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Meta-analysis

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

Vanesa Alonso-Ventura [a], Yangzhou Li [b], Vinay Pasupuleti [c], Yuani M. Roman [d], Adrian V. Hernandez [b,d,e], Faustino R. Pérez-López [f,*]

[a] Cardiology Department, Miguel Servet University Hospital, Zaragoza 50009, Spain
[b] University of Connecticut School of Pharmacy, Storrs, CT 06269, USA
[c] MedErgy HealthGroup Inc., Yardley, PA 19067, USA
[d] University of Connecticut/Hartford Hospital Evidence-based Practice Center, Hartford, CT 06102, USA
[e] School of Medicine, Universidad Peruana de Ciencias Aplicadas (UPC), Lima 9, Peru
[f] Department of Obstetrics and Gynecology, University of Zaragoza Faculty of Medicine, and Instituto de Investigaciones Sanitarias de Aragón, Zaragoza 50009, Spain

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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 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 1.2 to 4.0), insulin (MD = 19.1 pmol/L, 95%CI 11.9 to 26.2), HOMA-IR index (MD = 0.7, 95%CI 0.2 to 1.2), C reactive protein (MD = 0.05 mg/dL, 95%CI 0.01 to 0.09), and the risks of hypertension (RD = 0.24, 95%CI 0.15 to 0.33) and MetS (RD = 0.11, 95%CI 0.08 to 0.15). 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.

* Corresponding author at: Department of Obstetrics and Gynecology, Facultad de Medicina, Universidad de Zaragoza, Domingo Miral s/n, Zaragoza 50009, Spain.
E-mail addresses: vaventura.92@gmail.com (V. Alonso-Ventura), Yangzhou.li@uconn.edu (Y. Li), lepiscean@gmail.com (V. Pasupuleti), yuani.roman-morillo@hhchealth.org (Y.M. Roman), adrian.hernandez-diaz@uconn.edu (A.V. Hernandez), faustino.perez@unizar.es (F.R. Pérez-López).

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1. Introduction

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

PE/E have negative consequences on maternal and fetal health during pregnancy, including increased perinatal mortality, 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

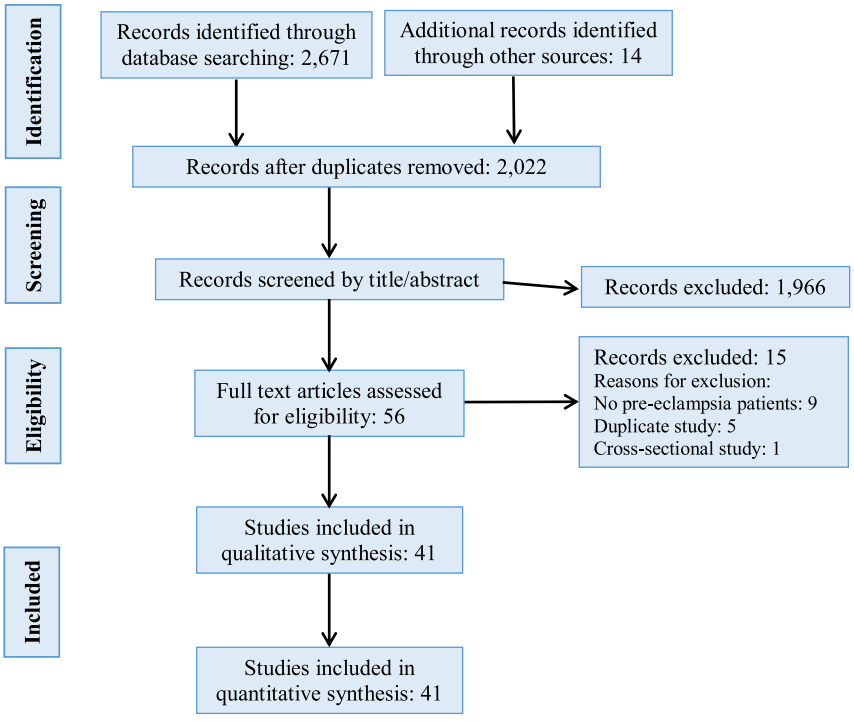

Fig. 1. Flow diagram of included studies.

Table 1
Characteristics of included studies.

Author, year [reference]	Country; study design	Exclusion reasons	Data during the index pregnancy: preeclampsia (PE)		Data during the index pregnancy: control (CG)		Time of follow up and/or age	Matching variables for controls
			Inclusion criteria; n (women); age at pregnancy	Parity index pregnancy; GAD, weeks	CG definition; n (women); age at pregnancy	Parity index pregnancy. GAD, weeks		
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][a]	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 ± 6.68 years	Pregnancies 1 (1–2); GAD: not reported	N = 20; Age: 27.25 ± 3.61 years	Pregnancies 2 (1–2); GAD: not reported	Follow-up period of PE group (6.12 ± 3.59 years and 6.05 ± 4.06 years in the CG	Age
Bar J, 1999 [26]	Israel; Prospective cohort study	None of the women had a previous definite diagnosis of hypertension or renal disease	PE according to the ACOG; N = 48 women according to the ACOG; Age: 36 ± 5 years	Parity not reported; Preterm delivery 30 (62.5%); IUGR: 27 (56%)	Pregnant women without PE. N = 48 women; Age = 35 ± 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; Retrospective cohort study	Known history of hypertension or renal disease	PE according to the ACOG; N = 62 women; Age: 27.5 ± 0.8 years	27 primiparous and 35 multiparous	Pregnant women without PE. N = 84 women; Age: 27.6 ± 0.6 years	30 primiparous and 54 multiparous	6 months postpartum	Age and gestation
Berends AL, 2008 [28]	The Netherlands; Retrospective cohort study	Multiple pregnancies	PE according to the ACOG; N = 36 women; Age = 36.2 ± 5.8 years.	Parity not reported; GAD: 37 ± 3.4 weeks	Pregnant women without PE. N = 100 women; Age 39.2 ± 5.6 years.	Parity not reported; GAD: 39.6 ± 1.4 weeks	Time interval delivery study: PE group 7 ± 5.6 years, and Control group 13.1 ± 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	PE according to the ISSHP; N = 131, including severe PE and one or more of the following conditions: (i) proteinuria ≥5 g/24 h (n = 59; 45.0%), (ii) HELLP syndrome (n = 43; 32.8%), (iii) eclampsia seizure (n = 10; 7.6%) or (iv) pulmonary edema (n = 6; 4.6%). Age: 30.9 ± 5.0 years	Primiparous: 101 (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 ± 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 ± 5.6 years; CG: 46.5 ± 4.8 years. Time post index pregnancy: PE group: 13.1 ± 2.2 years; CG: 14.2 ± 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 ± 4.0	Primiparous: 41/115 (36%); GAD 33.3 ± 4.3 weeks	Pregnant women without PE. N = 50 uncomplicated pregnancies; Age 36 ± 4.0.	Primiparous: 5/50 (10%); GAD 39.6 ± 2.3 weeks	Postpartum years: PE group: 5.4 8.0 ± 2.6 years; Control group: 8.0 ± 2.7 years;	Not matched
Carleton H, 1988 [31]	United States; Prospective cohort study	Not reported	PE according to the ACOG, N = 23 women; Age: <26 years.	23 Primiparous; GAD: not reported	23 matched controls (parity, ethnicity, age, weight) without PE.	Matched primiparous by year delivered, age and race; GAD: not reported	Follow-up assessment at least 3,5 years after delivery (1981–1985)	Year delivered, age, race, and weight ± 1/3
Chambers JC, 2001 [32]	United Kingdom; Retrospective cohort study	Exclusion criteria: atherosclerosis, malignancy, major organ failure, vasculitis, systemic infection, recent major surgery or trauma, and known diabetes	PE hypertension + proteinuria, N = 113 Single episode PE: 78 women; recurrent PE: 35 women; Age: Single episode: 34 ± 5; Recurrent episodes: 37 ± 5 years	Parity not reported; GAD: not reported	N = 48 women with uncomplicated pregnancies and deliveries; Age: 35 ± 6 years	Parity not reported; GAD: not reported	All were at least 3 months (median, 3 years) postpartum	Not matched

