Markers of Vascular Dysfunction After Hypertensive Disorders of Pregnancy

A Systematic Review and Meta-Analysis

Sophie Grand'Maison, Louise Pilote, Marisa Okano, Tara Landry, Natalie Dayan

Abstract—Women with prior hypertensive disorders of pregnancy (HDP) are at twice the risk of cardiovascular disease compared with women with prior normotensive pregnancy, possibly because of sustained vascular dysfunction after delivery. The aim of this systematic review and meta-analysis is to summarize evidence of vascular dysfunction at least 3 months after HDP. Articles in all languages were retrieved from principal databases. Studies included were observational, with HDP as the main exposure and measurements of vascular dysfunction via imaging modalities or serum biomarkers as the main outcome, assessed at least 3 months postpartum. We pooled results of modalities reported in >3 studies using a random effects model. Of 6109 potentially relevant studies, 72 were included that evaluated 10 imaging modalities and 11 serum biomarkers in 8702 women. There was evidence of vascular dysfunction in women post HDP compared with women with prior normal pregnancy when measured by carotid-femoral pulse wave velocity (0.64 m/s [0.17–1.11]), carotid intima–media thickness (0.025 mm [0.004–0.045]), and augmentation index (5.48% [1.58–9.37]), as well as mean levels of soluble fms-like tyrosine kinase (6.12 pg/mL [1.91–10.33]). Between-groups differences in measures of vascular dysfunction were more pronounced when assessments were performed in younger women (<40 years) or closer to the index pregnancy for almost all modalities. In conclusion, pooled data from studies evaluating vascular imaging suggest that some vascular dysfunction persists after HDP as compared with women with prior normal pregnancy. (***Hypertension***. 2016;68:1447-1458. DOI: 10.1161/HYPERTENSIONAHA.116.07907.) • Online Data Supplement

Key Words: biomarkers ■ endothelium ■ hypertension ■ imaging ■ preeclampsia/pregnancy ■ pregnancy and postpartum

Women who have had hypertensive disorders of pregnancy (HDP), including preeclampsia and gestational hypertension,[1,2] have twice the risk of subsequent cardiovascular disease (CVD) compared with women who have had normotensive pregnancies.[3,4] Furthermore, severity of HDP and fetal compromise seem most strongly associated with CVD and cardiovascular mortality.[5,6]

Vascular dysfunction, which could be preexisting or following HDP, including endothelial dysfunction, arterial stiffness, and subclinical atherosclerosis, has been suggested as a putative mechanism for this underlying association. Preeclampsia is a complex maternal syndrome characterized by placental hypoperfusion and subsequent widespread endothelial dysfunction because of the release of inflammatory cytokines and antiangiogenic proteins.[7,8] In particular, soluble fms-like tyrosine kinase 1 (sFlt-1), an antiangiogenic protein, is elevated within the placenta and serum of preeclamptic women.[9] This protein induces endothelial dysfunction by reducing the interaction of placental growth factor (PIGF) and vascular endothelial growth factor (VEGF) with their endothelial receptors.[10] An elevated ratio of sFlt-1 to PIGF has been found to be predictive of preeclampsia.[11] Soluble endoglin, an important agent in vascular homeostasis,[12] has also been observed at elevated levels in the serum of preeclamptic women and correlates with disease severity.[13]

It remains unclear whether some degree of vascular dysfunction persists in women after pregnancies complicated by HDP beyond what is captured through traditional atherosclerotic risk factors. Several vascular imaging modalities assessing function (eg, flow-mediated dilatation, pulse wave velocity, and augmentation index [AIx]) and structure (carotid intima–media thickness [cIMT]) and serum angiogenic biomarkers (eg, sFlt-1, VEGF, and PIGF) have been studied in the postpartum period. However, although some authors have reported persistent abnormalities after HDP,[14–17] others have not.[18–21] A 2014 meta-analysis of observational studies on nontraditional biomarkers after HDP concluded that there was evidence of endothelial dysfunction among women with a history of HDP when compared with women with previously uncomplicated

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pregnancies.[22] However, emphasis in this review was on biomarkers of unclear relevance to vascular disease (eg, serum homocysteine). Thus, the aim of the present systematic review and meta-analysis was to summarize and update evidence for vascular dysfunction at least 3 months after HDP, as measured by imaging modalities and a wide variety of relevant serum biomarkers involved in angiogenesis, thrombosis, and inflammation.

Methods

Data Sources and Searches

The following databases were searched for relevant studies: MEDLINE (via OvidSP 1946 to May 20, 2015; via PubMed 1946 to May 20, 2015); Embase Classic+Embase (via OvidSP 1947 to May 20, 2015); BIOSIS Previews (via OvidSP 1969 to 2015, Week 25); CINAHLPlus with full text (via Ebsco, 1937 to May 20, 2015); The Cochrane Central Register of Controlled Trials (via The Cochrane Library, issue 4 of 12, April 2015). The search strategies used text words and relevant indexing to answer the following question: are HDP associated with vascular dysfunction in the postpartum period? The full MEDLINE strategy (online-only Data Supplement) was applied to all databases, with modifications to search terms as necessary. Further studies were identified in Web of Science and Scopus (16/11/2015) by examining the reference lists of included studies. Clinical Trials registries were searched to identify relevant, ongoing research. Conference proceedings from the Society of Obstetricians and Gynaecologists of Canada (http://sogc.org/) were searched from 2013 to 2014. The Medline strategy was rerun before submission (3 studies were added).

Definitions of Exposure and Outcome

The exposure of interest was any HDP, including preeclampsia, eclampsia, gestational hypertension, or chronic hypertension with superimposed preeclampsia according to the current guidelines.[1,2,23] Preeclampsia was defined by a new onset of a blood pressure >140/90 mm Hg with proteinuria >0.3 g/24 h after 20 weeks of gestation, while eclampsia was the presence of seizures. Gestational hypertension was defined as a diastolic blood pressure >90 mm Hg after 20 weeks of gestation, and we also included systolic blood pressure >140 mm Hg according to the most recent guidelines.[1,2,23] Superimposed preeclampsia was defined as preexisting hypertension with new onset proteinuria >0.3 g/24 h after 20 weeks of gestation. The majority of the included studies used normotensive pregnancy as the main comparison group. Four studies also included a control group of nulliparous women.[24–27] We restricted our meta-analyses to comparisons with prior normotensive pregnancy.

The outcome of interest was any form of vascular dysfunction measured by imaging modalities and serum biomarkers. We included all imaging modalities assessing various types of vascular dysfunction: endothelial dysfunction by flow-mediated dilatation, forearm blood flow, laser doppler and endoPAT, arterial stiffness by pulse wave velocity, and AIx and subclinical atherosclerosis by cIMT.[28–30] Only serum biomarkers directly linked to vascular function either alone or in association with preeclampsia were considered, including markers of angiogenesis (sFlt-1, VEGF, PIGF, and soluble endoglin), inflammation (soluble intercellular adhesion molecule-1 [sICAM-1] and soluble vascular cellular adhesion molecule-1 [sVCAM-1]), and thrombosis (endothelin, and fibronectin).[9,31,32] We also included novel, yet promising, biomarkers (miRNA)[33] and growth arrest–specific protein 6.[34]

Study Selection

Publications were assessed for inclusion and quality in accordance with PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-Analysis).[35] Two independent reviewers (S. Grand'Maison and M. Okano) performed the study selection using specific inclusion criteria to ensure accuracy and reproducibility. The first screening was based on titles and abstracts of identified publications. All potentially relevant studies were retrieved for full-text evaluation. Both reviewers independently evaluated the full-text articles, and reasons for exclusion were recorded. Disagreement was resolved by discussion between the 2 reviewers and by a third reviewer (N. Dayan) as necessary. The inclusion criteria were human studies, observational studies with a control group, HDP (exposure), and vascular dysfunction assessed at least 3 months postpartum (to allow return to prepregnancy physiological baseline) by imaging modalities or serum biomarkers. If duplicate studies were found within the same data source, either the most recent or the most complete publication was selected.

Data Extraction

S. Grand'Maison and M. Okano completed data extraction for all articles that met inclusion criteria during the full-text review. Study design and details regarding exposure, including the definition provided by each study, were recorded. The following baseline characteristics of study participants were collected: number of participants in each group, mean or median age at the time of assessment, parity, mean time since the affected pregnancy, and presence of CVD risk factors at the time of the assessment (chronic hypertension, diabetes mellitus, cholesterol profile, prior history of symptomatic CVD, smoking status, and body mass index). The modalities used to assess vascular dysfunction (eg, dynamic vascular imaging or blood biomarkers) with associated mean or median values for each study population were recorded. Authors of articles with insufficient study details or incomplete reported results were contacted and allotted 3 weeks' time for response. The characteristics of the studies included in the meta-analysis are presented in Table and of those included in the systematic review only in Table S1 in the online-only Data Supplement.

Quality Assessment

The reviewers applied the Newcastle-Ottawa Scale[64] to assess study quality. The quality of observational studies was determined by assignment of stars to a series of questions that assess 3 categories of biases: selection, comparability, and exposure. Based on available literature, we considered age, chronic hypertension, and diabetes mellitus as the most

Table. Characteristics of Included Studies in the Meta-Analysis

Studies	Exposure (n)	Controls (n)	Age Exposed, y	Age Controls, y	Follow-Up Exposed, mo	Follow-Up Controls, mo	Modalities Used	Quality Score
Akhter et al[36] (CS)	Severe preeclampsia (42)	Normotensive (44)	44±3	44±3	132±60	132±60	cIMT	9
Aykas et al[37] (CS)	Preeclampsia (25)	Normotensive (20)	…	…	At least 60	At least 60	FMD, cIMT	8
Blaauw et al[25] (CS)	Early-onset preeclampsia (22)	Normotensive (22)/ never pregnant (22)	31±4	31±4/30±6	6.4±2.9	7.0±2.6	cIMT	6
Blaauw et al[38] (CS)	Preeclampsia (17)	Normotensive (16)	33±5	34±4	57	52	cIMT, sICAM-1	4
Chambers et al[18] (CS)	Single (78)/ recurrent (35) preeclampsia	Normotensive (48)	34±5/37±5	35±6	36 (median)	36 (median)	sICAM-1, FMD	7
Collen et al[39] (CS)	Previous preeclampsia and now normotensive (10)/and now with chronic hypertension (8)	Previous normotensive pregnancy and still normotensive (10)	60±5.4/62±4.2	63±3.1	≈480	≈480	cfPWV	5
Collen et al[40] (CS)	HDP (50)	Normotensive (55)	63±6	63±5	408–480	408–480	cfPWV, AIx, cIMT	6
Drost et al[41] (CC)	Early-onset preeclampsia (339)	Normotensive (332)	38.9±4.9	39.3±4.4	109±44	128±36	sICAM-1, sVCAM-1	8
Ehrenthal et al[42] (CC)	HDP (33)	Normotensive (41)	30.4	32.0	12	12	Carotid–radial PWV, AIx	7
Elvan-Taspinar et al[43] (CS)	Early-onset preeclampsia (44)	Normotensive (46)	32.4±4.8	35.1±4.1	13 (4–52) (mean range)	12 (5–46) (mean range)	cfPWV	6
Gaugler-Senden et al[44] (CS)	Severe early-onset (<24 wk) preeclampsia (20)	Normotensive (20)	38.8 (22.1–47.7)	37.7 (23.8–41.9)	66 (48–120)	70 (53–131)	cIMT	6
Gaugler-Senden et al[19] (CS)	Severe early-onset (<24 wk) preeclampsia (16)	Normotensive (18)	42.9 (38.8–45.1)	41.6 (38.8–45.7)	113 (110–124)	116 (112–131)	sFlt-1, VEGF	4
Goynumer et al[45] (CS)	Severe preeclampsia (34)	Normotensive (42)	30.94±4.37	29.67±4.29	19±4	19±4	cIMT, FMD	7
Hamad et al[20] (CS)	Preeclampsia (18)	Normotensive (17)	30±4	31±4	15±3	15±3	FMD, sICAM-1, sVCAM-1	8
Hamad et al[46] (CS)	Preeclampsia (35)	Normotensive (30)	…	…	5	5	FMD, PlGF, sFlt-1, VEGF, sICAM-1, sVCAM-1	8
Henriques et al[47] (CC)	Gestational hypertension (30)	Normotensive (30)	42.5±8.9	40.1±8.7	182±42	182±42	FMD	6
Hubel et al[15] (CS)	Preeclampsia (29)	Normotensive (35)	33.7±5.8	30.8±6.7	18±10	18±9	sFlt-1, VEGF	6
Kvehaugen et al[48] (CS)	Preeclampsia (26)	Normotensive (15)	37.2±4.4	40.5±4.2	77 (median)	84 (median)	sFlt-1, VEGF, PlGF, PAT, Endoglin	1
Lampinen et al[49] (CS)	Preeclampsia (30)	Normotensive (21)	38±6	36±4	66	66	FBF, AIx	5
Lampinen et al[50] (CS)	Preeclampsia (28)	Normotensive (20)	38±6	36±4	60–72	60–72	AIx, endothelin	6
McDonald et al[51] (CC)	Preeclampsia (109)	Normotensive (219)	49 (44–55)	49 (45–56)	240 (median)	240 (median)	cIMT	8
Mersich et al[52] (CS)	Preeclampsia (12)	Normotensive (12)	29.9±1 (SEM)	30.2±0.8 (SEM)	12±0.6	12±0.4	cIMT	4
Ostlund et al[21] (CS)	Severe preeclampsia (15)	Normotensive (16)	39.4±3.6	41.2±3.2	95±40	79±29	cfPWV, AIx, FMD, PlGF, sICAM-1, sVCAM-1, sFlt-1	7

