Cardiovascular Risk Factors in Offspring of Preeclamptic Pregnancies—Systematic Review and Meta-Analysis

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Objective To evaluate evidence for increased cardiovascular disease (CVD) risk factors in children exposed to preeclampsia in utero.

Study design PubMed, the Cumulative Index to Nursing and Allied Health Literature, the Cochrane Library, and EMBASE electronic databases were searched with an end of search date of June 4, 2018. Prospective and retrospective studies that compared CVD risk factors in those exposed to preeclampsia in utero with controls were eligible. Information was extracted on established CVD risk factors, including blood pressure, lipid profile, blood glucose, fasting insulin, body mass index, and endothelial/microvascular function.

Results Thirty-six studies provided cumulated data on 53 029 individuals. In utero exposure to preeclampsia was associated with 5.17 mm Hg (95% CI 1.60-8.73) greater mean systolic, 4.06 mm Hg (95% CI 0.67-7.44) greater mean diastolic blood pressure, and 0.36 kg/m^2 (95% CI 0.04-0.68) greater mean body mass index during childhood or young adulthood. No significant association was seen between exposure to preeclampsia in utero and other CVD risk factors.

Conclusions Offspring of preeclamptic pregnancies demonstrate risk factors for CVD during childhood and young adult life. Early blood pressure screening of children born after preeclamptic pregnancies may identify those that require interventions or preventive strategies to reduce later life CVD risk. *(J Pediatr 2019;208:104-13)*.

Cardiovascular disease (CVD) is a major global health burden that results in the greatest number of deaths worldwide. The World Health Organization estimates that 17.6 million people died from CVD in 2012, accounting for 31.4% of global mortality.[1] Research shows a strong link between preeclampsia and CVD.[2] Preeclampsia is a pregnancy complication that affects 2%-8% of pregnancies and is a leading case of maternal and infant morbidity and mortality.[3] Over the last decade, an accumulating body of research demonstrated that women who develop preeclampsia are at increased risk of CVD in later life.[2] A systematic review and meta-analysis that has assessed studies published until the end of 2012 shows that women who develop preeclampsia are at approximately twice the risk of developing or dying from overall CVD, ischemic heart disease, and stroke.[2] The likelihood of developing risk factors for CVD including hypertension and diabetes also is increased among women who develop preeclampsia compared with women who have normotensive pregnancies.[2] The bulk of evidence linking preeclampsia with CVD has resulted in preeclampsia being recognized by the American Heart Association as a female-specific cardiovascular risk factor.[4]

Emerging evidence also suggests that offspring of preeclamptic pregnancies also may be at increased risk of CVD in adult life. A long-term follow-up study reports that offspring of preeclamptic pregnancies are at twice the risk of stroke compared with offspring of normotensive pregnancies.[5] Davis et al performed a systematic review of studies published until mid-2011 that assessed CVD risk factors in offspring of preeclamptic pregnancies and reported that young offspring of preeclamptic pregnancies have increased blood pressure and body mass index (BMI).[6] At the time of the aforementioned review, there were not sufficient publications to perform meta-analyses on other conventional risk factors, including blood glucose and lipids. The aim of this study was to conduct an updated systematic review of all relevant studies published until June 2018 to assess risk factors for CVD, including systolic and diastolic blood pressure, BMI, blood glucose, lipids, and vascular function among those exposed to preeclampsia in utero.

BMI	Body mass index
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
SBP	Systolic blood pressure
SMD	Standard mean difference

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Methods

The review protocol is registered in PROSPERO (CRD42017074322). The following electronic databases were searched: PubMed, Cumulative Index to Nursing and Allied Health Literature, the Cochrane Library, and EMBASE with an end of search date of August 31, 2017. Subsequently, we conducted an updated search to include all relevant articles published until June 4, 2018. Our search strategy included terms such as "preeclampsia," "pre-eclampsia," "toxaemia," "toxemia," "gestation* hypertension," "pregnancy induced hypertension," and "eclampsia" AND "children," "offspring," "neonate," "infant" AND "pregnan*," "mother," "women," and "woman"; the search was limited to English and humans. The PRISMA guidelines were followed in conducting this systematic review.[7] Prospective and retrospective studies comparing CVD risk factors in those exposed to preeclampsia in utero with controls (either normotensive pregnancies or nonhypertensive pregnancies) were included. References of identified studies also were searched. We included studies that defined preeclampsia using the current International Society for the Study of Hypertension in Pregnancy guidelines.[8] However, as diagnostic criteria have changed over time, studies that used previous standard definitions of preeclampsia, including de novo onset of hypertension and proteinuria, also were included.[9] The definitions used in the individual studies are detailed in **Table I**. We excluded studies in which gestational hypertension and preeclampsia were considered together or when these 2 conditions were not distinguished. Studies were included if they reported the following outcomes in offspring: blood pressure (systolic or diastolic), BMI, lipid levels, blood glucose, insulin levels, and endothelial/microvascular function. All identified studies were sifted for relevance by 2 authors. Data were extracted from eligible studies by one author and cross-checked for accuracy by the second author. Discrepancies were resolved by discussion. The methodologic quality of each study was assessed independently by 2 authors using the Newcastle–Ottawa Quality Assessment Scale.[45]

The meta-analyses were conducted using Review Manager (RevMan) 5.3, with Mantel–Haenszel random-effects models. For each outcome measure, mean and SD were used in meta-analyses. The standard mean difference (SMD) or mean difference and the 95% CI were calculated. When mean and SD were not reported, the results were extracted as reported (ie, mean ± SEM, mean and CIs or range) and detailed in **Table II** (available at www.jpeds.com). Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the χ^2 P value was <.1. To assess publication bias, funnel plots were used for the primary outcomes.

Results

A total of 5162 articles were identified by the search and a further 15 from bibliographic search, of which 85 were eligible for full-text review (**Figure 1**). Of these, 36 were included in the review and 24 were included in the meta-analysis. The reasons for excluding 49 studies are detailed in **Figure 1**. Of the studies included in the meta analyses, 8.3% were of high quality (scored 7-8), 75% were of moderate quality (scored 4-6), and 8.3% were of low quality (scored 1-3) as assessed by the Newcastle–Ottawa Scale (**Table II**).

Systolic Blood Pressure

Systolic blood pressure (SBP) data were available from 20 studies. Of these, 15 were included in the meta-analyses providing data on 53 029 individuals, of whom 1599 were exposed to preeclampsia in utero (**Figure 2**, A).[16,18,20-22,24-27,34,35,37,39,41,46-48] Quantitative summary measures obtained by meta-analysis demonstrate that offspring of preeclamptic pregnancies have 5.17 mm Hg (95% CI 1.60-8.73) greater SBP compared with offspring of control pregnancies (**Figure 2**, A). Of the 5 studies that were not included in the meta-analysis, 3 report that offspring of preeclamptic pregnancies have greater SBP compared with controls,[30,38,43] and 1 reports that offspring of term preeclamptic pregnancies have greater mean SBP compared with controls but no significant difference between offspring of preterm preeclamptic pregnancies compared with controls (**Table III**; available at www.jpeds.com).[12] The other study reports that those born after early preeclampsia (defined as onset <34 weeks) have greater SBP compared with those born after late preeclampsia[28] (**Table III**).

Diastolic Blood Pressure

Diastolic blood pressure (DBP) data were available from 18 studies. Of these, 14 were included in the meta-analysis, providing data on 52 993 individuals, of whom 1583 were exposed to preeclampsia in utero (**Figure 2**, B).[15,16,18,20-22,26,27,31,34,35,37,39,41] Quantitative summary measures obtained by meta-analysis demonstrate that offspring of preeclamptic pregnancies have 4.06 mm Hg (95% CI 0.67-7.44) greater DBP compared with controls (**Figure 2**, B). The 3 studies that were not included in the meta-analysis also report greater DBP among offspring of preeclamptic pregnancies compared with controls (**Table III**).[12,30,38]

BMI

BMI data were available from 17 studies. Of these, 13 were included in the meta-analysis, providing data on 53 293 individuals, of whom 1752 were exposed to preeclampsia in utero (**Figure 3**). Quantitative summary measures obtained by meta-analysis demonstrate that offspring of preeclamptic pregnancies have 0.36 kg/m^2 (95% CI 0.04-0.68) greater BMI compared with controls (**Figure 3**).[5,16,18,24-27,31,37,39,41,42,46] The 4 studies that were not included in the meta-analysis reported greater BMI among offspring of preeclamptic pregnancies compared with controls (**Table III**).[12,30,40]

