substances produced in the fetal compartment that secondarily alter different maternal organs and functions that are permanently affected in comparison to women without hypertension and proteinuria. Pregnant women should be monitored with anthropometric, metabolic and renal function assessment due to the increased cardiovascular, endocrine and metabolic risks. This systematic review highlighted the close relationship between PE/E and future metabolic, body composition and glucose/insulin markers, and MetS risks that might end up in future cardiovascular and endocrine disease, negative change in BMI and other intermediate markers. In the past few years, a link between PE/E with subclinical cardiorenal syndrome of pregnancy has been suggested as the main cause of that specific hypertensive syndrome of pregnancy [74].

4.5. Conclusion

PE/E remains an under-recognized risk factor for future cardiovascular, metabolic, excessive BMI and kidney disease in women. In comparison to controls, PE/E significantly increased systolic BP and diastolic BP, BMI, waist, waist-to-hip ratio, weight, total cholesterol, LDL, triglycerides, glucose, insulin, HOMA-IR index, C reactive protein, and the risks of hypertension and MetS. Also, PE/E reduced HDL levels. Heterogeneity of effects was high for most outcomes.

The close relationships between findings reported here with future health risk, the identification of markers of cardiovascular and metabolic risks may recommend a close clinical follow up of pregnant women with the alterations reported in women with PE/E. Rigorous interventions to prevent obesity, hypertension and other metabolic alterations in years after PE/E pregnancy might provide clinical benefits although it remains to be determined decades after reproductive events.

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Author contributions

FRPL and AVH were involved in study conception and design; acquisition, and interpretation of data; drafting of the manuscript; and approval the final version of the manuscript. VAV, YL, VP, and YMR were involved in acquisition and interpretation of data; and approval of the final version of the manuscript. YL and AVH performed statistical analyses. FRPL and AVH have access to the data and are responsible for the accuracy of the manuscript.

Declaration of competing interest

The authors declared no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.154012.

References

[1] August P, Sibai BM. Preeclampsia: clinical features and diagnosis. UpToDate 2019. https://www.uptodate.com/contents/preeclampsia-clinical-features-and-diagnosis.

[2] ACCP Practice Bulletin No. 202: gestational hypertension and preeclampsia. Obstet Gynecol 2019;133:e1-25. https://doi.org/10.1097/AOG.00000000000003081.

[3] Magee LA, Pels A, Helewa M, Roy E, von Dadelszen P. Canadian Hypertensive Disorders of Pregnancy Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynecol Can 2014;36:416–41.

[4] Pitha KY, Cheddai P, Pérez-López FR, Wendtje JF, Ghiabi S, Vrijkotte T, et al. Perinatal outcomes in singleton pregnancies complicated with preeclampsia and eclampsia in Ecuador. J Obstet Gynecol 2016;36:581–4.

[5] August P. Management of hypertension in pregnant and postpartum women. UpToDate https://www.uptodate.com/contents/management-of-hypertension-in-pregnant-and-postpartum-women; 2019.

[6] Anzà C, Cifkova R, Kotsis V. Hypertensive complications of pregnancy: a clinical overview. Metab Clin Exp 2018;36:102–11.

[7] Jonsdottir LS, Arringtonsson R, Geirsson RT, Sigvaldaason H, Sigfusson N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. Acta Obstet Gynecol Scand 1995;74:772–6.

[8] Fraser A, Nelson SM, Macdonald-Wallis C. 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;125:1367–80.

[9] Alharbi FR, Ghanbari Andarieh M, Farokhkar A, Ahmad SA, Estimating rate of insulin resistance in women with preeclampsia using HOMA-IR index and comparison with non-preeclampsia pregnant women. Biomed Res Int 2014;2014:1–9.

[10] Pauli JM, Preeclampsia RJT. Short-term and long-term implications. Obstet Gynecol North Am 2015;42:299–317.

[11] Rana S, Lemoine E, Granger J, Karunamachi SA. Preeclampsia. Pathophysiology, challenges, and perspectives. Circ Res 2013;114:1094–112. https://doi.org/10.1161/ CircResAHA.113.313276.

[12] Wu P, Halthototutwa R, Kröv C, Rabu A, Kotronias RA, Rahuton C, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2017;10. https://doi.org/10.1161/CIRCOUTCOMES.116.003497 [pii: e003497].

[13] Wu P, Kröv C, Halthototutwa R, Kotronias RA, Rabu A, Fryer AA, et al. Pre-eclampsia is associated with a twofold increase in diabetes: a systematic review and meta-analysis. Diabetologia 2016;59:2518–26.