(*Continued*)

Table. Continued

Studies	Exposure (n)	Controls (n)	Age Exposed, y	Age Controls, y	Follow-Up Exposed, mo	Follow-Up Controls, mo	Modalities Used	Quality Score
Paez et al[26] (CS)	Preeclampsia (20)	Normotensive (20)/ never pregnant (15)	24.7±4.5	22±2.7/ 25±2.6	31±4.5	31±4.6	cfPWV, AIx, FMD	2
Paradisi et al[53] (CS)	Gestational hypertension (15)	Normotensive (15)	34.3±1.2 (SEM)	37.6±1.5 (SEM)	20.4±1.5	20.4±1.5	FMD	7
Polonia et al[54] (CS)	Preeclampsia (45)	Normotensive (55)	37.8±5.1	37.9±6.4	86±48	776±34	cfPWV	5
Portelinha et al[55] (CS)	Preeclampsia (58)	Normotensive (49)	34 (30–39)	34 (31–39)	72 (48–96)	72 (48–96)	sVCAM-1, sICAM-1	7
Ronnback et al[56] (CS)	Preeclampsia (22)	Normotensive (22)	36±1 (SEM)	37±1 (SEM)	At least 60	At least 60	AIx	6
Saarelainen et al[57] (CS)	HDP (16)	Normotensive (24)	…	…	At least 3	At least 3	FMD	2
Sandvik et al[17] (CS)	Preeclampsia (89)	Normotensive (69)	37.9±4.2	39±5.3	131±12	131±12	FMD, cIMT, sVCAM-1, VEGF, sFlt-1, PlGF	6
Tuzcu et al[58] (CS)	Preeclampsia (16)	Normotensive (24)	32.4±5.6	35.5±6.4	56.9±48	50.8±52.3	FMD, sFlt-1, sICAM-1, sVCAM-1	2
Yinon et al[59] (CS)	Early-onset (15)/late-onset preeclampsia (9)	Normotensive (16)	35±1/34±1 (SEM)	34±1 (SEM)	14±2/15±2 (SEM)	14±1 (SEM)	FMD	5
Yuan et al[60] (CS)	Late-onset preeclampsia (10)	Normotensive (11)	…	…	18	18	cIMT, carotid-brachial PWV, AIx	6
Abstracts								
Enkhmaa et al[61] (CC)	Preeclampsia (14)/gestational hypertension (11)	Normotensive (13)	32±6/32±6	32±6	16.6±8/16±8	16.6±8	PWV, AIx	4
Forest et al[62] (CC)	Preeclampsia (63)/gestational hypertension (105)	Normotensive (168)	35.4 (4.9)/34.5 (5.6)	35.4 (5.6)	94	94	sFlt-1, VEGF	3
Paez et al[27] (CS)	Preeclampsia (32)	Normotensive (30)/ never pregnant (30)	38.2±4.7	36.7±3.9/ 36.8±4.3	120	120	FMD	0
Tam et al[63] (CS)	Severe preeclampsia (50)	Normotensive (643)	37.1±4.6	46.6±3.2	84±5	142±18	cfPWV, AIx	1

Results are presented as mean±SD or median (IQR) if not specified otherwise. AIx indicates augmentation index; CC, cohort; cfPWV, carotid–femoral pulse wave velocity; cIMT, carotid intima–media thickness; CS, case–control; FBF, forearm blood flow; FMD, flow-mediated dilatation; HDP, hypertensive disorders of pregnancy; PAT, peripheral arterial tone; PlGF, placental growth factor; PWV, pulse wave velocity; SEM, standard error of mean; sFlt-1, soluble fms-like tyrosine kinase-1; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cellular adhesion molecule-1; and VEGF, vascular endothelial growth factor.

important confounders to be considered.[65–67] The Newcastle-Ottawa scale was selected as opposed to the Cochrane Risk of Bias Assessment Tool: for NonRandomized Studies of Interventions[68] as we did not evaluate an intervention. No study was excluded on the basis of quality alone.

Statistical Analysis

Results of studies were pooled using a random effects model if there were at least 3 studies evaluating the same technique or biomarker that reported means±standard deviation (SD) or standard error of mean (SEM). Results of the meta-analyses are presented as weighted mean difference (WMD) between HDP and normotensive pregnancy with the corresponding 95% confidence interval. Heterogeneity was assessed using the *I*-squared (I^2) method. If substantial heterogeneity was present, results were only pooled if subgroup analyses reduced heterogeneity. Predefined subgroup analyses included stratified results based on women's age at the time of assessment (dichotomized at 40 years), the delay since the index pregnancy (dichotomized at median duration of follow-up in months for each modality), study design (cohort or case–control), type of HDP (preeclampsia, gestational hypertension, or combined), and severity of cases. For modalities examined in 10 or more studies, visual inspection of funnel plot and an Egger's test were conducted to assess for possible publication bias. A 2-sided P value <0.05 was considered statistically significant for all analyses. Analyses were conducted using Stata, version 13 (StataCorp).

Results

Search Results and Characteristics of Included Studies

In the initial literature search, 6109 potentially relevant studies were identified, of which 177 full-text articles were retrieved for detailed assessment (Figure 1). Sixty-five studies

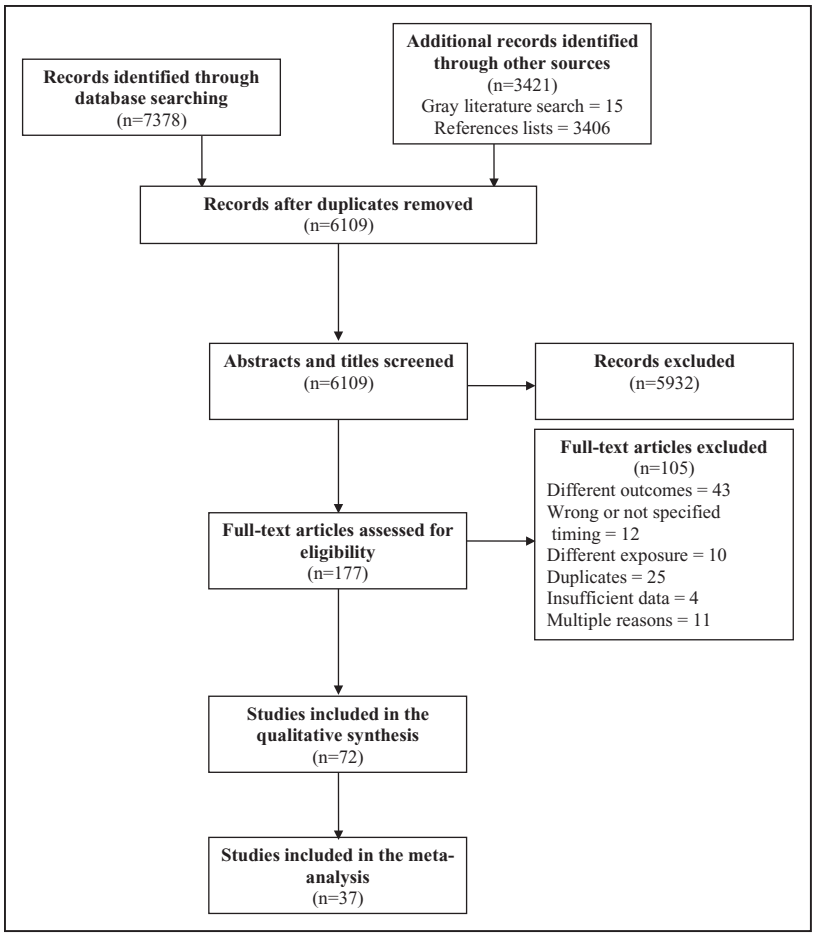

Figure 1. Flow diagram of the articles selection process.

and 7 abstracts with sufficient data were included in our final review: 59 case–control and 13 cohort studies for a total of 8702 women (3356 cases with HDP and 5346 controls). Thirty-seven studies were pooled in our analyses (Table). The characteristics of studies that were not pooled are presented in the Table S1.

The definitions of preeclampsia, gestational hypertension, and HDP were consistent with the guidelines of the International Society for the Study of Hypertension in Pregnancy, including the distinction between early (<34 weeks) and late (>34 weeks) preeclampsia.[23] However, one study used an unusual definition for early preeclampsia (<24 weeks),[19] as specified in Table.

The most frequently used modalities to assess different types of vascular dysfunction were cIMT, flow-mediated dilatation, carotid–femoral pulse wave velocity (cfPWV), AIx, sICAM-1, sVCAM-1, sFlt-1, and VEGF (Table S2), and results for these modalities were pooled if appropriate.

Imaging Modalities of Vascular Dysfunction

Measures of Arterial Stiffness

Arterial stiffness was assessed after any HDP using AIx in 1145 women (283 exposed and 862 controls) and more specifically after preeclampsia with cfPWV in 1087 women (242 exposed and 845 controls). Within these modalities, pooled results demonstrated persistence of arterial stiffness after the index pregnancy (AIx, WMD of 5.48% [1.58–9.37]; cfPWV, WMD of 0.64 m/s [0.17–1.11]; Figure 2). However, there was evidence of at least moderate heterogeneity measured by the I^2 method in these pooled modalities (AIx, 88.0%; cfPWV, 81.5%). We explored whether this was because of study quality, study design, or type of exposure. The heterogeneity in the AIx results seemed to be explained by study design because heterogeneity was not present in cohort studies (I^2=0.0%), but it was substantial in case–control studies (I^2=91.3%). Examining forest plots, the overall WMD for cfPWV was found to be influenced by the study by Tam et al, which was only available as an abstract.[63] Excluding this study, heterogeneity was diminished (I^2=0.0%), but findings of greater arterial stiffness in women post HDP persisted. Subgroup analyses based on mean age (<40 or ≥40 years) revealed that differences in vascular dysfunction were more pronounced in younger women as measured by AIx (WMD of 6.27% [1.86–10.69] versus 3.62% [−4.55 to 11.79]) and cfPWV (WMD of 0.372 m/s [0.153–0.592] versus 0.771 m/s [0.003–1.538]). Visual inspection of a funnel plot and the Egger's test revealed no evidence of publication bias for AIx (Figure S1).