Table I. Characteristics of the included studies

Study	Definition of preeclampsia SBP/DBP; proteinuria	Exposed to preeclampsia/controls	Birth weight cases/ controls, g	Gestational age cases/ controls, wk	Follow-up, y	Outcome measure considered
Akcakus et al, 2010[10]	>140/90, severe >160/110; 300 mg/24 h	30/30/30	1817/1693/1762	32.4/32.4/31.5	0	Lipids
Alsnes et al, 2014[11]	DBP ≥90 + increase of DBP >25; >0.3 g/L (1+)	228/383	Not reported	Not reported	11	Lipids/glucose
Alsnes et al, 2017[12]	≥140/90; 0.3 g/24 h (1+)	Term PE 343/preterm PE 27/ controls 15072	Term PE 3399/ Preterm PE 2094/No PE 3535	Term PE 100% ≥37 wk, preterm PE 25.9% <34 wk/ 74.1% 34-36 wk, No PE 0.9% <34 wk, 3% 34-36 wk, 96.1% ≥37 wk	28-29	SBP/DBP/BMI/lipids
Catarino et al, 2008[13]	DBP >110 or >90 on repeated measures; 0.3 g/24 h (1+)	46/42	2600/3400	37/38.5	0	Lipids
Davidge et al, 1996[14]	>140/90 or rise >30/15; 0.5 g/24 h (2+)	17/17	2920/3500	39.0/39.9	0	Endothelial function
Davis et al, 2015[15]	>140/90; 0.3 g/24 h (2+)	46/899	2658/3363	36.1/39.5	20	SBP/DBP/BMI/lipids/glucose/insulin
Fraser et al, 2013[16]	>140/90 × ≥2; 1+	53/2404	3217/3467	39.2/39.6	17	SBP/DBP/BMI/lipids/glucose/insulin
Fugelseth et al, 2011[17]	>140/90 × ≥2; 1+	25/15	1740/3500	32.3/38.6	5-8	Myocardial function
Geelhoed et al, 2010[18]	>139/89 × ≥2; 1+	205/5345	3103/3446	Not reported	9	SBP/DBP/BMI
Herzog et al, 2017[19]	>140/90; PCR ≥ 30	15 EPE, 15 LPE/164	1185 EPE, 3200 LPE/3560	30.7 EPE, 37.4 LPE/39.6	0	Placental and umbilical cord vasculature
Hiller et al, 2007[20]	DBP >110 or 2× DBP >90; 300 mg/ 24 h or 2× 2++ protein	10 and 78	Not reported	Not reported	4-7	SBP/DBP
Howlader et al, 2009[21]	>140/90 or rise >30/15; 3000 mg/24 h	15/20	1750/2570	33.25/36.9	0	SBP/DBP/lipids/markers of oxidative stress
Jayet et al, 2010[22]	>140/90 or rise >30/15; Consecutive dipstick tests proteinuria	48 and 90	2843 and 3244	>37 and <42	14	SBP/DBP/BMI/vascular dysfunction
Kajantie et al, 2009[5]	>140/90; 1+	Nonsevere 120, severe 164/4271	Nonsevere 3216, severe 2894/3435	Nonsevere 39.6, severe 39.3/40.0	Not reported	BMI
Kajantie et al, 2017[23]	>140/90; 1+	Nonsevere 97, severe 134/3524	Nonsevere 3227, severe 2881/3430	Nonsevere 39.7, severe 39.3/ 40.0	Not reported	Type 2 diabetes mellitus
Kvehaugen et al, 2010[24]	>140/90 × ≥2; ≥ 1+ on ≥2 samples	23 and 17	1740 and 3526	32.3 and 38.6	5-8	SBP/DBP/BMI
Kvehaugen et al, 2011[25]	>140/90 × ≥2; ≥ 1+ on ≥2 samples	26/15	Not reported	Not reported	5-8	Lipids/endothelial function
Lawlor et al, 2012[26]	>139/>89; 1+	143 and 5367	3042 and 3443	37.6 and 39.5	9-10	SBP/DBP/BMI/lipids
Lazdam et al, 2010[27]	>140/90; 2+	16 and 38	1323/?	30.93/>37	20-30	SBP/DBP/BMI/lipids/glucose/insulin
Lazdam et al, 2012[28]	>140/90; 2+	90/50	Not reported	Not reported	6-13	SBP
Libby et al, 2007[29]	DBP≥90 × 2; albuminuria	700/7948	3290/3320	40/40	45-49	Type 2 diabetes mellitus
Miettola et al, 2013[30]	>140/90; ≥0.3 g	197/5045	3378/3581	38.8/39.5	16	SBP/DBP/BMI/lipids/glucose/insulin
Oglaend et al, 2009[31]	> in DBP to >90; 1+	181/356	Not reported	37.6/40.1	10-12	SBP/DBP
Ogland et al, 2009[32]	> in DBP to >90; 1+	F: 91/194, M: 92/166	F: 3010/3510, M: 2970/3600	F: 37.5/39.7, M: 37.2/39.7	10-12	BMI
Ophir et al, 2006[33]	>140/90; >300 mg/24 h	36/35	2883/3274	37.7/38.8	0	Lipids
Palti et al, 1989[34]	>140/90 or rise >30/15; Edema and proteinuria	94 and 94	12.7% LBW cases/4.2% LBW controls	22% cases <37/ 4.3% controls <37	6	SBP/DBP
Reveret et al, 2015[35]	>140/90; >300 mg/24 h	72/83	1561/1856	31.3/31.3	0	SBP/DBP
Rodie et al, 2004[36]	DBP >110 or >90 repeatedly; ≥0.3 g/24 h	41/81	2510/3770	36.5/40	0	Lipids
Seidman et al, 1991[37]	1952 American Committee on Maternal Welfare Definition	428/33 117	M: 3175/3338, F: 3009/3215	Not reported	17	SBP/DBP/BMI

(*continued*)

Table I. Continued

Study	Definition of preeclampsia SBP/DBP; proteinuria	Exposed to preeclampsia/controls	Birth weight cases/ controls, g	Gestational age cases/ controls, wk	Follow-up, y	Outcome measure considered
Staley et al, 2015[38]	>140/90; 1+	161/6716	3029/3443	38.0/39.5	7	SBP/DBP
Tenhola et al, 2003[39]	>140/90 or rise >30/15; >300 mg/24 h	60/60	2622/2868	36.6/36.7	12	SBP/DBP/BMI/lipids/glucose/insulin
Timpka et al, 2016[40]	>140/90; proteinuria on dipstick	42/1260	3000/3440	38.5/40.0	17	BMI/cardiac structure and function
Vatten et al, 2003[41]	>140/90 or rise >30/15; >300 mg/24 h	220/3853	3421/3485	40.3/40.6	13-19	SBP/DBP/BMI
Washburn et al, 2013[42]	>140/90 or rise >30/15; >300 mg/24 h	51/121	1059/1033	29.0/27.1	14	BMI
Wen et al, 2011[43]	American Committee on Maternal Welfare Definition	5359/25102	Not reported	Not reported	7	BMI/SBP
Yavuz, et al 2006[44]	>140/90; >300 mg/24 h	7 and 26	2640/3500	38/39	0	Lipids

EPE, Early preeclampsia; *F*, female; *LBW*, low birth weight; *LPE*, Late preeclampsia; *M*, male; *PCR*, protein creatinine ratio; *PE*, preeclampsia.

Total Cholesterol

Total cholesterol data were available from 12 studies, of which 5 reported on cord blood and 7 on offspring blood. The meta-analyses on studies on cord blood (n = 3) showed no difference in total cholesterol between offspring of preeclamptic pregnancies compared with controls (SMD 1.23, 95% CI −0.59 to 3.05, **Figure 4** [available at www.jpeds.com]).[21,33,36] The 2 studies that were not included in the meta-analysis also showed no significant difference in total cholesterol between the 2 groups.[13,44] Of the 7 studies on offspring blood, 5 were included in the meta-analysis providing data on 3798 individuals, of whom 396 were exposed to preeclampsia in utero (**Figure 4**). Quantitative summary measures obtained by meta-analysis demonstrate no significant difference in total cholesterol levels in offspring of preeclamptic pregnancies and controls (SMD 0.47, 95% CI 0.21-1.16, **Figure 4**).[11,15,16,27,39] Of the 2 studies that were not included in the meta-analysis, one reports greater total cholesterol[25] and the other reports no significant difference in total cholesterol between the 2 groups (**Table III**).[30]

