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Item Type	info:eu-repo/semantics/article
Authors	Alonso-Ventura, Vanesa; Li, Yangzhou; Pasupuleti, Vinay; Roman, Yuani M.; Hernandez, Adrian V.; Pérez-López, Faustino R.
DOI	10.1016/j.metabol.2019.154012
Publisher	W.B. Saunders
Journal	Metabolism: Clinical and Experimental
Rights	info:eu-repo/semantics/openAccess; Attribution- NonCommercial-ShareAlike 4.0 International
Download date	22/05/2022 21:44:45
Item License	http://creativecommons.org/licenses/by-nc-sa/4.0/
Link to Item	http://hdl.handle.net/10757/652437

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Contents lists available at ScienceDirect

# Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Meta-analysis

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



Metabolism

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# ARTICLE INFO

Article history: Received 8 September 2019 Accepted 10 November 2019

Keywords: Preeclampsia Eclampsia HELLP syndrome Metabolic outcomes Biochemical outcomes Cardiovascular risk Meta-analysis

# ABSTRACT

*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 =  $2.0 \text{ kg/m}^2$ ; 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 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). Also, PE/E reduced HDL levels (MD = -2.15 mg/dL, 95%CI -3.46 to -0.85). 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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*Abbreviations:* ACOG, American College of Obstetrics and Gynecologists; ASSHPC, Australasian Society for the Study of Hypertension in Pregnancy Consensus; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CI, confidence interval; DBP, diastolic blood pressure; E, eclampsia; HbA1c, glycosilated hemoglobin; HDL, high density lipoprotein cholesterol; HELLP, hemolysis, elevated liver enzymes, and low platelet count; HOMA-IR, homeostatic model assessment insulin resistance; IGF, insulin growth factor 1; ICD, International Classification of Diseases; IQR, interquartile range; ISSHP, International Society for the study of Hypertension in Pregnancy; LDL, low density lipoprotein cholesterol; LP(a), lipoprotein (a); MD, mean difference; MetS, metabolic syndrome; NHBPEPWG, National High Blood Pressure Education Program Working Group; NOS, Newcastle–Ottawa Scale; PE, preeclampsia; RD, risk difference; RR, risk ratio; SBP, systolic blood pressure; SD, standard deviation; VLDL, very low density lipoprotein cholesterol; WHR, waist-to-hip ratio.

# 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, preterm 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

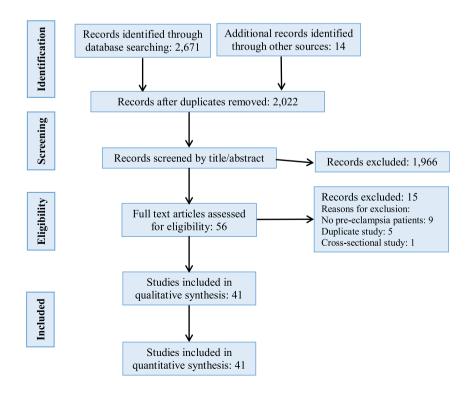


Fig. 1. Flow diagram of included studies.

Table 1Characteristics of included studies.

			Data during the index pregnam	cy: preeclampsia (PE)	Data during the index pregnar	ncy: control (CG)		
Author, year [reference]	Country; study design	Exclusion reasons	Inclusion criteria; n (women); age at pregnancy	Parity index pregnancy; GAD, weeks	CG definition; n (women); age at pregnancy	Parity index pregnancy. GAD, weeks	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	Normotensive pregnancies resulting in term delivery of a normal weight infant. n = 58; Age 30 [28, 33]	Primiparous = $32$ (50%); GAD = $40$ [39, 41] <sup>a</sup>	One year postpartum	Gestational duration
Andersgaard AB, 2012 [24]	Norway; Retrospective cohort study	Women with normoproteinuric hypertension and with normotensive hypertension	PE: hypertension $+$ proteinuria, N = 901 women; Age: 25.4 (24.4–26.4) years before the study of outcomes	Women reporting ≥1 childbirth; GAD: not reported	Pregnant women without hypertension and proteinuria. N = 7187; Age 24.0 (23.6–24.3) years before the study of outcomes.	Women reporting ≥1 child birth; GAD: not reported	Age 48.8 (25–87) years (PE group), and 47.4 (25–94) years (control group)	Age, parity
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 $\pm$ 6.68 years	Pregnancies 1 (1–2); GAD: not reported	N = 20; Age: 27.25 $\pm$ 3.61 years	Pregnancies 2 (1–2); GAD: not reported	Follow-up period of PE group (6.12 $\pm$ 3.59 years and 6.05 $\pm$ 4.06 years in the CG	Age
Bar J, 1999 [26]	Israel; Prospective cohort study	None of the women had a previous definite diagnosis of hypertension or renal disease	0	Parity not reported; Preterm delivery 30 (62.5%); IUGR: 27 (56%)	Pregnant women without PE. N = 48 women; Age = 35 $\pm$ 8 years.	Parity not reported; Preterm delivery 2 (4.5%), IUGR 1 (2.2%)	Examination of the study and control groups was performed 3–5 years after delivery	Not matched
Barden AE, 1999 [27]	Australia; Retrospec- tive cohort study	Known history of hypertension or renal disease	PE according to the ACOG; N = 62 women; Age: 27.5 $\pm$ 0.8 years	27 primiparous and 35 multiparous	Pregnant women without PE. N = 84 women; Age: 27.6 $\pm$ 0.6 years	30 primiparous and 54 multiparous	6 months postpartum	Age and gestation
Berends AL, 2008 [28]	The Netherlands; Retro- spective cohort study	Multiple pregnancies	PE according to the ACOG; N = 36 women; Age = $36.2 \pm 5.8$ years.	Parity not reported; GAD: $37 \pm 3.4$ weeks	Pregnant women without PE. N = 100 women; Age 39.2 $\pm$ 5.6 years.	Parity not reported; GAD: $39.6 \pm 1.4$ weeks	Time interval delivery study: PE group 7 $\pm$ 5.6 years, and Control group 13.1 $\pm$ 5.7 years	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	= 131, including severe PE and one or more of the following conditions: (i) proteinuria $\geq 5 g/24$ h (n = 59; 45.0%), (ii) HELLP syndrome	Primiparous: 101 (77.1%); GAD: 30.5 ± 2.1	N = 56 matched uncomplicated pregnancy, birth between 37 and 42 weeks gestation, after a normotensive pregnancy and with absence of IUGR. Births: 1998–2005. Age: 32.3 $\pm$ 4.1 years	Primiparous: 29 (51.8%); GAD: 40.0 ± 1.4 weeks	Time interval delivery risk assessment study: 9–16 years after index pregnancy. Age PE group: 44.0 $\pm$ 5.6 years; CG: 46.5 $\pm$ 4.8 years. Time post index pregnancy: PE group: 13.1 $\pm$ 2.2 years; CG: 14.2 $\pm$ 2.3 years	Maternal age (range ± 5 years) and date of delivery (range ± 1 year)
Breetveld 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 $\pm$ 4.0	Primiparous: 41/115 (36%); GAD 33.3 $\pm$ 4.3 weeks	Pregnant women without PE. N = 50 uncomplicated pregnancies; Age $36 \pm 4.0$ .	Primiparous: 5/50 (10%); GAD 39.6 ± 2.3 weeks	Postpartum years: PE group: $5.4 \ 8.0 \pm 2.6$ years; Control group: $8.0 \pm 2.7$ years;	Not matched
Carleton H, 1988 [31]	United States; Pro- spective 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.		Follow-up assessment at least 3,5 years after delivery (1981–1985)	Year delivered, age, race, and weight $\pm 1/3$
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	women; Age: Single episode:		$N=48$ women with uncomplicated pregnancies and deliveries; Age: 35 $\pm$ 6 years	Parity not reported;	All were at least 3 months (median, 3 years) postpartum	Not matched

Table	1 (	(continued)
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			Data during the index pregnan	cy: preeclampsia (PE)	Data during the index pregnan	cy: control (CG)		
Author, year [reference]	Country; study design	Exclusion reasons	Inclusion criteria; n (women); age at pregnancy	Parity index pregnancy; GAD, weeks	CG definition; n (women); age at pregnancy	Parity index pregnancy. GAD, weeks	Time of follow up and/or age	Matching variables for controls
Christensen M, 2016 [33]	Denmark; Retrospective cohort study.	experienced hypertensive disorder of pregnancy before or after 2001–2004 were	PE according to the ACOG. N = 21 patients with PE in 2001–2004; Age: time since delivery, years: $10.28 \pm 0.70$ m		N = 21 normotensive pregnant women without PE, in 2001–2004; Age: time since delivery, years: $10.27 \pm$	Primiparous n = 10 (48%); GAD: 280 $\pm$ 9 days	Ten year after delivery. Age: exposed women $40.75 \pm 2.7$ years; non-exposed women $40.67 \pm 2.2$ years	Age $(\pm 2 \text{ years})$ and time since delivery $(\pm 1 \text{ year})$
Coffeng SM, 2011 [34]	The Netherlands; Prospective cohort study	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.	0.70 years Severe early-onset PE according to the ISSHP; N = 16 severe early-onset PE; Age: 29.7 $\pm$ 4.8 years	Parity and GAD not reported	0.51. years N = 17 women with uncomplicated pregnancies; Age: 30.7 $\pm$ 3.6 years	Parity and GAD not reported	$40.67 \pm 2.3$ years Study 4 years after index delivery.	Not matched
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	Parity: median 0.5 [half interquartile 1.0]; GAD: 37.6 $\pm$ 3.2 weeks	Normotensive pregnancies. N = 17 women; Age: 26.0 $\pm$ 2.5 years	Parity: Median 1.0 [half interquartile 1.0]; GAD: $39.1 \pm$ 1.9 weeks	Study at 5 years follow-up.	Not matched
Drost JT, 2012 [36]	The Netherlands; Pro- spective cohort study	Pregnant or lactating women	PE < 32 weeks. N = 339 women with PE according to the ISSHP; Age: 29.8 $\pm$ 3.8 years	Number of pregnancies: 2.7 $\pm$ 1.4; GAD: not reported	Pregnant women without PE, $N = 332$ women without PE; Age: 28,6 $\pm$ 4,1 years	Number of pregnancies: 3.1 ± 1.4; GAD: not reported	Study 10 years post index-delivery.	Age
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 $\pm$	Parity: not reported GAD: $38.3 \pm 2.6$ weeks	Pregnant women without PE. $N = 168$ controls matched for age and year of index delivery; Age 27.0 $\pm$ 4.2 years	Parity not reported; GAD: $39.4 \pm 2.1$ weeks	Average period from the index pregnancy to the scheduled study 7.8 years (range 5.1–13.0 years).	Maternal age and year of delivery of the index pregnancy (within 1 year).
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 $\pm$ 5.2 years.	Primiparous and multiparous women; GAD: $35.3 \pm 3.8$ weeks	Women without PE, N = 38 pregnancies; Age: 24.7 $\pm$ 3.9 years.	38 women without adverse outcomes; GAD: $39.1 \pm 2.8$ weeks	Endpoints studied 20 years after pregnancies	Age- and parity-matched controls between 1975 and 1985
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: 40 women with preeclampsia according to the ICD 9 codes, who delivered between 1976 and 1982; Age: $24.2 \pm 3.7$	Parity: not reported; GAD: not reported	40 age- and parity-matched normotensive women, who delivered between 1976 and 1982; Age: 24.3 $\pm$ 3.4 years	Parity: parity matched; GAD: not reported	Women who delivered in 1976–1982, were studied in 2014–2015; Age: PE 59.4 $\pm$ 4.8; control: 59.7 $\pm$ 4.5 years	Age and parity
Girouard 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 $\pm$ 3.9 years	Parity: not reported; GAD: 38.3 $\pm$ 2.6	N = 168 women with normotensive pregnancy. Mean age: 27.0 $\pm$ 4.2 years	Parity: not reported; GAD: $39.4 \pm 2.1$		Maternal age and year of delivery of the index pregnancy (within 1 year)
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: $30 \pm 4$ years	Parity: one; GAD: not reported	$N=17$ age-matched controls; Mean age: 31 $\pm$ 4 years	Parity: one; GAD: not reported	Women were studied 7.8 years after delivery	Age and parity
He S, 1999 [42]	Sweden; Retrospective cohort study		PE 25 women (11 mild PE, and 14 severe PE); Age: 33 $\pm$ 6 years	Parity: 32 primipara; GAD: not reported	N=24 women; Age: Matched by age, parity and index of pregnancy $34 \pm 6$ years	Parity: 29 primiparous; GAD: not reported	Women were examined $2-5$ (4.5. $\pm$ 0.8) years after delivery	Age, parity at index pregnancy and time of delivery