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Table 1 (*continued*)

Author, year [reference]	Country; study design	Exclusion reasons	Data during the index pregnancy: preeclampsia (PE)		Data during the index pregnancy: control (CG)		Time of follow up and/or age	Matching variables for controls
			Inclusion criteria; n (women); age at pregnancy	Parity index pregnancy; GAD, weeks	CG definition; n (women); age at pregnancy	Parity index pregnancy. GAD, weeks		
Christensen M, 2016 [33]	Denmark; Retrospective cohort study.	Unexposed women who experienced hypertensive disorder of pregnancy before or after 2001–2004 were excluded.	PE according to the ACOG. N = 21 patients with PE in 2001–2004; Age: time since delivery, years: 10.28 ± 0.70 years	Primiparous n = 16 (76%); GAD: 262 ± 19 days	N = 21 normotensive pregnant women without PE, in 2001–2004; Age: time since delivery, years: 10.27 ± 0.51. years	Primiparous n = 10 (48%); GAD: 280 ± 9 days	Ten year after delivery. Age: exposed women 40.75 ± 2.7 years; non-exposed women 40.67 ± 2.3 years	Age (±2 years) and time since delivery (± 1 year)
Coffeng SM, 2011 [34]	The Netherlands; Prospective cohort study	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.	Severe early-onset PE according to the ISSHP; N = 16 severe early-onset PE; Age: 29.7 ± 4.8 years	Parity and GAD not reported	N = 17 women with uncomplicated pregnancies; Age: 30.7 ± 3.6 years	Parity and GAD not reported	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 ± 3.2 weeks	Normotensive pregnancies. N = 17 women; Age: 26.0 ± 2.5 years	Parity: Median 1.0 [half interquartile 1.0]; GAD: 39.1 ± 1.9 weeks	Study at 5 years follow-up.	Not matched
Drost JT, 2012 [36]	The Netherlands; Prospective cohort study	Pregnant or lactating women	PE < 32 weeks. N = 339 women with PE according to the ISSHP; Age: 29,8 ± 3,8 years	Number of pregnancies: 2.7 ± 1.4; GAD: not reported	Pregnant women without PE, N = 332 women without PE; Age: 28,6 ± 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 ± 3.9 years	Parity: not reported GAD: 38.3 ± 2.6 weeks	Pregnant women without PE. N = 168 controls matched for age and year of index delivery; Age 27.0 ± 4.2 years	Parity not reported; GAD: 39.4 ± 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 ± 5.2 years.	Primiparous and multiparous women; GAD: 35.3 ± 3.8 weeks	Women without PE, N = 38 pregnancies; Age: 24.7 ± 3.9 years.	38 women without adverse outcomes; GAD: 39.1 ± 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 ± 3.7	Parity: not reported; GAD: not reported	40 age- and parity-matched normotensive women, who delivered between 1976 and 1982; Age: 24.3 ± 3.4 years	Parity: parity matched; GAD: not reported	Women who delivered in 1976–1982, were studied in 2014–2015; Age: PE 59.4 ± 4.8; control: 59.7 ± 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 ± 3.9 years	Parity: not reported; GAD: 38.3 ± 2.6	N = 168 women with normotensive pregnancy. Mean age: 27.0 ± 4.2 years	Parity: not reported; GAD: 39.4_ ± 2.1	Women were studied 7.8 years after their first delivery. Case women were more overweight compared with controls	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 ± 4 years	Parity: one; GAD: not reported	N = 17 age-matched controls; Mean age: 31 ± 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	Negative history of hematological, cardiovascular, hepatic or renal disorder before index pregnancy	PE 25 women (11 mild PE, and 14 severe PE); Age: 33 ± 6 years	Parity: 32 primipara; GAD: not reported	N = 24 women; Age: Matched by age, parity and index of pregnancy 34 ± 6 years	Parity: 29 primiparous; GAD: not reported	Women were examined 2–5 (4.5. ± 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 ± 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 ± 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 ± 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	PE or eclampsia in 22 women; Age: 24.8 ± 2 0.9 years	Parity: First pregnancy; GAD: 36.2 ± 0.5 weeks	Control women: 22; Age: 25.0 ± 0.9 years	Parity: First pregnancy; GAD: 40.1 ± 0.4 weeks	Years since delivery: PE-eclampsia group: 41.8 ± 0.9 years; Control group: 41.8 ± 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 ± 5 years	Primiparity: 14/28 (50%); GAD: 33 [29, 36] weeks	Control women: 20 women with a previous normotensive pregnancy; Age 30 ± 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, prior essential hypertension in pregnancy or renal disease	PE: 39 women according to the ASSHPC Statement criteria for the diagnosis preeclampsia; Age: 37 ± 6 years	Multiparous: 26 (67%); GAD: not reported	Control group: 35 women; Age: 38 ± 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 ± 4	Primiparous 203 (79%); GAD: 217 ± 28 days	Control group: 53 women; Age: 33 ± 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 ± 3 years and child's age ± 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 ±	61 normal pregnancies; Age:	Parity: 0.874 ±	Elapse time from	Age, parity,

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Table 1 (*continued*)

Author, year [reference]	Country; study design	Exclusion reasons	Data during the index pregnancy: preeclampsia (PE)		Data during the index pregnancy: control (CG)		Time of follow up and/or age	Matching variables for controls
			Inclusion criteria; n (women); age at pregnancy	Parity index pregnancy; GAD, weeks	CG definition; n (women); age at pregnancy	Parity index pregnancy. GAD, weeks		
	cohort study	pregnancy were excluded.	preeclampsia; Age: 27.37 ± 3.44 years	1.344; GAD: not reported	28.13 ± 4.26 years	1.286; GAD: not reported	delivery: PE group: 12.3 ± 3.17 (Age: 38.26 ± 12.63); Control group: 12.7 ± 3.33 years (Age: 39.54 ± 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 ± 3.6 years	Parity: 1.8 ± 0.9; GAD: 245 ± 6 days	Control: 16 non-complicated pregnant women; Age: 11 years after delivery 41.2 ± 3.2 years	Parity: 2.5 ± 0.7; GAD: 281 ± 6 days	Study performed 11.2 ± 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]	Parity: not reported. GAD: 39 [38, 40]; Cesarean rate: 28.6%	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]	Parity: not reported; GAD: 35 [32.5, 37.0]	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 ± 5.7	Parity (%): Primiparous 43 ± 61.4; Previous pregnancy with PE 11 (15.9%); GAD: 35.6 ± 3.8.weeks	Control group: 70 normotensive pregnancies; Age: 30.3 ± 4.1	Parity (%): Primiparous 42 ± 60.0; Previous pregnancy with PE 0 (0%); GAD: 39.2 ± 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 ± 3.9 years (postmenopausal n = 8, 36%), and control group 49.8 ± 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 ± 8 years	Parity: not reported; GAD: not reported	Control: 201 normotensive pregnant women; Age at first pregnancy 28 ± 1 years	Parity: not reported; GAD: not reported	Age (years) at recall: PE group 49 ± 3.0, and control group: 48.5 ± 1.5	Not matched
White WM, 2016 [62]	United States; Retrospective cohort study	Myocardial infarction, congestive heart failure, stroke, dementia, any cancer, autoimmune disease and neurological conditions	PE: 40 women with PE according to the ICD 9, who delivered between 1976 and 1982; Age: mean age 24 years	Parity: matched; GAD: not reported	40 age- and parity-matched women without histories of preeclampsia, who delivered between 1976 and 1982	Parity: matched; GAD: not reported	Mean age of the study participants at the time of imaging was 59.5 ± 4.6 years	Parity and age at index birth; Mean age at delivery: 24 years
Zoet GA, 2018 [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)]. [a]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
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 kg/m^2 (1.6 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%

