Evaluation of Cardiac Function in Women With a History of Preeclampsia: A Systematic Review and Meta-Analysis

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***Background*—**Women with a history of preeclampsia are at increased risk of cardiovascular morbidity and mortality. However, the underlying mechanisms of disease association, and the ideal method of monitoring this high-risk group, remains unclear. This review aims to determine whether women with a history of preeclampsia show clinical or subclinical cardiac changes when evaluated with an echocardiogram.

***Methods and Results*—**A systematic search of MEDLINE, EMBASE, and CINAHL databases was performed to identify studies that examined cardiac function in women with a history of preeclampsia, in comparison with those with normotensive pregnancies. In the 27 included studies, we found no significant differences between preeclampsia and nonpreeclampsia women with regard to left ventricular ejection fraction, isovolumetric relaxation time, or deceleration time. Women with a history of preeclampsia demonstrated a higher left ventricular mass index and relative wall thickness with a mean difference of 4.25 g/m^2 (95% CI, 2.08, 6.42) and 0.03 (95% CI, 0.01, 0.05), respectively. In comparison with the nonpreeclampsia population, they also demonstrated a lower E/A and a higher E/e′ ratio with a mean difference of −0.08 (95% CI, −0.15, −0.01) and 0.84 (95% CI, 0.41, 1.27), respectively.

***Conclusions*—**In comparison with women who had a normotensive pregnancy, women with a history of preeclampsia demonstrated a trend toward altered cardiac structure and function. Further studies with larger sample sizes and consistent echocardiogram reporting with the use of sensitive preclinical markers are required to assess the role of echocardiography in monitoring this high-risk population group. **(*J Am Heart Assoc*. 2019;8:e013545. DOI: 10.1161/JAHA.119.013545.)**

Key Words: diastolic dysfunction • left ventricular remodeling • preeclampsia/pregnancy • pregnancy and postpartum • systolic dysfunction

Preeclampsia is a heterogenous disorder of pregnancy that affects 3% to 5% of women and is characterized by a final common pathway of endothelial dysfunction resulting in hypertension and end-organ damage.[1,2] The underlying etiology of preeclampsia is unclear, and there is increasing evidence to support that there are different pathophysiological subtypes of this disease.[3,4] These subtypes include: (1) the characteristic placental mediated disorder that results in placental ischemia and the release of antiangiogenic factors into the maternal circulation and (2) a syndrome where preeclampsia is a symptom of underlying vascular dysfunction and a failure of the physiological stress test of pregnancy.[3] The latter in particular is now supported by epidemiological evidence that preeclampsia does not resolve with delivery of the placenta, but, rather, is associated with an increased risk of long-term cardiovascular sequelae.[5] For example, 20% of women with preeclampsia remain hypertensive at 6 months postpartum, and these women have a 3-fold increased risk of chronic hypertension.[6,7] A recent systematic review of 22 studies also illustrated that a history of preeclampsia is associated with a 2- to 4-fold increased risk of heart failure, coronary artery disease, stroke, and cardiovascular disease–related death.[5] The American Heart Association has now recognized both gestational hypertension and preeclampsia as risk factors for cardiovascular disease.[8,9] However, it is unclear whether increased cardiovascular morbidity is a result of shared risk factors between preeclampsia and cardiovascular

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Accompanying Tables S1 through S4 and Figures S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013545

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Clinical Perspective

What Is New?

- Women with a history of preeclampsia have an increased left ventricular mass index, increased relative wall thickness, lower E/A ratio, and higher E/e′ ratio in comparison with those with a history of normotensive pregnancies.
- Given that women with a history of preeclampsia demonstrate altered cardiac structure and function preceding the development of cardiovascular disease, echocardiography may play an important role in the ongoing evaluation of this high-risk population group.

What Are the Clinical Implications?

- Further research with larger sample sizes, consistent reporting, and assessment of sensitive preclinical markers, such as myocardial deformation, is required to clarify these findings.

disease or a direct result of the hypertensive disorder of pregnancy.[10] There is also insufficient evidence or consensus regarding the most appropriate method and timing of cardiovascular monitoring within this population group.