Hubel CA, 2008 [43]	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	Eclampsia: 25 women; Age: not reported	Parity: not reported; GAD: not reported	Control 28 women with uncomplicated pregnancy; Age not reported	Parity: not reported; GAD: not reported	Deliveries between 1931 and 1996. Women were 50 to 67 years old at reexamination (32 years after delivery)	Age, age at pregnancy, and parity
Innes KE, 2005 [44]	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	Cases: 13 women with PE according to the ACOG in their first pregnancies; Age: $33.9 \pm 0.9$ years	Parity: primiparous; GAD: not reported	13 pregnant women matched to cases on race/ethnicity, current age, and age at delivery. Age: $33.3 \pm 0.9$ years	Parity: Primiparous; GAD: not reported	All subjects were menstruating regularly at the time of the study. Follow up interval ranged from 1 to 10 years and averaged $3.69 \pm 0.47$ years	Cases on race/ethnicity, current age, and age at delivery
Kvehaugen AS, 2010 [45]	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	PE: 23 women with preeeclampsia; Age: 30.0 [27.0, 32.0]	Parity: 2.0 [1.0, 2.0], Multiparous 60%; GAD: Median 32.3 weeks	15 control matched normotensive pregnancy at the same hospital; Age: 34.0 [32.0, 37.0]	Parity: 2.0 [2.0, 3.0], Multiparous 30%; GAD: Median 38.6 weeks	Age at the study: PE women 36.0 [33.0, 39.0]; Controls: 40.5 [39.0, 44.0]	Not matched
Laivuori H, 1996 [46]	Finland; Retrospective cohort study	Women with hysterectomy; use of levonorgestrel-release intrauterine device, hormone replacement therapy, or progestin-only contraception		Parity: First pregnancy; GAD: $36.2 \pm 0.5$ weeks	Control women: 22; Age: 25.0 $\pm$ 0.9 years	Parity: First pregnancy; GAD: $40.1 \pm 0.4$ weeks	Years since delivery: PE-eclampsia group: $41.8 \pm 0.9$ years; Control group: $41.8 \pm 0.9$ years	Age
Lampinen KH, 2008 [47]	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	Severe PE: 28 non-obese women with previous severe preeclampsia or eclampsia; Age: $33 \pm 5$ years	Primiparity: 14/28 (50%); GAD: 33 [29, 36] weeks	Control women: 20 women with a previous normotensive pregnancy; Age 30 $\pm$ 4	Primiparity: 3/20 (15%); GAD: 40 ([40 to 41]:	Women were studied 5 to 6 years after the index pregnancy.	Not matched
Mangos GJ, 2012 [48]	Australia; Retrospective cohort study	Pregnant women were excluded who had DM,	PE: 39 women according to the ASSHPC Statement criteria for the diagnosis preeclampsia; Age: $37 \pm 6$ years	Multiparous: 26 (67%); GAD: not reported	Control group: 35 women; Age: 38 $\pm$ 6 years	Multiparous women 30 (86%); GAD: not reported	Years postpartum: PE group: 3.8 (2.5–5.0); control group: 4.3 (2.8–7.0)	BMI
Manten GTR, 2007 [49]	The Netherlands; Retrospective cohort study	Women with fasting glucose levels ≥7.0 mmol/L	PE: 256 women with preeclampsia according to the ACOG criteria, HELLP syndrome $n = 163 (64\%)$ ; Age: $31 \pm 4$	Primiparous 203 (79%); GAD: 217 ± 28 days	Control group: 53 women; Age: $33 \pm 4$	Primiparous 31 (58%); GAD: 283 ± 10 days	Women were studied at least 3 months after delivery, and after ending lactation	
McDonald SD, 2013 [50]	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	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	Control group: 219 women without PE; Age of oldest child, median 21 [16, 28]; Age at index pregnancy: not reported	Parity not reported; GAD not reported	Study performed two decades after delivery; Age: PE group 49 ([QR 44–55] years; Control group: 49 [IQR 45–56] years	Maternal age $\pm$ 3 years and child's age $\pm$ 5 years
Nisell H, 1999 [51]	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	PE: 21 women with preeclampsia according to the ACOG criteria; Age: 30 SEM 1	Parity: Primiparous 14; GAD: 37.1 SEM 0.8	Control group; 22 women; Age: 30 SEM 1	Parity: Primiparous 9; GAD: 40.1 SEM 0.3	Women were followed up to 26-119 weeks after delivery	Age, pregnancy during 1995
Nohira T, 2013 [52]	Japan; Retrospective	Patients who had CVD prior to	PE: 58 women with severe	Parity: 0.896 $\pm$	61 normal pregnancies; Age:	Parity: 0.874 $\pm$	Elapse time from	Age, parity,

Table 1 (continued)

			Data during the index pregnan	cy: preeclampsia (PE)	Data during the index pregnan	cy: control (CG)		
Author, year Country; study [reference]	Country; study design	Exclusion reasons	Inclusion criteria; n (women); age at pregnancy	Parity index pregnancy; GAD, weeks	CG definition; n (women); age at pregnancy	Parity index pregnancy. GAD, weeks	Time of follow up and/or age	Matching variables for controls
	cohort study	pregnancy were excluded.	preeclampsia; Age: 27.37 ± 3.44 years	1.344; GAD: not reported	$28.13 \pm 4.26 \text{ years}$	1.286; GAD: not reported	delivery: PE group: $12.3 \pm 3.17$ (Age: $38.26 \pm 12.63$ ); Control group: $12.7 \pm 3.33$ years (Age: $39.54 \pm 10.26$ )	prepregnancy BMI, smoking habits and family history of DM, CVD and preeclampsia
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: $39.4 \pm 3.6$ years	Parity: $1.8 \pm 0.9$ ; GAD: 245 $\pm$ 6 days	Control: 16 non-complicated pregnant women; Age: 11 years after delivery $41.2 \pm 3.2$ years	Parity: $2.5 \pm 0.7$ ; GAD: $281 \pm 6$ days	Study performed 11.2 $\pm$ 0.6 years following the index pregnancy	Age, parity and date of delivery
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. Patients with hepatitis A or B were identified	PE: 58 women according to the ISSHP; Age: 27 [24, 3]	Parity: not reported. GAD: 34 [33, 37] weeks; Cesarean rate: 74.1%	48 women without medical complications associated to pregnancy; Age: 28 [25, 33]	GAD: 39 [38, 40];	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]	Age, BMI, time since pregnancy, smoking, contraceptive intake, alcohol consumption
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]	<b>J</b> 1	Control group 60 women; Age: 28 [25, 33]	Parity: not reported; GAD: 39.0 [38.1, 40.0]	Data at recall: women with PE: Age 34 [31, 39] years; control group 34 [31, 40] years	Age
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: Primiparous; GAD: not reported	1369 control pregnant women; Age: average 25 years	Parity: Primiparous; GAD: not reported	The median interval from first delivery to examination at 31 years was 6 years in all groups [IQR: 5 months to 11 years].	Not matched
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	Control group: 2964 normotensive pregnant women; Age: not reported	Parity: not reported; GAD: not reported	Recall for study 21 years after delivery.	Not matched
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: 36	Control: 40 uncomplicated pregnant women matched as a	Parity: Primiparous women; GAD: 40	Gravids delivering between 1975 and	Time of index pregnancy, smoking

	study	or had a recent infection within the last 10 days.	to the ISSHP criteria; Age: 24 [21.2, 26] years	[33.2, 38] weeks	group for time of index pregnancy, smoking, and current BMI; Age: 25 [21, 27] years	[38, 41] weeks	1985. Ages at recall were in the PE group 43 [40, 47], and 44 [43, 47] years	and current body mass index
Smith GN, 2009 [59]	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: $30.5 \pm 5.7$	Parity (%): Primiparous 43 $\pm$ 61.4; Previous pregnancy with PE 11 (15.9%); GAD: 35.6 $\pm$ 3.8.weeks	Control group: 70 normotensive pregnancies; Age: $30.3 \pm 4.1$	Parity (%): Primiparous 42 $\pm$ 60.0; Previous pregnancy with PE 0 (0%); GAD: 39.2 $\pm$ 1.6 weeks	Comparison of physical and biochemical parameters at year 1 follow-up between women with and without preeclampsia	Age, parity, and race
Spaan JJ, 2010 [60]	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	Age at recall (23 years after PE): PE group $49.0 \pm 3.9$ years (postmenopausal n = 8, 36%), and control group $49.8 \pm 3.9$ years (postmenopausal n = 5, 17%)	Matched for age, BMI and date of delivery
Suzuki H, 2008 [61]	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: $34 \pm 8$ years	Parity: not reported; GAD: not reported	Control: 201 normotensive pregnant women; Age at first pregnancy $28 \pm 1$ years	Parity: not reported; GAD: not reported	Age (years) at recall: PE group $49 \pm 3.0$ , and control group: $48.5 \pm 1.5$	Not matched
White WM, 2016 [62]	United States; Retro- spective 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 $59.5 \pm 4.6$ years	Parity and age at index birth; Mean age at delivery: 24 years
Zoet GA, 2018 [63]	The Netherlands; Retrospective cohort study	Women aged < 45 or > 55 years	PE: 164 women withhypertension + 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; GAD: 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)]. <sup>a</sup>P < 0.001; ACOG: American College of Obstetrics and Gynecology; ASSHPC: 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.

# Table 2

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	$I^2$
Systolic blood pressure	38 (17,267)	MD = 8.3  mmHg (6.8  to  9.7)	< 0.00001	78%
Diastolic blood pressure	37 (17,232)	MD = 6.8  mmHg (5.6  to  8.0)	< 0.00001	83%
Hypertension	12 (2261)	RD = 0.24% (0.15  to  0.33)	< 0.00001	89%
Body mass index	34 (17,039)	$MD = 2.0 \text{ kg/m}^2 (1.6 \text{ to } 2.4)$	< 0.00001	56%
Waist circumference	13 (11,371)	MD = 4.3  cm (3.1  to 5.5)	< 0.00001	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)	0.0005	0%
Lipoprotein (a)	4 (445)	MD = 1.9  mg/dL (-0.8  to  4.7)	0.17	7%
Total cholesterol	29 (13,477)	MD = 4.6  mg/dL (1.5  to  7.7)	0.003	56%
HDL-cholesterol	29 (13,367)	MD = -2.1  mg/dL (-3.5  to -0.8)	0.001	57%
LDL-cholesterol	24 (5220)	MD = 4.6  mg/dL (0.2  to  8.9)	0.04	81%
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 (1.2  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)	< 0.00001	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)	< 0.000001	0%

Cl: 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.