Low-Density Lipoprotein Cholesterol

Low-density lipoprotein (LDL) cholesterol data were available from 12 studies, which included 5 on cord blood and 7 on offspring blood. The 3 studies on cord blood that were included in the meta-analysis report an increase in LDL cholesterol in offspring of preeclamptic pregnancies compared with controls with the quantitative analysis demonstrating a 0.30 mean difference (95% CI 0.29-4.31, **Figure 5** [available at www.jpeds.com]).[21,33,36] The 2 studies that were not included in the meta-analysis report no significant difference between the 2 groups (**Table III**).[13,44] Of the 7 studies on offspring blood, 5 were included in the meta-analysis, providing data on 3465 individuals, of whom 258 were exposed to preeclampsia in utero (**Figure 5**). Quantitative summary measures obtained by meta-analysis demonstrate no difference in LDL cholesterol between offspring of preeclamptic pregnancies and controls (SMD 0.12, 95% CI −0.09 to 0.34, **Figure 5**).[15,16,27,28,39] Both studies that were not included in the meta-analysis report that there is no difference in LDL cholesterol between offspring of preeclamptic pregnancies and controls (**Table III**).[25,30]

High-Density Lipoprotein Cholesterol

High-density lipoprotein (HDL) cholesterol data were available from 14 studies, which included 5 on cord blood and 9 on offspring blood. The 5 studies on cord blood could not be included in the meta-analysis. Of these, 3 reported a significant reduction[10,13,21] and 2 reported no significant difference[36,44] in cord blood HDL between offspring of preeclamptic pregnancies and controls (**Table III**). Of the 9 studies reporting on HDL cholesterol in offspring blood, 7 were included in the meta-analysis, providing data on 7684 individuals, of whom 503 were exposed to preeclampsia in utero (**Figure 6**; available at

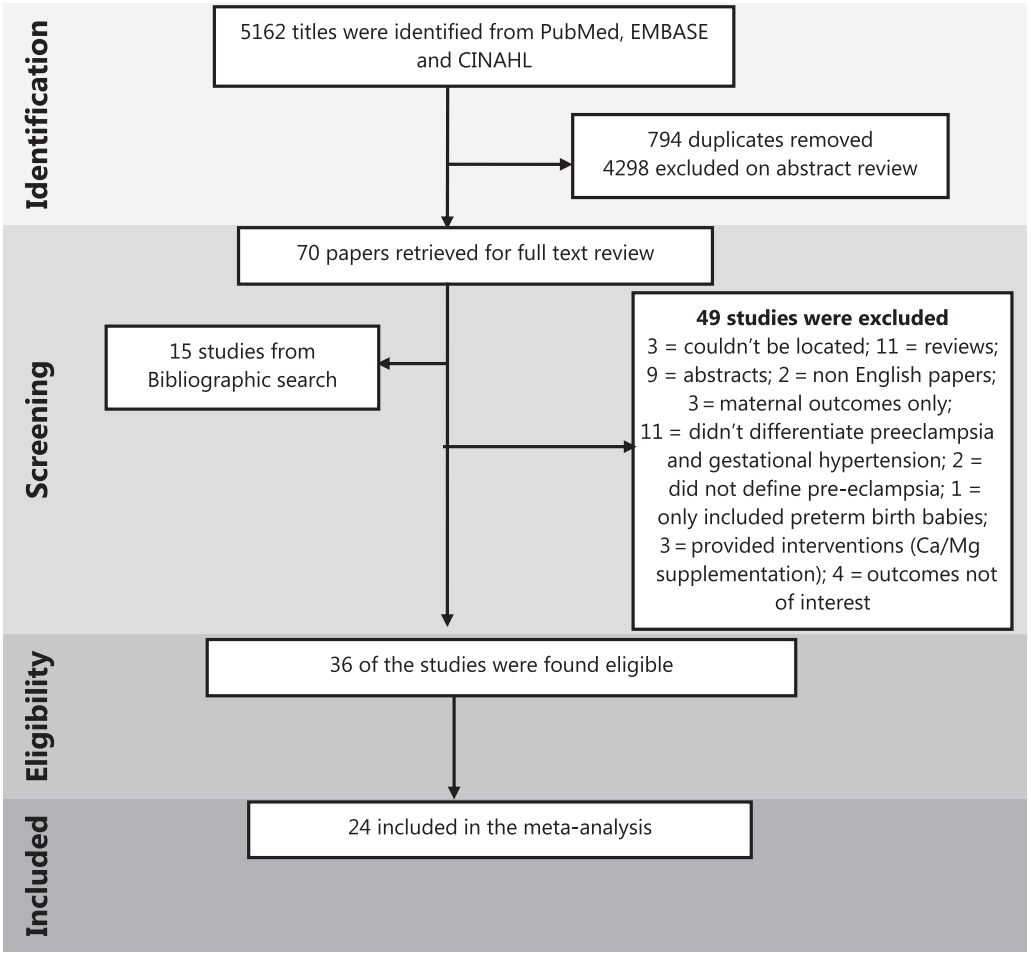


Figure 1. Study selection process. *CINAHL*, Cumulative Index to Nursing and Allied Health Literature.

www.jpeds.com). Quantitative summary measures obtained by meta-analysis did not demonstrate a significant difference in HDL cholesterol between offspring of preeclamptic pregnancies and controls (SMD 0.24, 95% CI −0.79 to 0.31, **Figure 6**).[11,15,16,21,25,27,39] Both studies that were not included in the meta-analysis reported that there was no significant difference in HDL levels in blood between the 2 groups (**Table III**).[12,30]

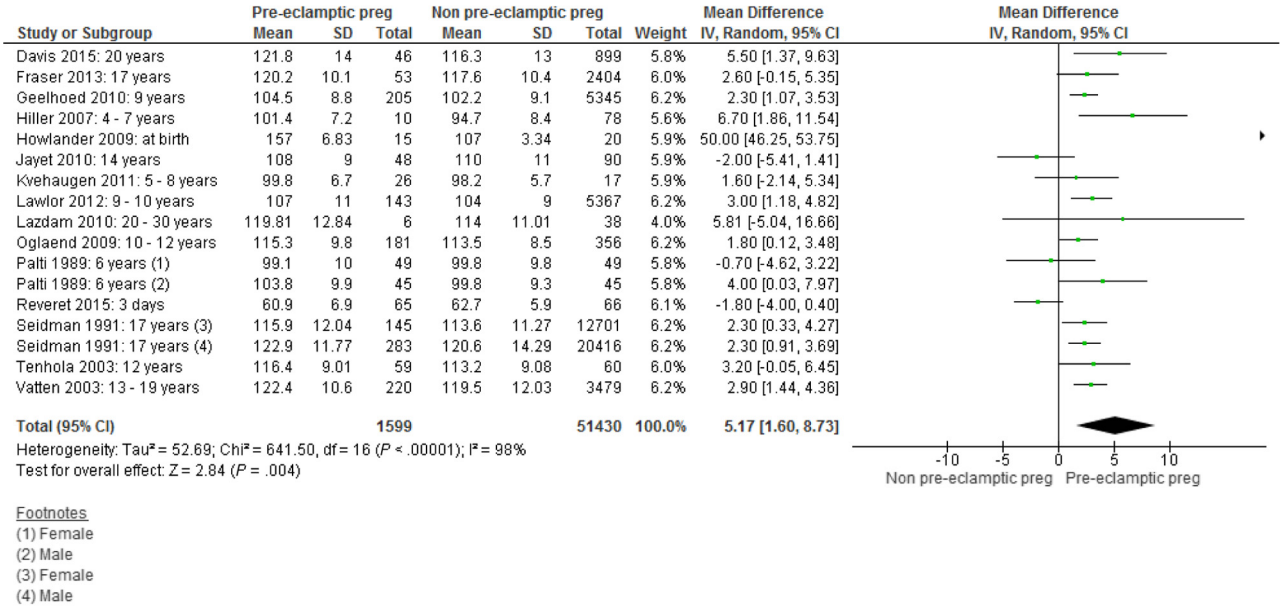
Non-HDL Cholesterol

Non-HDL cholesterol data were available from 3 studies. Of these, 2 were included in the meta-analysis, providing data on 4058 individuals, of whom 306 were exposed to pre-eclampsia in utero (**Figure 7**; available at www.jpeds.com). Quantitative summary measures obtained by meta-analysis demonstrate no difference in non-HDL cholesterol between offspring of preeclamptic pregnancies compared with controls (SMD 0.06, 95% CI −0.07 to 0.18, **Figure 7**).[11,26] The study that was not included in the meta-analysis reports that offspring of term preeclamptic pregnancies have greater mean non-HDL cholesterol compared with controls but that no difference was observed among offspring of preterm preeclamptic pregnancies compared with controls (**Table III**).[12]