Transthoracic echocardiography is the gold standard for noninvasive evaluation of cardiac structure and function. However, there is little research examining the use of echocardiography to assess cardiovascular risk in women with a history of preeclampsia. The studies that have been conducted are limited by small sample sizes and have reported inconsistent results. Significant limitations to postpartum follow-up studies in preeclampsia include the low incidence of disease, heterogeneity of the population group, and significant loss to follow-up. With this in mind, a systematic review and meta-analysis may be of benefit in identifying potential structural and functional changes to the cardiovascular system in women with a history of preeclampsia.

With this review, we aimed to determine whether women with a history of preeclampsia show clinical or subclinical cardiac changes when evaluated by echocardiography. We hypothesize that women with a history of preeclampsia demonstrate altered cardiac function in comparison with those with a history of normotensive pregnancies. Identified associations between echocardiogram abnormalities and preeclampsia provide a logical framework for prospective risk evaluations and interventions.

Methods

Literature Search

This systematic review is registered with PROSPERO (The International Prospective Register of Systematic Reviews; ID, CRD42018115554) and conducted in accord with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (Table S1). There was no deviation from the original protocol submitted to PROSPERO, and the authors declare that all supporting data are available within the article and its online supplementary files.

We performed a systematic search of MEDLINE, EMBASE, and CINAHL databases from inception to December 2018. The search strategy, described in detail in Table S2, focused on identifying studies that examined cardiac function in women with a history of preeclampsia in comparison with those with normotensive pregnancies. The reference lists of the included articles and other published reviews were also examined to identify additional relevant studies for this review. Both librarians and investigators were involved in developing the search strategy.

Inclusion and Exclusion Criteria

Studies were included if they assessed cardiac structure and function in women with a history of preeclampsia at >6 weeks postpartum using echocardiography. Studies were excluded if: (1) cardiac assessments were performed within 6 weeks of delivery; (2) detailed assessment of cardiac structure and function by echocardiography was not performed; (3) the timing of echocardiography was not reported; (4) no matched normotensive pregnancies were evaluated as part of the study; (5) the study evaluated gestational hypertensives only; or (6) the manuscript was not available for review in English or only available in abstract form. The decision to exclude conference abstracts was based on the: (1) limitations in assessing study quality of conference abstracts alone and (2) difficulty in extracting the required depth of information from such abstracts. Studies that assessed cardiac function within 6 weeks of delivery were excluded because of the known hemodynamic changes that occur in the immediate postpartum period.

Study Selection

Two reviewers (M.R., L.W.) independently screened the titles and abstracts and excluded articles that were irrelevant to the topic. The reviewers then evaluated the full text of eligible articles for suitability based on the strict inclusion and exclusion criteria. A third reviewer (D.L.R.) was used to resolve discrepancies.

Data Extraction

The research question, study design, patient demographic data, and cardiac indices reported in each study were recorded. Cardiac indices of interest were identified according to the American Society of Echocardiography and European Association of Cardiovascular Imaging Guidelines.[11,12] For evaluation of diastolic function, the 2009 American Society of

Table 1. Cardiac Indices Assessed and Their Implications as Identified by the American Society of Echocardiography and European Association of Cardiovascular Imaging[12,13]

Cardiac Indices	Definition/Measurement Method	Normal Ranges	Implications
LVMI, g/m^2	Measured at the end of diastole using, linear method, 2D echocardiography, or 3D echocardiography and indexed to body surface area.	Linear measurement: 43 to 95 2D measurement: 44 to 88	Increased LVMI suggests hypertrophy. The type of hypertrophy (eccentric or concentric) is determined by the RWT.
RWT	Calculated using the formula - RWT=(2×posterior wall thickness)/(LV internal diameter at end diastole)	RWT>0.42 RWT≤0.42	RWT>0.42 suggests concentric remodeling. RWT≤0.42 suggests eccentric remodeling.
LVEF	Ejection fraction is calculated through measurement of end-diastolic velocity (EDV) and end-systolic velocity (ESV). EF = (EDV-ESV)/EDV	53% to 73%	Reduced ejection fraction is suggestive of systolic dysfunction.
E/A ratio	The mitral E/A ratio is made up of 2 components which reflect the pressure gradient between the left atria and ventricle during early and late diastole. E wave: Early diastole is characterized by rapid flow across the mitral valve resulting in a peak in flow called the E wave. A wave: The "a wave" reflects increased filling velocities in late diastole attributed to an atrial contraction.	0.8 to 2.0*	The E/A ratio in combination with DT and IVRT can be used to identify LV filling patterns that are suggestive of diastolic dysfunction. **Mild diastolic dysfunction** Characterized by decreased E/A ratio, prolonged DT, and prolonged IVRT. **Pseudo-normal phase** E/A ratio, DT and IVRT return to within normal range. Increased E/e′ ratio and a decrease in E/A ratio with Valsalva maneuver. **Severe dysfunction with restrictive filling pattern** Characterized by increased E/A ratio, shortened DT, and IVRT.
DT	Interval between the peak of the E wave to the beginning of diastasis. Diastasis refers to the period where flow across the mitral valve decreases as a result of rising ventricular pressures. Deceleration time is influenced by LV relaxation and stiffness.	140 to 200 ms*	
IVRT	Time between closure of the aortic valve at the end of systole to the opening of the mitral valve at the beginning of diastole.	70 to 100 ms*	
Mean E/e′ ratio	Ratio of flow across the mitral valve through early diastole (the E wave) and the mitral annular early diastolic velocity (e′ wave).	E/e′<8=normal E/e′>14=abnormal	An elevated E/e′ ratio is indicative of raised LV filling pressures.