Measures of Subclinical Large Vessel Atherosclerosis

Persistence of subclinical large-vessel atherosclerosis in women with HDP as compared with controls was also found. Pooled analysis of cIMT measured in 802 women (341 exposed and 461 controls) revealed an overall WMD of 0.025 mm [0.004–0.045]; Figure 2). However, there was

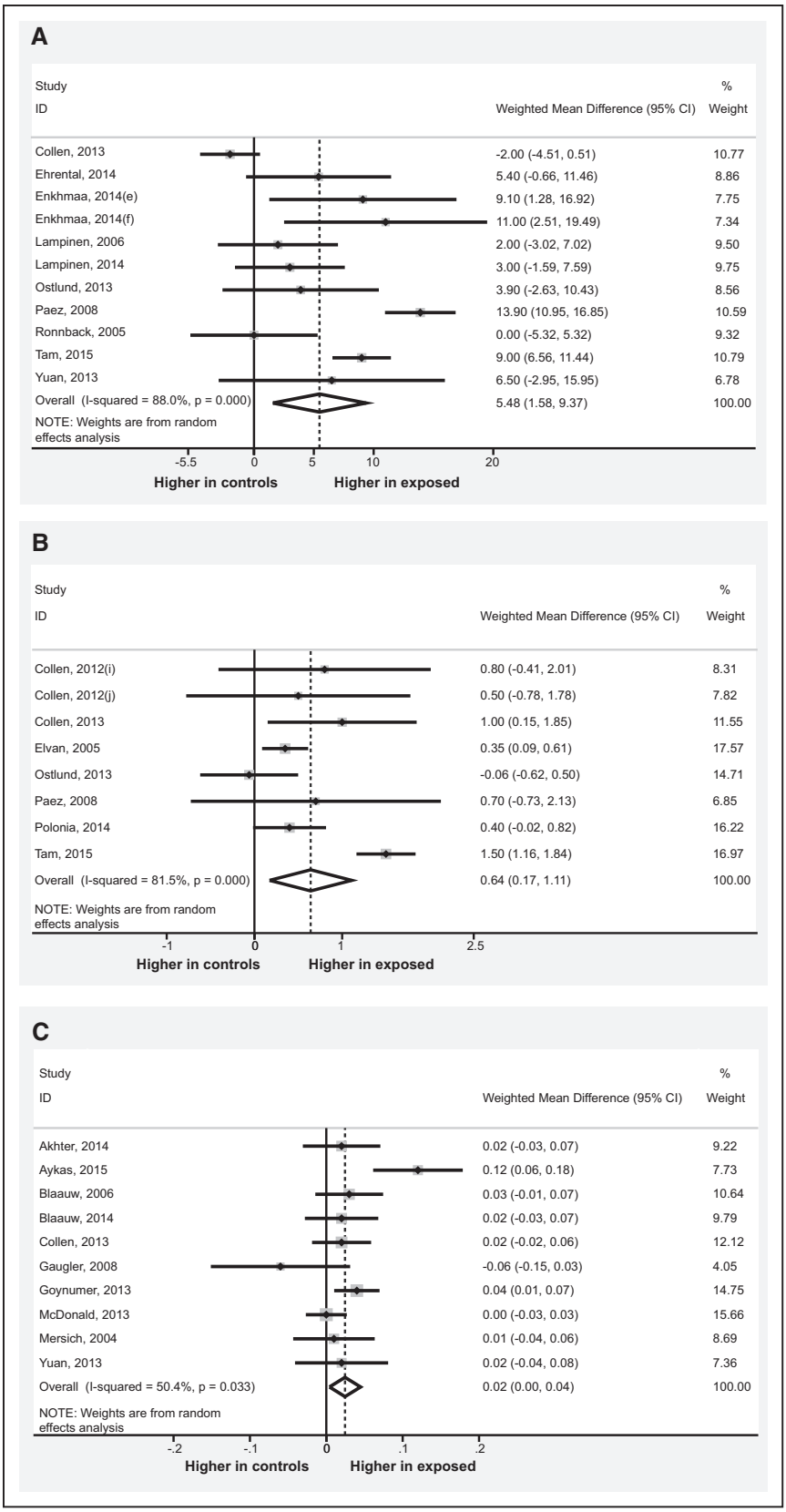

Figure 2. Results of weighted mean difference (WMD) between women with and without prior hypertensive disorders of pregnancy (HDP) of pooled imaging modalities. Augmentation index (AIx, %; **A**); carotid–femoral pulse wave velocity (cfPWV, m/s; **B**); and carotid intima-media thickness (cIMT, mm; **C**). *Higher values of AIx, cIMT, and cfPWV means more vascular impairment.

evidence of moderate heterogeneity (50.4%) measured by the I^2 method. Results of cIMT were influenced by the study by Aykas et al,[37] without a readily apparent explanation: the population and definition of preeclampsia were similar, and the study was at low risk of bias. Nevertheless, pooled analyses excluding this study reduced heterogeneity (I^2=0.0%) without affecting the overall WMD. Subgroup analyses based on mean age (<40 or ≥40 years) were similar as with arterial stiffness

modalities (WMD of 0.031 mm [0.002–0.061] versus 0.009 mm [−0.012 to 0.029]). Visual inspection of a funnel plot and the Egger's test revealed no evidence of publication bias for cIMT (Figure S2).

The magnitude of between-group differences in various measures of vascular dysfunction (cIMT, AIx, and cfPWV) diminished over time, as might be expected based on the development of traditional atherosclerotic risk factors in the control groups as they age (cIMT, WMD of 0.03 mm [0.01–0.05] before 48 months post delivery versus 0.02 mm [−0.02 to 0.07] after 48 months post delivery; AIx, WMD of 9.92% [5.92–13.92] before 60 months post delivery versus 2.69% [−1.79 to 7.17] after 60 months post delivery; cfPWV WMD of 0.63 m/s [−0.16 to 1.42] before 287 months post delivery versus 0.54 m/s [0.19–0.88] after 287 months post delivery). To test this hypothesis, we evaluated the absolute values in exposed and control women before and after the overall median follow up time (Table S3). We found that, indeed, cfPWV and cIMT increased over time (eg, with age) in the control groups. This same trend was not as apparent with AIx, but the duration of follow-up was shorter than the other marker of arterial stiffness (cfPWV).

General Measures of Endothelial Dysfunction

There was high heterogeneity between studies assessing endothelial dysfunction through flow-mediated dilatation, which was not reduced by our subgroup analyses. Thus, results of these studies were not pooled.

Serum Biomarkers of Vascular Dysfunction

Markers of Angiogenesis

Our included studies evaluated sFlt-1 (704 women [359 exposed and 345 controls]) and VEGF (528 women [273 cases and 255 controls]) to assess impaired angiogenesis in women with previous HDP. In pooled analyses, mean levels of sFlt-1 were modestly higher in women with previous HDP compared with women without (WMD of 6.12 pg/mL [1.91–10.33]; Figure 3), which represents a mean difference of 12% between women with and without prior HDP. However, pooled results revealed no significant difference between groups in mean levels of VEGF (WMD of 1.15 pg/mL [−26.12 to 28.42]; Figure 3). There was moderate heterogeneity in studies assessing sFlt-1 and VEGF (I^2=49.3% and 44.9%, respectively). We were unable to account for this heterogeneity after evaluating the impact of study quality, study design, or type of HDP. In subgroup analyses based on maternal age and delay since pregnancy, a difference was only observed for sFlt-1. Differences in mean levels of sFlt-1 post HDP were more pronounced when measured closer to the index pregnancy (WMD of 10.44 pm/mL [1.38–19.51] before 94 months post delivery versus 3.23 pg/mL [−0.18 to 6.23] after 94 months post delivery). We were unable to adequately assess publication bias for studies on these serum biomarkers because there were fewer than 10 pooled studies for each marker.

Markers of Inflammation

Studies measuring markers of vascular inflammation in women with and without previous preeclampsia included sICAM-1 (1010 women [541 cases and 469 controls]) and sVCAM-1 (1007 women [517 cases and 490 controls]). Pooled analyses of these biomarkers revealed similar levels in women with and without previous preeclampsia (WMD of 0.68 ng/mL [−16.12 to 17.47] and 3.94 ng/mL [−18.04 to 25.92], respectively; Figure 3). There was moderate heterogeneity in studies assessing sICAM-1 (I^2=59.0%), but not in studies measuring sVCAM-1 (I^2=0.0%). As with the angiogenesis biomarkers, we were unable to account for the heterogeneity in sICAM-1 studies after evaluating the impact of study quality, study design, or type of HDP. In subgroup analyses based on maternal age and delay since pregnancy, no difference was observed with these biomarkers. There were not enough studies included to adequately assess publications bias.

Other Modalities

Our search strategy revealed studies evaluating other markers and techniques to measure vascular dysfunction. However, pooled analyses were not conducted either because there were 3 or fewer available studies (ie, PIGF, EndoPAT, fibronectin, soluble endoglin, miRNA, large and small artery elasticity index, growth arrest–specific protein 6, ambulatory stiffness index, $CD34^+$-$VEGF\text{-}2^+$, CD133-$VEGF\text{-}2^+$, and vascular compliance) or because reported results were insufficient (laser doppler, forearm blood flow, and endothelin).

Quality Assessment

Quality assessment results are presented in Table and Table S1, with 53.5% (38/71) of the studies at medium risk of bias (4–6 stars) and 25.3% (18/71) at high risk (0–3 stars), which is mostly because of the inclusion of abstracts. Of the 37 pooled studies, 18 (48.6%) were at medium risk of bias.

Discussion

Our systematic review and meta-analysis represent the most recent and updated work summarizing the evidence for subclinical vascular dysfunction in women with prior HDP compared with women with prior normotensive pregnancies, which is a hypothesized mechanism explaining the increased risk of premature CVD in these women. We included case–control and cohort studies without language restriction and pooled studies stratified by modality to reduce potential heterogeneity. We explored reasons for heterogeneity in all pooled studies. We used a validated quality assessment tool (Newcastle-Ottawa Scale)[64] and multiple reviewers to avoid selection bias. We summarized evidence from studies evaluating various types of vascular dysfunction through imaging modalities (arterial stiffness: cfPWV, AIx; and subclinical atherosclerosis: cIMT), as well as soluble biomarkers (angiogenesis: sFlt-1, VEGF; and inflammation: sICAM-1, sVCAM-1), in women with prior HDP. All of the pooled studies on imaging modalities demonstrated more vascular dysfunction in women with prior HDP as compared with women with prior normotensive pregnancy. In contrast, sFlt-1 was the only biomarker consistently higher in women with prior preeclampsia relative to women with recent normotensive pregnancy. Results for other biomarkers were varied and could not be pooled. To date, literature on serum biomarker involvement in angiogenesis or inflammation after HDP has been inconsistent, with reports of lower[41] or higher[21] levels in women with preeclampsia

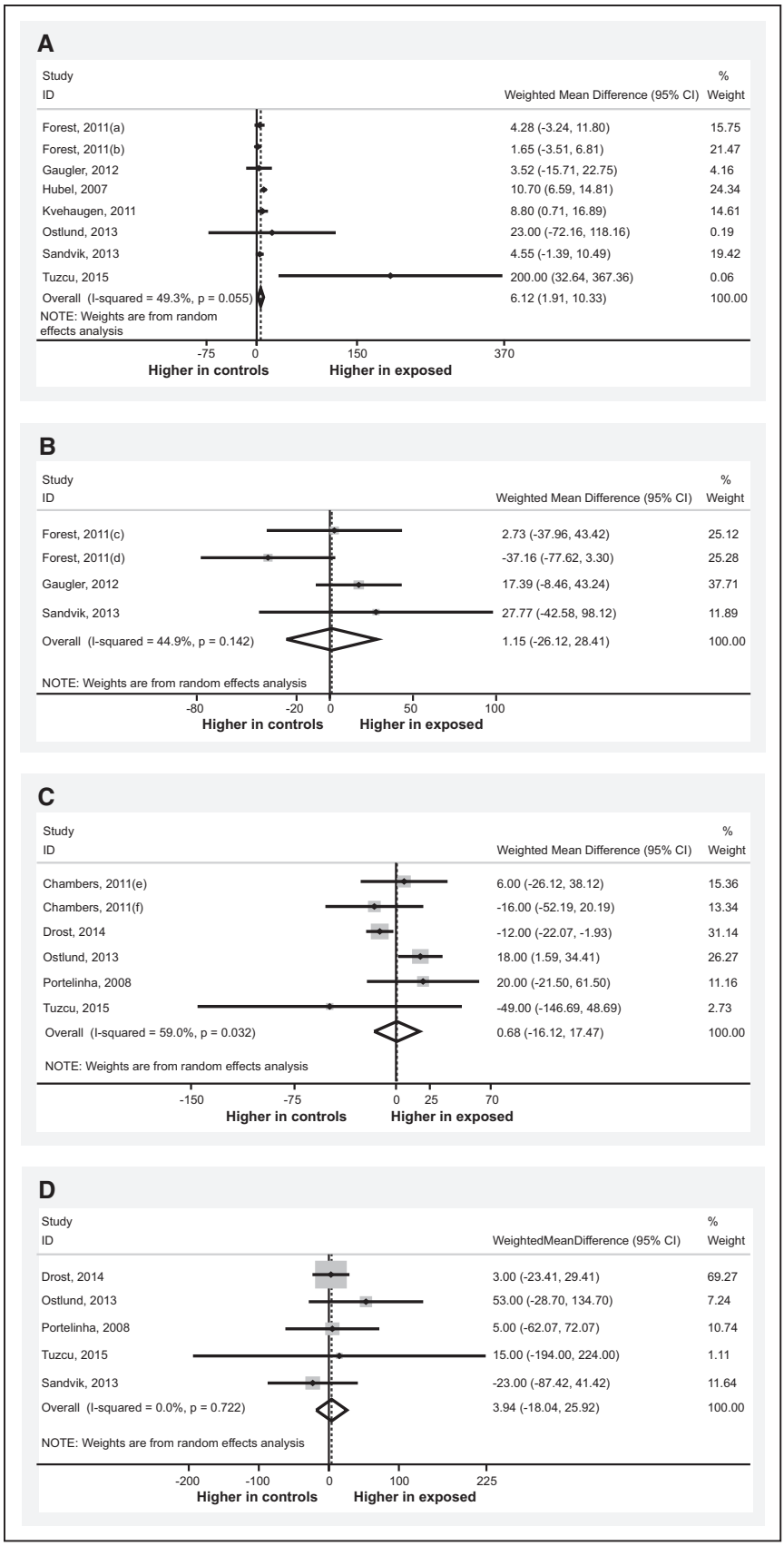

Figure 3. Results of weighted mean difference (WMD) between women with and without prior hypertensive disorders of pregnancy (HDP) of pooled serum biomarkers. Soluble fms-like tyrosine kinase 1 (sFlt-1, pg/mL; **A**); vascular endothelial growth factor (VEGF, pg/mL; **B**); soluble intercellular adhesion molecule-1 (sICAM-1, ng/mL; **C**); soluble vascular cellular adhesion molecule-1 (sVCAM-1, ng/mL; **D**). *Higher values of sFlt-1, sICAM-1, and sVCAM-1 mean more vascular impairment, whereas higher values of VEGF mean less vascular impairment.