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

(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

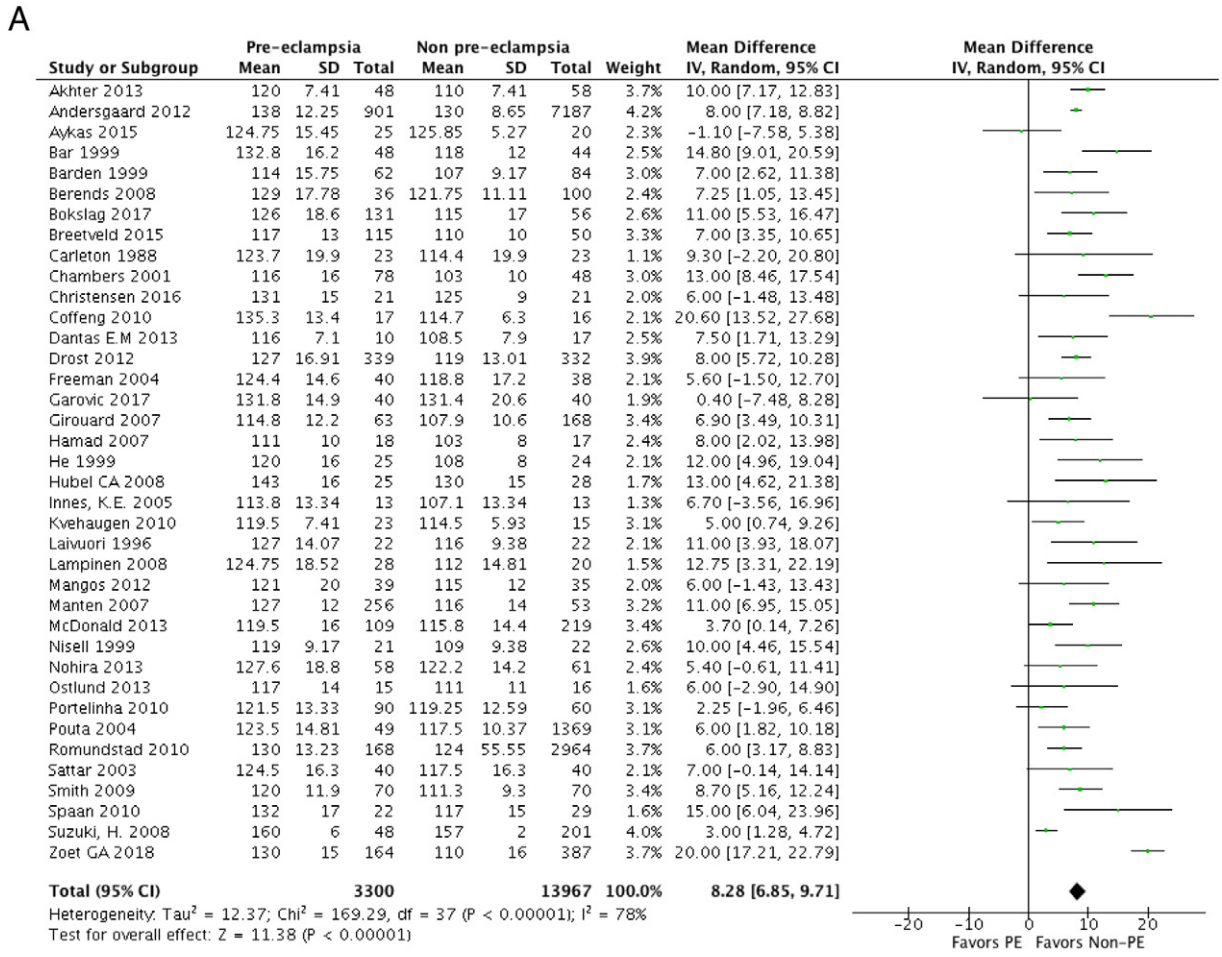
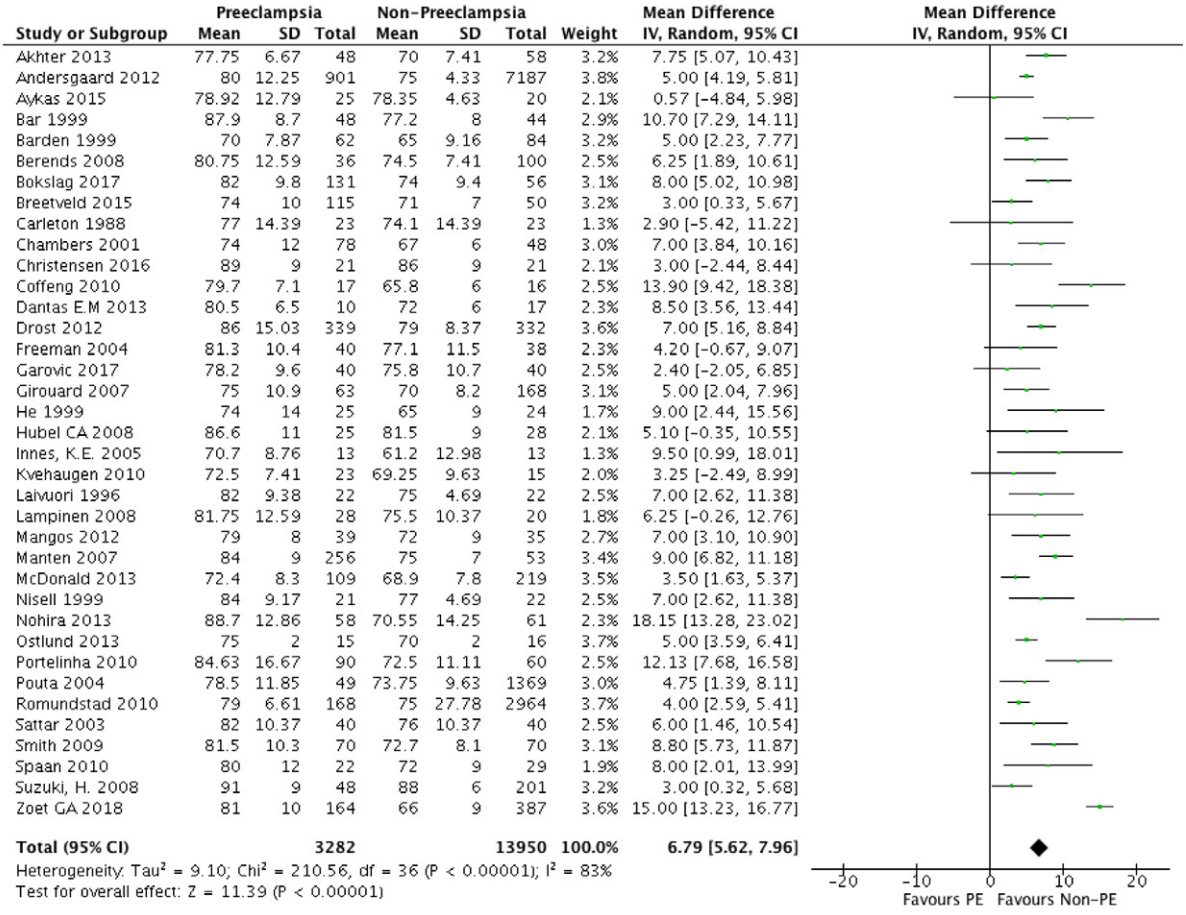


Fig. 2. Meta-analyses of blood pressure-related outcomes: Mean differences of systolic blood pressure (Fig. 2A) and diastolic blood pressure (Fig. 2B), and risk difference of hypertension (Fig. 2C). A. Mean systolic blood pressure, n = 38 studies (I^2=78%). B. Mean diastolic blood pressure, n = 37 studies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