DT indicates deceleration time; IVRT, isovolumetric relaxation time; LV, left ventricular; LVMI, left ventricular mass index; RWT, relative wall thickness.
*With increasing age E/A ratio decreases, and DT and IVRT increase. Therefore, age-specific ranges must be used.

Echocardiography/European Association of Cardiovascular Imaging guidelines were used, given that a significant proportion of the studies were performed before the release of the new 2016 guidelines. Indices assessed included left ventricular mass index (LVMI), relative wall thickness (RWT), left ventricular ejection fraction (LVEF), mean E/A ratio, mean E/e′ ratio, isovolumetric relaxation time, and deceleration time. These indices were chosen because they are key to assessing cardiac morphology, systolic function, and diastolic function and are further defined in Table 1.[12,13]

Quality Assessment

Quality assessment was performed by 2 independent blinded authors (M.R., D.L.R.) using the Newcastle–Ottawa Scale for cohort studies.[14] Risk of bias was analyzed within the 3 categories of case selection, comparability between cases and controls, and outcome. A study was considered good quality if it obtained ≥3 points in the selection domain, ≥1 point in the comparability domain, and ≥2 points in the outcome domain. A study was considered fair quality if it obtained 2 points in the selection domain, ≥1 point in the comparability domain, and ≥2 in the outcome domain. A study was assessed as poor quality if it obtained a score of 0 to 1 in the selection domain, a score of 0 in the comparability domain, or a score of 0 to 1 in the outcome domain.[15]

Statistical Analysis

Data regarding the variables of interest were extracted from each study for the preeclampsia and nonpreeclampsia groups. The primary outcome was the mean difference (MD) between the preeclampsia and nonpreeclampsia groups in relation to various cardiac indices. Most studies reported the data as a continuous variable using mean and SD. To ensure consistency and allow for aggregation of results, when the central tendency and the spread of the distribution were reported respectively as median and interquartile range (IQR), mean

and SD were estimated according to the method devised by Hozo et al.[16] In order to assess the potential influence of data transformation on analysis, a sensitivity analysis was performed with the exclusion of studies that used median/IQR. MD and a random-effects model was used to compare the difference in cardiac indices between preeclampsia and nonpreeclampsia groups. A random-effects model was used in preference to a common effect size, given that the studies included in the analysis were observational studies with different population groups.

Publication bias was assessed with funnel plot symmetry. The presence or absence of heterogeneity was determined using the chi-square test, and the magnitude of heterogeneity was assessed with the I^2 statistic. Heterogeneity was considered to be present when the chi-square test revealed a $P<0.05$ and the magnitude of heterogeneity considered to be low, moderate, and high with an I^2 statistic of <25%, 50%, and >75%, respectively.[17] When high heterogeneity ($I^2>75\%$) was identified, a subgroup analysis was performed to suggest potential sources of heterogeneity. The demographic and study characteristics assessed in the subgroup analysis included sample size, quality of study, age at assessment, time from index pregnancy, and body mass index (BMI). A subgroup analysis was also performed to assess the influence of the method of data reporting (mean/SD or median/IQR) on heterogeneity. The analysis was performed using Review Manager 5.3 (RevMan, version 5.3.5; The Cochrane collaboration, 2014).