[14] Stroup DF, Berlin JA, Morton SC, et al. For the meta-analysis of observational studies in epidemiology (MOOSE) group. Meta-analysis of observational studies in epidemiology. A proposal for reporting. JAMA 2000;283:208–12. 2010.1001/jama.283.15.2008.

[15] Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISHHP. Pregnancy Hypertens 2014;4:97–104. https://doi.org/10.1016/j.preghy.2014.02.001.

[16] Kattath AG, Garovic VD. The management of hypertension in pregnancy. Adv Chronic Kidney Dis 2013;20:259–39.

[17] IC10Data.com Preeclampsia 014. https://www.icd10data.com/ICD10CM/Codes/000-09A/010-016/014-InternationalClassificationofDiseases (ICD). https://www.who.int/classifications/icd/en/.

[18] ICD10Data.com Preeclampsia 014. https://www.icd10data.com/ICD10CM/Codes/000-09A/010-016/014-InternationalClassificationofDiseases (ICD).

[19] Peek MJ, Horvath JS, Child AC, Henderson-Smart DJ, Peat B, Gillin A. Maternal and infant outcome in singleton pregnancies complicated with preeclampsia and eclampsia in Ecuador. J Obstet Gynecol 2016;36:581–4.

[20] Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Canadian Hypertensive Disorders of Pregnancy Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynecol Can 2014;36:416–41.

[21] August P. Management of hypertension in pregnant and postpartum women. UpToDate https://www.uptodate.com/contents/management-of-hypertension-in-pregnant-and-postpartum-women; 2019.

[22] August P. Management of hypertension in pregnant and postpartum women. UpToDate https://www.uptodate.com/contents/management-of-hypertension-in-pregnant-and-postpartum-women; 2019.

[23] August P. Management of hypertension in pregnant and postpartum women. UpToDate https://www.uptodate.com/contents/management-of-hypertension-in-pregnant-and-postpartum-women; 2019.
adhesion molecules (VCAM-1 and ICAM-1) and C-reactive protein in women with history of preeclampsia. Acta Obstet Gynecol Scand 2008;87:969–71. https://doi.org/10.1080/00016340802232653.

Portelinha A, Belo L, Cerdeira AS, Braga J, Tejera E, Pinto F, et al. Lipid levels including oxidized LDL in women with history of preeclampsia. Hypertens Pregnancy 2010;29:253–60. https://doi.org/10.1080/01619775.2009.1080659.

Poult A, Harkaralainen AO, Suvio U, Gissler M, Laitinen J, McCarthy MJ, et al. Manifestations of metabolic syndrome after preeclampsia pregnancy. Hypertension 2004;43:825–31.

Roumen RD, Magnusson EB, Smith GD, Vatten LJ. Hypertension in pregnancy and later cardiovascular risk: common antecedents? Circulation 2012;126:579–84. https://doi.org/10.1161/CIRCULATIONAHA.110.934607.

Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classical and novel risk factor pathways in women with a history of preeclampsia. Hypertension 2003;42:43–52.

Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H, et al. Pre-Eclampsia New Emerging Team (PE-NET). A history of preeclampsia identifies women who have worse cardiovascular risk factors. Am J Obstet Gynecol 2009;200(5):e1–8. https://doi.org/10.1016/j.ajog.2008.06.035.

Spaan JJ, Houven AJ, Musella A, Ekhar T, Spandanndr ME, et al. Insulin resistance relates to microvascular reactive 23 years after preeclampsia. Microvasc Res 2010;80:417–21.

Suzuki H, Watanabe Y, Aima H, Kobayashi K, Ohno Y, Kanno Y. Short- and long-term prognosis of blood pressure and kidney disease in women with a past history of preeclampsia. Clin Exp Nephrol 2008;12:102–9. https://doi.org/10.1007/s12245-007-0018-1.

White WM, Miekle MM, Araoz PA, Lahr BD, Bailey KR, Jayachandran M, et al. A history of preeclampsia is associated with a risk for coronary artery calcification 3 decades later. Am J Obstet Gynecol 2016;214:519.e1–519.e8. https://doi.org/10.1016/j.ajog.2016.04.033.

Zoet GA, Benschop L, Boersma E, Budde RPJ, Fauser BCJM, van der Graaf Y, et al. CREW Consortium. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45–55-year-old women with a history of preeclampsia. Circulation 2018;137:877–89. https://doi.org/10.1161/CIRCULATIONAHA.117.026955.

Hernández-Díaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ 2009;338:b2255. https://doi.org/10.1136/bmj.b2255.

Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kulkina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. Am J Obstet Gynecol 2012 Feb;206(2):134.e1–8. https://doi.org/10.1016/j.ajog.2011.08.017.