Triglycerides

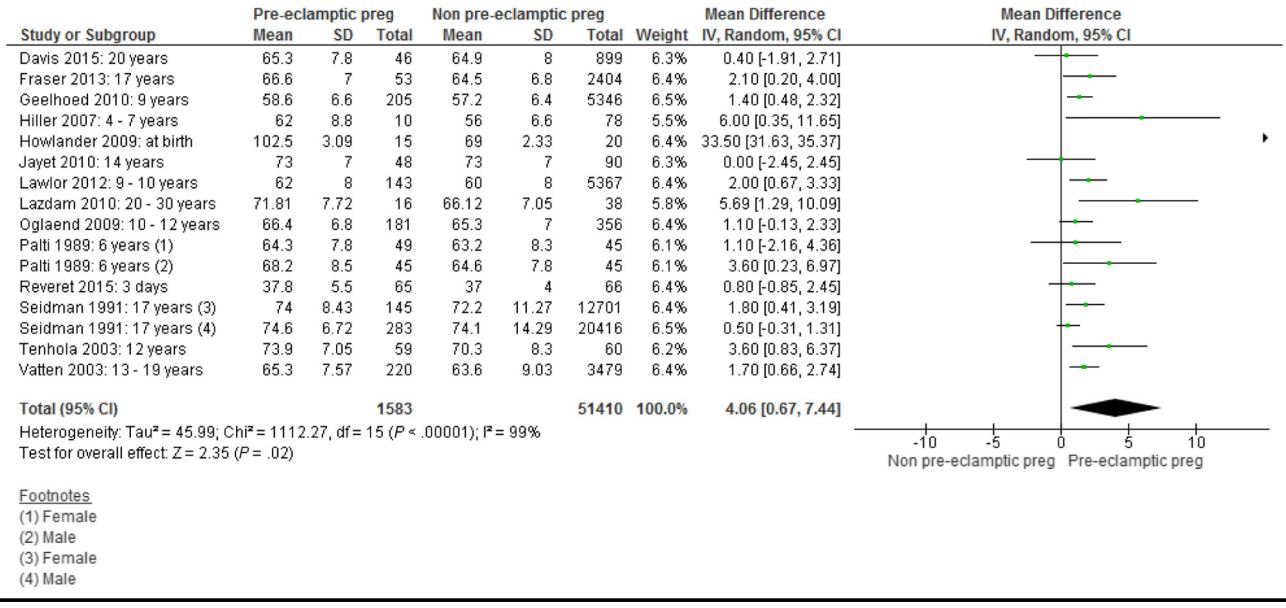
Triglyceride data were available from 13 studies, which included 6 on cord blood and 7 on offspring blood. Of the 6 studies on cord blood, 2 were included in the meta-analysis, providing data on 55 offspring from preeclamptic pregnancies and 51 controls. Quantitative summary measures obtained by meta-analysis demonstrate that offspring of preeclamptic pregnancies have greater cord blood triglyceride levels compared with controls (SMD 1.33, 95% CI −1.25 to 3.90, **Figure 8** [available at www.jpeds.com]).[21,33] Of the 4 studies that were not included in the meta-analysis, 2 report greater cord blood triglyceride levels in offspring of preeclamptic pregnancies[10,13] and the other 2 report no difference between the 2 groups (**Table II**).[36,44] Of the 7 studies reporting on offspring blood triglyceride levels, 4 were included in the meta-analysis, providing data on 1276 individuals of whom 216 were exposed to preeclampsia in utero. Quantitative summary measures obtained by

A Systolic Blood pressure



Footnotes
(1) Female
(2) Male
(3) Female
(4) Male

B Diastolic Blood pressure



Footnotes
(1) Female
(2) Male
(3) Female
(4) Male

Figure 2. **A,** Mean difference in SBP in mm Hg between those who were exposed to preeclampsia in utero and controls. **B,** Mean difference in DBP in mm Hg between those who were exposed to preeclampsia in utero and controls. *IV*, inverse variance.

meta-analysis demonstrate no difference in serum triglyceride levels between the 2 groups (SMD 0.05, 95% CI −0.13 to 0.23, **Figure 8**).[15,27,28,39] Of the 4 studies that were not included in the meta-analyses, 3 report that serum triglyceride levels are not significantly different between the 2 groups (**Table III**).[16,25,30] A study linking triglycerides in young adulthood with data from birth registries reports that offspring of term preeclamptic pregnancies have greater mean triglyceride levels but no difference between offspring of preterm preeclamptic pregnancies and controls (**Table III**).[12]

Glucose

Fasting blood glucose data were available from 7 studies. Of these, 6 were included in the meta-analysis, providing data on 4334 individuals, of whom 486 were exposed to preeclampsia in utero (**Figure 9**; available at www.jpeds.com). Quantitative summary measures obtained by meta-analysis

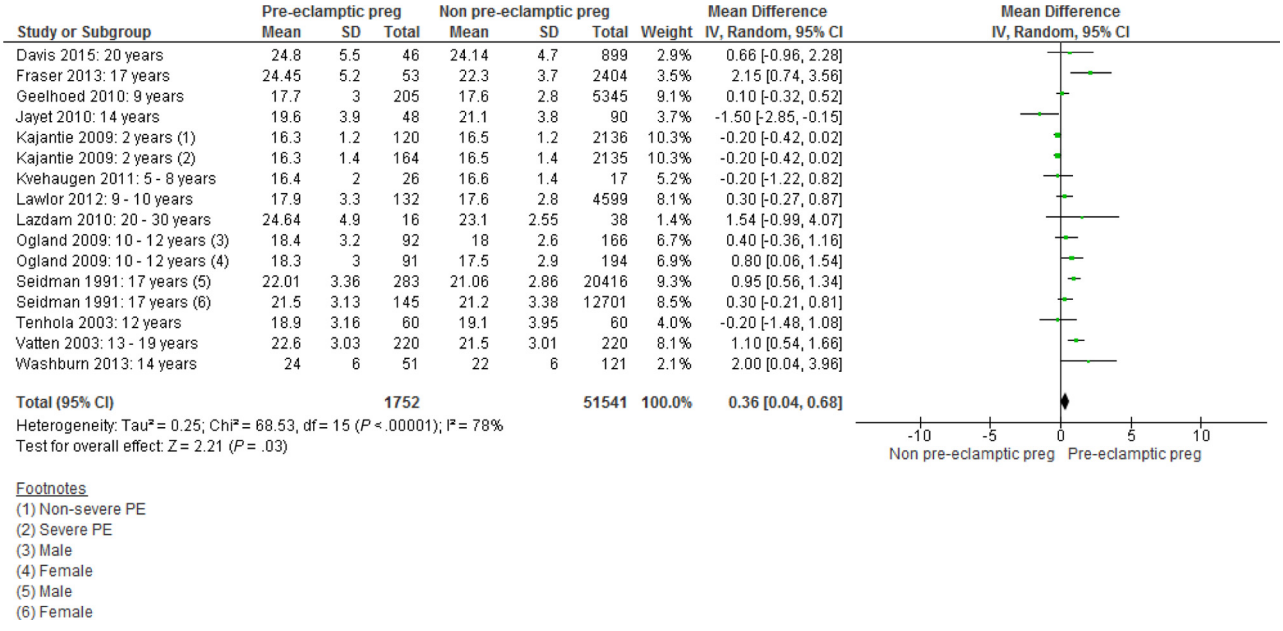


Figure 3. Mean difference in BMI in kg/m^2 between those who were exposed to preeclampsia in utero and controls. *PE*, preeclampsia.

did not demonstrate a significant difference in blood glucose between offspring of preeclamptic pregnancies and controls (mean difference 0.01 mmol/L, 95% CI −0.03 to 0.05, **Figure 6**).[11,15,16,27,28,39] The study that was not included in the meta-analysis reports that there is no difference in plasma glucose between the 2 groups (5.14 mmol/L [IQR 4.90, 5.50] vs 5.14 mmol/L [IQR 4.90, 5.40], **Table III**).[30]

Insulin

Fasting insulin data were available from 6 studies. Of these, 4 were included in the meta-analysis, providing data on 1276 individuals, of whom 215 were exposed to preeclampsia in utero (**Figure 10**; available at www.jpeds.com). Quantitative summary measures obtained by meta-analysis demonstrate no difference in fasting insulin levels between the 2 groups (SMD 0.25, 95% CI −0.0.03 to 0.53, **Figure 10**).[15,27,28,39] The 2 studies that were not included in the meta-analysis report no difference in plasma insulin between offspring of preeclamptic pregnancies and controls (**Table III**).[16,30]