Results

Study and Data Selection

The electronic search of MEDLINE, EMBASE, and CINAHL databases identified 3456 potential studies (Figure 1). After the removal of duplicates, 2839 articles were screened for eligibility. Subsequently, 2778 publications were excluded through screening of titles and abstracts. The full text of the remaining 61 articles was assessed for eligibility, and, of those, 34 studies were excluded because of: (1) single-arm study (n=8); (2) assessment within 6 weeks of delivery (n=5); (3) no or minimal echocardiogram data (n=8); (4) uncertain echocardiogram results (n=1); (5) duplicate reporting (n=6); (6) assessment of participants with gestational hypertension only (n=4); and (7) wrong study design (n=2). Of the 27 studies included, a further 2 studies were excluded from the meta-analysis because they did not provide data regarding the echocardiogram variables of interest. One study assessed cardiac function at 1 and 14 years postpartum, and another assessed those with a history of early and late preeclampsia as separate groups. Thus, within these studies, the subgroups were analyzed as separate entities.

Quality Assessment

Nine studies (33%) were considered high quality, 1 (4%) fair quality, and 17 (63%) poor quality (Table S3). Most studies performed well in the domain of cohort selection and were representative of the preeclampsia and normotensive population in the community. With regard to comparability of cohorts, 41% of the studies failed to control for important factors such as age, BMI, and smoking. Most studies did not blind echocardiogram assessment to disease exposure, and 63% failed to report or had inadequate follow-up.

Study Characteristics

Study characteristics and demographic data are illustrated in Table 2.[18–44] A total of 5058 women were reviewed beyond pregnancy, of which 1797 had a history of preeclampsia. The majority of studies defined preeclampsia using the traditional criteria of hypertension and proteinuria after 20 weeks of gestation. Few studies (n=3) utilized the updated definition of hypertension with evidence of end-organ dysfunction. With regard to superimposed preeclampsia, a large proportion of the studies excluded women with pre-existing hypertension, diabetes mellitus, and renal disease (n=15). Of the remaining, the addition of proteinuria or end-organ dysfunction was required to confirm the diagnosis of preeclampsia.

In the preeclampsia group, cardiac function was assessed within 12 months of delivery in 11 studies (41%), between 12 months and 5 years in 7 studies (26%), between 5 and 10 years in 1 study (4%), and >10 years from the index pregnancy in 7 studies (26%). In the nonpreeclampsia group, cardiac function was assessed within 12 months of delivery in 11 studies (41%), between 12 months and 5 years in 6 studies (22%), between 5 and 10 years in 2 studies (7%), >10 years in 6 studies (22%), and was not reported in 1 study (4%). Furthermore, 1 study assessed cardiac function at both 1 and 14 years postpartum in both preeclampsia and nonpreeclampsia groups. The mean age of assessment was <50 years in 23 of 27 (85%) and 24 of 27 studies (89%) in the preeclampsia and nonpreeclampsia groups, respectively. Two studies assessed women at a mean age >50 years in both the preeclampsia and nonpreeclampsia groups. Two studies did not report age of assessment in the preeclampsia group, and 1 study did not report age of assessment in the nonpreeclampsia group. Of the 24 studies (89%) that reported BMI, the mean BMI was normal in 42% of the studies in the preeclampsia group and 71% of the studies in the nonpreeclampsia group. Three studies reported a mean BMI≥30 kg/m^2 in the preeclampsia group, and 1 reported a mean BMI≥30 kg/m^2 in the nonpreeclampsia group. Mean arterial pressure was reported in 25 of 27 studies (93%). Most studies reported a normal mean arterial pressure of