B



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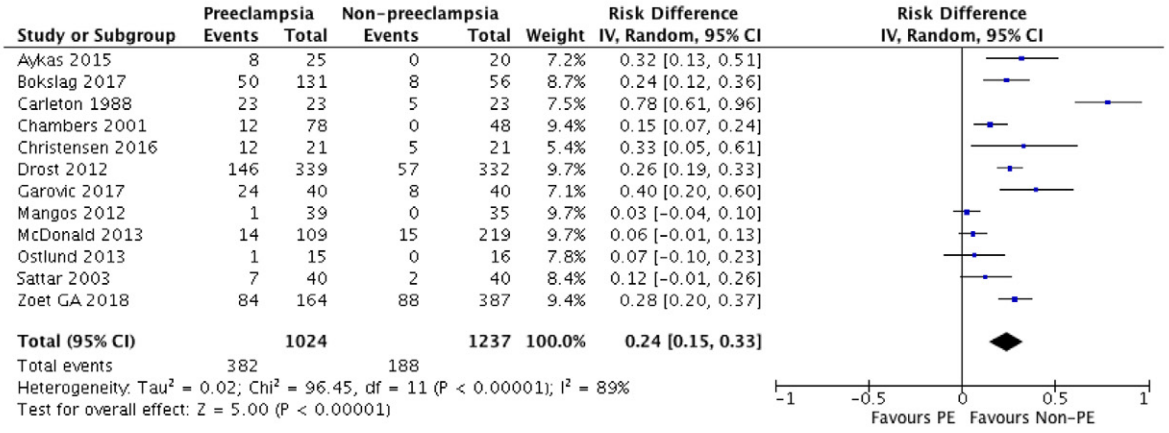

Fig. 2 (*continued*).

without previous hypertension or kidney disease. Proteinuria may be visually assessed by dipstick or by an automated device and confirmed by a 24 h urine collection.

2.2. Outcomes of interest

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

2.3. Study selection and data extraction

We included prospective or retrospective observational studies evaluating singleton PE and/or E and without previous kidney diseases.

Normotensive uncomplicated pregnancies reported in the respective publication were considered as control groups. Published studies were eligible for inclusion if they reported metabolic or biochemical outcomes of interest three months after delivery or later. Exclusion criteria were: (a) PE data was not available or could not be extracted from the study groups; (b) no appropriate control group; (c) other hypertensive disorders different from PE, E and HELLP syndrome; (d) chronic pregestational diseases; and (e) metabolic or biochemical outcomes of interest measured within three months after delivery. Three of the authors (VAV, FRPL, YL) independently evaluated full-text articles for compliance with inclusion and exclusion criteria. Disagreements were managed through discussion with the other authors (FRPL, AVH) to reach a consensus. Authors were contacted if supplementary information or clarification was required in order to analyze study eligibility.

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

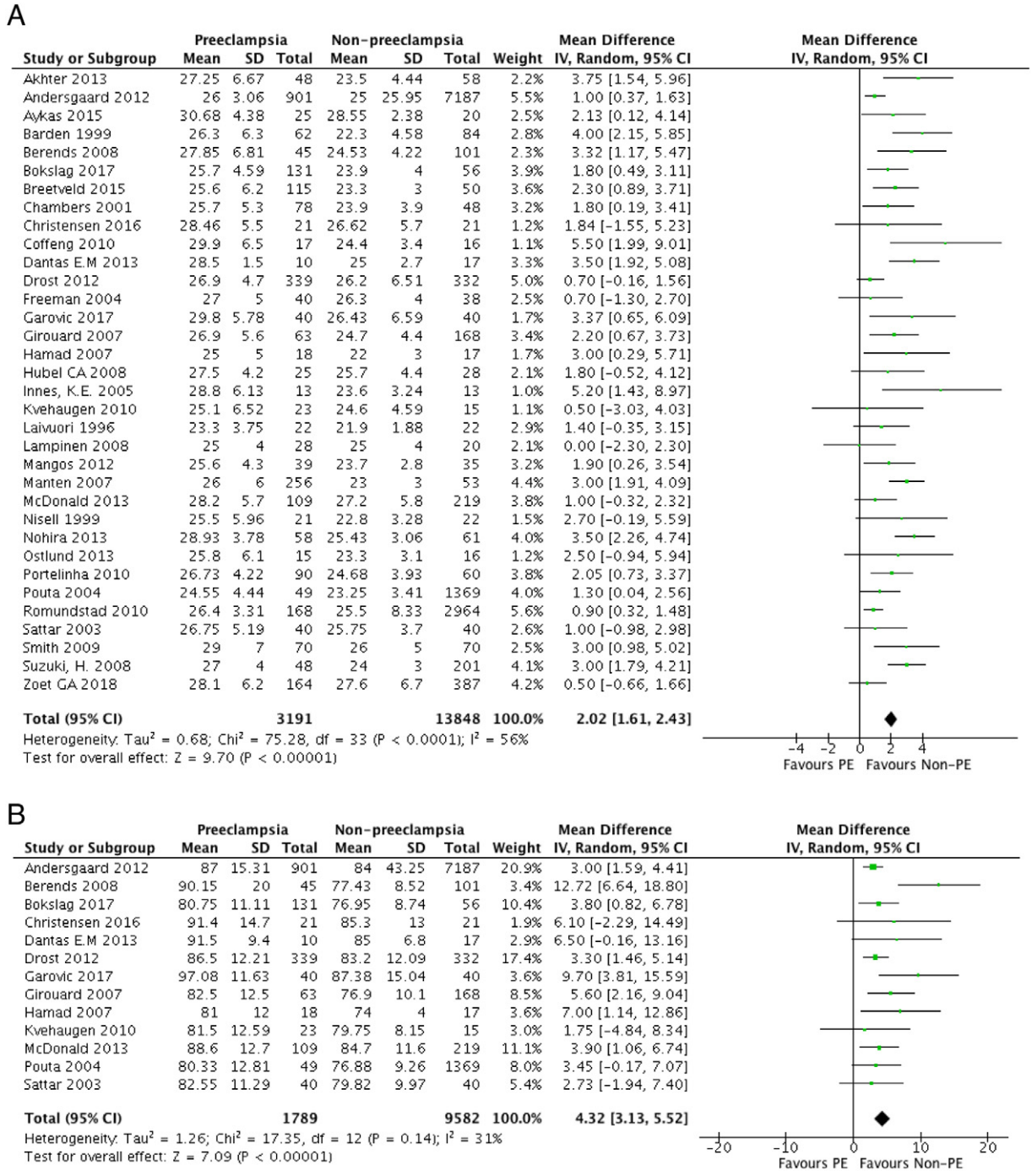

Fig. 3. Meta-analyses of anthropometric outcomes: Mean differences of body mass index (BMI) (Fig. 3A), waist circumference (Fig. 3B), waist-to-hip ratio (WHR), (Fig. 3C), and weight (Fig. 3d). A. BMI, n=34 studies (I^2=56%). B. Waist circumference, n=13 studies (I^2=31%). C. Waist-to-hip ratio, n=10 studies (I^2=59%). D. Weight, n=5 studies (I^2=0%)