MacDonald DJ, Eepine P, Pledger M, Geller SE, Lawton B, Stone P. Pre-eclampsia causing severe maternal morbidity – a national retrospective review of pre-eclampsia and maternal morbidity and mortality improved care. Aust N Z J Obstet Gynaecol 2019 Mar 18;59(1):119–271. https://doi.org/10.1111/ajog.12971.

Harville E, Violari JS, Raitakari OT. Preconception cardiovascular risk factors and pregnancy outcome. Epidemiology 2011;22:724–30. https://doi.org/10.1097/EDE.0b013e31822a59e0.

Magnusson EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol 2009;114:961–70. https://doi.org/10.1097/OG.0b013e3181b80d1c.

Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease in women with preeclampsia: systematic review and meta-analysis. Eur J Epidemiol 2013;28:1–19. https://doi.org/10.1007/s10654-012-9762-5.

Covella B, Vitruccio AE, Cadigalli A, Attini R, Gesualdo L, Versino E, et al. A systematic review and meta-analysis of preeclampsia: long-term risk of chronic and end-stage kidney disease after preeclampsia. Kidney Int 2019;97:761–72. https://doi.org/10.1016/j.kint.2019.01.033.

Semrami J, Naranjo M, McCullough PA. Preeclampsia as a form of type 5 cardiorenal syndrome: an underrecognized entity in women’s cardiovascular health. Cardiol Med 2018;8:160–72. https://doi.org/10.1159/000487846.

Peterhazi E, Karczmarczyk B. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation 2011;123:2856–69. https://doi.org/10.1161/CIRCULATIONAHA.110.943407.

Benschop L, Schalekamp-Timmersmann S, Schelling SCJ, Steegers EAP, Roeters van Lennep JE. Early pregnancy cardiovascular health and subclinical atherosclerosis. J Am Heart Assoc. 2019 Aug 6;8(15):e011394. https://doi.org/10.1161/JAHA.118.011394.

Houven AJ, Lichtenstein P, Brison D, Vatten LJ, Jacobsson C, Gibon A, Cnattingius S. Serum insulin-like growth factors in normal pregnancy and subsequently measured cardiovascular risk factors. Acta Obstet Gynecol Scand 2003;82(10):1105–13. https://doi.org/10.1080/0001634031000142932.

Adank MC, Benschop L, Peterhrboers KR, Smak Gregoor AM, Kors AW, Mulder MT, et al. Maternal lipid profile in early pregnancy associated with pregnancy complications and blood pressure in pregnancy and long term postpartum? Am J Obstet Gynecol 2019;221:150.e1–150.e13. https://doi.org/10.1016/j.ajog.2019.03.025.

Rozwadowski T, Banach M, McCullough PA. Artificial intelligence and machine learning for preeclampsia: a health-care revolution? Hypertension 2019;73(6):1246–8. https://doi.org/10.1161/HYPERTENSIONAHA.119.130458.

Rozwadowski T, Banach M, McCullough PA. A history of preeclampsia in women: a cardiovascular health concern. Am J Obstet Gynecol 2019;221:150.e1–150.e13. https://doi.org/10.1016/j.ajog.2019.03.025.

Rozwadowski T, Banach M, McCullough PA. Preeclampsia as a form of type 5 cardiorenal syndrome: an underrecognized entity in women’s cardiovascular health. Cardiol Med 2018;8:160–72. https://doi.org/10.1159/000487846.

Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation 2011;123:2856–69. https://doi.org/10.1161/CIRCULATIONAHA.110.943407.

Benschop L, Schalekamp-Timmersmann S, Schelling SCJ, Steegers EAP, Roeters van Lennep JE. Early pregnancy cardiovascular health and subclinical atherosclerosis. J Am Heart Assoc. 2019 Aug 6;8(15):e011394. https://doi.org/10.1161/JAHA.118.011394.

Houven AJ, Lichtenstein P, Brison D, Vatten LJ, Jacobsson C, Gibon A, Cnattingius S. Serum insulin-like growth factors in normal pregnancy and in pregnancies complicated by preeclampsia. Acta Obstet Gynecol Scand 2003;82(10):1105–13. https://doi.org/10.1080/0001634031000142932.

Benschop L, Schalekamp-Timmersmann S, Schelling SCJ, Steegers EAP, Roeters van Lennep JE. Early pregnancy cardiovascular health and subclinical atherosclerosis. J Am Heart Assoc. 2019 Aug 6;8(15):e011394. https://doi.org/10.1161/JAHA.118.011394.

Houven AJ, Lichtenstein P, Brison D, Vatten LJ, Jacobsson C, Gibon A, Cnattingius S. Serum insulin-like growth factors in normal pregnancy and in pregnancies complicated by preeclampsia. Acta Obstet Gynecol Scand 2003;82(10):1105–13. https://doi.org/10.1080/0001634031000142932.