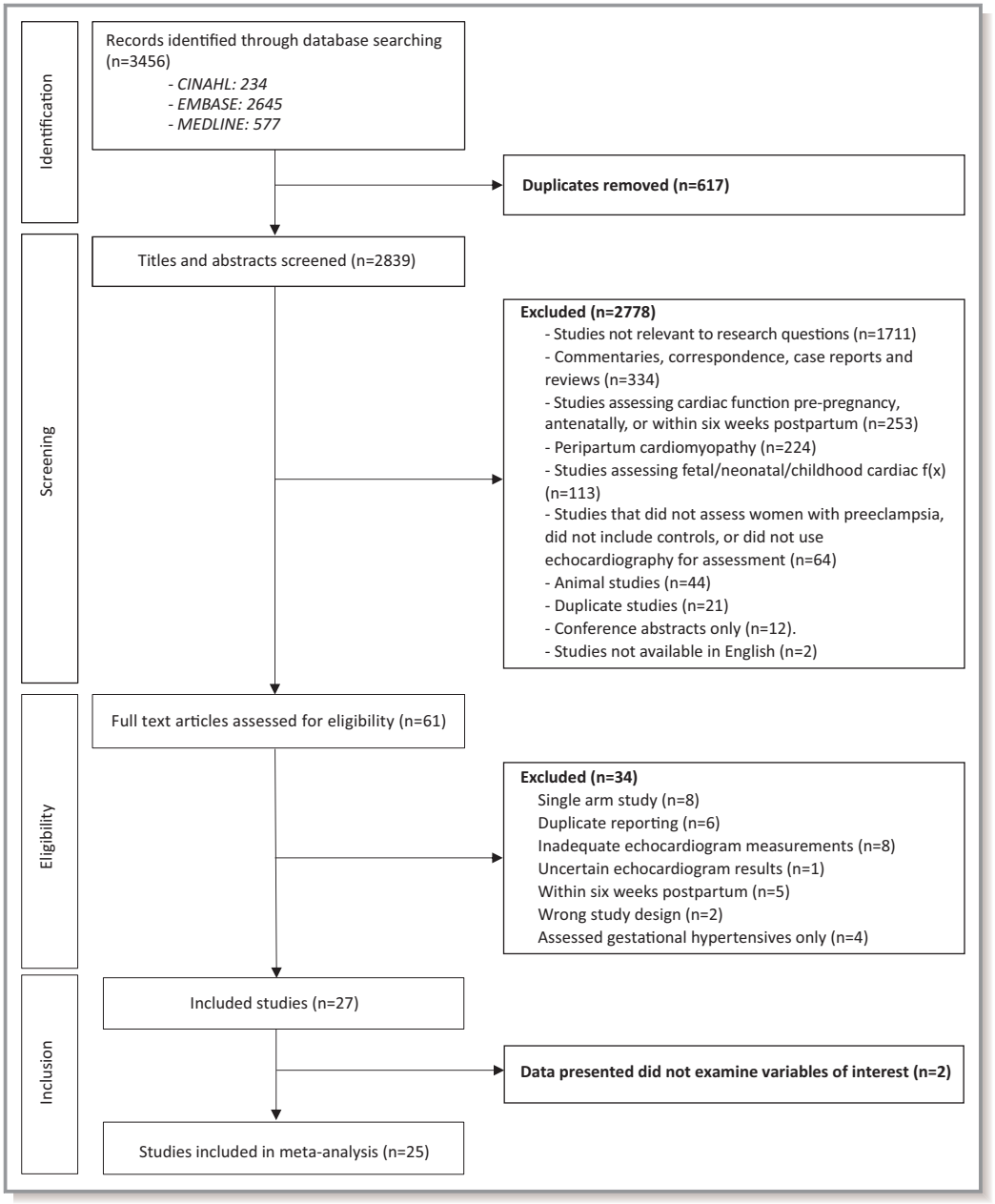

Figure 1. PRISMA flowchart of study selection process.

<100 mm Hg in both the preeclampsia and nonpreeclampsia groups. A mean mean arterial pressure of ≥100 mm Hg was reported in 4 studies in the preeclampsia group and 2 studies in the nonpreeclampsia group.

With regard to cardiovascular risk factors, most studies either excluded or did not report cardiovascular risk factors (Table S4). Of the studies that included women with cardiovascular risk factors, hypertension was more common in the preeclampsia group in comparison with the nonpreeclampsia group. The rate of current or past smoking was similar in both groups. Few studies included or reported the presence of diabetes mellitus, renal disease, or cardiovascular disease at the time of evaluation.

Furthermore, 3 studies within the preeclampsia group included participants with a history of gestational hypertension or preeclampsia. Two of the 3 studies reported that the majority of participants were identified to have preeclampsia, and 1 did not report this information. Analysis was performed with inclusion and exclusion of these studies and showed no difference in results (data not presented).