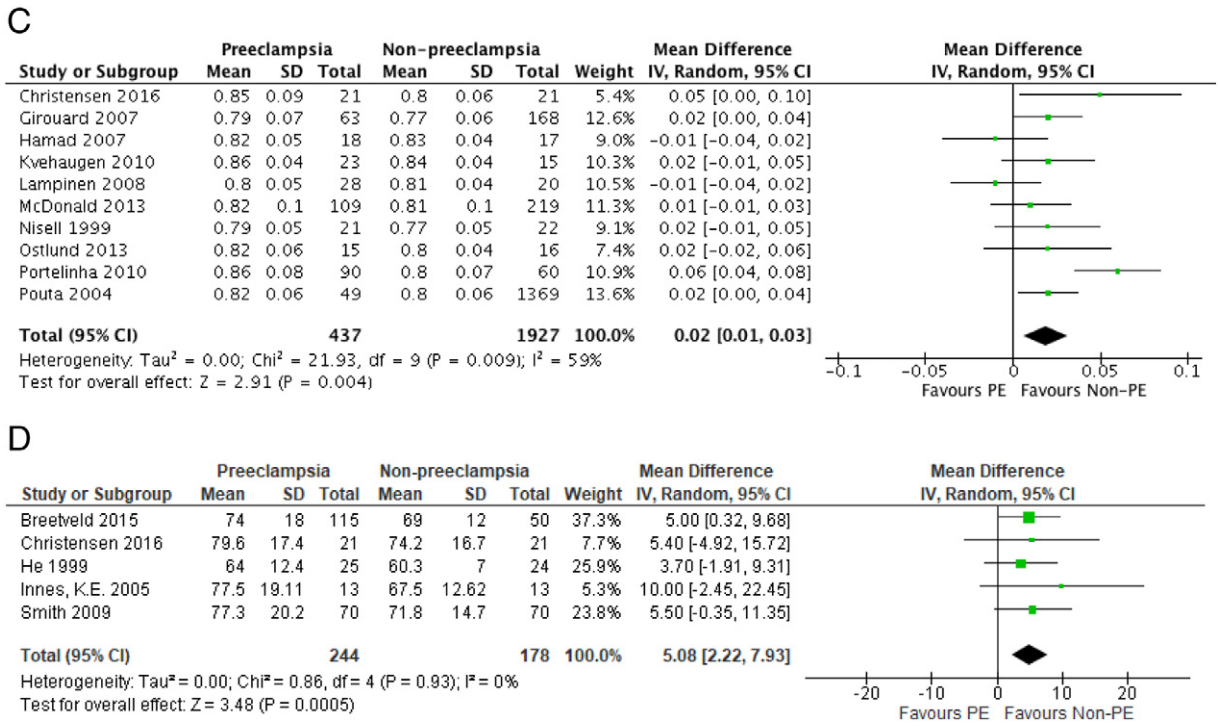

Fig. 3 (*continued*).

2.4. Risk of bias assessment

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

2.5. Statistical analyses

Inverse variance random-effects models were used for meta-analyses. Effects were reported as risk difference (RD) for dichotomous outcomes or mean differences (MD) for continuous outcomes and their 95% CIs. Continuous outcomes were adjusted for baseline values per exposure arm. For studies reporting medians (m) and interquartile ranges (IQR), means were estimated by $x = (a + 2\,m + b)/4$, 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 $Tau^2 > 1$ was defined as the presence of substantial statistical heterogeneity. An I^2 value of 0–30% was used to define low heterogeneity, 30–60% moderate heterogeneity, and >60% substantial heterogeneity [21]. Potential publication bias was estimated by the Begg's funnel plot and the Egger's linear regression test [22].

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

3. Results

3.1. Selection of studies

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

3.2. Characteristics of included studies

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

Diagnoses of PE and E were based on definitions from different scientific organizations such as ACOG (n = 14 studies), ISSHP (n = 9 studies), NHBPEWG (n = 4 studies), ICD (n = 2 studies), and ASSHPC (n = 1 study), and standard clinical diagnosis of PE/E (n = 10 studies) (Table 1). Other publications defined PE without referring to scientific

societies and as an association of conventional hypertension and proteinuria developing after 20 weeks of pregnancy (n = 10 studies) which remitted within a few days after delivery. All included studies had similar PE/E definitions: new onset hypertension and proteinuria after 20 weeks of gestation and in the case of E also included coma and/or seizures in previously normotensive women without renal pathology.

3.3. Risk of bias assessment

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

3.4. Meta-analyses of outcomes

3.4.1. Blood pressure

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

3.4.2. Anthropometric outcomes

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

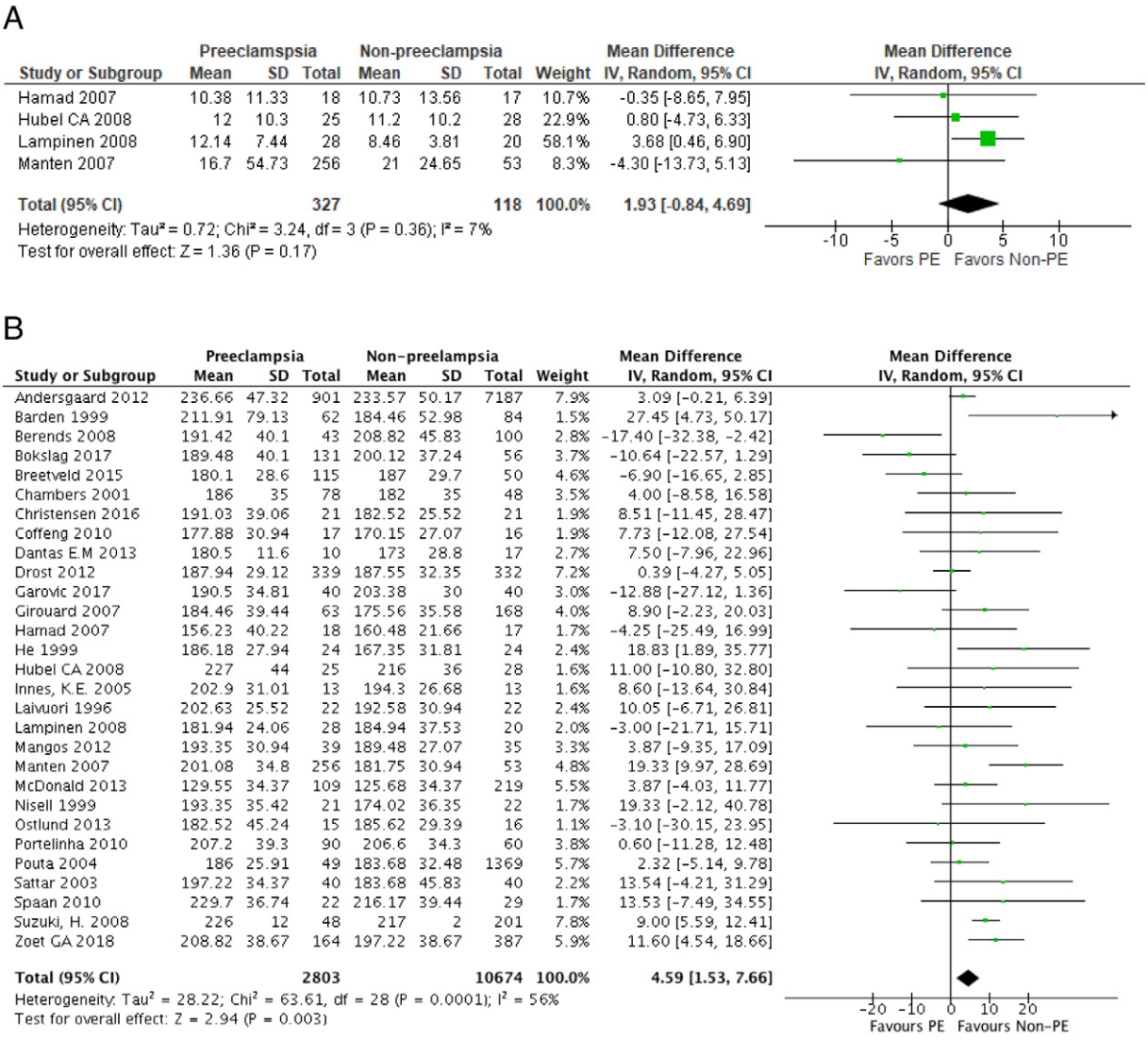

Fig. 4. Meta-analyses of lipid-related outcomes: Mean differences of serum lipoprotein (a) [Lp(a)] (Fig. 4A), total cholesterol (Fig. 4B), HDL-cholesterol (Fig. 4C), LDL-cholesterol (Fig. 4D), VLDL-cholesterol (Fig. 4E) and triglycerides (Fig. 4F). A. Lipoprotein (a), n=4 studies (I^2=7%). B. Total cholesterol, n=29 studies (I^2=56%). C. HDL-cholesterol, n=29 studies (I^2=57%). D. LDL-cholesterol, n=24 studies (I^2=81%). E. VLDL-cholesterol, n=3 studies (I^2=15%). F. Triglycerides, n=28 studies (I^2=46%).