compared with normotensive pregnancy after a 3-month follow-up period. Our hypothesis is that serum biomarkers, which are responsible for the initial endothelial insult during pregnancy and are more expressed in placental tissue than in the endothelium,[9] may not be detected at elevated levels after the index pregnancy. Furthermore, commercial kits might not

be sensitive enough to measure lower levels of these circulating or protein-bound biomarkers later in life. However, the endothelial damage they caused during the index pregnancy is sustained and captured by other more sensitive vascular imaging modalities years after delivery.

Thus, we think that our pooled results of vascular imaging techniques (cfPWV, cIMT, and AIx) provide more robust evidence of vascular dysfunction after HDP. cIMT is a well-established marker of subclinical atherosclerosis.[69] Specifically, a value of >0.6 mm has been associated with a high risk of coronary artery disease.[70] We found a pooled WMD of 0.025 mm (0.004–0.045), which is small but may, nevertheless, indicate the beginning of large-vessel atherosclerosis in women post HDP. Furthermore, cfPWV, the gold standard measure of arterial stiffness, has been directly associated with increased risk of vascular disease and events.[29] A recent meta-analysis demonstrated that an increase of cfPWV by 1 m/s corresponds to an adjusted risk increase of 14% in total vascular events after mean follow-up of 7.7 years.[71] By extension, the WMD of 0.64 m/s (0.17–1.11) as demonstrated in our meta-analysis indicates greater arterial stiffness and a heightened risk of vascular disease in young women with prior HDP.

We found that the difference of vascular dysfunction between women with and without prior HDP was more pronounced in younger women. This may indicate that damage is present in early years after complicated pregnancy, which is generally a period where traditional CVD risk factors are not experienced.[72] This difference appeared to be attenuated with time, possibly because with the development of traditional atherosclerotic risk factors, the disparity between groups becomes less evident. Other factors that change over time may also explain this observed phenomenon. For example, older women might become more aware of CVD and choose to modify their lifestyle or start medications for CVD risk factors, both of which may have influenced the results of vascular imaging techniques.

Regardless, these finding have important potential implications for management and surveillance of young women after HDP. In an effort to prevent CVD in these women, it is currently recommended that women with HDP be screened for CVD risk factors in the postpartum period.[1,2] Our study results suggest that systematic measurement of vascular dysfunction with imaging modalities might be considered as part of global CVD screening among this population. The utilization of one of these imaging modalities could help to distinguish women with previous HDP at high risk (with preclinical atherosclerosis) who could benefit from a more aggressive control of CVD risk factors and specific reduction strategies even if their absolute risk of CVD is low. Furthermore, use of techniques that seem to persist regardless of age or time since delivery might be the most appropriate choices to follow high-risk women over time. Thus, future prospective studies are required to determine whether the presence of vascular dysfunction on imaging is correlated with a greater rate of vascular events and should prompt specific vascular risk reduction therapies.

Our study contributes to the knowledge gained from the recent meta-analysis by Visser et al[22] on CVD biomarkers after HDP. In our study, we included more biomarkers directly linked to vascular function because our hypothesis was that global endothelial dysfunction results in accelerated vascular aging and persistent dysfunction years after delivery. Additional studies on fibronectin,[14] sICAM-1,[16] sVCAM-1,[16] endothelin,[73] VEGF,[48,62] and sFlt-1[48,62] are featured in our meta-analysis because our search strategy included a supplemental database (BIOSIS Previews), as well as references of the included articles. The complete search strategy of the meta-analysis by Visser et al was not available in the full text of the article or the supplemental material; thus, we were unable to directly compare the MeSH and non-MeSH terms used. Our meta-analysis, to our knowledge, is the first to pool results of vascular dysfunction measured by validated imaging modalities, which most closely reflected the vascular endothelium function and structure.

We restricted our review to studies that assessed vascular dysfunction at least 3 months postpartum to allow time to return to prepregnancy physiology. We wanted to answer the question whether events occurring during pregnancy resulted in accelerated vascular aging beyond the immediate postpartum period. The delay since pregnancy varied significantly between the studies (range 3–480 months), suggesting that damage persists well beyond the immediate postpartum period in most cases and is unlikely to completely regress spontaneously. Large-scale prospective studies would better address the trajectory of vascular dysfunction after HDP to eventually assess whether vascular dysfunction is present prepartum in these women.

Limitations

Our review has several limitations. First, there was substantial heterogeneity in some of our results that could not be explained by the age of women at the time of assessment, study design, or time elapsed since the index pregnancy. Thus, the pooled results for those modalities should be interpreted with caution. However, heterogeneity for other results has been explained by study design (AIx) or by the results of one specific study (cIMT[37] and cfPWV[63]). Second, the duration of follow-up since the index pregnancy was reported in various ways and precluded preplanned subgroup analyses to address whether a longer or shorter delay affected the heterogeneity of some of our pooled results. However, by estimating the median duration of follow-up in months for each modality, we were able to show that for studies assessing cIMT and AIx, the difference between both groups was more pronounced in the earlier period after the index pregnancy. This finding corroborates the results of our subgroup analyses based on age because it shows that women have more vascular dysfunction near the index pregnancy when they usually are younger and have a less important burden of traditional CVD risk factors. The definitions of HDP, preeclampsia, and gestational hypertension were mainly uniform; however, studies published after 2014 may have used slightly different definitions of preeclampsia owing to the release of new guidelines on HDP, which added systolic blood pressure >140 mm Hg to diastolic blood pressure of >90 mm Hg as a diagnosis criteria.[1,2] Because studies were conducted during and after pregnancy, it is unclear whether vascular dysfunction was already present prepartum, contributing to the development of HDP. However, studies evaluating vascular function in young women before

and throughout pregnancy until the development of CVD many years later do not exist. Longitudinal prospective cohort studies beginning in the prepregnancy phase would be laborious but informative on the trajectory between HDP and CVD. In addition, our review did not include cardiac echocardiography because our focus was on vascular impairment. A future systematic review on this topic would contribute to our understanding of overall cardiac function after HDP. Moreover, to completely evaluate the confounding effect of traditional atherosclerotic risk factors on the vascular dysfunction measurements, an individual patient analysis would be preferable, but could not be done with available data. Finally, owing to small numbers of studies for some modalities, mostly for biomarkers, we were unable to assess for publication bias. Thus, it remains possible that unpublished studies exist, which could have led us to overestimate the presence of vascular dysfunction post HDP with imaging modalities or underestimate it with biomarkers.

Despite these limitations, we think that our results complement previous findings and provide further evidence for vascular dysfunction after HDP. Risk stratification of women after HDP using vascular imaging modalities in addition to atherosclerotic factors might identify subgroup who would benefit from aggressive risk reduction approaches.

Perspectives

This systematic review and meta-analysis demonstrated the presence of vascular dysfunction in women with previous HDP when compared with women with previous normotensive pregnancies. Vascular imaging techniques seem to be useful tools in identifying women with vascular dysfunction in the postpartum period after HDP. In contrast, serum biomarkers measured after HDP appeared not as sensitive to accurately measure underlying dynamic endothelial damage. The use of vascular imaging modalities in the postpartum period might help further define an at-risk group to be targeted for more aggressive risk factor modification.

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Disclosures

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References

1. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P; SOGC Hypertension Guideline Committee. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. *J Obstet Gynaecol Can*. 2014;36:575–576.
2. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists. Task Force on Hypertension in Pregnancy. *Obstetrics and Gynecology*. 2013;122:1122–1131.
3. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974. doi: 10.1136/bmj.39335.385301.BE.
4. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol*. 2013;28:1–19. doi: 10.1007/s10654-013-9762-6.
5. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001;323:1213–1217.
6. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005;366:1797–1803. doi: 10.1016/S0140-6736(05)67726-4.
7. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation*. 2011;123:2856–2869. doi: 10.1161/CIRCULATIONAHA.109.853127.
8. Mutter WP, Karumanchi SA. Molecular mechanisms of preeclampsia. *Microvasc Res*. 2008;75:1–8. doi: 10.1016/j.mvr.2007.04.009.
9. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111:649–658. doi: 10.1172/JCI17189.
10. Maynard SE, Venkatesha S, Thadhani R, Karumanchi SA. Soluble Fms-like tyrosine kinase 1 and endothelial dysfunction in the pathogenesis of preeclampsia. *Pediatr Res*. 2005;57(5 Pt 2):1R–7R. doi: 10.1203/01.PDR.0000159567.85157.B7.
11. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, Dilba P, Schoedl M, Hund M, Verlohren S. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. *N Engl J Med*. 2016;374:13–22. doi: 10.1056/NEJMoa1414838.
12. Toporsian M, Gros R, Kabir MG, Vera S, Govindaraju K, Eidelman DH, Husain M, Letarte M. A role for endoglin in coupling eNOS activity and regulating vascular tone revealed in hereditary hemorrhagic telangiectasia. *Circ Res*. 2005;96:684–692. doi: 10.1161/01.RES.0000159936.38601.22.
13. Venkatesha S, Toporsian M, Lam C, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med*. 2006;12:642–649. doi: 10.1038/nm1429.
14. Evans CS, Gooch L, Flotta D, Lykins D, Powers RW, Landsittel D, Roberts JM, Shroff SG. Cardiovascular system during the postpartum state in women with a history of preeclampsia. *Hypertension*. 2011;58:57–62. doi: 10.1161/HYPERTENSIONAHA.111.173278.
15. Hubel CA, Wallukat G, Wolf M, Herse F, Rajakumar A, Roberts JM, Markovic N, Thadhani R, Luft FC, Dechend R. Agonistic angiotensin II type 1 receptor autoantibodies in postpartum women with a history of preeclampsia. *Hypertension*. 2007;49:612–617. doi: 10.1161/01.HYP.0000256565.20983.d4.
16. Lazzarin N, Desideri G, Ferri C, Valensise H, Gagliardi G, Tiralongo GM, Manfellotto D. Hypertension in pregnancy and endothelial activation: An emerging risk factor for cardiovascular disease. *Pregnancy Hypertens*. 2012;2:393–397. doi: 10.1016/j.preghy.2012.02.002.
17. Sandvik MK, Leirgul E, Nygård O, Ueland PM, Berg A, Svarstad E, Vikse BE. Preeclampsia in healthy women and endothelial dysfunction 10 years later. *Am J Obstet Gynecol*. 2013;209:569.e1–569.e10. doi: 10.1016/j.ajog.2013.07.024.
18. Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. *JAMA*. 2001;285:1607–1612.
19. Gaugler-Senden IP, Tamsma JT, van der Bent C, Kusters R, Steegers EA, de Groot CJ. Angiogenic factors in women ten years after severe very early onset preeclampsia. *PLoS One*. 2012;7:e43637. doi: 10.1371/journal.pone.0043637.
20. Hamad RR, Eriksson MJ, Silveira A, Hamsten A, Bremme K. Decreased flow-mediated dilation is present 1 year after a pre-eclamptic pregnancy. *J Hypertens*. 2007;25:2301–2307. doi: 10.1097/HJH.0b013e3282ef5fc0.
21. Östlund E, Al-Nashi M, Hamad RR, Larsson A, Eriksson M, Bremme K, Kahan T. Normalized endothelial function but sustained cardiovascular risk profile 11 years following a pregnancy complicated by preeclampsia. *Hypertens Res*. 2013;36:1081–1087. doi: 10.1038/hr.2013.81.
22. Visser S, Hermes W, Ket JC, Otten RH, van Pampus MG, Bloemenkamp KW, Franx A, Mol BW, de Groot CJ. Systematic review and metaanalysis on nonclassic cardiovascular biomarkers after hypertensive pregnancy disorders. *Am J Obstet Gynecol*. 2014;211:373.e1–373.e9. doi: 10.1016/j.ajog.2014.03.032.
23. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens*. 2014;4:97–104. doi: 10.1016/j.preghy.2014.02.001.