Vascular Function

Studies on umbilical cord and placenta have shown that cellular fibronectin (a marker of endothelial cell activation) is greater in cord blood of infants born of preeclamptic pregnancies compared with controls (n = 17 in each group, 3 ± 0.15 μg/mL vs 2.6 ± 0.14 μg/mL, $P < .001$) and that preeclampsia (n = 29) is associated with a smaller umbilical cord vein area and wall thickness compared with controls (n = 76).[14,19] Studies on endothelial and cardiac function demonstrate smaller hearts, increased heart rates, and increased late diastolic velocity at the mitral valve at age 5-8 years, greater mean wall thickness (0.025; 95% CI 0.008-0.043), and smaller mean left ventricular end-diastolic volume (−9.0 mL; 95% CI −15 to −3.1) at age 17 years and 30% reduction in flow-mediated dilatation of the brachial artery at age 13-20 years (6.3 ± 1.2% vs 8.3 ± 1.4%, $P < .0001$) among those exposed to preeclampsia compared with controls.[17,22,40] One study reported no difference in endothelial function at age 5-8 years between offspring of preeclamptic pregnancies compared with controls but a significant reduction in endothelial function in children of preeclamptic pregnancies who were also born small for gestational age compared with controls.[25]

Discussion

This review demonstrates that offspring of preeclamptic pregnancies have greater SBP and DBP and a small increase in BMI, compared with controls. Our meta-analysis of 53 029 individuals of whom 1599 were exposed to preeclampsia in utero demonstrates a 5.17-mm Hg greater SBP among those exposed to preeclampsia compared with controls, and our meta-analyses of 52 993 individuals, of whom 1583 were exposed to preeclampsia in utero demonstrates a 4.06-mm Hg greater DBP among those exposed to preeclampsia compared with controls. The previous review by Davis et al reports a 2.39-mm Hg greater SBP (43 917 individuals, 1221 exposed to preeclampsia) and 1.35-mm Hg greater DBP (43 913 individuals, 1221 exposed to preeclampsia) among those exposed to preeclampsia in utero compared with controls.[6] Our findings demonstrate a stronger association with the increase in sample size. Both SBP and DBP track from childhood to adulthood, with average reported tracking correlation being greater for SBP than for DBP.[49] Because elevated blood pressure in

childhood is proposed to help predict adult hypertension,[49] these findings warrant further investigation.

The previous review by Davis et al reported a 0.62 kg/m^2 increase in BMI among those exposed to preeclampsia compared with controls (39 473 individuals, 1062 exposed to preeclampsia).[6] Consistent with the above, our current meta analyses, which includes 53 293 individuals, of whom 1752 were exposed to preeclampsia in utero, also demonstrates a small increase in BMI of 0.36 kg/m^2 among offspring of preeclamptic pregnancies compared with controls. Although commonly used, the accuracy of BMI as a predictor of adiposity in children is debatable. Among relatively fat children, BMI is shown to be a good indicator of excess adiposity, but the differences in BMI in relatively thin children can be largely due to fat-free mass.[50] A BMI for age or the BMI percentile of the Centers for Disease Control and Prevention reference population is considered a better predictor of adiposity among children.[50] The data on childhood adiposity using the aforementioned measures are limited for the populations relevant for this review and hence could not be assessed.

Our meta-analyses of studies on cord blood demonstrated greater LDL cholesterol and triglycerides and lower HDL cholesterol levels in offspring of preeclamptic pregnancies but no difference in offspring blood. The lack of translation of findings in cord blood to later years suggests that factors during pregnancy and labor including oxidative stress may influence the results in cord blood and that there is no difference in lipids between offspring of preeclamptic and control pregnancies.

The results on blood glucose and fasting insulin demonstrated no significant difference between offspring of preeclamptic pregnancies and controls. Two previous studies have assessed long-term risk for type 2 diabetes mellitus among offspring of preeclamptic pregnancies. The Helsinki birth cohort study of 5335 individuals reports that there is no association between the offspring risk for type 2 diabetes mellitus and maternal severe (n = 134) and nonsevere preeclampsia (n = 97) when offspring data were obtained at age 50-61 years.[23] Similar findings were reported in another study of 8648 individuals of whom 700 were exposed to preeclampsia in utero.[29] The results of fasting blood glucose and insulin levels found in our meta-analyses are consistent with the aforementioned findings that offspring of preeclamptic pregnancies are not at increased risk of developing type 2 diabetes mellitus compared with controls.

Only a limited number of studies have assessed vascular function in offspring of preeclamptic pregnancies. Therefore, we were not able to perform meta-meta-analysis on this variable. Although a few studies suggest that offspring of preeclamptic pregnancies show evidence of vascular dysfunction, current literature is not sufficient to draw conclusions on the effects if any of preeclampsia on offspring vascular health.

There are several potential limitations in our analyses that should be acknowledged. Both preeclampsia and CVD are multifactorial disorders with many genetic, environmental, and lifestyle factors contributing to disease risk. The data available to us did not allow for detailed exploration of potential confounding factors. For example, a genetic link between preeclampsia and CVD is increasingly being discovered and hence, the association between preeclampsia and CVD risk factors in offspring could be due to shared genetic factors that contribute to both diseases.[51-55] Another example is increased maternal BMI, which associates with increased risk of preeclampsia, offspring BMI, and offspring blood pressure, although the association with offspring blood pressure attenuates when childhood BMI is considered.[43,56,57] There are also other confounders that have opposite effects on preeclampsia and CVD. Maternal smoking during pregnancy is associated with a 33% reduction in the risk of preeclampsia[58] but an increase in the risk of offspring blood pressure and BMI in adult life,[59] which could lead to an underestimation of the true effects of preeclampsia on offspring health. We considered the fact that observational studies are likely to be subject to publication bias and constructed funnel plots for all the outcome measures in meta-analyses and these were symmetrical. Meta-analysis of continuous outcome variables also is affected by heterogeneity among studies but our review did not demonstrate significant heterogeneity.

The finding of greater blood pressure among offspring of preeclamptic pregnancies warrants further review, since even a 2-mm Hg reduction in systolic blood pressure is shown to be associated with 10% lower mortality from stroke and 7% lower mortality from ischemic heart disease in middle age.[60] The studies eligible for this review do not report on the prevalence of hypertension requiring treatment or the prevalence of obesity among those exposed to preeclampsia in utero. Therefore, the finding of mild elevations in SBP, DBP, and BMI in the meta-analyses raises the question of clinical applicability of the findings.

At present, there is limited literature on this topic. However, a recent large population-based study of 231 298 deliveries between 1991 and 2014 compared cardiovascular risk factors among singletons exposed to preeclampsia in utero with those unexposed.[61] In total, 4.1% of births in the cohort were to mothers diagnosed with preeclampsia, of whom 3.2% (n = 7286) had mild preeclampsia, 0.9% (n = 2174) had severe preeclampsia, and 0.03% (n = 73) had eclampsia. Cardiovascular risk was assessed in children up until 18 years of age. This study reports a significant linear relationship between the severity of preeclampsia and hypertension in the offspring. During the follow-up period, children exposed to mild preeclampsia, severe preeclampsia, and eclampsia had significantly greater rates of hypertension compared with children born after non–preeclamptic pregnancies (0.11%, 0.14%, and 1.37% vs 0.06%, $P < .001$) respectively. The prevalence of obesity showed a similar relationship with children exposed to mild preeclampsia, severe preeclampsia, and eclampsia having significantly greater rates of obesity compared with children born after non–preeclamptic pregnancies (0.4%, 0.4%, and 1.4% vs 0.2%, $P < .001$) respectively.[61] Because elevated blood

pressure during childhood has been shown to predict the development of hypertension,[49] the findings of this meta-analyses support current literature and suggest that children born after preeclamptic pregnancies may benefit from routine blood pressure monitoring and targeted interventions when required. ■