Left Ventricular Mass Index

LVMI was assessed in 19 of 27 studies (70%). LVMI was significantly higher in those with a history of preeclampsia in comparison with those with normotensive pregnancies (MD,

Table 2. Patient Characteristics in Included Studies

Study	Sample Size		Age (y), Mean/Median				Time From Index Pregnancy (mo)				Body Mass Index (kg/m), Mean/Median				Mean Arterial Pressure, Mean/Median			
	preeclampsia	nonpreeclampsia	preeclampsia	SD/IQR	nonpreeclampsia	SD/IQR	preeclampsia	SD/IQR	nonpreeclampsia	SD/IQR	preeclampsia	SD/IQR	nonpreeclampsia	SD/IQR	preeclampsia	SD/IQR	nonpreeclampsia	SD/IQR
Abdel Wahab (2018)[18]*	101	42	25	4	25	4	14	5	14	6	25	1	24	1	90	8	82	6
Al-Nashi (2016)[19]	15	16	39	4	41	3	134	7	134	7	26	6	23	3	93	9	92	10
Andrietti (2008)[20]†	55	9	NPV (31), LPV (31)	NPV (28–34), LPV (29–33)	32	30 to 32	>5	…	>5	…	NPV (22), LPV (24)	NPV (20–26), LPV (24–29)	23	20 to 25	NPV (86), LPV (94)	NPV (79–95), LPV (80–100)	85	80 to 90
Attalla (2015)[21]	72	50	29	11	30	13	7	1	7	1	25	3	25	3	95	11	91	10
Bokslag (2018)[22]†	131	56	44	6	47	5	157	26	170	28	26*	23 to 29	24*	21 to 27	97	12	87	11
Breetveld (2018)[23]†	67	37	36	33 to 39	40	37 to 43	64	53 to 77	100	79 to 119	24	21 to 29	23	21 to 25	85	81 to 91	83	75 to 89
Ciftci (2014)[24]	40	27	34	8	36	10	60	…	60	…	27	4	26	4	89	10	90	9
Clemmensen (2018)[25]	53	40	41	6	41	6	150	43	144	36	29	6	27	5	109	15	104	12
Collen (2013)[26]	50	55	63	6	63	5	480	…	480	…	28	5	26	5	106	13	104	14
Estensen (2013)[27]	75	63	33	5	32	5	6	…	6	…	…	…	…	…	100	14	86	7
Evans (2011)[28]*	18	50	28	1	30	1	17	1	17	1	26	2	26	1	86	3	80	1
Ghi (2014)[29]†	16	18	37	17 to 49	31	24 to 38	6 to 12	…	6 to 12	…	20	19 to 29	22	17 to 32	92	67 to 117	78	67 to 98
Ghossein-Doha (2013)—1 y[30]†	20	8	31	30 to 32	33	32 to 34	12	…	12	…	22	20 to 26	21	19 to 25	88	81 to 84	91	79 to 95
Ghossein-Doha (2013)—14 y[30]†	20	8	43	42 to 45	45	44 to 47	168	…	168	…	24	23 to 30	23	20 to 27	98	84 to 111	97	85 to 104
Ghossein-Doha (2017)[31]†	107	41	36	4	40	4	58	48 to 76	94	76 to 119	26	6	23	3	86	10	82	9
Melchiorre (2011)—Preterm preeclampsia[32]†	27	40	31	29 to 36	33	29 to 37	12	…	12	…	26	24 to 31	24	23 to 27	93	80 to 102	83	73 to 93
Melchiorre (2011)—Term preeclampsia[32]†	37	38	33	29 to 37	34	29 to 38	12	…	12	…	26	23 to 33	23	21 to 26	90	80 to 99	80	70 to 87
Orabona (2017)[33]	109	60	37	5	37	4	30	12	26	7	23	3	23	2	93	12	89	7
Rafik Hamad (2009)[34]‡	35	30	31	5	31	4	6 to 12	…	6 to 12	…	…	…	…	…	92	2	86	2
Scantlebury (2015)[35]	427	2210	54	13	56	13	312	168	…	…	34	8	31	7	95	17	91	16
Shahul (2018)[36]†	32	25	32	7	31	5	12	…	12	…	31	27–35	27	24 to 31	…	…	…	…
Simmons (2002)[37]	15	44	32	6	29	5	3	1	3	1	…	…	…	…	…	…	…	…