(ASSHPC) [18]. 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

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tudy or Subgroup	Mann								
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Akhter 2013	120	7.41	48	110	7.41	58	3.7%	10.00 [7.17, 12.83]	
ndersgaard 2012	138	12.25	901	130	8.65	7187	4.2%	8.00 [7.18, 8.82]	-
wkas 2015	124.75	15.45	25	125.85	5.27	20	2.3%	-1.10 [-7.58, 5.38]	
lar 1999	132.8	16.2	48	118	12	44	2.5%	14.80 [9.01, 20.59]	
larden 1999	114	15.75	62	107	9.17	84	3.0%	7.00 [2.62, 11.38]	
lerends 2008	129	17.78	36	121.75	11.11	100	2.4%	7.25 [1.05, 13.45]	
lokslag 2017	126	18.6	131	115	17	56	2.6%	11.00 [5.53, 16.47]	
reetveld 2015	117	13	115	110	10	50	3.3%	7.00 [3.35, 10.65]	
arleton 1988	123.7	19.9	23	114.4	19.9	23	1.1%	9.30 [-2.20, 20.80]	
hambers 2001	116	16	78	103	10	48	3.0%	13.00 [8.46, 17.54]	
hristensen 2016	131	15	21	125	9	21	2.0%	6.00 [-1.48, 13.48]	
offeng 2010	135.3	13.4	17	114.7	6.3	16	2.1%	20.60 [13.52, 27.68]	
Dantas E.M 2013	116	7.1	10	108.5	7.9	17	2.5%	7.50 [1.71, 13.29]	
Drost 2012	127	16.91	339	119	13.01	332	3.9%	8.00 [5.72, 10.28]	
reeman 2004	124.4	14.6	40	118.8	17.2	38	2.1%	5.60 [-1.50, 12.70]	
Sarovic 2017	131.8	14.9	40	131.4	20.6	40	1.9%	0.40 [-7.48, 8.28]	
Sirouard 2007	114.8	12.2	63	107.9	10.6	168	3.4%	6.90 [3.49, 10.31]	
lamad 2007	111	10	18	103	8	17	2.4%	8.00 [2.02, 13.98]	—
le 1999	120	16	25	108	8	24	2.1%	12.00 [4.96, 19.04]	
lubel CA 2008	143	16	25	130	15	28	1.7%	13.00 [4.62, 21.38]	
nnes, K.E. 2005	113.8	13.34	13	107.1	13.34	13	1.3%	6.70 [-3.56, 16.96]	
(vehaugen 2010	119.5	7.41	23	114.5	5.93	15	3.1%	5.00 [0.74, 9.26]	
aivuori 1996.	127	14.07	22	116	9.38	22	2.1%	11.00 [3.93, 18.07]	
ampinen 2008.	124.75	18.52	28	112	14.81	20	1.5%	12.75 [3.31, 22.19]	
langos 2012	121	20	39	115	12	35	2.0%	6.00 [-1.43, 13.43]	+
fanten 2007	127	12	256	116	14	53	3.2%	11.00 [6.95, 15.05]	
1cDonald 2013	119.5	16	109	115.8	14.4	219	3.4%	3.70 [0.14, 7.26]	<u> </u>
Visell 1999	119	9.17	21	109	9.38	22	2.6%	10.00 [4.46, 15.54]	
Vohira 2013	127.6	18.8	58	122.2	14.2	61	2.4%	5.40 [-0.61, 11.41]	
Ostlund 2013	117	14	15	111	11	16	1.6%	6.00 [-2.90, 14.90]	+
ortelinha 2010	121.5	13.33	90	119.25	12.59	60	3.1%	2.25 [-1.96, 6.46]	
outa 2004	123.5	14.81	49	117.5	10.37	1369	3.1%	6.00 [1.82, 10.18]	
Romundstad 2010	130	13.23	168	124	55.55	2964	3.7%	6.00 [3.17, 8.83]	
attar 2003	124.5	16.3	40	117.5	16.3	40	2.1%	7.00 [-0.14, 14.14]	
mith 2009	120	11.9	70	111.3	9.3	70	3.4%	8.70 [5.16, 12.24]	
paan 2010	132	17	22	117	15	29	1.6%	15.00 [6.04, 23.96]	
uzuki, H. 2008	160	6	48	157	2	201	4.0%	3.00 [1.28, 4.72]	
loet GA 2018	130	15	164	110	16	387	3.7%	20.00 [17.21, 22.79]	
otal (95% CI)			3300			13967	100.0%	8.28 [6.85, 9.71]	•

**Fig. 2.** Meta-analyses of blood pressure-related outcomes: Mean differences of systolic blood pressure (Fig. 2A) and diastolic blood pressure (Fig. 2B), and risk difference of hypertension (Fig. 2C). A. Mean systolic blood pressure, n = 38 studies ( $l^2 = 78\%$ ). B. Mean diastolic blood pressure, n = 37 studies ( $l^2 = 83\%$ ). C. Hypertension, n = 12 studies ( $l^2 = 89\%$ ).