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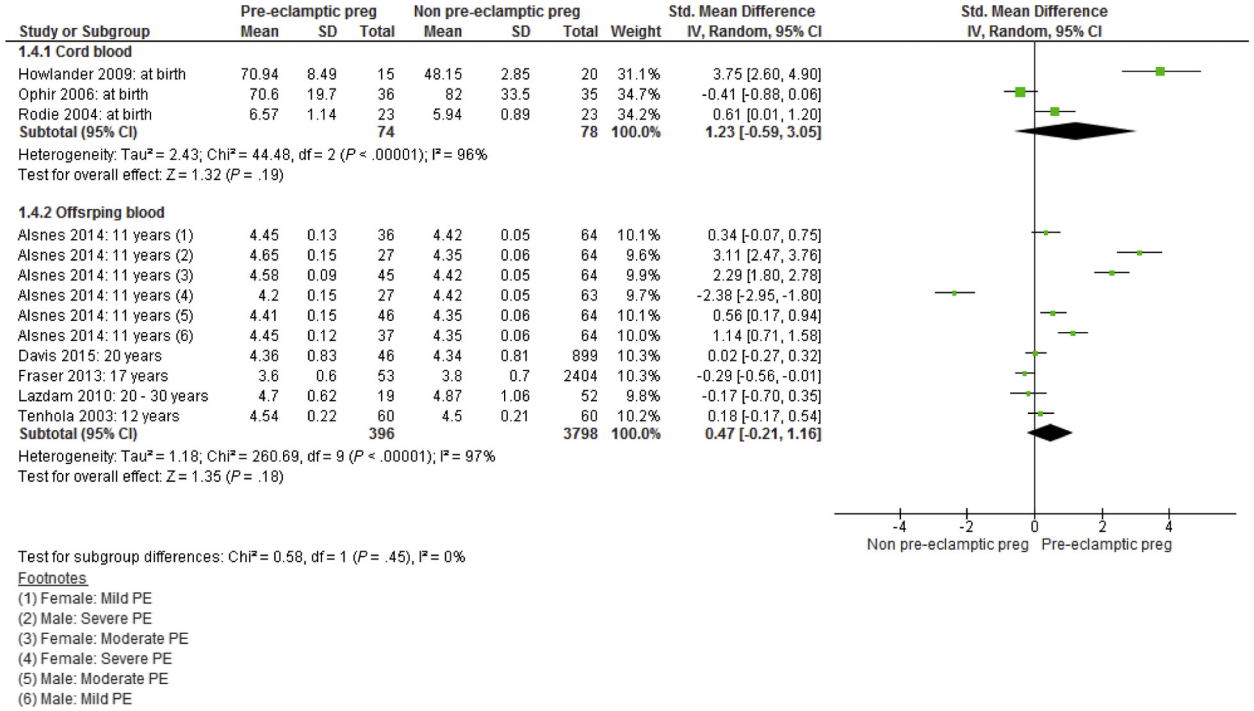

Figure 4. SMD in total cholesterol between those who were exposed to preeclampsia in utero and controls.

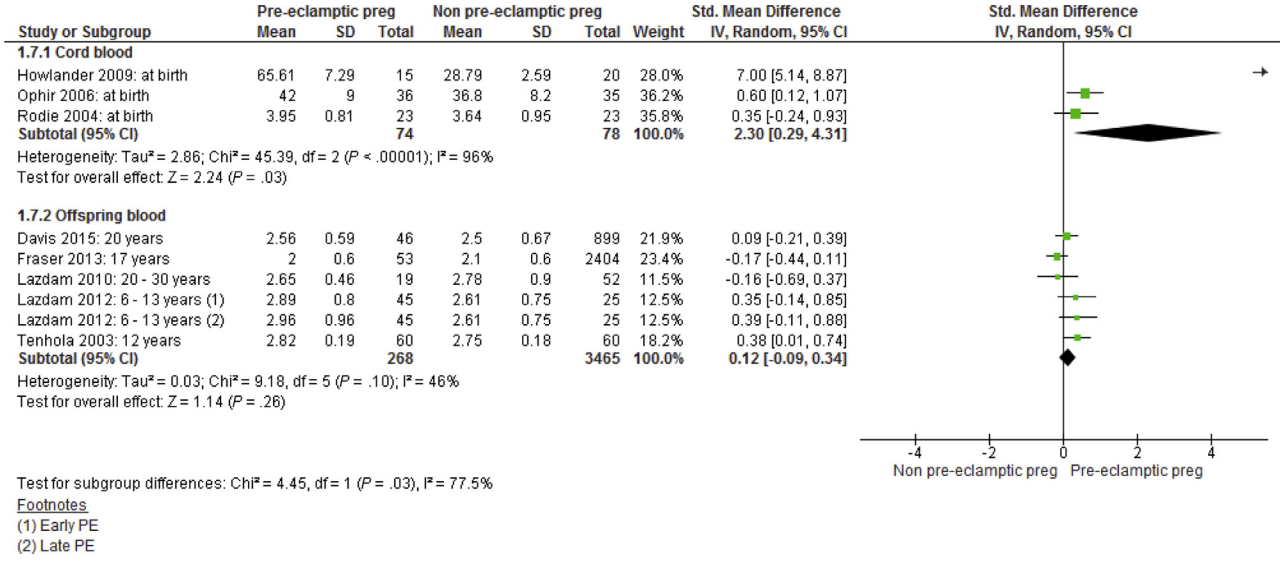

Figure 5. SMD in LDL cholesterol between those who were exposed to preeclampsia in utero and controls.

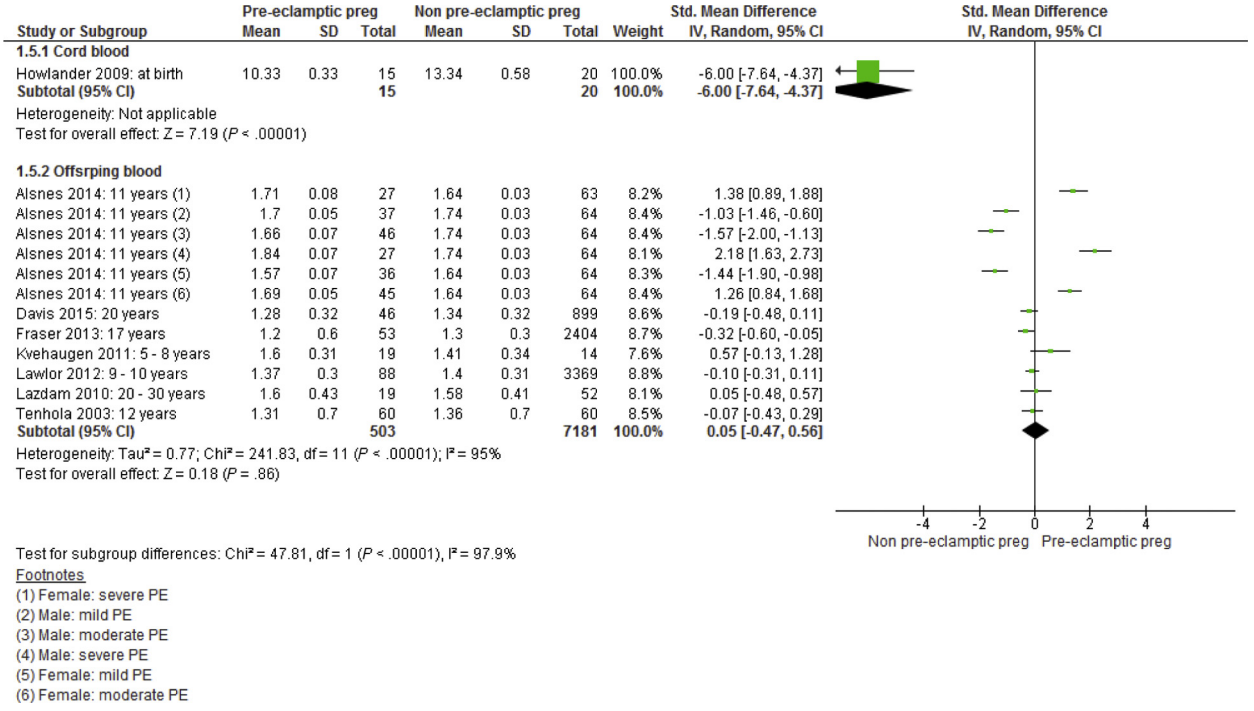

Figure 6. SMD in HDL cholesterol between those who were exposed to preeclampsia in utero and controls.

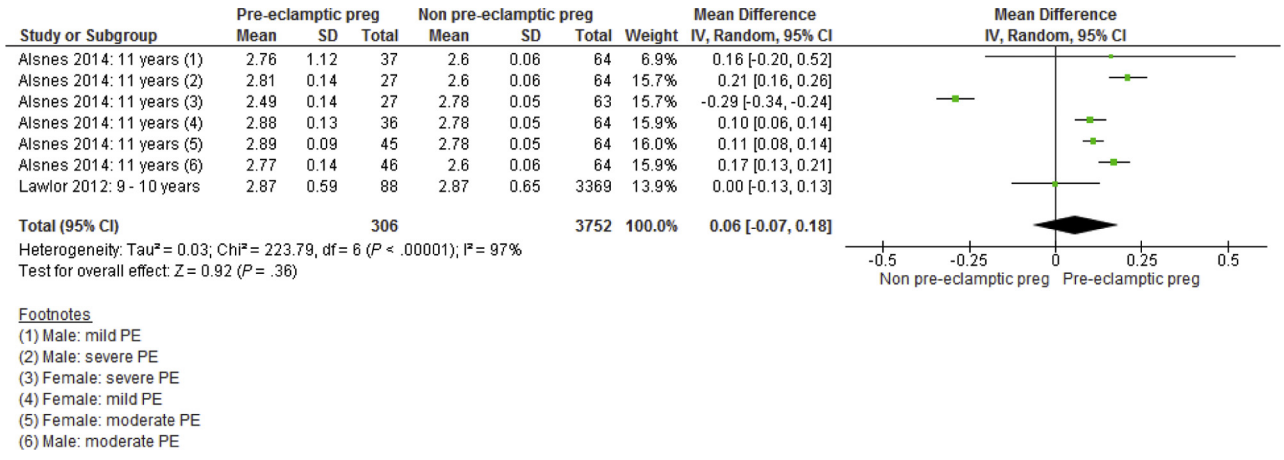

Figure 7. Mean difference in non-HDL cholesterol between those who were exposed to preeclampsia in utero and controls.