Continued

Table 2. Continued

Study	Sample Size		Age (y), Mean/Median			Time From Index Pregnancy (mo)			Body Mass Index (kg/m), Mean/Median			Mean Arterial Pressure, Mean/Median		
	preeclampsia	nonpreeclampsia	preeclampsia	SD/IQR	nonpreeclampsia	preeclampsia	SD/IQR	nonpreeclampsia	preeclampsia	SD/IQR	nonpreeclampsia	preeclampsia	SD/IQR	nonpreeclampsia	SD/IQR
Soma—Pillay (2018)[38]	96	45	29	7	27	12	…	12	30	8	28	97	14	87	9
Spaan (2009)[39]	22	29	49	4	50	276	20 to 28	276	25	4	26	100	12	88	10
Strobl (2011)[40]	31	17	43	4	44	180	23	179	24	2	24	93	7	95	4
Tyldum (2012)[41]	19	19	29	5	27	3	…	3	29	4	24	91	9	84	6
Valensise (2016)[42]	75	147	34	4	34	12 to 18	…	12 to 18	23	4	23	88	12	85	10
Yu (2018)[43]	25	30	…	…	29	3	…	3	22	2	20	92	8	86	8
Yuan (2014)[44]	7	7	…	…	…	16 to 20	…	16 to 20	…	…	…	97	12	87	9

IQR indicates interquartile range; LPV, low plasma volume; NPV, normal plasma volume.
*These studies were excluded from the meta-analysis because they did not provide echocardiogram data on the variables of interest.
†Studies reported median and interquartile range.
‡Studies reported mean and standard error.

4.25 g/m^2; 95% CI, 2.08–6.42; P=0.0001; Figure 2A).[19,20,22–26,29–37,39,42,44] While there was no evidence of funnel plot asymmetry suggesting publication bias (Figure S1), the heterogeneity between studies was significant (I^2=93%; P<0.00001). Subgroup analysis to determine the source of heterogeneity showed that study quality, sample size, age of assessment, BMI, and time from index pregnancy did not reduce heterogeneity. However, when studies that required transformation of median/IQR were removed from analysis, heterogeneity reduced from high to moderate (I^2=50%; P=0.02). LVMI remained significantly higher in women with a history of preeclampsia despite the removal of these studies from analysis (MD, 3.85 g/m^2; 95% CI, 1.79–5.91; P=0.0003).

Relative Wall Thickness

RWT was reported in 13 of 27 studies (48%). The pooled RWT was marginally higher in women with a history of preeclampsia in comparison with those with normotensive pregnancies (MD, 0.03; 95% CI, 0.01–0.05; P=0.02; Figure 2B).[19,23,26,29–35,37,42,44] When we performed a sensitivity analysis and removed studies that reported data as median/IQR, we identified no differences in RWT between groups (MD, 0.01; 95% CI, −0.01–0.04; P=0.26). There was no evidence of funnel plot asymmetry to suggest publication bias (Figure S1). Again, there was significant heterogeneity between studies (I^2=94%; P<0.00001). Subgroup analysis did not reduce heterogeneity when assessed for method of data reporting (mean/SD or median/IQR), sample size, study quality, age at assessment, time from index pregnancy, and BMI.

Left Ventricular Systolic Function

Most studies assessed systolic function using LVEF. LVEF was reported in 19 of 27 studies (70%), and all studies reported a normal mean ejection fraction in both the preeclampsia and nonpreeclampsia groups. There were no differences in LVEF between women with a history of preeclampsia and normotensive pregnancies (MD, −0.69%; 95% CI, −1.77–0.38; P=0.21; Figure 3).[19–25,27,29,31–33,35,36,38,39,41,43,44] There was no evidence of funnel plot asymmetry to suggest publication bias (Figure S1). However, there was heterogeneity between studies (I^2=86%; P<0.00001). A subgroup and sensitivity analysis showed that when studies that reported median/IQR were removed, women with a history of preeclampsia had a lower LVEF (MD, −1.05%; 95% CI, −1.92 to −0.18; P=0.02). Furthermore, heterogeneity between studies improved from high to moderate (I^2=51%; P=0.01). Subgroup analysis did not suggest any difference in heterogeneity when assessed for sample size, study quality, age at assessment, BMI, or time from index pregnancy.