24. Agatisa PK, Ness RB, Roberts JM, Costantino JP, Kuller LH, McLaughlin MK. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. *Am J Physiol Heart Circ Physiol*. 2004;286:H1389–H1393. doi: 10.1152/ajpheart.00298.2003.
25. Blaauw J, van Pampus MG, Van Doormaal JJ, Fokkema MR, Fidler V, Smit AJ, Aarnoudse JG. Increased intima-media thickness after early-onset preeclampsia. *Obstet Gynecol*. 2006;107:1345–1351. doi: 10.1097/01.AOG.0000218097.22464.b4.
26. Pàez O, Alfie J, Gorosito M, Puleio P, de Maria M, Prieto N, Majul C. Parallel decrease in arterial distensibility and in endothelium-dependent dilatation in young women with a history of pre-eclampsia. *Clin Exp Hypertens*. 2009;31:544–552. doi: 10.3109/10641960902890176.
27. Paez O, De Maria M, Puleio P, Majul C, Zilberman J, Gorosito M. Assessment of left ventricular structure and flow-mediated dilation in women ten years after a preeclamptic pregnancy. *J Hypertens*. 2010;28:e213.
28. Bots ML, Dijk JM, Oren A, Grobbee DE. Carotid intima-media thickness, arterial stiffness and risk of cardiovascular disease: current evidence. *J Hypertens*. 2002;20:2317–2325.
29. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37:1236–1241.
30. Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. *Circulation*. 2007;115:2390–2397. doi: 10.1161/CIRCULATIONAHA.106.678276.
31. Nattel S. Targeting MicroRNA-208a to Suppress Adverse Postmyocardial Infarction Remodelling Related to RNA Activation of Endoglin Gene Expression. *Can J Cardiol*. 2015;31:591–592. doi: 10.1016/j.cjca.2015.03.013.
32. Rohde LE, Lee RT, Rivero J, Jamacochian M, Arroyo LH, Briggs W, Rifai N, Libby P, Creager MA, Ridker PM. Circulating cell adhesion molecules are correlated with ultrasound-based assessment of carotid atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1998;18:1765–1770.
33. Murphy MS, Casselman RC, Tayade C, Smith GN. Differential expression of plasma microRNA in preeclamptic patients at delivery and 1 year postpartum. *Am J Obstet Gynecol*. 2015;213:367.e1–e9.
34. Stepan H, Richter J, Kley K, Kralisch S, Jank A, Schaarschmidt W, Ebert T, Lössner U, Jessnitzer B, Kratzsch J, Blüher M, Stumvoll M, Fasshauer M. Serum levels of growth arrest specific protein 6 are increased in preeclampsia. *Regul Pept*. 2013;182:7–11. doi: 10.1016/j.regpep.2012.12.013.
35. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006–1012. doi: 10.1016/j.jclinepi.2009.06.005.
36. Akhter T, Larsson M, Wikström AK, Naessen T. Thicknesses of individual layers of artery wall indicate increased cardiovascular risk in severe preeclampsia. *Ultrasound Obstet Gynecol*. 2014;43:675–680. doi: 10.1002/uog.13289.
37. Aykas F, Solak Y, Erden A, Bulut K, Dogan S, Sarli B, Acmaz G, Afsar B, Siriopol D, Covic A, Sharma S, Johnson RJ, Kanbay M. Persistence of cardiovascular risk factors in women with previous preeclampsia: a long-term follow-up study. *J Investig Med*. 2015;63:641–645. doi: 10.1097/JIM.0000000000000189.
38. Blaauw J, Souwer ET, Coffeng SM, Smit AJ, van Doormaal JJ, Faas MM, van Pampus MG. Follow up of intima-media thickness after severe early-onset preeclampsia. *Acta Obstet Gynecol Scand*. 2014;93:1309–1316. doi: 10.1111/aogs.12499.
39. Collén AC, Manhem K, Sverrisdóttir YB. Sympathetic nerve activity in women 40 years after a hypertensive pregnancy. *J Hypertens*. 2012;30:1203–1210. doi: 10.1097/HJH.0b013e3283531ed2.
40. Collén AC, Hellgren M, Gustafsson H, Johansson MC, Manhem K. Cardiovascular and metabolic characteristics 40 years after hypertensive pregnancies: a long-term follow-up study of mothers. *J Hypertens*. 2013;31:758–765. doi: 10.1097/HJH.0b013e32835e2a9b.
41. Drost JT, Maas AH, Holewijn S, Joosten LA, van Eyck J, van der Schouw YT, de Graaf J. Novel cardiovascular biomarkers in women with a history of early preeclampsia. *Atherosclerosis*. 2014;237:117–122. doi: 10.1016/j.atherosclerosis.2014.09.009.
42. Ehrenthal DB, Goldstein ND, Wu P, Rogers S, Townsend RR, Edwards DG. Arterial stiffness and wave reflection 1 year after a pregnancy complicated by hypertension. *J Clin Hypertens (Greenwich)*. 2014;16:695–699. doi: 10.1111/jch.12398.
43. Elvan-Taşpinar A, Bots ML, Franx A, Bruinse HW, Engelbert RH. Stiffness of the arterial wall, joints and skin in women with a history of pre-eclampsia. *J Hypertens*. 2005;23:147–151.
44. Gaugler-Senden IP, Berends AL, de Groot CJ, Steegers EA. Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health. *Eur J Obstet Gynecol Reprod Biol*. 2008;140:171–177. doi: 10.1016/j.ejogrb.2008.03.004.
45. Goynumer G, Yucel N, Adali E, Tan T, Baskent E, Karadag C. Vascular risk in women with a history of severe preeclampsia. *J Clin Ultrasound*. 2013;41:145–150. doi: 10.1002/jcu.21962.
46. Hamad RR, Eriksson MJ, Berg E, Larsson A, Bremme K. Impaired endothelial function and elevated levels of pentraxin 3 in early-onset preeclampsia. *Acta Obstet Gynecol Scand*. 2012;91:50–56. doi: 10.1111/j.1600-0412.2011.01238.x.
47. Henriques AC, Carvalho FH, Feitosa HN, Macena RH, Mota RM, Alencar JC. Endothelial dysfunction after pregnancy-induced hypertension. *Int J Gynaecol Obstet*. 2014;124:230–234. doi: 10.1016/j.ijgo.2013.08.016.
48. Kvehaugen AS, Dechend R, Ramstad HB, Troisi R, Fugelseth D, Staff AC. Endothelial function and circulating biomarkers are disturbed in women and children after preeclampsia. *Hypertension*. 2011;58:63–69. doi: 10.1161/HYPERTENSIONAHA.111.172387.
49. Lampinen KH, Rönnback M, Kaaja RJ, Groop PH. Impaired vascular dilatation in women with a history of pre-eclampsia. *J Hypertens*. 2006;24:751–756. doi: 10.1097/01.hjh.0000217859.27864.19.
50. Lampinen KH, Rönnback M, Groop PH, Nicholls MG, Yandle TG, Kaaja RJ. Increased plasma norepinephrine levels in previously pre-eclamptic women. *J Hum Hypertens*. 2014;28:269–273. doi: 10.1038/jhh.2013.84.
51. McDonald SD, Ray J, Teo K, Jung H, Salehian O, Yusuf S, Lonn E. Measures of cardiovascular risk and subclinical atherosclerosis in a cohort of women with a remote history of preeclampsia. *Atherosclerosis*. 2013;229:234–239. doi: 10.1016/j.atherosclerosis.2013.04.020.
52. Mersich B, RigO J, LEnArd Z, Studinger P, Visontai Z, Kollai M. Carotid artery stiffening does not explain baroreflex impairment in pre-eclampsia. *Clin Sci (Lond)*. 2004;107:407–413. doi: 10.1042/CS20040137.
53. Paradisi G, Biaggi A, Savone R, Ianniello F, Tomei C, Caforio L, Caruso A. Cardiovascular risk factors in healthy women with previous gestational hypertension. *J Clin Endocrinol Metab*. 2006;91:1233–1238. doi: 10.1210/jc.2005-1337.
54. Polónia J, Olival C, Ribeiro S, Silva JA, Barbosa L. [Assessment of central hemodynamic properties of the arterial wall in women with previous preeclampsia]. *Rev Port Cardiol*. 2014;33:345–351. doi: 10.1016/j.repc.2013.11.006.
55. Portelinha A, Belo L, Tejera E, Rebelo I. Adhesion molecules (VCAM-1 and ICAM-1) and C-reactive protein in women with history of preeclampsia. *Acta Obstet Gynecol Scand*. 2008;87:969–971. doi: 10.1080/00016340802322265.
56. Rönnback M, Lampinen K, Groop PH, Kaaja R. Pulse wave reflection in currently and previously preeclamptic women. *Hypertens Pregnancy*. 2005;24:171–180. doi: 10.1081/PRG-200059871.
57. Saarelainen H, Kärkkäinen H, Valtonen P, Punnonen K, Laitinen T, Heiskanen N, Lyyra-Laitinen T, Vanninen E, Heinonen S. Flow-mediated vasodilation is not attenuated in hypertensive pregnancies despite biochemical signs of inflammation. *ISRN Obstet Gynecol*. 2012;2012:709464. doi: 10.5402/2012/709464.
58. Tuzcu ZB, Asicioglu E, Sunbul M, Ozben B, Arikan H, Koc M. Circulating endothelial cell number and markers of endothelial dysfunction in previously preeclamptic women. *Am J Obstet Gynecol*. 2015;213:533.e1–533.e7. doi: 10.1016/j.ajog.2015.06.043.
59. Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, Lai V, Cherney DZ, Hladunewich MA. Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: insights into future vascular risk. *Circulation*. 2010;122:1846–1853. doi: 10.1161/CIRCULATIONAHA.110.948455.
60. Yuan LJ, Xue D, Duan YY, Cao TS, Yang HG, Zhou N. Carotid arterial intima–media thickness and arterial stiffness in pre-eclampsia: analysis with a radiofrequency ultrasound technique. *Ultrasound Obstet Gynecol*. 2013;42:644–652. doi: 10.1002/uog.12409.
61. Enkhmaa D, Shufelt C, Rich-Edwards J, Merz NB. Vascular endothelial function in mongolian women with a history of preeclampsia or gestational hypertension. *Journal of Women's Health*. 2014;23:P70–25.
62. Forest JC, Girouard J, Bujold E, Guerette D, Giguere Y. Vascular endothelial growth factor (VEGF) levels and insulin resistance are modified in women with a past history of severe preeclampsia. *Clin Chem Lab Med*. 2011;49:S300.