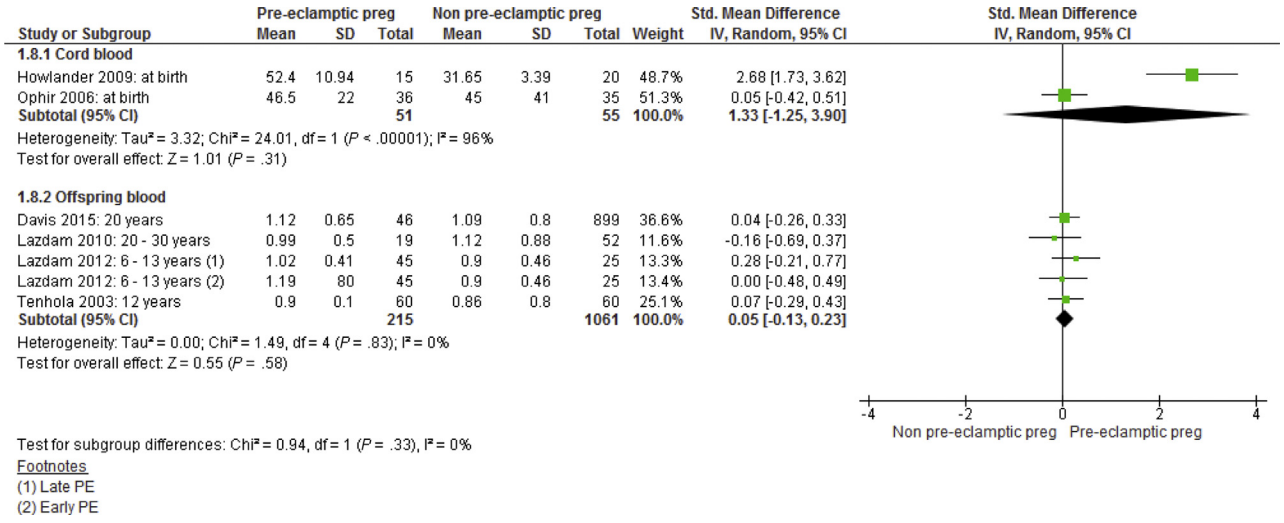

Figure 8. SMD in triglycerides between those who were exposed to preeclampsia in utero and controls.

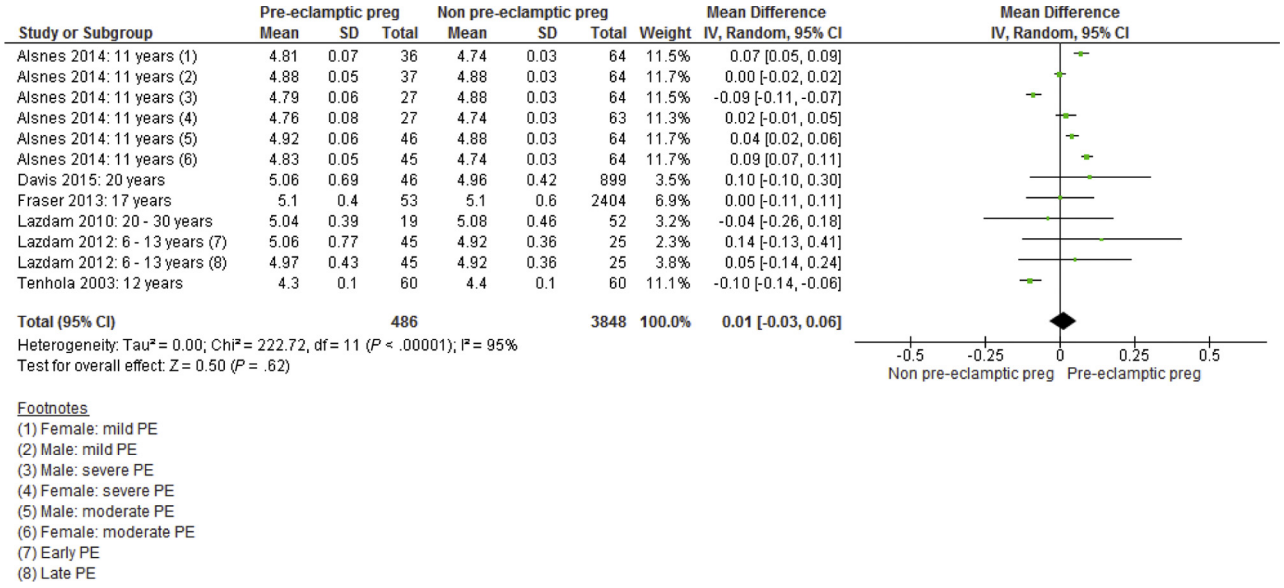

Figure 9. Mean difference in blood glucose in mmol/L between those who were exposed to preeclampsia in utero and controls.

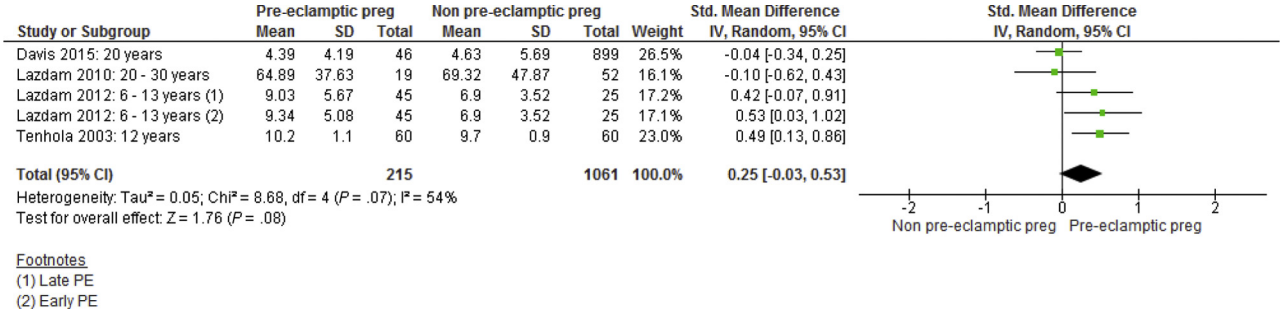

Figure 10. SMD in fasting insulin levels between those who were exposed to preeclampsia in utero and controls.

Table II. Quality assessment using the adapted Newcastle–Ottawa Scale

	Selection				Comparability	Exposure			
Manuscript	**1**	**2**	**3**	**4**	**1**	**1**	**2**	**3**	**Total score**
Akcakus et al, 2010[10]									N/A
Alsnes et al, 2014[11]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Alsnes et al, 2017[12]	a*	a*	b	a*	a+b**	a*	a*	b	7 of 8
Catarino et al, 2008[13]	a*	a*	b	b	not cont	a*	a*	c	4 of 8
Davidge et al, 1996[14]	a*	b	b	b	not cont	a*	b	c	2 of 8
Davis et al, 2015[15]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Fraser et al, 2013[16]	a*	a*	a*	b	a+b**	a*	a*	b	7 of 8
Fugelseth et al, 2011[17]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Geelhoed et al, 2010[18]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Herzog et al, 2017[19]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Hiller et al, 2007[20]	c	a*	b	b	a+b**	b*	a *	b	5 of 8
Howlader et al, 2009[21]	a*	a*	b	b	not cont	a*	a*	b	4 of 8
Jayet et al, 2010[22]	a*	a*	c	b	not cont	a*	a*	c	4 of 8
Kajantie et al, 2009[5]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Kajantie et al, 2017[23]	a*	a*	a*	b	a+b**	a*	a*	b	7 of 8
Kvehaugen et al, 2010[24]	c	b	b	b	not cont	a*	a*	c	2 of 8
Kvehaugen et al, 2011[25]	a*	a*	b	b	not cont	a*	a*	b	4 of 8
Lawlor et al, 2012[26]	a*	a*	b	b	not cont	a*	a*	b	4 of 8
Lazdam et al, 2010[27]	a*	b	b	a*	a+b**	a*	a*	c	6 of 8
Lazdam et al, 2012[28]	a*	b	a*	a*	not cont	a*	a*	c	5 of 8
Libby et al, 2007[29]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Miettola et al, 2013[30]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Ogland et al, 2009[31]	a*	b	b	a*	a+b**	a*	a*	c	6 of 8
Ogland et al, 2017	a*	a*	b	b	a*	a*	a*	b	5 of 8
Ophir et al, 2006[32]	a*	a*	b	b	not cont	a*	a*	b	4 of 8
Palti et al, 1989[33]	a*	b	a*	a*	not cont	a*	a*	c	5 of 8
Reveret et al, 2015[34]	a*	a*	b	b	a*	a*	a*	b	5 of 8
Rodie et al, 2004[35]	a*	a*	b	b	a*	a*	a*	b	5 of 8
Seidman et al, 1991[36]	a*	b	c	b	a+b**	a*	b	c	4 of 8
Staley et al, 2015[37]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Tenhola et al, 2003[38]	a*	b	b	b	not cont	a*	b	c	2 of 8
Timpka et al, 2016[39]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Vatten et al, 2003[40]									N/A
Washburn et al, 2013[41]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Wen et al, 2011[42]	a*	a*	b	b	a+b**	a*	a*	b	6 of 8
Yavuz, et al 2006[43]	a*	b	a*	b	not cont	e	a*	c	3 of 8