В

Akhter 2013   77.75   6.67   48   70   7.41   58   3.2%   7.75   [5.07, 10.43]			clamps			Preeclam		1000 V 2	Mean Difference	Mean Difference
Andersgaard 2012   80   12.25   90.1   75   4.33   7187   3.88   5.00[419,5.81]   +     Aqkas 2015   78.92   12.79   25   78.35   4.63   20   2.1%   0.57[-4.84,5.98]     Bar 1999   87.9   8.7   4.72   8   44   2.9%   10.70[7.29, 14.11]	Study or Subgroup	Mean			Mean	SD		-	IV, Random, 95% CI	IV, Random, 95% CI
Axkas 2015   78.92   12.79   25   78.35   4.63   20   2.1%   0.57(-18.4)   5.98]     Bar 1999   87.9   8.7   48   77.2   8   44   2.9%   10.70(7.29, 14.11)     Berents 2008   80.75   12.59   36   74.5   7.41   100   2.5%   6.25(1.89, 10.61)     Berents 2008   80.75   12.59   36   74.5   7.41   100   2.5%   6.25(1.89, 10.61)     Breetveld 2015   74   10   115   71   7   50   3.2%   3.00[0.33, 5.67]     Carleton 1988   77   14.39   23   1.3%   2.90[5.42, 11.22]      Chambers 2010   79,7   71   76   6   48   3.00   7.00 [3.84, 10.16]      Coffeng 2010   79,7   71   75   8   2.3%   7.00 [3.64, 10.16]      Coffeng 2010   79,7   71   11.5   38   2.36%   7.00 [3.64, 13.44]      Drost 2012   86   10.4   0   7.11   11.5   3.13%   4.	Akhter 2013								7.75 [5.07, 10.43]	
Bar 1999   87.9   8.7   48   77.2   8   44   2.9%   10.70[7.29,14,11]	Andersgaard 2012			901	75	4.33	7187	3.8%	5.00 [4.19, 5.81]	+
Barden 1999   70   7.87   62   65   9.16   84   3.2%   5.00[2.3, 7.77]     Berends 2008   80.75   12.59   36   74.5   7.41   100   2.5%   6.25[1.89, 10.61]     Breateds 2008   80.75   12.59   36   74.5   7.41   100   2.5%   6.25[1.89, 10.98]     Breetveld 2015   74   10   115   71   7   50   3.2%   3.00[0.33, 5.67]     Carleon 1388   77   14.39   23   74.1   14.39   23   13.3   2.90[-5.42, 11.22]     Chambers 2001   74   12   78   67   6   48   3.0%   7.00[3.84, 10.16]      Coffeng 2010   79.7   7.1   77.6   6   17   2.3%   8.50[3.56, 13.44]      Drost 2012   86   15.03   339   79   8.37   332   3.6%   7.00[5.16, 8.84]      Freeman 2004   81.3   1.04   40   77.1   11.5   38   2.3%   4.20[-0.67, 9.07]      Garowic 2007	Aykas 2015					4.63			0.57 [-4.84, 5.98]	
Berends 2008     80.75     12.59     36     74.5     7.41     100     2.5%     6.25     [1.89, 10.61]       Bokslag 2017     82     9.8     131     74     9.4     56     3.1%     8.00 [5.02, 10.98]       Breetveld 2015     74     10     115     71     7     50     3.2%     3.00 [0.33, 5.67]       Carleton 1988     77     14.39     23     74.1     14.39     23     13%     2.90 [5.42, 11.22]       Chambers 2001     74     12     78     67     6     48     3.0%     7.00 [3.84, 10.16]       Christensen 2016     89     9     21     86     9     21.1%     3.00 [-2.44, 8.44]       Coffen 2010     79.7     7.1     17     65.8     16.14	Bar 1999			48		8	44	2.9%	10.70 [7.29, 14.11]	n
Bokslag 2017   82   9.8   131   74   9.4   56   3.1%   8.00 [5.02, 10.98]	Barden 1999				65	9.16	84		5.00 [2.23, 7.77]	
Breetveld 2015   74   10   115   71   7   50   3.2%   3.00 [0.33, 5.67]     Carleton 1988   77   14.39   23   74.1   14.39   23   1.3%   2.300 [-5.42, 11.22]     Chambers 2001   74   12   78   67   6   48   3.0%   7.00 [3.44, 10.16]     Christensen 2016   89   9   21   86   9   21   2.1%   3.00 [-2.44, 8.44]     Coffeng 2010   79.7   7.1   17   65.8   6   16   2.5%   13.90 [9.42, 18.38]     Drost 2012   86   15.03   339   79   8.37   332   3.6%   7.00 [5.16, 8.84]     Freeman 2004   81.3   10.4   40   77.1   11.5   38   2.3%   4.20 [-0.67, 9.07]     Garovic 2017   78.2   9.6   40   75.8   10.7   40   2.5%   2.40 [-2.05, 6.85]     He 1999   74   14   25   65   9   21.1%   5.10 [-0.35, 10.55]     Hubel CA 2008   86.6   11   25   81.5   9	Berends 2008	80.75	12.59	36	74.5	7.41	100	2.5%	6.25 [1.89, 10.61]	
Carleton 1988   77   14.39   23   7.4.1   14.39   23   1.3%   2.90 [-5.42, 11.22]     Chambers 2001   74   12   78   67   6   48   3.0%   7.00 [3.84, 10.16]     Christensen 2016   89   9   21   86   9   21 [3%   3.00 [-2.44, 8.44]     Coffeng 2010   79.7   7.1   17   65.8   6   16   2.5%   13.90 [9.42, 18.38]     Dantas E M 2013   80.5   6.5   10   72   6   17   2.3%   8.50 [3.56, 13.44]     Torst 2012   86   15.03   339   79   8.37   332   3.6%   7.00 [2.04, 7.96]     Garowic 2017   78.2   9.6   40   75.8   10.7   40   2.5%   2.40 [-2.05, 6.85]     Giroward 2007   75   10.9   63   70   82   2.1%   5.10 [-0.35, 10.55]     Hubel CA 2008   86.6   11   25   81.5   9   28   2.1%   7.00 [2.62, 11.38]     Lawyoni 1996   82   9.38   22   75   7.00 [2.62, 11.38]	Bokslag 2017	82	9.8	131	74	9.4	56	3.1%	8.00 [5.02, 10.98]	
Chambers 2001   74   12   78   67   6   48   3.0%   7.00   [3.84, 10.16]	Breetveld 2015	74	10	115	71	7	50	3.2%	3.00 [0.33, 5.67]	
Christensen 2016   89   9   21   86   9   21   2.1%   3.00[-2.44, 8.44]     Coffeng 2010   79.7   7.1   17   65.8   6   16   2.5%   13.90 [9.42, 18.38]     Dartas EM 2013   80.5   6.5   10   72   6   17   2.3%   8.50 [3.56, 13.44]     Drost 2012   86   15.03   339   79   8.37   332   3.6%   7.00 [5.16, 8.84]     Freeman 2004   81.3   10.4   40   77.1   11.5   38   2.3%   4.20 [-0.67, 9.07]     Garovic 2017   78.2   9.6   40   75.8   10.7   40   2.5%   2.40 [-2.05, 6.65]     Girouard 2007   75   10.9   63   70   8.2   168   3.1%   5.00 [2.04, 7.96]     Hubel CA2008   86.6   11   25   81.5   9   28   2.1%   5.10 [-2.65, 12.76]     Innes, K.E 2005   70.7   8.76   13   61.2   2.9%   7.00 [2.62, 11.38]   1.41     Lampinen 2008   81.75   12.59   28   75.5	Carleton 1988	77	14.39	23	74.1	14.39	23	1.3%	2.90 [-5.42, 11.22]	
Coffeng 2010   79.7   7.1   17   65.8   6   16   2.5%   13.90   [9.42, 18.38]	Chambers 2001	74	12	78	67	6	48	3.0%	7.00 [3.84, 10.16]	
Dantas E M 2013   80.5   6.5   10   72   6   17   2.3%   8.50 [3.56, 13.44]     Drost 2012   86   15.03   339   79   8.37   332   3.6%   7.00 [5.16, 8.84]     Freeman 2004   81.3   10.4   40   77.1   11.5   38   2.3%   4.20 [-0.67, 9.07]     Garovic 2017   78.2   9.6   40   75.8   10.7   40   2.5%   2.40 [-2.05, 6.85]     Girouard 2007   75   10.9   63   70   8.2   168   3.1%   5.00 [2.04, 7.96]     Hubel CA 2008   86.6   11   25   81.5   9   28   2.1%   5.10 [-0.35, 10.55]     Innes, K.E. 2005   7.07   8.76   13   61.2   12.98   13   1.3%   9.50 [0.99, 18.01]     Laivari 1996   82   9.38   22   75   1.69   22   5.5%   7.00 [3.10, 10.90]     Mangos 2012   79   8   39   72   9   35   3.7%   7.00 [3.10, 10.90]     Mante 2007   84   9.17   21   77 <td>Christensen 2016</td> <td>89</td> <td>9</td> <td>21</td> <td>86</td> <td>9</td> <td>21</td> <td>2.1%</td> <td>3.00 [-2.44, 8.44]</td> <td></td>	Christensen 2016	89	9	21	86	9	21	2.1%	3.00 [-2.44, 8.44]	
Drost 2012   86   15.03   339   79   8.37   332   3.6%   7.00   [5.16, 8.84]      Freeman 2004   81.3   10.4   40   77.1   11.5   38   2.3%   4.20   [-0.67, 9.07]     Garovic 2017   78.2   9.6   40   75.8   10.7   40   2.5%   2.40   [-2.05, 6.85]     Girouard 2007   75   10.9   63   70   8.2   168   3.1%   5.00   [2.04, 7.96]     He 1999   74   14   25   65   9   24   1.7%   9.00   [2.44, 15.56]     Hubel CA 2008   86.6   11   25   81.5   9   28   2.1%   5.10   [-0.35, 10.55]     Innes, K.E. 2005   70.7   8.61   61.2   2.9   8.3   1.3%   9.50   [0.99, 18.01]	Coffeng 2010	79.7	7.1	17	65.8	6	16	2.5%	13.90 [9.42, 18.38]	
Drost 2012   86   15.03   339   79   8.37   332   3.6%   7.00 [5.16, 8.84]		80.5	6.5	10	72	6	17			· · · · · · · · · · · · · · · · · · ·
Freeman 2004   81.3   10.4   40   77.1   11.5   38   2.3%   4.20 [-0.67, 9.07]     Garovic 2017   78.2   9.6   40   75.8   10.7   40   2.5%   2.40 [-2.05, 6.85]     Girouard 2007   75   10.9   63   70   8.2   168   3.1%   5.00 [2.04, 7.96]     Hubel CA 2008   86.6   11   25   65   9   24   1.7%   9.00 [2.44, 15.56]     Hubel CA 2008   86.6   11   25   81.5   9   28   2.1%   5.10 [-0.35, 10.55]     Innes, K.E. 2005   70.7   8.76   13   61.2   12.98   13   1.3%   9.50 [0.99, 18.01]     Kvehaugen 2010   72.5   7.41   23   69.25   9.63   15   2.0%   3.25 [-2.49, 8.99]     Lawori 1996   82   9.38   22   75   7.00 [2.62, 11.38]	Drost 2012	86	15.03	339	79	8.37	332	3.6%		
Garovic 2017   78.2   9.6   40   75.8   10.7   40   2.5%   2.40 [-2.05, 6.85]     Girouard 2007   75   10.9   63   70   8.2   168   3.1%   5.00 [2.04, 7.96]     He 1999   74   14   25   65   9   24   1.7%   9.00 [2.44, 15.56]     Hubel CA 2008   86.6   11   25   81.5   9   28   2.1%   5.10 [-0.35, 10.55]     Innes, K.E. 2005   70.7   8.76   13   61.2   12.98   13   1.3%   9.50 [0.99, 18.01]     Kvehaugen 2010   72.5   7.41   23   69.25   9.63   15   2.0%   3.25 [-2.49, 8.99]     Laivori 1996   82   9.38   22   75   4.69   22   2.5%   7.00 [2.62, 11.38]     Lampinen 2008   81.75   12.59   28   75.5   10.37   20   1.8%   6.25 [-0.26, 12.76]     Manten 2007   84   9   256   75   7   53   3.4%   9.00 [6.82, 11.18]     McDonald 2013   72.4   8.3   109 <t< td=""><td>Freeman 2004</td><td>81.3</td><td>10.4</td><td>40</td><td>77.1</td><td>11.5</td><td>38</td><td>2.3%</td><td></td><td></td></t<>	Freeman 2004	81.3	10.4	40	77.1	11.5	38	2.3%		
Girouard 2007   75   10.9   63   70   8.2   168   3.1%   5.00 [2.04, 7.96]     He 1999   74   14   25   65   9   24   1.7%   9.00 [2.44, 15.56]     Hubel CA 2008   86.6   11   25   81.5   9   28   2.1%   5.10 [-0.35, 10.55]     Innes, K.E. 2005   70.7   8.76   13   69.25   9.63   15   2.0%   3.25 [-2.49, 8.99]     Laivuori 1996   82   9.38   22   7.5   10.37   20   1.8%   6.25 [-0.26, 12.76]     Mangos 2012   79   8   39   72   9   35   2.7%   7.00 [2.62, 11.38]     Marten 2007   84   9   256   75   7   53   3.4%   9.00 [2.62, 11.38]     McDonald 2013   72.4   8.3   109   68.9   7.8   219   3.5%   3.50 [1.63, 5.37]     Nisell 1999   84   9.17   21   77   4.69   22   2.5%   7.00 [2.62, 11.38]     Ostlund 2013   75   2   15   70   2 <td>Garovic 2017</td> <td>78.2</td> <td>9.6</td> <td>40</td> <td>75.8</td> <td>10.7</td> <td>40</td> <td></td> <td></td> <td></td>	Garovic 2017	78.2	9.6	40	75.8	10.7	40			
He 1999   74   14   25   65   9   24   1.7%   9.00 [2.44, 15.56]     Hubel CA 2008   86.6   11   25   81.5   9   28   2.1%   5.10 [-0.35, 10.55]     Innes, K.E. 2005   70.7   8.76   13   61.2   12.98   13   1.3%   9.50 [0.99, 18.01]     Kvehaugen 2010   72.5   7.41   23   69.25   9.63   15   2.0%   3.25 [-2.49, 8.99]     Laivuori 1996   82   9.38   22   75   4.69   22   2.5%   7.00 [2.62, 11.38]     Lampinen 2008   81.75   12.59   28   75.5   10.37   20   1.8%   6.25 [-0.26, 12.76]     Manten 2007   84   9   256   75   7   53   3.4%   9.00 [6.82, 11.18]     McDonald 2013   72.4   8.3   109   68.9   7.8   219   3.5%   3.50 [1.63, 5.37]     Nohira 2013   88.7   12.86   58   70.55   14.25   61   2.3%   18.15 [13.28, 23.02]     Ostlund 2013   75   2   15	Girouard 2007	75	10.9	63	70	8.2	168	3.1%	5.00 [2.04, 7.96]	
Hubel CA 2008   86.6   11   25   81.5   9   28   2.1%   5.10 [-0.35, 10.55]     Innes, K.E. 2005   70.7   8.76   13   61.2   12.98   13   1.3%   9.50 [0.99, 18.01]     Kvehaugen 2010   72.5   7.41   23   69.25   9.63   15   2.0%   3.25 [-2.49, 8.99]     Laivuori 1996   82   9.38   22   75   10.37   20   1.8%   6.25 [-0.26, 12.76]     Mangos 2012   79   8   39   72   9   35   2.7%   7.00 [3.10, 10.90]     Manten 2007   84   9   256   75   7   53   3.4%   9.00 [6.82, 11.18]     McDonald 2013   72.4   8.3   109   68.9   7.8   219   3.5%   3.50 [1.63, 5.37]     Nisell 1999   84   9.17   21   77   4.69   22   2.5%   7.00 [2.62, 11.38]      Nohira 2013   85.7   2.86   58   70.55   14.25   61   2.3%   18.15 [13.28, 23.02]      Ostlund 2013   75   <		74	14	25	65	9	24	1.7%		· · · · · · · · · · · · · · · · · · ·
Innes, K.E. 2005   70.7   8.76   13   61.2   12.98   13   1.3%   9.50 [0.99, 18.01]     Kvehaugen 2010   72.5   7.41   23   69.25   9.63   15   2.0%   3.25 [-2.49, 8.99]     Lawuori 1996   82   9.38   22   75   4.69   22   2.5%   7.00 [2.62, 11.38]     Lampinen 2008   81.75   12.59   28   75.5   10.37   20   1.8%   6.25 [-0.26, 12.76]     Mangos 2012   79   8   39   72   9   35   2.7%   7.00 [3.10, 10.90]     Manten 2007   84   9   256   75   7   53   3.4%   9.00 [6.82, 11.18]     McDonald 2013   72.4   8.3   109   68.9   7.8   219   3.5%   3.50 [1.63, 5.37]     Nisell 1999   84   9.17   21   77   4.69   22   2.5%   7.00 [2.62, 11.38]     Nohira 2013   85.7   12.86   58   70.55   14.25   61   2.3%   18.15 [13.28, 23.02]      Ostlund 2013   75   2	Hubel CA 2008	86.6	11	25	81.5	9	28	2.1%		
Kvehaugen 2010   72.5   7.41   23   69.25   9.63   15   2.0%   3.25   [-2.49, 8.99]     Laivuori 1996   82   9.38   22   75   4.69   22   2.5%   7.00   [2.62, 11.38]     Lampinen 2008   81.75   12.59   28   75.5   10.37   20   1.8%   62.5   [-0.26, 12.76]     Mangos 2012   79   8   39   72   9   35   2.7%   7.00 [3.10, 10.90]     Manten 2007   84   9   256   75   7   53   3.4%   9.00 [6.82, 11.18]     McDonald 2013   72.4   8.3   109   68.9   7.8   219   3.5%   3.50 [1.63, 5.37]     Nisell 1999   84   9.17   21   77   4.69   22   2.5%   7.00 [2.62, 11.38]     Ostlund 2013   75   2   15   70   2   16   3.7%   5.00 [3.59, 6.41]      Portelinha 2010   84.63   16.67   90   72.5   11.11   60   2.5%   12.13 [7.68, 16.58] <tr< td=""><td></td><td></td><td></td><td></td><td></td><td>12.98</td><td></td><td></td><td></td><td></td></tr<>						12.98				
Laivuori 1996   82   9.38   22   75   4.69   22   2.5%   7.00 [2.62, 11.38]										
Lampinen 2008   81.75   12.59   28   75.5   10.37   20   1.8%   6.25   [-0.26, 12.76]     Mangos 2012   79   8   39   72   9   35   2.7%   7.00   [3.10, 10.90]     Manten 2007   84   9   256   75   7   53   3.4%   9.00   [6.82, 11.18]										
Mangos 2012   79   8   39   72   9   35   2.7%   7.00 [3.10, 10.90]     Manten 2007   84   9   256   75   7   53   3.4%   9.00 [6.82, 11.18]     McDonald 2013   72.4   8.3   109   68.9   7.8   219   3.5%   3.50 [1.63, 5.37]										· · · · · ·
Manten 2007   84   9   256   75   7   53   3.4%   9.00 [6.82, 11.18]										
McDonald 2013   72.4   8.3   109   68.9   7.8   219   3.5%   3.50   [1.63, 5.37]										
Nisell 1999   84   9.17   21   77   4.69   22   2.5%   7.00 [2.62, 11.38]										
Nohira 2013   88.7   12.86   58   70.55   14.25   61   2.3%   18.15   [13.28, 23.02]										
Ostlund 2013   75   2   15   70   2   16   3.7%   5.00 [3.59, 6.41]										
Portelinha 2010   84.63   16.67   90   72.5   11.11   60   2.5%   12.13 [7.68, 16.58]										-
Pouta 2004   78.5   11.85   49   73.75   9.63   1369   3.0%   4.75   [1.39, 8.11]										
Romundstad 2010   79   6.61   168   75   27.78   2964   3.7%   4.00 [2.59, 5.41]										
Sattar 2003     82     10.37     40     76     10.37     40     2.5%     6.00 [1.46, 10.54]										
Smith 2009     81.5     10.3     70     72.7     8.1     70     3.1%     8.80 [5.73, 11.87]        Spaan 2010     80     12     22     72     9     29     1.9%     8.00 [2.01, 13.99]        Suzuki, H. 2008     91     9     48     88     6     201     3.2%     3.00 [0.32, 5.68]        Zoet GA 2018     81     10     164     66     9     387     3.6%     15.00 [13.23, 16.77]										
Spaan 2010     80     12     22     72     9     29     1.9%     8.00 [2.01, 13.99]										
Suzuki, H. 2008 91 9 48 88 6 201 3.2% 3.00 [0.32, 5.68]										
Zoet GA 2018 81 10 164 66 9 387 3.6% 15.00 [13.23, 16.77]										
Total (95% Cl) 3282 13950 100.0% 6.79 [5.62, 7.96]	Total (95% CI)			3282			13950	100.0%	6.79 [5.62, 7.96]	•