63. Tam WH, Ma RC, Ozaki R, Lao TT, Liu EK, Singh SD, Chan MH, Chan JC. [189-POS]: Cardiometabolic risk among women with a prior history of pre-eclampsia. *Pregnancy Hypertension*. 2015;5:96.
64. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605. doi: 10.1007/s10654-010-9491-z.
65. Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *J Am Coll Cardiol*. 1994;24:1468–1474.
66. Sanchez PL, Morinigo JL, Pabon P, Martin F, Piedra I, Palacios IF, Martin-Luengo C. Prognostic relations between inflammatory markers and mortality in diabetic patients with non-ST elevation acute coronary syndrome. *Heart*. 2004;90:264–269.
67. Vita JA, Treasure CB, Nabel EG, McLenachan JM, Fish RD, Yeung AC, Vekshtein VI, Selwyn AP, Ganz P. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. *Circulation*. 1990;81:491–497.
68. Sterne J, Higghins J, Reeves B. ACROBAT-NRSI. obotdgf. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0. 2015.
69. Gepner AD, Keevil JG, Wyman RA, Korcarz CE, Aeschlimann SE, Busse KL, Stein JH. Use of carotid intima-media thickness and vascular age to modify cardiovascular risk prediction. *J Am Soc Echocardiogr*. 2006;19:1170–1174. doi: 10.1016/j.echo.2006.04.009.
70. Kłosiewicz-Wasek B, Ceremuzyński L, Poloński L, Lukaszewicz R, Wasilewski J. Association between carotid artery atherosclerosis and coronary artery disease in young females. Reference to sex hormone profile. *Kardiol Pol*. 2008;66:127–132; discussion 133.
71. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55:1318–1327. doi: 10.1016/j.jacc.2009.10.061.
72. Lee DS, Chiu M, Manuel DG, Tu K, Wang X, Austin PC, Mattern MY, Mitiku TF, Svenson LW, Putnam W, Flanagan WM, Tu JV; Canadian Cardiovascular Outcomes Research Team. Trends in risk factors for cardiovascular disease in Canada: temporal, socio-demographic and geographic factors. *CMAJ*. 2009;181:E55–E66. doi: 10.1503/cmaj.081629.
73. Barden A, Beilin LJ, Ritchie J, Walters BN, Michael CA. Plasma and urinary endothelin 1, prostacyclin metabolites and platelet consumption in pre-eclampsia and essential hypertensive pregnancy. *Blood Press*. 1994;3:38–46.

Novelty and Significance

What Is New?

- This study summarizes evidence for measurable subclinical vascular dysfunction, including vascular imaging techniques and soluble fms-like tyrosine kinase 1, months to years after pregnancies complicated by hypertensive disorders of pregnancy.
- Vascular imaging techniques seem to be useful tools to distinguish women at risk for vascular disease in the postpartum period after hypertensive disorders of pregnancy.

What Is Relevant?

- There is uncertainty regarding the mechanism of increased cardiovascular disease in women who have had hypertensive disorders of pregnancy.
- This study provides further evidence for vascular dysfunction after initial hypertensive injury. Further, the optimal method of screening women after hypertensive disorders of pregnancy is not known.
- Results of this study suggest that use of vascular imaging techniques might further define an at-risk population in the postpartum period to be targeted for assessment of more aggressive risk factor modification.

Summary

Vascular dysfunction is present in women after hypertensive disorders of pregnancy. It is currently recommended that women with a history of complicated pregnancy be screened for cardiovascular risk factors in the postpartum period. Risk stratification of women after these pregnancy complications using vascular imaging modalities in addition to measurement of usual atherosclerotic factors might identify subgroup who would benefit from aggressive risk reduction approaches.

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Markers of Vascular Dysfunction After Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-Analysis

Sophie Grand'Maison, Louise Pilote, Marisa Okano, Tara Landry and Natalie Dayan

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MARKERS OF VASCULAR DYSFUNCTION AFTER HYPERTENSIVE DISORDERS OF PREGNANCY: A SYSTEMATIC REVIEW AND META-ANALYSIS SUPPLEMENTAL MATERIAL

Short title : Pregnancy Complications And Vascular Dysfunction

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Supplemental text: Medline Search Strategy

1 exp Hypertension, Pregnancy-Induced/
2 Hypertension/
3 limit 2 to yr="1970 - 2004"
4 pregnancy/
5 3 and 4
6 Pregnancy Complications, Cardiovascular/
7 limit 6 to yr="1970 - 2004"
8 ((pregnant or pregnancy or pregnancies or maternal or gestation* or proteinuria or gestosis) adj3 (hypertens* or hyper-tens* or toxemia* or toxaemia*)).tw,kf.
9 (eclamp* or preclamp* or preeclamp*).tw,kf.
10 (EPH adj3 (complex* or gestosis or toxemia* or toxaemia*)).tw,kf.
11 (PIH or PPEP).tw,kf.
12 1 or 5 or 7 or 8 or 9 or 10 or 11
13 Endothelium/
14 Epithelium/
15 limit 14 to yr="1966 - 1972"
16 exp Endothelium, Vascular/
17 capillaries/
18 limit 17 to yr="1966 - 1987"
19 Blood Vessels/
20 limit 19 to yr="1966 - 1987"
21 exp Arteries/
22 Cardiovascular Diseases/
23 Vascular Diseases/
24 13 or 15 or 16 or 18 or 20 or 21 or 22 or 23
25 (ph or us or pp or pa).fs.
26 blood flow velocity/
27 Carotid Intima-Media Thickness/
28 Laser-Doppler Flowmetry/
29 Pulse Wave Analysis/
30 exp echocardiography/
31 exp Ultrasonography, Doppler/
32 vascular stiffness/
33 elasticity/
34 limit 33 to yr="1990 - 2011"
35 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 34
36 24 and 35
37 exp biological markers/
38 ((arter* or aort* or vascular or endotheli* or endo-theli* or flow or intra-media or media*) adj3 (stiffness or distensibility or dis-tensibility or elast* or function* or dysfunction* or dilat* or resist* or thickness* or thicken* or complian*)).tw,kf.
39 (echocardiograph* or echo-cardiograph*).tw,kf.
40 (pulse wave adj2 (analys* or velocit*)).tw,kf.
41 augment* inde*.tw,kf.
42 (FMD or IMT).tw,kf.

43 ((bio or biological or biochemical or circulat* or vascular or cardiovasc* or cardio-vasc* or disease*) adj3 marker*).tw,kf.
44 biomarker*.tw,kf.
45 or/36-44
46 12 and 45
47 Epidemiologic Studies/
48 exp case-control studies/
49 Control Groups/
50 exp cohort studies/
51 cross-sectional studies/
52 Postpartum Period/
53 ep.fs.
54 (case-control* or (control* adj1 group*) or longitudinal or long-term* or retrospective* or cohort* or prospective* or cross-sectional*).tw,kf.
55 (postpartum or post-partum or puerper*).tw,kf.
56 ((after or follow* or post) adj2 (deliver* or pregnan*)).tw,kf.
57 or/47-56
58 46 and 57
59 Animals/ not (Animals/ and Humans/)
60 (animals or animal or mice or mus or mouse or murine or woodmouse or rats or rat or murinae or muridae or cottonrat or cottonrats or hamster or hamsters or cricetinae or rodentia or rodent or rodents or pigs or pig or porcine or swine or swines or piglets or piglet or boar or boars or "sus scrofa" or ferrets or ferret or polecat or polecats or "mustela putorius" or "guinea pigs" or "guinea pig" or cavia or callithrix or marmoset or marmosets or cebuella or hapale or octodon or chinchilla or chinchillas or gerbillinae or gerbil or gerbils or jird or jirds or merione or meriones or rabbits or rabbit or hares or hare or diptera or flies or fly or dipteral or drosphila or drosophilidae or cats or cat or carus or felis or nematoda or nematode or nematoda or nematode or nematodes or sipunculida or dogs or dog or canine or canines or canis or sheep or sheeps or mouflon or mouflons or ovis or goats or goat or capra or capras or rupicapra or chamois or haplorhini or monkey or monkeys or macaque or macaques or primate or primates or anthropoidea or anthropoids or saguinus or tamarin or tamarins or leontopithecus or hominidae or ape or apes or paniscus or "pan paniscus" or bonobo or bonobos or troglodytes or "pan troglodytes" or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or chimpanzee or chimpanzees or prosimians or "bush baby" or prosimian or "bush babies" or galagos or galago or pongidae or gorilla or gorillas or pongo or pygmaeus or "pongo pygmaeus" or orangutans or pygmaeus or lemur or lemurs or lemuridae or horse or horses or pongo or equus or cow or calf or bull or chicken or chickens or gallus or quail or bird or birds or quails or poultry or poultries or fowl or fowls or reptile or reptilia or reptiles or snakes or snake or lizard or lizards or alligator or alligators or crocodile or crocodiles or turtle or turtles or amphibian or amphibians or amphibia or frog or frogs or bombina or salientia or toad or toads or "epidalea calamita" or salamander or salamanders or eel or eels or fish or fishes or pisces or catfish or catfishes or siluriformes or arius or heteropneustes or sheatfish or perch or perches or percidae or perca or trout or trouts or char or chars or salvelinus or "fathead minnow" or minnow or cyprinidae or carps or carp or zebrafish or zebrafishes or goldfish or goldfishes or guppy or guppies or chub or chubs or tinca or barbels or barbus or pimephales or promelas or "poecilia reticulata" or mullet

or mullets or seahorse or seahorses or "mugil curema" or "atlantic cod" or shark or sharks or catshark or anguilla or salmonid or salmonids or whitefish or whitefishes or salmon or salmons or sole or solea or "sea lamprey" or lamprey or lampreys or pumpkinseed or sunfish or sunfishes or tilapia or tilapias or turbot or turbots or flatfish or flatfishes or sciuridae or squirrel or squirrels or chipmunk or chipmunks or suslik or susliks or vole or voles or lemming or lemmings or muskrat or muskrats or lemmus or otter or otters or marten or martens or martes or weasel or badger or badgers or ermine or mink or minks or sable or sables or gulo or gulos or wolverine or wolverines or minks or mustela or llama or llamas or alpaca or alpacas or camelid or camelids or guanaco or guanacos or chiroptera or chiropteras or bat or bats or fox or foxes or iguana or iguanas or "xenopus laevis" or parakeet or parakeets or parrot or parrots or donkey or donkeys or mule or mules or zebra or zebras or shrew or shrews or bison or bisons or buffalo or buffaloes or deer or deers or bear or bears or panda or pandas or "wild hog" or "wild boar" or fitchew or fitch or beaver or beavers or jerboa or jerboas or capybara or capybaras).ti.

61 58 not (59 or 60)
62 limit 61 to (case reports or comment or editorial or letter)
63 61 not 62
64 limit 63 to "review articles"
65 limit 63 to systematic reviews
66 63 not (64 or 65)
67 remove duplicates from 66
68 limit 67 to yr="1990 -Current"

Supplemental References:

1. Agatisa PK, Ness RB, Roberts JM, Costantino JP, Kuller LH, McLaughlin MK. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. *Am J Physiol Heart Circ Physiol*. 2004;286:H1389-H1393.
2. Akhter T, Wikstrom AK, Larsson M, Naessen T. Individual common carotid artery wall layer dimensions, but not carotid intima-media thickness, indicate increased cardiovascular risk in women with preeclampsia: an investigation using noninvasive high-frequency ultrasound. *Circ Cardiovasc Imaging*. 2013;6:762-768.
3. Andersgaard AB, Acharya G, Mathiesen EB, Johnsen SH, Straume B, Oian P. Recurrence and long-term maternal health risks of hypertensive disorders of pregnancy: a population-based study. *Am J Obstet Gynecol*. 2012;206:143.e1-e8.
4. Barden A, Beilin LJ, Ritchie J, Walters BN, Michael CA. Plasma and urinary endothelin 1, prostacyclin metabolites and platelet consumption in pre-eclampsia and essential hypertensive pregnancy. *Blood Pressure*. 1994;3:38-46.
5. Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop pre-eclampsia? *J Hypertens*. 1999;17:1307-1315.
6. Barry DR, Utzschneider KM, Tong J, Gaba K, Leotta DF, Brunzell JD, Easterling TR. Intraabdominal fat, insulin sensitivity, and cardiovascular risk factors in postpartum women with a history of preeclampsia. *Am J Obstet Gynecol*. 2015;213:104 e1-e11.
7. Berends AL, de Groot CJ, Sijbrands EJ, Sie MP, Benneheij SH, Pal R, Heydanus R, Oostra BA, van Dujin CM, Steegers EA. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. *Hypertension*. 2008;51:1034-1041.
8. Blaauw J, Graaff R, van Pampus MG, van Doormaal JJ, Smit AJ, Rakhorst G, Aarnoudse JG. Abnormal endothelium-dependent microvascular reactivity in recently preeclamptic women. *Obstetrics & Gynecology*. 2005;105:626-632.
9. Bremme K and Blomback M. Hemostatic abnormalities may predict chronic hypertension after preeclampsia. Gynecologic and obstetric investigation. 1996;41:20-26.
10. Carty DM, Anderson LA, Duncan CN, Baird DP, Rooney LD, Dominiczak AF, Delles C. Peripheral arterial tone: assessment of microcirculatory function in pregnancy. *J Hypertens*. 2012;30:117-123.
11. Ciftci FC, Caliskan M, Ciftci O, Gullu H, Uckuyu A, Toprak E, Yanik F. Impaired coronary microvascular function and increased intima-media thickness in preeclampsia. *J Am Soc Hypertens*. 2014;8:820-826.
12. Deng L, Bremme K, Hansson LO and Blomback M. Plasma levels of von Willebrand factor and fibronectin as markers of persisting endothelial damage in preeclampsia. *Obstetrics & Gynecology*. 1994;84:941-945.
13. Estensen ME, Remme EW, Grindheim G, Smiseth OA, Segers P, Henriksen T, Aakhus S. Increased arterial stiffness in pre-eclamptic pregnancy at term and early and late postpartum: a combined echocardiographic and tonometric study. *Am J Hypertens*. 2013;26:549-556.
14. Estensen ME, Grindheim G, Remme EW, Godang K, Henriksen T, Aukrust P, Aakhus S, Gullestad L, Ueland T. Elevated inflammatory markers in preeclamptic pregnancies, but no relation to systemic arterial stiffness. *Pregnancy Hypertens*. 2015;5:325-329.
15. Evans CS, Gooch L, Flotta D, Lykins D, Powers RW, Landsittel D, Roberts JD, Shroff SG. Cardiovascular system during the postpartum state in women with a history of preeclampsia. *Hypertension*. 2011;58:57-62.