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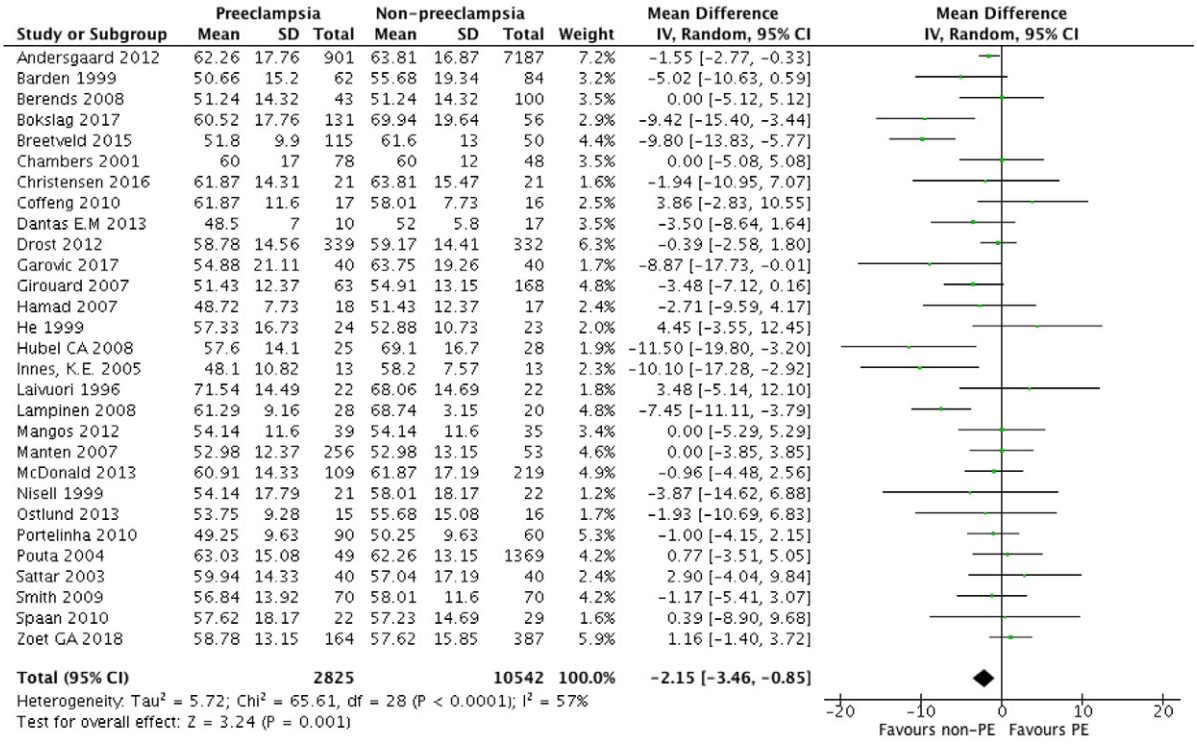

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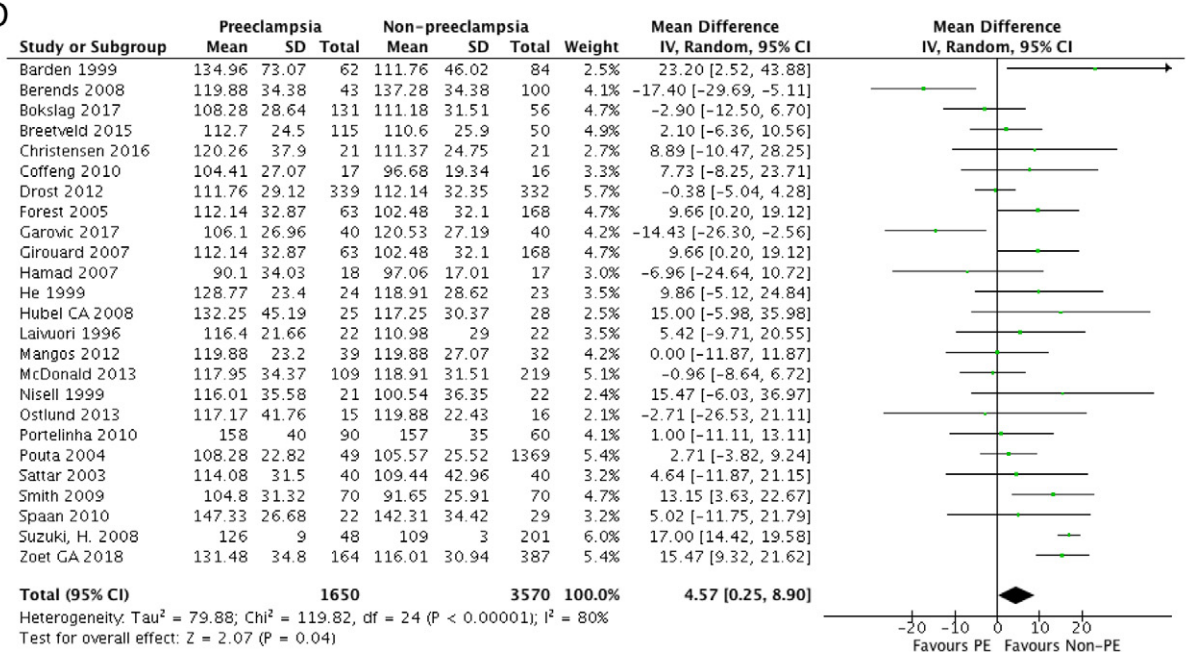

Fig. 4 (*continued*).

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)

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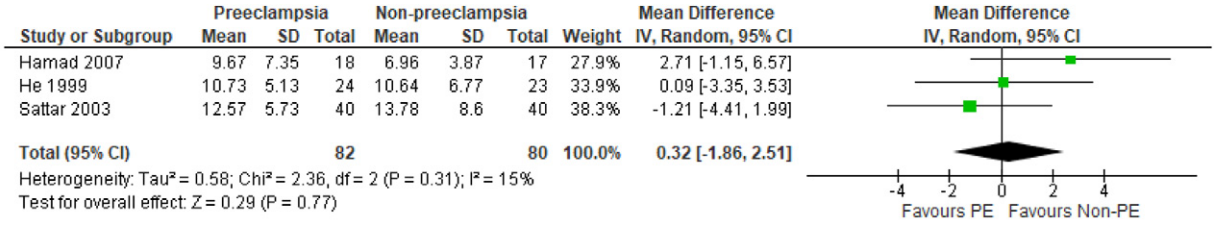