	Preeclan	npsia	Non-preecla	mpsia		<b>Risk Difference</b>	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Aykas 2015	8	25	0	20	7.2%	0.32 [0.13, 0.51]	
Bokslag 2017	50	131	8	56	8.7%	0.24 [0.12, 0.36]	
Carleton 1988	23	23	5	23	7.5%	0.78 [0.61, 0.96]	
Chambers 2001	12	78	0	48	9.4%	0.15 [0.07, 0.24]	
Christensen 2016	12	21	5	21	5.4%	0.33 [0.05, 0.61]	
Drost 2012	146	339	57	332	9.7%	0.26 [0.19, 0.33]	
Garovic 2017	24	40	8	40	7.1%	0.40 [0.20, 0.60]	
Mangos 2012	1	39	0	35	9.7%	0.03 [-0.04, 0.10]	
McDonald 2013	14	109	15	219	9.7%	0.06 [-0.01, 0.13]	<b>+-</b> -
Ostlund 2013	1	15	0	16	7.8%	0.07 [-0.10, 0.23]	
Sattar 2003	7	40	2	40	8.4%	0.12 [-0.01, 0.26]	
Zoet GA 2018	84	164	88	387	9.4%	0.28 [0.20, 0.37]	
Total (95% CI)		1024		1237	100.0%	0.24 [0.15, 0.33]	◆
Total events	382		188				
Heterogeneity. Tau <sup>2</sup> =	0.02; Ch	i <sup>2</sup> = 96.	45, df = 11 (P	< 0.000	$(001);  ^2 =$	89%	-1 -0.5 0 0.5
Test for overall effect:	Z = 5.00	(P < 0.)	000011				Favours PE Favours Non-PE



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.

	Pree	clamp	sia	Non-p	reeclan	npsia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Akhter 2013	27.25	6.67	48	23.5	4.44	58	2.2%	3.75 [1.54, 5.96]	
Andersgaard 2012	26	3.06	901	25	25.95	7187	5.5%	1.00 [0.37, 1.63]	
Aykas 2015	30.68	4.38	25	28.55	2.38	20	2.5%	2.13 [0.12, 4.14]	
Barden 1999	26.3	6.3	62	22.3	4.58	84	2.8%	4.00 [2.15, 5.85]	
Berends 2008	27.85	6.81	45	24.53	4.22	101	2.3%	3.32 [1.17, 5.47]	
Bokslag 2017	25.7	4.59	131	23.9	4	56	3.9%	1.80 [0.49, 3.11]	
Breetveld 2015	25.6	6.2	115	23.3	3	50	3.6%	2.30 [0.89, 3.71]	
Chambers 2001	25.7	5.3	78	23.9	3.9	48	3.2%	1.80 [0.19, 3.41]	
Christensen 2016	28.46	5.5	21	26.62	5.7	21	1.2%	1.84 [-1.55, 5.23]	
Coffeng 2010	29.9	6.5	17	24.4	3.4	16	1.1%	5.50 [1.99, 9.01]	
Dantas E.M 2013	28.5	1.5	10	25	2.7	17	3.3%	3.50 [1.92, 5.08]	<u> </u>
Drost 2012	26.9	4.7	339	26.2	6.51	332	5.0%	0.70 [-0.16, 1.56]	
Freeman 2004	27	5	40	26.3	4	38	2.5%	0.70 [-1.30, 2.70]	
Garovic 2017		5.78	40	26.43	6.59	40	1.7%	3.37 [0.65, 6.09]	
Girouard 2007	26.9	5.6	63	24.7	4.4	168	3.4%	2.20 [0.67, 3.73]	
Hamad 2007	25	5	18	22	3	17	1.7%	3.00 [0.29, 5.71]	
Hubel CA 2008	27.5	4.2	25	25.7	4.4	28	2.1%	1.80 [-0.52, 4.12]	
Innes, K.E. 2005		6.13	13	23.6	3.24	13	1.0%	5.20 [1.43, 8.97]	
Kvehaugen 2010		6.52	23	24.6	4.59	15	1.1%	0.50 [-3.03, 4.03]	
Laivuori 1996		3.75	22	21.9	1.88	22	2.9%	1.40 [-0.35, 3.15]	<u> </u>
Lampinen 2008	25	4	28	25	4	20	2.1%	0.00 [-2.30, 2.30]	
Mangos 2012	25.6	4.3	39	23.7	2.8	35	3.2%	1.90 [0.26, 3.54]	<del></del>
Manten 2007	26	6	256	23	3	53	4.4%	3.00 [1.91, 4.09]	
McDonald 2013	28.2	5.7	109	27.2	5.8	219	3.8%	1.00 [-0.32, 2.32]	
Nisell 1999	25.5		21	22.8	3.28	22	1.5%	2.70 [-0.19, 5.59]	
Nohira 2013	28.93		58	25.43	3.06	61	4.0%	3.50 [2.26, 4.74]	
Ostlund 2013	25.8	6.1	15	23.3	3.1	16	1.2%	2.50 [-0.94, 5.94]	
Portelinha 2010	26.73		90	24.68	3.93	60	3.8%	2.05 [0.73, 3.37]	
Pouta 2004	24.55			23.25	3.41	1369	4.0%	1.30 [0.04, 2.56]	
Romundstad 2010		3.31	168	25.5	8.33	2964	5.6%	0.90 [0.32, 1.48]	
Sattar 2003	26.75		40	25.75	3.7	40	2.6%	1.00 [-0.98, 2.98]	
5mith 2009	20.75	7	70	25.75	5.7	70	2.5%	3.00 [0.98, 5.02]	
Suzuki, H. 2008	27	4	48	24	3	201	4.1%	3.00 [1.79, 4.21]	
Zoet GA 2018	28.1	6.2	164	27.6	6.7	387	4.2%	0.50 [-0.66, 1.66]	
	20.1	0.2		27.0	0.7				
Total (95% CI)			3191				100.0%	2.02 [1.61, 2.43]	•
Heterogeneity: Tau² =					(P < 0.0	001); I <sup>2</sup>	= 56%		-4 -2 0 2 4
Test for overall effect:	7 - 07	0 /P /	0.0000	111					Favours PE Favours Non-Pl

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	Pree	87     15.31     901       90.15     20     45       80.75     11.11     131       91.4     14.7     21       91.5     9.4     10       86.5     12.21     339       97.08     11.63     40       82.5     12.5     63       81     12     18       81.5     12.59     23       88.6     12.7     109			reeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Andersgaard 2012	87	15.31	901	84	43.25	7187	20.9%	3.00 [1.59, 4.41]	-
Berends 2008	90.15	20	45	77.43	8.52	101	3.4%	12.72 [6.64, 18.80]	
Bokslag 2017	80.75	11.11	131	76.95	8.74	56	10.4%	3.80 [0.82, 6.78]	
Christensen 2016	91.4	14.7	21	85.3	13	21	1.9%	6.10 [-2.29, 14.49]	
Dantas E.M 2013	91.5	9.4	10	85	6.8	17	2.9%	6.50 [-0.16, 13.16]	
Drost 2012	86.5	12.21	339	83.2	12.09	332	17.4%	3.30 [1.46, 5.14]	-
Garovic 2017	97.08	11.63	40	87.38	15.04	40	3.6%	9.70 [3.81, 15.59]	
Girouard 2007	82.5	12.5	63	76.9	10.1	168	8.5%	5.60 [2.16, 9.04]	
Hamad 2007	81	12	18	74	4	17	3.6%	7.00 [1.14, 12.86]	
Kvehaugen 2010	81.5	12.59	23	79.75	8.15	15	3.0%	1.75 [-4.84, 8.34]	
McDonald 2013	88.6	12.7	109	84.7	11.6	219	11.1%	3.90 [1.06, 6.74]	
Pouta 2004	80.33	12.81	49	76.88	9.26	1369	8.0%	3.45 [-0.17, 7.07]	
Sattar 2003	82.55	11.29	40	79.82	9.97	40	5.4%	2.73 [-1.94, 7.40]	+
Total (95% CI)			1789			9582	100.0%	4.32 [3.13, 5.52]	•
Heterogeneity: Tau <sup>2</sup> =	1.26; C	$hi^2 = 17$	7.35, dt	f = 12 (F	= 0.14	); $I^2 = 3$	1%		-20 -10 0 10 20
Test for overall effect	Z = 7.0	9 (P < C	0.0000	1)					Favours PE Favours Non-PE

**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 (l<sup>2</sup>=56%). B. Waist circumference, n=13 studies (l<sup>2</sup>=31%). C. Waist-to-hip ratio, n=10 studies (l<sup>2</sup>=59%). D. Weight, n=5 studies (l<sup>2</sup>=0%)

А

5.4%

9.0%

10.3%

10.5%

11.3%

9.1%

7.4%

10.9%

13.6%

12.6%

Mean Difference

0.05 [0.00. 0.10]

0.02 [0.00, 0.04]

-0.01 [-0.04, 0.02]

0.02 [-0.01, 0.05]

-0.01 [-0.04, 0.02]

0.01 [-0.01, 0.03]

0.02 [-0.01. 0.05]

0.02 [-0.02, 0.06]

0.06 [0.04, 0.08] 0.02 [0.00, 0.04]

0.02 [0.01, 0.03]