16. Karkkainen H, Saarelainen H, Laitinen T, Heiskanen N, Valtonen P, Laitinen T, Vanninen E, Heinonen S. Ambulatory arterial stiffness index and nocturnal blood pressure dipping in pregnancies complicated by hypertension. *Clin Physiol Funct Imaging*. 2014;34:39-46.
17. Laivuori H, Kaaja R, Rutanen EM, Viinikka L, Ylikorkala O. Evidence of high circulating testosterone in women with prior preeclampsia. *Journal of Clinical Endocrinology and Metabolism*. 1998;83:344-347.
18. Lampinen KH, Ronnback M, Groop PH, Kaaja RJ. Renal and vascular function in women with previous preeclampsia: a comparison of low- and high-degree proteinuria. *Kidney Int*. 2006;70:1818-1822.
19. Lazzarin N, Desideri G, Ferri C, Valensise H, Gagliardi G, Tiralongo GM, Manfellotto D. Hypertension in pregnancy and endothelial activation: An emerging risk factor for cardiovascular disease. *Pregnancy Hypertension*. 2012;2:393-397.
20. Lommerse T, Aardenburg R, Houben A, Peeters LL. Endothelium-dependent vasodilatation in formerly preeclamptic women correlates inversely with body mass index and varies independently of plasma volume. *Reproductive Sciences*. 2007;14:765-770.
21. Mangos GJ, Spaan JJ, Pirabhahar S, Brown MA. Markers of cardiovascular disease risk after hypertension in pregnancy. *J Hypertens*. 2012;30:351-358.
22. Murphy MSQ, Casselman RC, Smith GN. Postpartum alterations in circulating endothelial progenitor cells in women with a history of pre-eclampsia. *Pregnancy Hypertension*. 2013;3:178-185.
23. Murphy MS, Casselman RC, Tayade C, Smith GN. Differential expression of plasma microRNA in preeclamptic patients at delivery and 1 year postpartum. *Am J Obstet Gynecol*. 2015: dx.doi.org/10.1016/j.ajog.2015.05.013
24. Orabona R, Sciatti E, Vizzardi E, Bonadei I, Valcamonico A, Metra M, Frusca T. Elastic properties of ascending aorta in patients with a previous pregnancy complicated by early or late preeclampsia. *Ultrasound in Obstetrics & Gynecology*. 2015: doi: 10.1002/uog.14838
25. Ramsay JE, Stewart F, Greer IA, Sattar N. Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. *BJOG*. 2003;110:1029-1031.
26. Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. *Hypertension*. 2003;42:39-42.
27. Souwer ET, Blaauw J, Coffeng SM, Smit AJ, Van Doormaal JJ, Faas MM, Van Pampus MG. Decreased arterial elasticity in formerly early-onset preeclamptic women. *Acta Obstet Gynecol Scand*. 2011;90:797-801.
28. Spaanderman ME, Willekes C, Hoeks AP, Ekhart TH, Peeters LL. The effect of pregnancy on the compliance of large arteries and veins in healthy parous control subjects and women with a history of preeclampsia. *Am J Obstet Gynecol*. 2000;183:1278-1286.
29. Spaan JJ, Houben AJ, Musella A, Ekhart T, Spaanderman ME, Peeters LL. Insulin resistance relates to microvascular reactivity 23 years after preeclampsia. *Microvascular research*. 2010;80:417-421.
30. Stepan H, Richter J, Kley K, Kralisch S, Jank A, Schaarschmidt W, Ebert T, Lössner U, Jessnitzer B, Kratzsch J, Blüher M, Stumvoll M, Fasshauer M. Serum levels of growth arrest specific protein 6 are increased in preeclampsia. *Regul Pept*. 2013;182:7-11.
31. Tyldum EV, Backe B, Stoylen A, Slordahl SA. Maternal left ventricular and endothelial functions in preeclampsia. *Acta Obstet Gynecol Scand*. 2012;91:566-573.
32. van Rijn BB, Franx A, Steegers EA, de Groot CJ, Bertina RM, Pasterkamp G, Voorbij HA, Bruinse HW, Roest M. Maternal TLR4 and NOD2 gene variants, pro-inflammatory phenotype and susceptibility to early-onset preeclampsia and HELLP syndrome. *PLoS ONE*.

2008;3:e1865.
33. Christensen M, Kronborg CJ, Knudsen UB. [139-POS]: Preeclampsia and arterial stiffness - A 10-year follow up of previous preeclamptic women. *Pregnancy Hypertension*. 2015;5:72-73.
34. Lazdam M, De La Horra A, Diesch J, Francis J, Kenworthy Y, Shore A, Neubauer S, Kharbanda R, Alp N, Redman C, Kelly B, Leeson P. Unique features of long-term cardiovascular phenotype in young women with early-onset preeclampsia. *Pregnancy Hypertension*. 2012;2:259-260.
35. Murphy MSQ, Smith GN. Pre-eclampsia is associated with early postpartum endothelial dysfunction as measured by laser doppler flowmetry and iontophoresis. *Reproductive Sciences*. 2014;1:123A.

Table S1: Studies Characteristics of those Included in the Systematic Review

Studies	Exposure (n)	Controls (n)	Age exposed (years)	Age controls (years)	Follow-up exposed (months)	Follow-up controls (months)	Modalities used	Quality score
Agatisa, 2004[1] (CS)	Preeclampsia (16)	Normotensive pregnancy (14) / Never pregnant (20)	29±1 (SEM)	26±2 / 26±1 (SEM)	9.9±0.5 (SEM)	9.5±0.5 (SEM)	FBF	6
Akhter, 2013[2] (CS)	Preeclampsia (48)	Normotensive pregnancy (58)	30 (26-34)	30 (28-33)	12	12	cIMT	7
Anders-gaard, 2012[3] (CC)	Preeclampsia (250) / gestational hypertension (138)	Normotensive pregnancy (1778)	-	-	At least 228	At least 228	cIMT	4
Barden, 1994[4] (CS)	Preeclampsia (20)	Normotensive pregnancy (28)	27.4±1.5 (SEM)	26.8±1.2 (SEM)	6	6	Endothelin	6
Barden, 1999[5] (CS)	Preeclampsia (62)	Normotensive pregnancy (84)	27.5±0.8	27.6±0.6	6	6	Endothelin	6
Barry, 2015[6] (CS)	Severe (32) / Mild Preeclampsia (17)	Normotensive pregnancy (22)	32.5±5.9 / 35.0±7.5	34.6±4.3	17.5 (13-39) / 15 (11-35)	16.5 (13-25)	FMD	7
Berends, 2008[7] (CS)	Preeclampsia (48)	Normotensive pregnancy (100)	36.2±5.8	39.2±5.6	84±67	157±68	cIMT	5
Blaauw, 2005[8] (CS)	Severe preeclampsia	Normotensive pregnancy	29.9±4.2	32.3±2.7	7.0±2.8	6.0±2.2	Laser doppler	6

	(25)	(23)						
Bremme, 1996[9] (CS)	Severe (28) / Mild preeclampsia (14)	Normotensive pregnancy (26)	29 (21-38)/ 28 (23-34)	Range of 20-40	9 (6-15)	-	Fibronectin	1
Carty, 2012[10] (CC)	Preeclampsia (27)	Normotensive pregnancy (68)	29 (22-36)	35 (20-44)	6 to 9	6 to 9	PAT	6
Ciftci, 2014[11] (CS)	Mild preeclampsia (46)	Gestational hypertension (38)	33.28± 7.34	34.00± 9.48	63.54± 2.19	63.57± 2.77	cIMT	8
Deng, 1994[12] (CS)	Severe (21) / Mild preeclampsia (10)	Normotensive pregnancy (11)	-	-	5 to 15	5 to 15	Fibronectin	0
Estensen, 2013[13] (CC)	Preeclampsia (75)	Normotensive pregnancy (63)	32±6	32±5	6	6	Vascular compliance	5
Estensen, 2015[14] (CS)	Preeclampsia (34)	Normotensive pregnancy (61)	-	-	6	6	sVCAM-1	7
Evans, 2011[15] (CC)	Preeclampsia (18)	Normotensive pregnancy (50)	28.1±1.3	29.9±0.6	16.5±1.1	16.5±0.6	PWV, FBF, Fibronectin	6
Karkkainen, 2013[16] (CC)	HDP (15)	Normotensive pregnancy (27)	-	-	At least 3	At least 3	AASI	5
Laivuori, 1998[17] (CS)	Severe preeclampsia or eclampsia (21)	Normotensive pregnancy (20)	41.8±0.9	41.8±0.9	202±1	204±1	Endothelin	3
Lampinen, 2006[18] (CS)	Preeclampsia with	Normotensive pregnancy	37.7±7 / 38±5	36±4	60 to 72	60 to 72	FMD	6

	proteinuria <5g/d (8) / >5g/d (22)	(22)						
Lazzarin, 2012[19] (CS)	HDP (25)	Normotensive pregnancy (25)	33±5.6	32.9±4.5	3	3	sICAM-1, sVCAM-1	6
Lommerse, 2007[20] (CS)	Preeclampsia (32)	Normotensive pregnancy (10)	31 (27-34)	33 (31-36)	9 (7-19)	20 (10-40)	FBF	2
Mangos, 2012[21] (CC)	Preeclampsia (39) / Gestational Hypertension (27)	Normotensive pregnancy (35)	37±6 / 36±6	38±6	46 (30-60)/ 35 (26-72)	52 (34-84)	FBF	6
Murphy, 2013[22] (CS)	Preeclampsia (17)	Normotensive pregnancy (13)	31.5±5.4	31.8±3.7	6	6	CD34+ VEGFR-2+, CD133+ VEGFR-2+	6
Murphy, 2015[23] (CS)	Severe (6) / Mild preeclampsia (7)	Normotensive pregnancy (17)	-	-	12	12	miRNA	3
Orabona, 2015[24] (CS)	Early-onset (30) / Late-onset preeclampsia (30)	Normotensive pregnancy (30)	38±4 / 36±6	37±4	6 to 48	6 to 48	PWV	5
Ramsay, 2003[25] (CS)	Preeclampsia (10)	Normotensive pregnancy (10)	46 (40-49)	45 (43-48)	264 (192-276)	246 (216-288)	Laser doppler	1
Sattar,	Preeclampsia	Normotensive	43 (40-	44 (43-47)	At least 226	At lest 226	sICAM-1,	5