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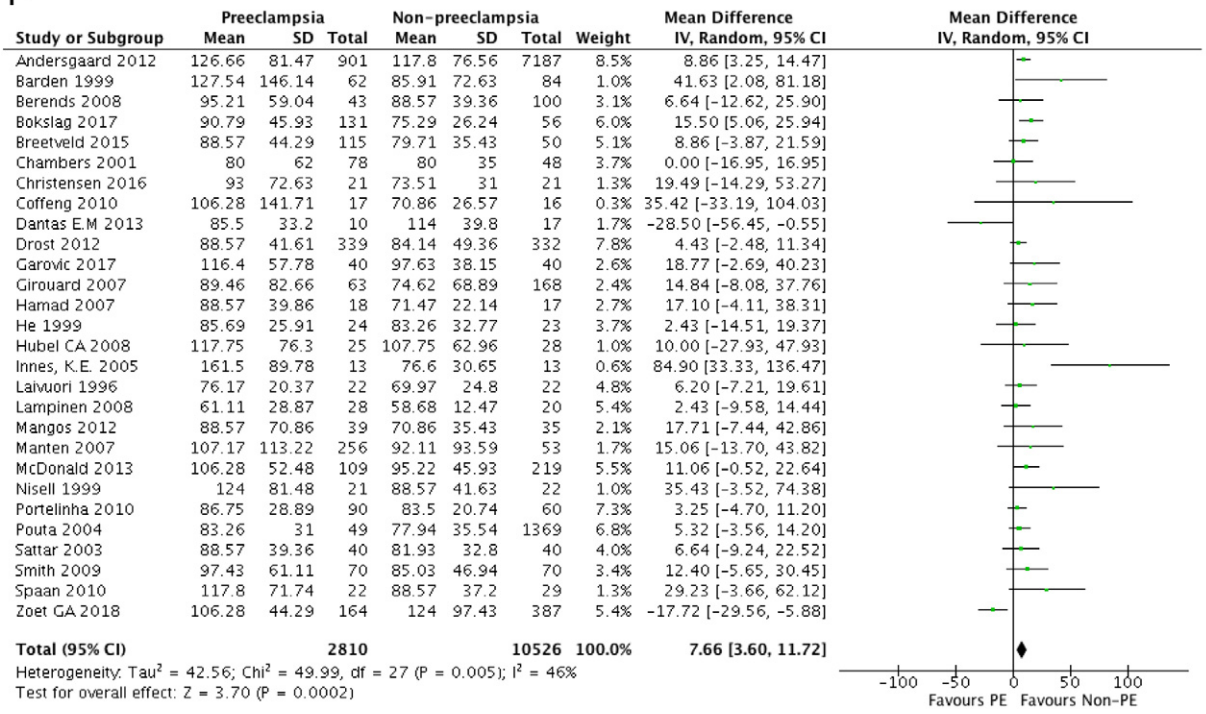


Fig. 4 (*continued*).

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

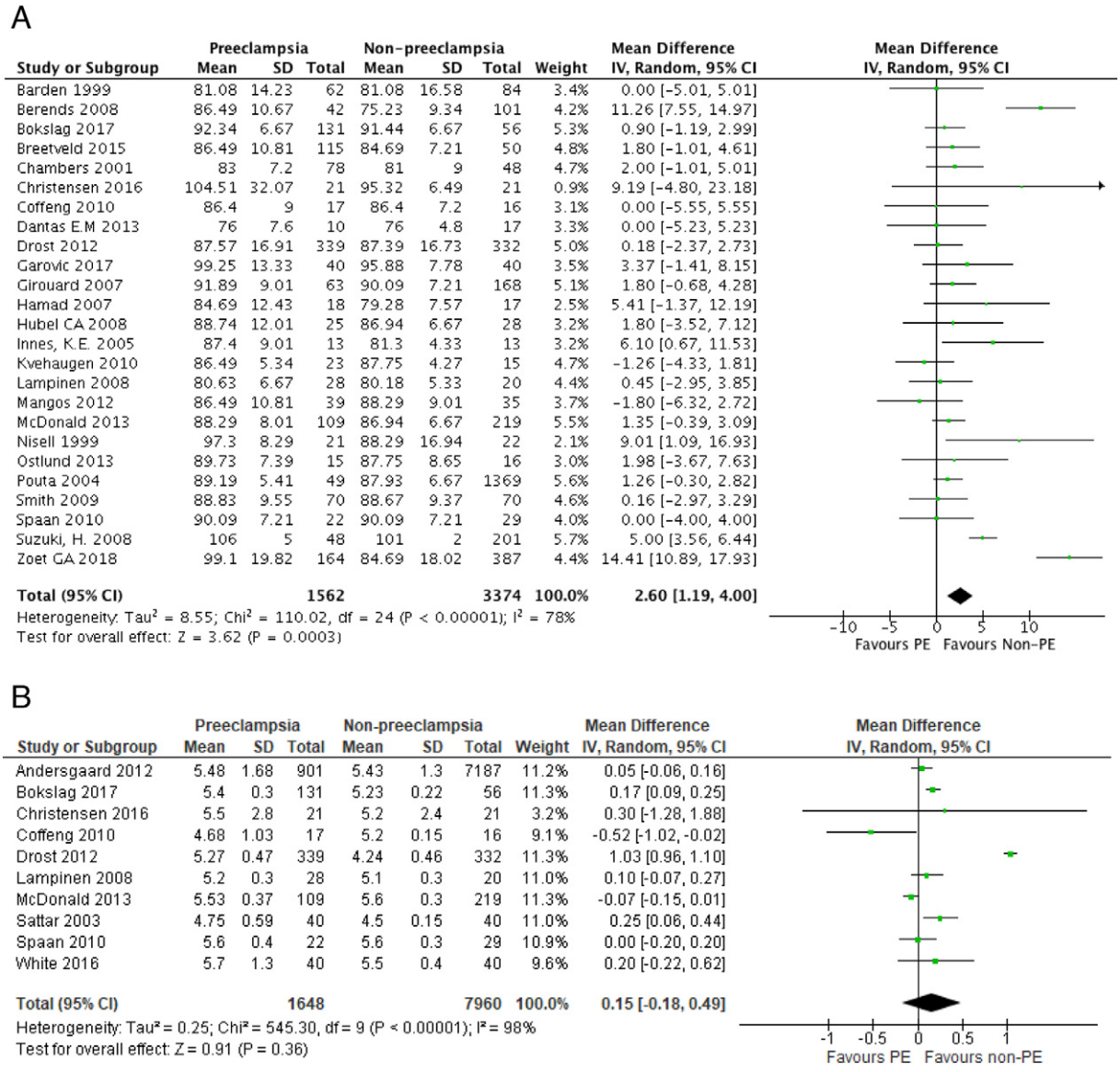
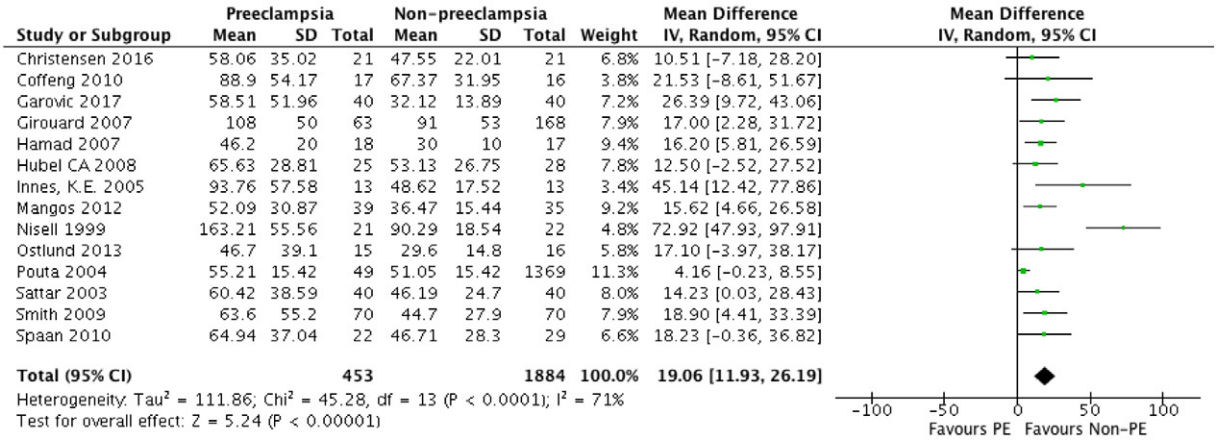


Fig. 5. Meta-analyses of glucose- and insulin-related outcomes: Mean differences of serum glucose (Fig. 5A), HbA1c (Fig. 5B), insulin (Fig. 5C), HOMA-IR index (Fig. 5d), and serum IGF-1 (Fig. 5e). A. Serum glucose, n=25 studies (I^2=78%). B. Glycosilated hemoglobin (HbA1c), n=10 studies (I^2=98%). C.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