-0.1

-0.05

Weight IV, Random, 95% CI

Non-preeclampsia

SD

0.06

0.06

0.04

0.04

0.04

0.05

0.04

0.07

0.06

0.1

Total

21

168

17

15

20

219

22

16

60

1369

Mean

0.77

0.83

0.84

0.81

0.81

0.77

0.8

0.8

0.8

0.8

Total (95% Cl)4371927100.0%Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 21.93, df = 9 (P = 0.009); I<sup>2</sup> = 59%Test for overall effect: Z = 2.91 (P = 0.004)

Preeclampsia

SD Total

21

63

18

23

28

109

21

15

90

49

Mean

0.85 0.09

0.82

0.79

0.82 0.06

0.86 0.08

0.79 0.07

0.82 0.05

0.86 0.04

0.8 0.05

0.82 0.06

0.1

0.05

D

С

**Study or Subgroup** 

Christensen 2016

Kvehaugen 2010

Lampinen 2008

McDonald 2013

Portelinha 2010

Nisell 1999

Pouta 2004

Ostlund 2013

Girouard 2007

Hamad 2007

	Pree	clamps	sia	Non-pi	reeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Breetveld 2015	74	18	115	69	12	50	37.3%	5.00 [0.32, 9.68]	
Christensen 2016	79.6	17.4	21	74.2	16.7	21	7.7%	5.40 [-4.92, 15.72]	
He 1999	64	12.4	25	60.3	7	24	25.9%	3.70 [-1.91, 9.31]	
Innes, K.E. 2005	77.5	19.11	13	67.5	12.62	13	5.3%	10.00 [-2.45, 22.45]	
Smith 2009	77.3	20.2	70	71.8	14.7	70	23.8%	5.50 [-0.35, 11.35]	
Total (95% CI)			244			178	100.0%	5.08 [2.22, 7.93]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	hi² = 0.8	6, df =	4 (P = 0.	93); I <sup>z</sup> = I	0%		-	
Test for overall effect:									-20 -10 0 10 20 Favours PE Favours Non-PE



#### 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  $\geq$ 7 were considered as high-quality studies and NOS scores of 5–6 were considered moderate quality. Any discrepancies were addressed by a reevaluation of the original article to reach consensus.

# 2.5. Statistical analyses

Inverse variance random-effects models were used for metaanalyses. 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 + 2 m + 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 + 2 m + 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<sup>2</sup>>1 was defined as the presence of substantial statistical heterogeneity. An I<sup>2</sup> 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 Metaanalysis (Version 2; Biostat, Englewood, NJ).

Mean Difference

IV, Random, 95% CI

0.05

Favours PE Favours Non-PE

0.1

#### 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 crosssectional 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

# А

	Pree	clamsp	sia	Non-p	reeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Hamad 2007	10.38	11.33	18	10.73	13.56	17	10.7%	-0.35 [-8.65, 7.95]	
Hubel CA 2008	12	10.3	25	11.2	10.2	28	22.9%	0.80 [-4.73, 6.33]	
Lampinen 2008	12.14	7.44	28	8.46	3.81	20	58.1%	3.68 [0.46, 6.90]	<b>─</b> ∎──
Manten 2007	16.7	54.73	256	21	24.65	53	8.3%	-4.30 [-13.73, 5.13]	
Total (95% CI)			327			118	100.0%	1.93 [-0.84, 4.69]	•
Heterogeneity: Tau² =				3 (P = 0.	36); I <sup>z</sup> =	7%			-10 -5 0 5 10
Test for overall effect	:Z=1.30	6 (P = 0.)	17)						Favors PE Favors Non-PE

# В

	Pree	Preeclampsia Non-preelampsia Mean Difference					Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Andersgaard 2012	236.66	47.32	901	233.57	50.17	7187	7.9%	3.09 [-0.21, 6.39]	
Barden 1999	211.91	79.13	62	184.46	52.98	84	1.5%	27.45 [4.73, 50.17]	
Berends 2008	191.42	40.1	43	208.82	45.83	100	2.8%	-17.40 [-32.38, -2.42]	
Bokslag 2017	189.48	40.1	131	200.12	37.24	56	3.7%	-10.64 [-22.57, 1.29]	
Breetveld 2015	180.1	28.6	115	187	29.7	50	4.6%	-6.90 [-16.65, 2.85]	
Chambers 2001	186	35	78	182	35	48	3.5%	4.00 [-8.58, 16.58]	<del></del>
Christensen 2016	191.03	39.06	21	182.52	25.52	21	1.9%	8.51 [-11.45, 28.47]	
Coffeng 2010	177.88	30.94	17	170.15	27.07	16	1.9%	7.73 [-12.08, 27.54]	
Dantas E.M 2013	180.5	11.6	10	173	28.8	17	2.7%	7.50 [-7.96, 22.96]	
Drost 2012	187.94	29.12	339	187.55	32.35	332	7.2%	0.39 [-4.27, 5.05]	+-
Garovic 2017	190.5	34.81	40	203.38	30	40	3.0%	-12.88 [-27.12, 1.36]	
Girouard 2007	184.46	39.44	63	175.56	35.58	168	4.0%	8.90 [-2.23, 20.03]	+
Hamad 2007	156.23	40.22	18	160.48	21.66	17	1.7%	-4.25 [-25.49, 16.99]	
He 1999	186.18	27.94	24	167.35	31.81	24	2.4%	18.83 [1.89, 35.77]	
lubel CA 2008	227	44	25	216	36	28	1.6%	11.00 [-10.80, 32.80]	
nnes, K.E. 2005	202.9	31.01	13	194.3	26.68	13	1.6%	8.60 [-13.64, 30.84]	
aivuori 1996	202.63	25.52	22	192.58	30.94	22	2.4%	10.05 [-6.71, 26.81]	
ampinen 2008	181.94	24.06	28	184.94	37.53	20	2.0%	-3.00 [-21.71, 15.71]	
Mangos 2012	193.35	30.94	39	189.48	27.07	35	3.3%	3.87 [-9.35, 17.09]	
Manten 2007	201.08	34.8	256	181.75	30.94	53	4.8%	19.33 [9.97, 28.69]	
McDonald 2013	129.55	34.37	109	125.68	34.37	219	5.5%	3.87 [-4.03, 11.77]	
visell 1999	193.35	35.42	21	174.02	36.35	22	1.7%	19.33 [-2.12, 40.78]	
Ostlund 2013	182.52	45.24	15	185.62	29.39	16	1.1%	-3.10 [-30.15, 23.95]	
ortelinha 2010	207.2	39.3	90	206.6	34.3	60	3.8%	0.60 [-11.28, 12.48]	
outa 2004	186	25.91	49	183.68	32.48	1369	5.7%	2.32 [-5.14, 9.78]	
attar 2003	197.22	34.37	40	183.68	45.83	40	2.2%	13.54 [-4.21, 31.29]	
5paan 2010	229.7	36.74	22	216.17	39.44	29	1.7%	13.53 [-7.49, 34.55]	
Suzuki, H. 2008	226	12	48	217	2	201	7.8%	9.00 [5.59, 12.41]	
20et GA 2018	208.82	38.67	164	197.22	38.67	387	5.9%	11.60 [4.54, 18.66]	
Fotal (95% CI)			2803			10674	100.0%	4.59 [1.53, 7.66]	<b>◆</b>
Heterogeneity: Tau <sup>2</sup> =	= 28.22: 0	hi <sup>2</sup> = 63	3.61, d	f = 28 (P	= 0.000	$(11);  ^2 =$	56%		
Fest for overall effect									-20 -10 6 10 20
		v. v.							Favours PE Favours Non-PE

**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 (l<sup>2</sup>=7%). B. Total cholesterol, n=29 studies (l<sup>2</sup>=56%). C. HDL-cholesterol, n=29 studies (l<sup>2</sup>=57%). D. LDL-cholesterol, n=24 studies (l<sup>2</sup>=81%). E. VLDL-cholesterol, n=3 studies (l<sup>2</sup>=15%). F. Triglycerides, n=28 studies (l<sup>2</sup>=46%).

С

	Pree					ipsia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Andersgaard 2012	62.26	17.76	901	63.81	16.87	7187	7.2%	-1.55 [-2.77, -0.33]	-
Barden 1999	50.66	15.2	62	55.68	19.34	84	3.2%	-5.02 [-10.63, 0.59]	
Berends 2008	51.24	14.32	43	51.24	14.32	100	3.5%	0.00 [-5.12, 5.12]	
Bokslag 2017	60.52	17.76	131	69.94	19.64	56	2.9%	-9.42 [-15.40, -3.44]	
Breetveld 2015	51.8	9.9	115	61.6	13	50	4.4%	-9.80 [-13.83, -5.77]	
Chambers 2001	60	17	78	60	12	48	3.5%	0.00 [-5.08, 5.08]	
Christensen 2016	61.87	14.31	21	63.81	15.47	21	1.6%	-1.94 [-10.95, 7.07]	
Coffeng 2010	61.87	11.6	17	58.01	7.73	16	2.5%	3.86 [-2.83, 10.55]	
Dantas E.M 2013	48.5	7	10	52	5.8	17	3.5%	-3.50 [-8.64, 1.64]	
Drost 2012	58.78	14.56	339	59.17	14.41	332	6.3%	-0.39 [-2.58, 1.80]	
Garovic 2017	54.88	21.11	40	63.75	19.26	40	1.7%	-8.87 [-17.73, -0.01]	
Girouard 2007	51.43	12.37	63	54.91	13.15	168	4.8%	-3.48 [-7.12, 0.16]	
Hamad 2007	48.72	7.73	18	51.43	12.37	17	2.4%	-2.71 [-9.59, 4.17]	
He 1999	57.33	16.73	24	52.88	10.73	23	2.0%	4.45 [-3.55, 12.45]	
Hubel CA 2008	57.6	14.1	25	69.1	16.7	28	1.9%	-11.50 [-19.80, -3.20]	
nnes, K.E. 2005	48.1	10.82	13	58.2	7.57	13	2.3%	-10.10 [-17.28, -2.92]	
aivuori 1996	71.54	14.49	22	68.06	14.69	22	1.8%	3.48 [-5.14, 12.10]	
Lampinen 2008	61.29	9.16	28	68.74	3.15	20	4.8%	-7.45 [-11.11, -3.79]	<u> </u>
Mangos 2012	54.14	11.6	39	54.14	11.6	35	3.4%	0.00 [-5.29, 5.29]	
Manten 2007	52.98	12.37	256	52.98	13.15	53	4.6%	0.00 [-3.85, 3.85]	
McDonald 2013	60.91	14.33	109	61.87	17.19	219	4.9%	-0.96 [-4.48, 2.56]	
Visell 1999	54.14	17.79	21	58.01	18.17	22	1.2%	-3.87 [-14.62, 6.88]	
Ostlund 2013	53.75	9.28	15	55.68	15.08	16	1.7%	-1.93 [-10.69, 6.83]	
Portelinha 2010	49.25	9.63	90	50.25	9.63	60	5.3%	-1.00 [-4.15, 2.15]	
Pouta 2004	63.03	15.08	49	62.26	13.15	1369	4.2%	0.77 [-3.51, 5.05]	
5attar 2003	59.94	14.33	40	57.04	17.19	40	2.4%	2.90 [-4.04, 9.84]	
Smith 2009	56.84	13.92	70	58.01	11.6	70	4.2%	-1.17 [-5.41, 3.07]	
5paan 2010	57.62	18.17	22	57.23	14.69	29	1.6%	0.39 [-8.90, 9.68]	
Zoet GA 2018	58.78	13.15	164	57.62	15.85	387	5.9%	1.16 [-1.40, 3.72]	+
Total (95% CI)			2825			10542	100.0%	-2.15 [-3.46, -0.85]	•
Heterogeneity. Tau <sup>2</sup> =	5.72; C	$hi^2 = 65$	5.61, df	= 28 (P	< 0.00	01); $ ^2 =$	57%		
Fest for overall effect:									-20 -10 0 10 2
									Favours non-PE Favours PE