2003[26] **(CS)**	(40)	pregnancy (40)	47)				sVCAM-1	
Souwer, 2011[27] **(CS)**	Early onset preeclampsia (14)	Normotensive pregnancy (16)	33±5	34±4	55±7	52±2	Large and small artery elasticity index	3
Spaander-man, 2000[28] **(CS)**	Preeclampsia and thrombophilia (18) / and chronic hypertension (11) / and no other disease (13)	Normotensive pregnancy (10)	29±4 / 33±4 / 29±3	31±2	12 (6-46) / 11 (6-29) / 20 (6-46)	18 (6-48)	Vascular compliance	3
Spaan, 2010[29] **(CS)**	Preeclampsia (22)	Normotensive pregnancy (29)	49±3.9	49.8±3.9	276 (240-336)	276 (240-336)	Laser doppler	6
Stepan, 2013[30] **(CS)**	Preeclampsia (44)	Normotensive pregnancy (45)	31 (27-35)	30 (37-36)	312 (300-336)	324 (276-372)	Growth arrest specific protein 6	5
Tyldum, 2012[31] **(CS)**	Preeclampsia (19)	Normotensive pregnancy (19)	29±5	27±4	At least 3	At least 3	FMD	6
Van Rijn, 2008[32] **(CS)**	Early onset preeclampsia (144)	Normotensive pregnancy (70)	-	-	At least 6	At least 6	sICAM-1	5
			ABSTRACTS					
Christensen, 2015[33] **(CC)**	Preeclampsia (19)	Normotensive pregnancy (19)	-	-	120	120	PWV, AIx, cIMT	1
Lazdam,	Preeclampsia	Normotensive	40	40	72-156	72-156	cIMT,	2

2012[34] **(CS)**	(90)	pregnancy (50)					PWV, AIx	
Murphy, 2014[35] **(CS)**	Preeclampsia (10)	Normotensive pregnancy (40)	32.1±6.1	30.4±4.2	7±0.7	6±0.9	Laser doppler	0

* Results are presented as mean +/-SD or median (IQR) if not specified otherwise

**The sample size for each group represents the number of patients not lost to follow-up

AASI: ambulatory arterial stiffness index; AIx: augmentation index; CC: Cohort; CS: Case-control; cIMT: carotid intima-media thickness; CVD; Cardiovascular disease; FBF: Forearm blood flow; FMD: Flow mediated dilatation; GDM: Gestational diabetes; HDP: Hypertensive Disorders of Pregnancy; miRNA: microRNA; PAT: peripheral arterial tone; PIGF: placental growth factor; PWV: pulse wave velocity; sICAM-1: soluble intercellular adhesion molecule-1; SLE: Systemic lupus erythematous; sVCAM-1: soluble vascular cellular adhesion molecule-1; SEM: standard error of mean; VEGF: vascular endothelial growth factor.

Table S2: Summary of Assessed Modalities

Modalities	Number of studies	Type of Vascular Measurements
Carotid intima-media thickness (cIMT)	16 (10)	Subclinical atherosclerosis (large vessels)
Flow-mediated dilatation (FMD)	17 (13)	Endothelial dysfunction (small vessels)
Pulse wave velocity (PWV)	13 (7)	Arterial stiffness (small vessels)
Augmentation index (AIx)	11 (10)	Arterial stiffness (small vessels)
Laser doppler	4	Endothelial dysfunction (small vessels)
Forearm blood flow (FBF)	5	Endothelial dysfunction (small vessels)
Peripheral arterial tone (PAT)	2	Endothelial dysfunction (small vessels)
Vascular compliance	2	Vascular compliance (large vessels)
Ambulatory stiffness index	1	Arterial stiffness (small vessels)
Large and small artery elasticity index	1	Vascular compliance (large and small vessels)
BIOMARKERS		
Soluble intercellular adhesion molecule (sICAM-1)	11 (5)	Inflammation
Soluble vascular cellular adhesion molecule (sVCAM-1)	10 (5)	Inflammation
Soluble fms-like tyrosine kinase-1 (sFlt-1)	8 (7)	Angiogenesis
Vascular endothelial growth factor (VEGF)	6 (3)	Angiogenesis
Endothelin	4	Thrombosis
Placental growth factor (PIGF)	4	Angiogenesis
Fibronectin	3	Thrombosis
Endoglin	1	Angiogenesis
microRNA	1	Posttranscriptional regulation of gene expression
Growth arrest specific protein 6	1	Angiogenesis
CD33+VEGR1+, CD34+VEGR2+	1	Angiogenesis

Some studies assessed more than 1 modality. Modalities in bold font have been pooled. Numbers in parentheses correspond to the number of studies included in the meta-analysis

Table S3: Absolute Values and Weight Mean Differences Stratified on Median Duration of Follow-up

	Median follow-up (months)	N < median follow-up	Mean value for exposed	Mean value for controls	WMD < median follow-up	N > median follow-up	Mean value for exposed	Mean value for controls	WMD > median follow-up
cIMT (mm)	48	198	0.57	0.54	0·03 [0·01 to 0·05]	604	0.64	0.60	0·02 [-0·02 to 0·07]
AIx (%)	60	173	23.02	11.84	9·92 [5·92 to 13·92]	972	19.92	17.27	2·69 [-1·79 to 7·17]
cfPWV (m/s)	287	854	7.64	7.02	0·63 [-0·16 to 1·42]	233	7.75	7.08	0·54 [0·19 to 0·88]
sFlt-1	94	145	207.1	133.93	10·44 [1·38 to 19·51]	559	140.66	133.13	3·23 [-0·18 to 6·23]

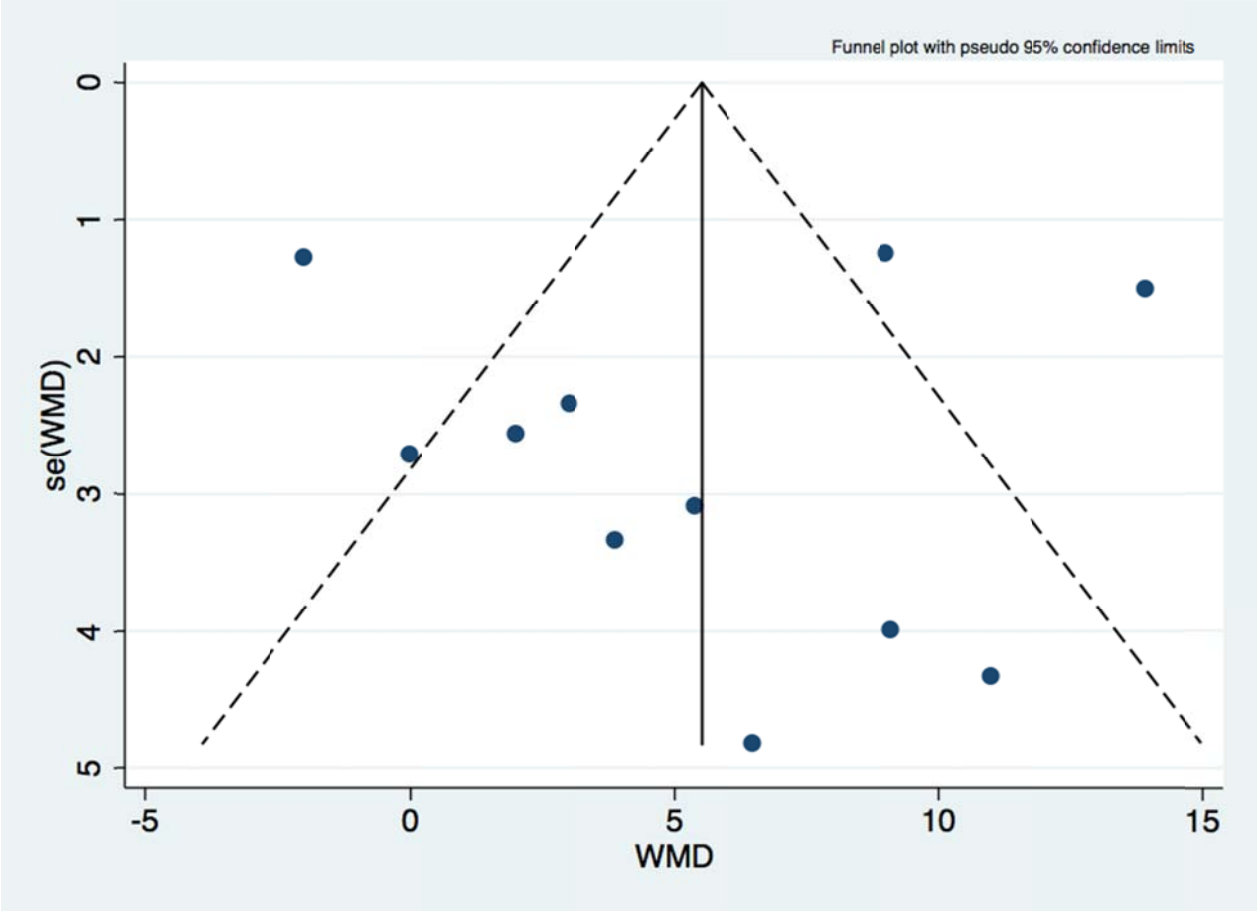

Figure S1: Funnel Plot of Studies Assessing Augmentation Index

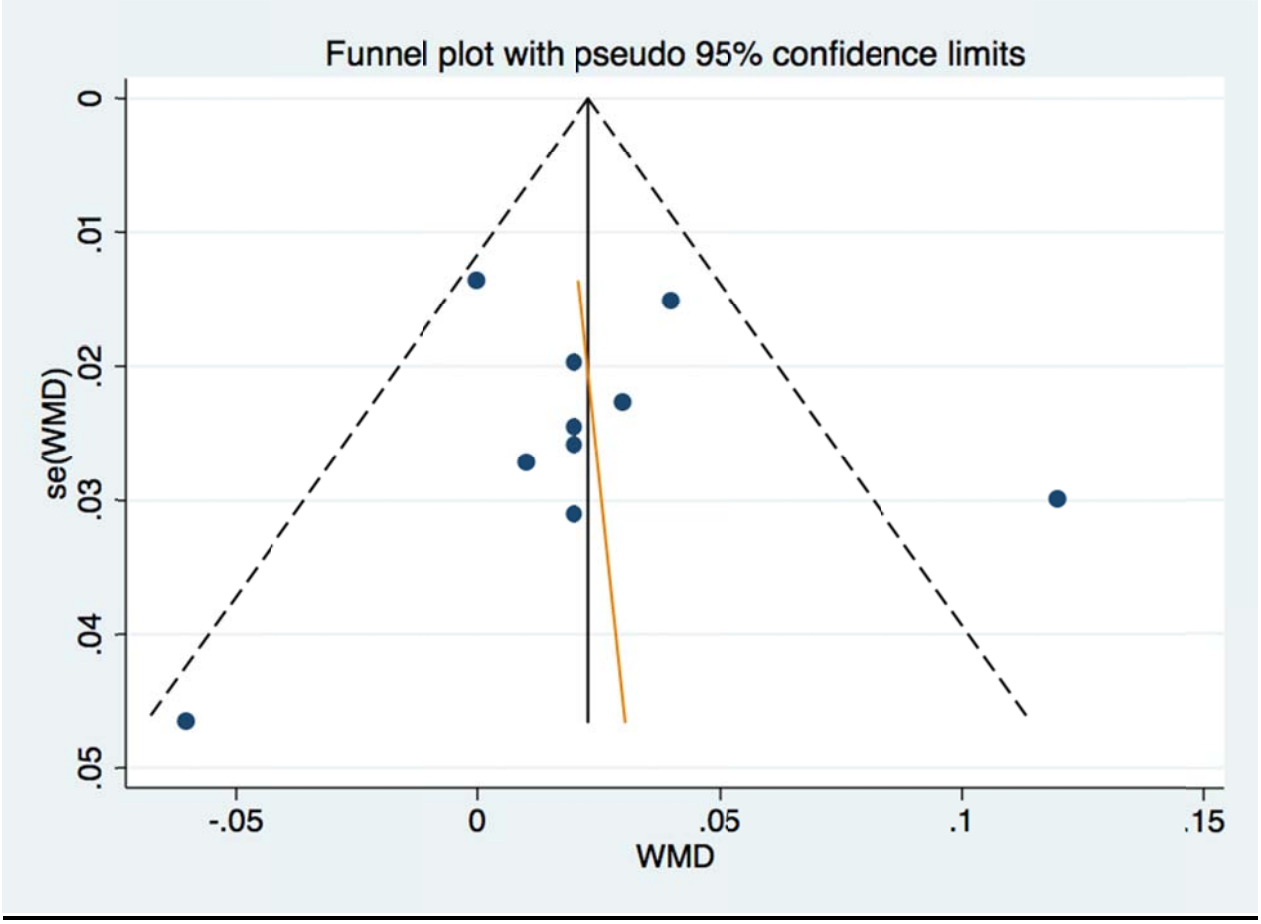

Figure S2: Funnel Plot of Studies Assessing Carotid Intima-Media Thickness