C



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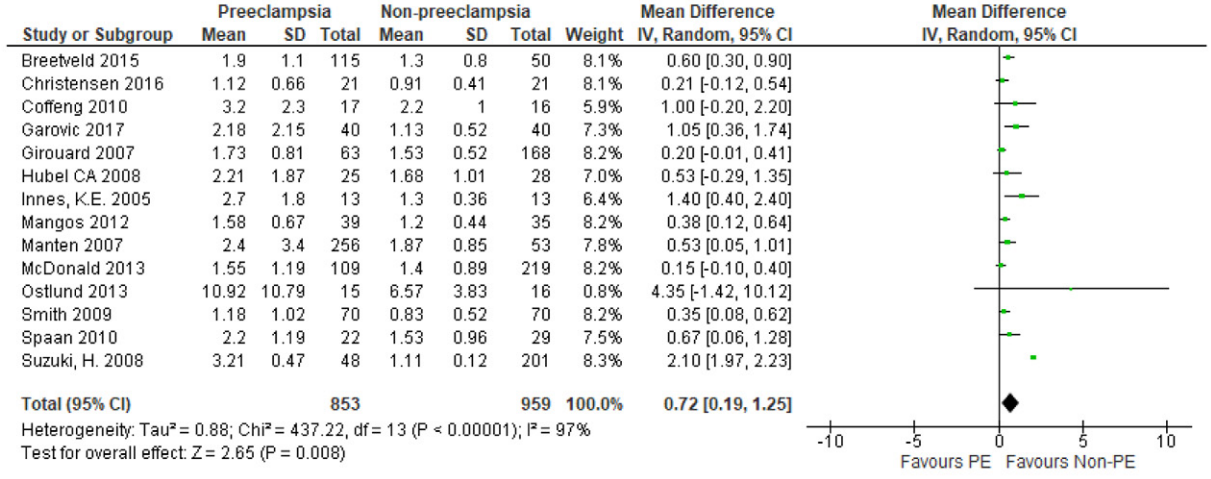

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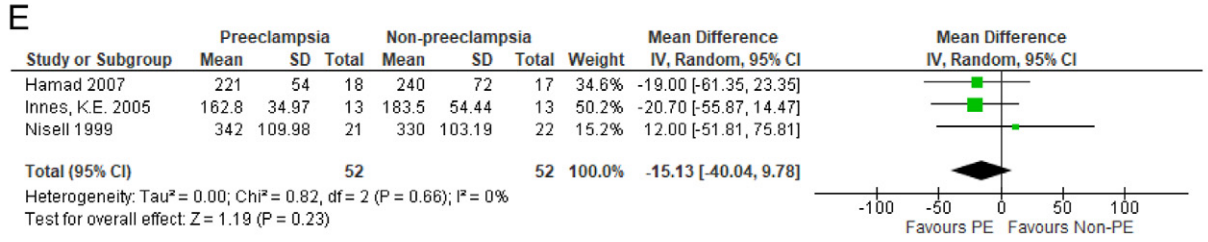

Fig. 5 (*continued*).

adjustment during pregnancy. Recent evidence from a population-based prospective cohort suggested that women with high blood pressure during pregnancy and postpartum have altered maternal lipid profile during early pregnancy [72].

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

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

4.3. Strengths and limitations

Our systematic review has several strengths: it was centered in PE/E, including women who suffered HELLP syndrome, without considering other hypertensive disorders of pregnancy which may have different

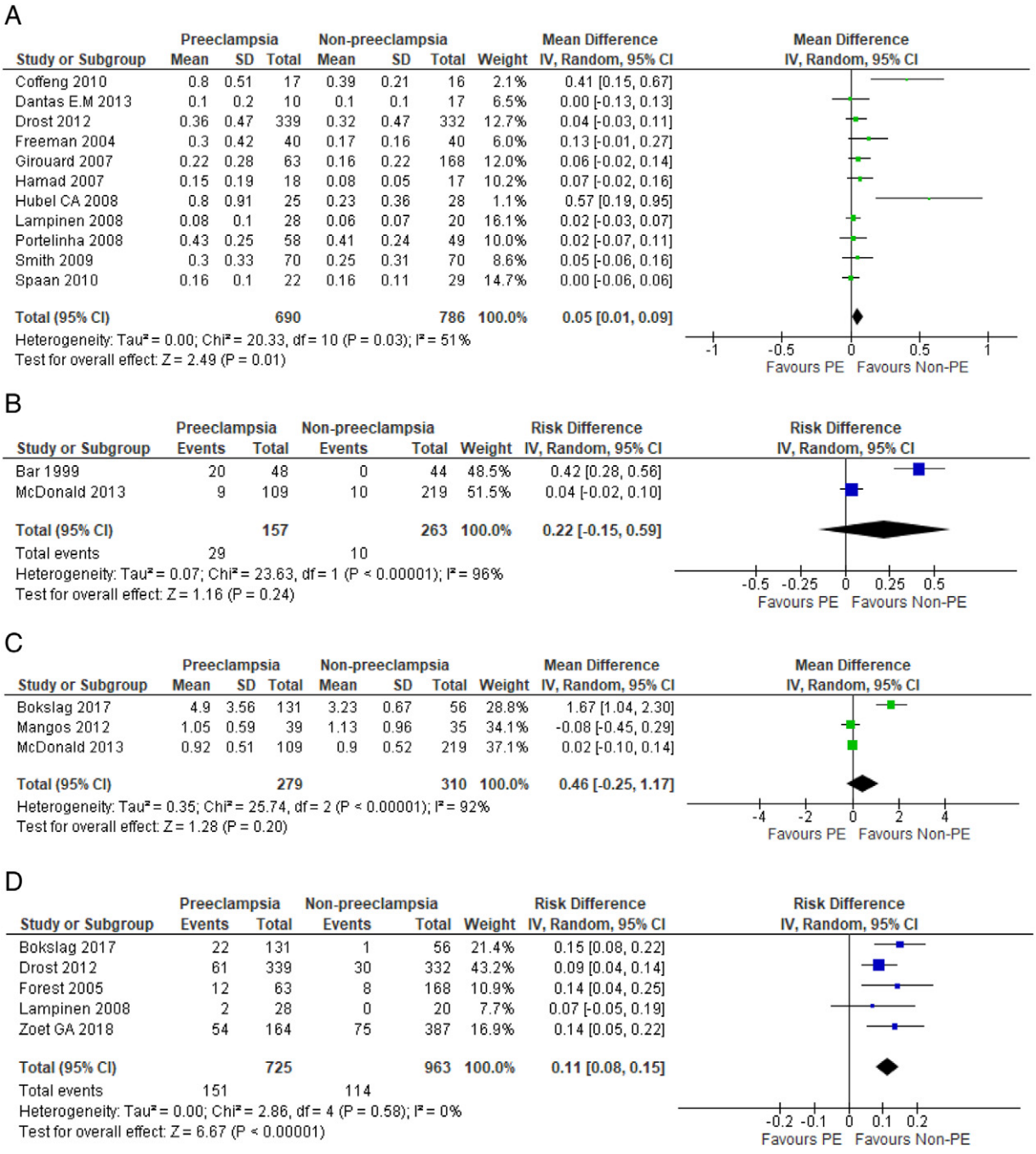

Fig. 6. Meta-analyses of other outcomes: Mean difference (MD) of serum CRP (Fig. 6a), risk difference (RD) of microalbuminuria (Fig. 6b), MD of albuminuria levels (Fig. 6c), and RD of metabolic syndrome (MetS) (Fig. 6d). a. C-reactive protein, n=11 studies (I^2=51%). b. Microalbuminuria, n=2 studies (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.

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Author contributions

FRPL and AVH were involved in study conception and design; acquisition, and interpretation of data; drafting of the manuscript; and approval the final version of the manuscript.

VAV, YL, VP, and YMR were involved in acquisition and interpretation of data; and approval of the final version of the manuscript.

YL and AVH performed statistical analyses.

FRPL and AVH have access to the data and are responsible for the accuracy of the manuscript.

Declaration of competing interest

The authors declared no conflict of interest.

Appendix A. Supplementary data

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

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