	_								
		clampsi			reeclam			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean	SD		Weight	IV, Random, 95% CI	IV, Random, 95% CI
Barden 1999	134.96		62	111.76	46.02	84	2.5%	23.20 [2.52, 43.88]	
Berends 2008	119.88		43	137.28	34.38	100	4.1%	-17.40 [-29.69, -5.11]	
Bokslag 2017	108.28	28.64	131	111.18	31.51	56	4.7%	-2.90 [-12.50, 6.70]	
Breetveld 2015	112.7	24.5	115	110.6	25.9	50	4.9%	2.10 [-6.36, 10.56]	
Christensen 2016	120.26	37.9	21	111.37	24.75	21	2.7%	8.89 [-10.47, 28.25]	
Coffeng 2010	104.41	27.07	17	96.68	19.34	16	3.3%	7.73 [-8.25, 23.71]	
Drost 2012	111.76	29.12	339	112.14	32.35	332	5.7%	-0.38 [-5.04, 4.28]	
Forest 2005	112.14	32.87	63	102.48	32.1	168	4.7%	9.66 [0.20, 19.12]	
Garovic 2017	106.1	26.96	40	120.53	27.19	40	4.2%	-14.43 [-26.30, -2.56]	
Girouard 2007	112.14	32.87	63	102.48	32.1	168	4.7%	9.66 [0.20, 19.12]	
Hamad 2007	90.1	34.03	18	97.06	17.01	17	3.0%	-6.96 [-24.64, 10.72]	
He 1999	128.77	23.4	24	118.91	28.62	23	3.5%	9.86 [-5.12, 24.84]	
Hubel CA 2008	132.25	45.19	25	117.25	30.37	28	2.5%	15.00 [-5.98, 35.98]	
Laivuori 1996	116.4	21.66	22	110.98	29	22	3.5%	5.42 [-9.71, 20.55]	
Mangos 2012	119.88	23.2	39	119.88	27.07	32	4.2%	0.00 [-11.87, 11.87]	· · · · · · · · · · · · · · · · · · ·
McDonald 2013	117.95	34.37	109	118.91	31.51	219	5.1%	-0.96 [-8.64, 6.72]	
Nisell 1999	116.01	35.58	21	100.54	36.35	22	2.4%	15.47 [-6.03, 36.97]	
Ostlund 2013	117.17	41.76	15	119.88	22.43	16	2.1%	-2.71 [-26.53, 21.11]	
Portelinha 2010	158	40	90	157	35	60	4.1%	1.00 [-11.11, 13.11]	
Pouta 2004	108.28	22.82	49	105.57	25.52	1369	5.4%	2.71 [-3.82, 9.24]	_ <del>_</del>
Sattar 2003	114.08	31.5	40	109.44	42.96	40	3.2%	4.64 [-11.87, 21.15]	
Smith 2009	104.8	31.32	70	91.65	25.91	70	4.7%	13.15 [3.63, 22.67]	
Spaan 2010	147.33	26.68	22	142.31	34.42	29	3.2%	5.02 [-11.75, 21.79]	
Suzuki, H. 2008	126	9	48	109	3	201	6.0%	17.00 [14.42, 19.58]	-
Zoet GA 2018	131.48	34.8	164	116.01	30.94	387	5.4%	15.47 [9.32, 21.62]	
Total (95% CI)			1650			3570	100.0%	4.57 [0.25, 8.90]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	,			df = 24 (I	P < 0.00	001); l²	= 80%		-20 -10 0 10 20 Favours PE Favours Non-PE



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). 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.

# 3.4.4. 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)

1	4	

	Pree	clamp	sia	Non-pr	eeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Hamad 2007	9.67	7.35	18	6.96	3.87	17	27.9%	2.71 [-1.15, 6.57]	
He 1999	10.73	5.13	24	10.64	6.77	23	33.9%	0.09 [-3.35, 3.53]	
Sattar 2003	12.57	5.73	40	13.78	8.6	40	38.3%	-1.21 [-4.41, 1.99]	
Total (95% CI)			82			80	100.0%	0.32 [-1.86, 2.51]	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				2 (P = 0	.31); I² =	15%			-4 -2 0 2 4 Favours PE Favours Non-PE

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Е

	Pree	clampsi	a	Non-p	reeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Andersgaard 2012	126.66	81.47	901	117.8	76.56	7187	8.5%	8.86 [3.25, 14.47]	+
Barden 1999	127.54	146.14	62	85.91	72.63	84	1.0%	41.63 [2.08, 81.18]	
Berends 2008	95.21	59.04	43	88.57	39.36	100	3.1%	6.64 [-12.62, 25.90]	+
Bokslag 2017	90.79	45.93	131	75.29	26.24	56	6.0%	15.50 [5.06, 25.94]	
Breetveld 2015	88.57	44.29	115	79.71	35.43	50	5.1%	8.86 [-3.87, 21.59]	
Chambers 2001	80	62	78	80	35	48	3.7%	0.00 [-16.95, 16.95]	-+-
Christensen 2016	93	72.63	21	73.51	31	21	1.3%	19.49 [-14.29, 53.27]	
Coffeng 2010	106.28	141.71	17	70.86	26.57	16	0.3%	35.42 [-33.19, 104.03]	
Dantas E.M 2013	85.5	33.2	10	114	39.8	17	1.7%	-28.50 [-56.45, -0.55]	
Drost 2012	88.57	41.61	339	84.14	49.36	332	7.8%	4.43 [-2.48, 11.34]	-
Garovic 2017	116.4	57.78	40	97.63	38.15	40	2.6%	18.77 [-2.69, 40.23]	
Girouard 2007	89.46	82.66	63	74.62	68.89	168	2.4%	14.84 [-8.08, 37.76]	+
Hamad 2007	88.57	39.86	18	71.47	22.14	17	2.7%	17.10 [-4.11, 38.31]	<u> </u>
He 1999	85.69	25.91	24	83.26	32.77	23	3.7%	2.43 [-14.51, 19.37]	
Hubel CA 2008	117.75	76.3	25	107.75	62.96	28	1.0%	10.00 [-27.93, 47.93]	<del></del>
Innes, K.E. 2005	161.5	89.78	13	76.6	30.65	13	0.6%	84.90 [33.33, 136.47]	
Laivuori 1996	76.17	20.37	22	69.97	24.8	22	4.8%	6.20 [-7.21, 19.61]	+
Lampinen 2008	61.11	28.87	28	58.68	12.47	20	5.4%	2.43 [-9.58, 14.44]	+-
Mangos 2012	88.57	70.86	39	70.86	35.43	35	2.1%	17.71 [-7.44, 42.86]	+
Manten 2007	107.17	113.22	256	92.11	93.59	53	1.7%	15.06 [-13.70, 43.82]	
McDonald 2013	106.28	52.48	109	95.22	45.93	219	5.5%	11.06 [-0.52, 22.64]	
Nisell 1999	124	81.48	21	88.57	41.63	22	1.0%	35.43 [-3.52, 74.38]	+
Portelinha 2010	86.75	28.89	90	83.5	20.74	60	7.3%	3.25 [-4.70, 11.20]	+
Pouta 2004	83.26	31	49	77.94	35.54	1369	6.8%	5.32 [-3.56, 14.20]	-
5attar 2003	88.57	39.36	40	81.93	32.8	40	4.0%	6.64 [-9.24, 22.52]	+
5mith 2009	97.43	61.11	70	85.03	46.94	70	3.4%	12.40 [-5.65, 30.45]	+
Spaan 2010	117.8	71.74	22	88.57	37.2	29	1.3%	29.23 [-3.66, 62.12]	<u> </u>
Zoet GA 2018	106.28	44.29	164	124	97.43	387	5.4%	-17.72 [-29.56, -5.88]	
Total (95% CI)			2810			10526	100.0%	7.66 [3.60, 11.72]	•
Heterogeneity: Tau <sup>2</sup> =				= 27 (P =	0.005);	l <sup>2</sup> = 46	%		-100 -50 0 50 100
Fest for overall effect:	Z = 3.70	(P = 0.0	002)						Favours PE Favours Non-PE

Fig. 4 (continued).

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

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	Pree	clampsi	a	Non-p	reeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Barden 1999	81.08	14.23	62	81.08	16.58	84	3.4%	0.00 [-5.01, 5.01]	
Berends 2008	86.49	10.67	42	75.23	9.34	101	4.2%	11.26 [7.55, 14.97]	
Bokslag 2017	92.34	6.67	131	91.44	6.67	56	5.3%	0.90 [-1.19, 2.99]	
Breetveld 2015	86.49	10.81	115	84.69	7.21	50	4.8%	1.80 [-1.01, 4.61]	
Chambers 2001	83	7.2	78	81	9	48	4.7%	2.00 [-1.01, 5.01]	
Christensen 2016	104.51	32.07	21	95.32	6.49	21	0.9%	9.19 [-4.80, 23.18]	
Coffeng 2010	86.4	9	17	86.4	7.2	16	3.1%	0.00 [-5.55, 5.55]	
Dantas E.M 2013	76	7.6	10	76	4.8	17	3.3%	0.00 [-5.23, 5.23]	
Drost 2012	87.57	16.91	339	87.39	16.73	332	5.0%	0.18 [-2.37, 2.73]	
Garovic 2017	99.25	13.33	40	95.88	7.78	40	3.5%	3.37 [-1.41, 8.15]	
Girouard 2007	91.89	9.01	63	90.09	7.21	168	5.1%	1.80 [-0.68, 4.28]	<b></b>
Hamad 2007	84.69	12.43	18	79.28	7.57	17	2.5%	5.41 [-1.37, 12.19]	
Hubel CA 2008	88.74	12.01	25	86.94	6.67	28	3.2%	1.80 [-3.52, 7.12]	
Innes, K.E. 2005	87.4	9.01	13	81.3	4.33	13	3.2%	6.10 [0.67, 11.53]	
Kvehaugen 2010	86.49	5.34	23	87.75	4.27	15	4.7%	-1.26 [-4.33, 1.81]	
Lampinen 2008	80.63	6.67	28	80.18	5.33	20	4.4%	0.45 [-2.95, 3.85]	
Mangos 2012	86.49	10.81	39	88.29	9.01	35	3.7%	-1.80 [-6.32, 2.72]	
McDonald 2013	88.29	8.01	109	86.94	6.67	219	5.5%	1.35 [-0.39, 3.09]	
Nisell 1999	97.3	8.29	21	88.29	16.94	22	2.1%	9.01 [1.09, 16.93]	
Ostlund 2013	89.73	7.39	15	87.75	8.65	16	3.0%	1.98 [-3.67, 7.63]	
Pouta 2004	89.19	5.41	49	87.93	6.67	1369	5.6%	1.26 [-0.30, 2.82]	
Smith 2009	88.83	9.55	70	88.67	9.37	70	4.6%	0.16 [-2.97, 3.29]	
Spaan 2010	90.09	7.21	22	90.09	7.21	29	4.0%	0.00 [-4.00, 4.00]	
Suzuki, H. 2008	106	5	48	101	2	201	5.7%	5.00 [3.56, 6.44]	
Zoet GA 2018	99.1	19.82	164	84.69	18.02	387	4.4%	14.41 [10.89, 17.93]	
Total (95% CI)			1562			3374	100.0%	2.60 [1.19, 4.00]	◆
Heterogeneity: Tau <sup>2</sup> =	8.55; Ch	$i^2 = 110$	0.02, df	= 24 (F	< 0.00	001); I <sup>2</sup>	= 78%		
Test for overall effect:						.,			-10 -5 0 5 10 Favours PE Favours Non-PE
									Favours PE Favours Non-PE