N/A, not available; *not cont*, study does not control for any factor; ** and ***, A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Table III. Results of studies not included in the meta-analyses

Outcome and study	Age at follow-up, y	PE, n	Controls, n	PE results	Control results	*P*
SBP						
Alsnes et al 2017[12*]	29	343 term 27 preterm	15 072	+2.3 mm Hg (95% CI 1.1-3.5) −0.6 mm Hg (95% CI −4.3 to 3.1)		
Lazdam et al, 2012[28]	6 to 13	47 all (early and late)		early PE vs late PE 96.27 ± 7.30 mm Hg vs 88.39 mm Hg ± 7.57 mm Hg		.005
Miettola et al, 2013[30]	16	174	4518	116 mm Hg (IQR 108, 125)	114 mm Hg (106, 123)	
Staley et al, 2015[37]	7	161	6716	1.22 mm Hg (95% CI −0.52 to 2.97)		
Wen et al, 2011[42]	7	30461 all		102.1 ± 10.4 mm Hg	101.7 ± 10.1 mm Hg	
DBP						
Alsnes et al, 2017[12*]	29	343 term 27 preterm	15 072	+1.0 mm Hg (95% CI 0.1-1.9) 0.00 mm Hg (95% CI −2.1 to 2.2)		
Miettola et al, 2013[30]	16	174	4518	68 mm Hg (IQR 64, 74)	67 mm Hg (62, 72)	
Staley et al, 2015[37]	7	161	6716	+0.49 mm Hg (95% CI −0.85 to 1.83)		
BMI						
Alsnes et al, 2017[12*]	29	343 term 27 preterm	15 072	0.93 kg/m^2 (95% CI 0.41-1.44) mean difference –0.78 kg/m^2, 95% CI −2.05 to 0.49		
Miettola et al, 2013[30]	16	174	4518	21.1 kg/m^2 (IQR 19.0, 23.3)	20.9 kg/m^2 (IQR 18.9, 22.4)	
Timpka et al, 2016[39]	12	42	1260	22.7 kg/m^2 (IQR 19.9, 24.8)	21.7 kg/m^2 (IQR 19.9, 24.4)	
Total cholesterol						
In cord blood						
Catarino et al, 2008[13]	At birth	41	39	73 mg/dL (IQR 57, 97.5)	86 mg/dL (IQR 72, 109)	.09 < .001
Yavuz et al, 2006[43†]	At birth	7	26	65.0 mg/dL	56.03 mg/dL	NS
In offspring blood						
Kvehaugen et al, 2011[25]	5-8 y	19	14	5.01 mmol/L (IQR 4.44, 5.39)	4.43 mmol/L (IQR 4.00, 5.00)	.04
Miettola et al, 2013[30]	16	174	4518	4.19 mmol/L (IQR 3.70, 4.70)	4.19 mmol/L (IQR 3.70, 4.70)	
LDL cholesterol						
In cord blood						
Catarino et al, 2008[13]	At birth	41	39	34 mg/dL (IQR 28, 52)	32 mg/dL (IQR 25, 50)	.68
Yavuz et al, 2006[43†]	At birth	7	26	30.42 mg/dL	25.53 mg/dL	NS
In offspring blood						
Kvehaugen et al, 2011[25]	5-8 y	19	14	1.8 mmol/L (IQR 1.2, 2.4)	0.3	.04
Miettola et al 2013[30]	16	174	4518	2.18 mmol/L (IQR 1.80, 2.60)	2.17 mmol/L (IQR 1.90, 2.60)	
HDL in cord blood						
Howlader et al, 2009[21]	At birth	15	20	10.33 ± 0.33 mg/dL	13.34 ± 0.58 mg/dL	<.01
Akcakus et al, 2010[10]	At birth	30 PE and 30 severe PE	30	PE 17.3 ±12.3 mg/dL Severe PE 17.1 ± 12.8 mg/dL	27.6 ± 13.0 mg/dL	.002
Catarino et al, 2008[13]	At birth	41	39	32.0 mg/dL (IQR 25.5, 39.5)	53 mg/dL (IQR 48, 57)	<.001
Yavuz et al, 2006[43†]	At birth	7	26	28.28 mg/dL	25.18 mg/dL	NS
Rodie et al, 2004[35]	At birth	23	23	0.19 ± 0.12 mmol/L	0.17 ± 0.09 mmol/L	.53
HDL in blood						
Alsnes et al, 2017[12*]	29	343 term 27 preterm	15 072	−0.01 (−0.05 to 0.02) mmol/L −0.02 (−0.16 to 0.12) mmol/L		
Miettola et al, 2013[30]	16	174	4518	1.36 mmol/L (IQR 1.17, 1.62)	1.38 mmol/L (IQR 1.20, 1.59)	.77
Non-HDL cholesterol						
Alsnes et al, 2017[12*]	29	343 term 27 preterm	15 072	0.14 (95% CI 0.03-0.25) 0.14 (95% CI −0.17 to 0.44)		

(*continued*)

Table III. Continued

Outcome and study	Age at follow-up, y	PE, n	Controls, n	PE results	Control results	*P*
Triglycerides in cord blood						
Akcakus et al, 2010[10]	At birth	30 PE and 30 severe PE	30	PE 39.2 ± 42.0 mg/dL Severe PE 39.5 ± 56.5 mg/dL	14.9 ± 18.8 mg/dL	.039
Catarino et al, 2008[13]	At birth	41	39	49.0 mg/dL (IQR 33.5, 63.5)	39.0 mg/dL (IQR 29.0, 52.0)	<.001
Rodie et al, 2004[35]	At birth	23	23	0.50 ± 0.14 mmol/L	0.44 ± 0.10 mmol/L	.09
Yavuz et al, 2006[43†]	At birth	2	26	30.57 mg/dL	32.57 mg/dL	NS
Triglycerides in blood						
Fraser et al, 2013[16]	17	53	2404	0.7 mmol/L (IQR 0.6, 1.1)	0.8 mmol/L (IQR 0.6, 1.0)	.56
Kvehaugen et al, 2011[25]	5-8 y	19	14	0.60 mmol/L (IQR, 0.53, 0.73)	0.58 mmol/L (IQR, 0.53, 0.82)	
Miettola et al, 2013[30]	16	174	4518	0.75 mmol/L (IQR 0.56, 1.02)	0.75 mmol/L (IQR 0.57, 0.97)	
Alsnes et al, 2017[12*]	29	343 term 27 preterm	15 072	0.13 mmol/L (95% CI 0.06-0.21) (0.17 mmol/L, 95% CI −0.06 to 0.43)		
Blood glucose						
Miettola et al, 2013[30]	16	174	4518	5.14 mmol/L (IQR 4.90, 5.50)	5.14 mmol/L (IQR 4.90, 5.40)	
Insulin						
Fraser et al, 2013[16]	17	53	2404	7.30 mU/L (IQR 5.3, 10.2)	7.0 mU/L (IQR 5.1, 9.9)	
Miettola et al, 2013[30]	16	174	4518	9.90 mU/L (IQR 7.30, 13.00)	9.57 mU/L (IQR 7.30, 12.10)	

*Results reported as mean difference compared with the control group.
†Results reported as median.