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	Pree	clamp	sia	Non-pr	eeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Andersgaard 2012	5.48	1.68	901	5.43	1.3	7187	11.2%	0.05 [-0.06, 0.16]	+
Bokslag 2017	5.4	0.3	131	5.23	0.22	56	11.3%	0.17 [0.09, 0.25]	+
Christensen 2016	5.5	2.8	21	5.2	2.4	21	3.2%	0.30 [-1.28, 1.88]	
Coffeng 2010	4.68	1.03	17	5.2	0.15	16	9.1%	-0.52 [-1.02, -0.02]	
Drost 2012	5.27	0.47	339	4.24	0.46	332	11.3%	1.03 [0.96, 1.10]	+
Lampinen 2008	5.2	0.3	28	5.1	0.3	20	11.0%	0.10 [-0.07, 0.27]	+
McDonald 2013	5.53	0.37	109	5.6	0.3	219	11.3%	-0.07 [-0.15, 0.01]	-
Sattar 2003	4.75	0.59	40	4.5	0.15	40	11.0%	0.25 [0.06, 0.44]	
Spaan 2010	5.6	0.4	22	5.6	0.3	29	10.9%	0.00 [-0.20, 0.20]	
White 2016	5.7	1.3	40	5.5	0.4	40	9.6%	0.20 [-0.22, 0.62]	
Total (95% CI)			1648			7960	100.0%	0.15 [-0.18, 0.49]	-
Heterogeneity: Tau <sup>2</sup> =	= 0.25; C	hi² = 54	45.30, c	lf=9 (P	< 0.0000	)1); I <sup>z</sup> = !	98%	-	
Test for overall effect	Z = 0.91	(P = 0)	1.36)						-1 -0.5 0 0.5 1 Favours PE Favours non-PE

**Fig. 5.** Meta-analyses of glucose- and insulin-related outcomes: Mean differences of serum glucose (Fig. 5A), HbA1c (Fig. 5B), insulin (Fig. 5C), HOMA-IR index (Fig. 5d), and serum IGF-1 (Fig. 5e). A. Serum glucose, n=25 studies (I<sup>2</sup>=78%). B. Glycosilated hemoglobin (HbA1c), n=10 studies (I<sup>2</sup>=98%). C. Insulin, n=14 studies (I<sup>2</sup>=71%) D. HOMA-IR, n=14 studies (I<sup>2</sup>=97%). E. IGF-1, n=3 studies (I<sup>2</sup>=0%).

		clampsi			preeclam			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI
Christensen 2016	58.06	35.02	21	47.55	22.01	21	6.8%	10.51 [-7.18, 28.20]		+
Coffeng 2010	88.9	54.17	17	67.37	31.95	16	3.8%	21.53 [-8.61, 51.67]		
Garovic 2017	58.51	51.96	40	32.12	13.89	40	7.2%	26.39 [9.72, 43.06]		
Girouard 2007	108	50	63	91	53	168	7.9%	17.00 [2.28, 31.72]		_ <b>-</b>
Hamad 2007	46.2	20	18	30	10	17	9.4%	16.20 [5.81, 26.59]		
Hubel CA 2008	65.63	28.81	25	53.13	26.75	28	7.8%	12.50 [-2.52, 27.52]		+
Innes, K.E. 2005	93.76	57.58	13	48.62	17.52	13	3.4%	45.14 [12.42, 77.86]		
Mangos 2012	52.09	30.87	39	36.47	15.44	35	9.2%	15.62 [4.66, 26.58]		
Nisell 1999	163.21	55.56	21	90.29	18.54	22	4.8%	72.92 [47.93, 97.91]		
Ostlund 2013	46.7	39.1	15	29.6	14.8	16	5.8%	17.10 [-3.97, 38.17]		<b>—</b> —
Pouta 2004	55.21	15.42	49	51.05	15.42	1369	11.3%	4.16 [-0.23, 8.55]		-
Sattar 2003	60.42	38.59	40	46.19	24.7	40	8.0%	14.23 [0.03, 28.43]		
Smith 2009	63.6	55.2	70	44.7	27.9	70	7.9%	18.90 [4.41, 33.39]		
Spaan 2010	64.94	37.04	22	46.71	28.3	29	6.6%	18.23 [-0.36, 36.82]		
Total (95% CI)			453			1884	100.0%	19.06 [11.93, 26.19]		•
Heterogeneity: Tau <sup>2</sup> =	= 111.86;	$Chi^2 = 4$	15.28. (	df = 13	(P < 0.0	001); I <sup>2</sup>	= 71%			
Test for overall effect									-100	-50 Ó 50 100 Favours PE Favours Non-PE
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	Pree	clamps	sia	Non-pr	eeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Breetveld 2015	1.9	1.1	115	1.3	0.8	50	8.1%	0.60 [0.30, 0.90]	+
Christensen 2016	1.12	0.66	21	0.91	0.41	21	8.1%	0.21 [-0.12, 0.54]	+
Coffeng 2010	3.2	2.3	17	2.2	1	16	5.9%	1.00 [-0.20, 2.20]	+
Garovic 2017	2.18	2.15	40	1.13	0.52	40	7.3%	1.05 [0.36, 1.74]	
Girouard 2007	1.73	0.81	63	1.53	0.52	168	8.2%	0.20 [-0.01, 0.41]	+
Hubel CA 2008	2.21	1.87	25	1.68	1.01	28	7.0%	0.53 [-0.29, 1.35]	
Innes, K.E. 2005	2.7	1.8	13	1.3	0.36	13	6.4%	1.40 [0.40, 2.40]	_ <del></del>
Mangos 2012	1.58	0.67	39	1.2	0.44	35	8.2%	0.38 [0.12, 0.64]	-
Manten 2007	2.4	3.4	256	1.87	0.85	53	7.8%	0.53 [0.05, 1.01]	-
McDonald 2013	1.55	1.19	109	1.4	0.89	219	8.2%	0.15 [-0.10, 0.40]	+
Ostlund 2013	10.92	10.79	15	6.57	3.83	16	0.8%	4.35 [-1.42, 10.12]	
Smith 2009	1.18	1.02	70	0.83	0.52	70	8.2%	0.35 [0.08, 0.62]	-
Spaan 2010	2.2	1.19	22	1.53	0.96	29	7.5%	0.67 [0.06, 1.28]	-
Suzuki, H. 2008	3.21	0.47	48	1.11	0.12	201	8.3%	2.10 [1.97, 2.23]	-
Total (95% CI)			853			959	100.0%	0.72 [0.19, 1.25]	◆
Heterogeneity: Tau <sup>2</sup> =	0.88; CI	hi² = 43	7.22. df	f = 13 (P ·	< 0.0000	)1);   <sup>2</sup> =	97%		
Test for overall effect:						~			-10 -5 0 5 10
			ć						Favours PE Favours Non-PE
Е									
	Pree	clamps	sia	Non-p	reeclam	psia		Mean Difference	Mean Difference

	Preeclampsia				reeclam	osia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Hamad 2007	221	54	18	240	72	17	34.6%	-19.00 [-61.35, 23.35]	
Innes, K.E. 2005	162.8	34.97	13	183.5	54.44	13	50.2%	-20.70 [-55.87, 14.47]	
Nisell 1999	342	109.98	21	330	103.19	22	15.2%	12.00 [-51.81, 75.81]	
Total (95% CI)			52			52	100.0%	-15.13 [-40.04, 9.78]	-
Heterogeneity: Tau² = Test for overall effect				(P = 0.6	i6); I² = 09	6			-100 -50 0 50 100 Favours PE Favours Non-PE

Fig. 5 (continued).

adjustment during pregnancy. Recent evidence from a populationbased 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

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	Pree	clamp	sia	Non-pr	eeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Coffeng 2010	0.8	0.51	17	0.39	0.21	16	2.1%	0.41 [0.15, 0.67]	· · · · · · · · · · · · · · · · · · ·
Dantas E.M 2013	0.1	0.2	10	0.1	0.1	17	6.5%	0.00 [-0.13, 0.13]	
Drost 2012	0.36	0.47	339	0.32	0.47	332	12.7%	0.04 [-0.03, 0.11]	
Freeman 2004	0.3	0.42	40	0.17	0.16	40	6.0%	0.13 [-0.01, 0.27]	<b>—</b> —
Girouard 2007	0.22	0.28	63	0.16	0.22	168	12.0%	0.06 [-0.02, 0.14]	-
Hamad 2007	0.15	0.19	18	0.08	0.05	17	10.2%	0.07 [-0.02, 0.16]	+-
Hubel CA 2008	0.8	0.91	25	0.23	0.36	28	1.1%	0.57 [0.19, 0.95]	
Lampinen 2008	0.08	0.1	28	0.06	0.07	20	16.1%	0.02 [-0.03, 0.07]	+
Portelinha 2008	0.43	0.25	58	0.41	0.24	49	10.0%	0.02 [-0.07, 0.11]	+
Smith 2009	0.3	0.33	70	0.25	0.31	70	8.6%	0.05 [-0.06, 0.16]	
Spaan 2010	0.16	0.1	22	0.16	0.11	29	14.7%	0.00 [-0.06, 0.06]	+
Total (95% CI)			690			786	100.0%	0.05 [0.01, 0.09]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	hi <b>≃</b> = 20	0.33, df	= 10 (P =	= 0.03); I	<sup>2</sup> = 51%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 2.49	(P = 0	.01)						Favours PE Favours Non-PE

В

	Preeclan	npsia	Non-preeclar	npsia		Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Bar 1999	20	48	0	44	48.5%	0.42 [0.28, 0.56]			
McDonald 2013	9	109	10	219	51.5%	0.04 [-0.02, 0.10]	-		
Total (95% CI)		157		263	100.0%	0.22 [-0.15, 0.59]			
Total events	29		10						
Heterogeneity: Tau <sup>z</sup> =	0.07; Chi <sup>z</sup>	= 23.63	, df = 1 (P ≤ 0.0	)0001); P	²= 96%		-0.5 -0.25 0 0.25 0.5		
Test for overall effect:	Z=1.16 (P	P = 0.24)					Favours PE Favours Non-PE		

# С

	Pree	clamp	sia	Non-pr	eeclam	psia		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bokslag 2017	4.9	3.56	131	3.23	0.67	56	28.8%	1.67 [1.04, 2.30]	
Mangos 2012	1.05	0.59	39	1.13	0.96	35	34.1%	-0.08 [-0.45, 0.29]	+
McDonald 2013	0.92	0.51	109	0.9	0.52	219	37.1%	0.02 [-0.10, 0.14]	•
Total (95% CI)			279			310	100.0%	0.46 [-0.25, 1.17]	•
Heterogeneity: Tau² = Test for overall effect:			-	-4 -2 0 2 4 Favours PE Favours Non-PE					

	Preeclan	npsia	Non-preecla	mpsia		<b>Risk Difference</b>	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bokslag 2017	22	131	1	56	21.4%	0.15 [0.08, 0.22]	
Drost 2012	61	339	30	332	43.2%	0.09 [0.04, 0.14]	
Forest 2005	12	63	8	168	10.9%	0.14 [0.04, 0.25]	
Lampinen 2008	2	28	0	20	7.7%	0.07 [-0.05, 0.19]	
Zoet GA 2018	54	164	75	387	16.9%	0.14 [0.05, 0.22]	
Total (95% CI)		725		963	100.0%	0.11 [0.08, 0.15]	•
Total events	151		114				
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chi <sup>z</sup>	= 2.86,	df = 4 (P = 0.5)	8); I <b>2</b> = 09	6		
Test for overall effect:	Z= 6.67 (F	P < 0.00	001)				Favours PE Favours Non-PE

**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 ( $I^2=51\%$ ). b. Microalbuminuria, n=2 studies ( $I^2=96\%$ ). c. Albuminuria levels, n=3 studies ( $I^2=92\%$ ). d. MetS, n=5 studies ( $I^2=0\%$ ).

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.

# 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 [1,5,6,71]. 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.

# Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### 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.

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