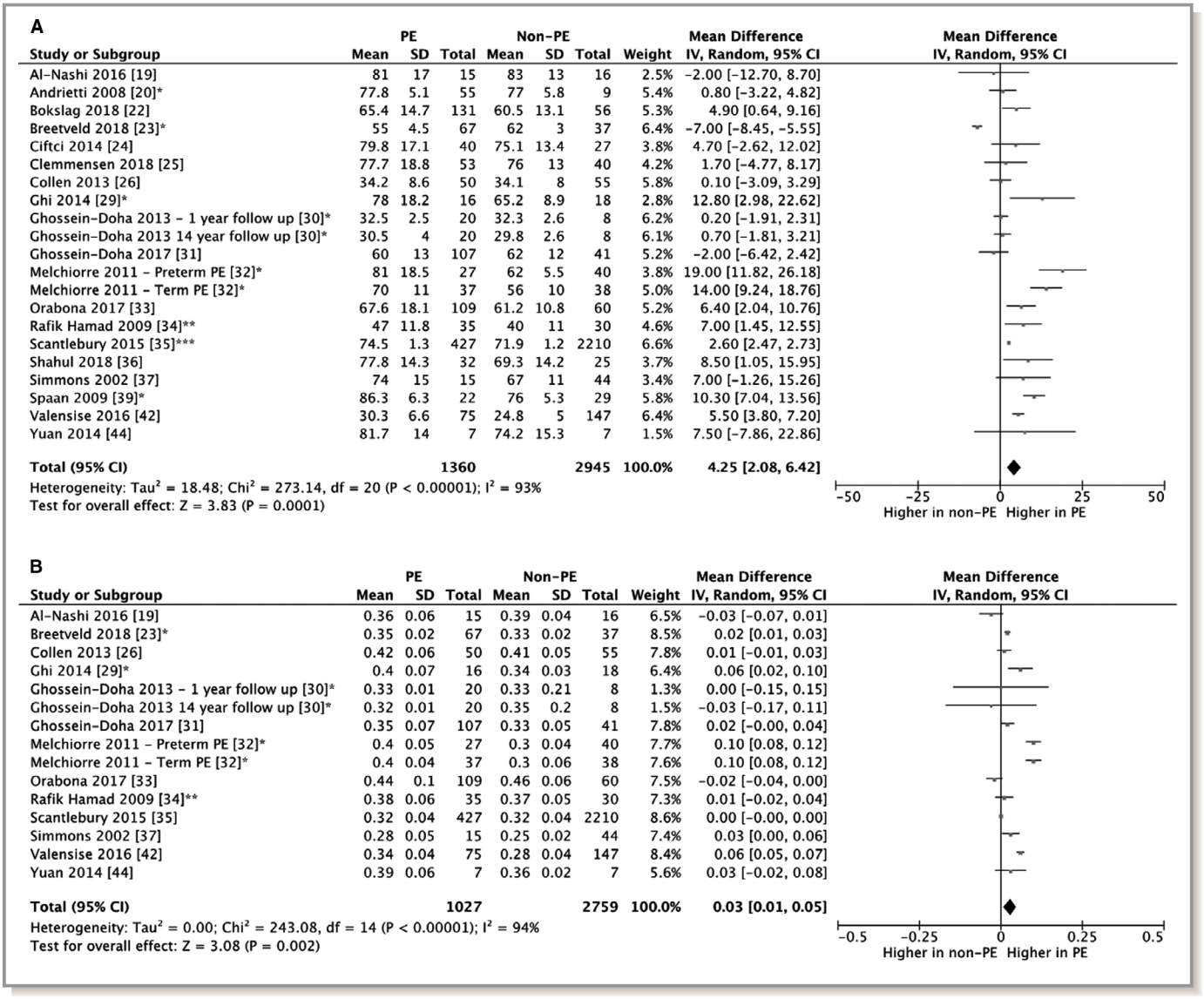

Figure 2. Forest plot illustrating the mean difference in indices of left ventricular hypertrophy. **A**, Mean difference in left ventricular mass index (g/m^2) between PE and non-PE groups. (**B**) Mean difference in relative wall thickness between PE and non-PE groups. *Data transformed from median and IQR to mean and SD. **Data originally reported as mean and standard error. ***Data originally reported as geometric mean and SD. IQR indicates interquartile range; PE, preeclampsia.

Left Ventricular Diastolic Function

The most common diastolic parameters reported were E/e′ ratio, E/A ratio, isovolumetric relaxation time, and DT. The E/e′ ratio was reported in 11 of 27 studies (41%) and was higher in women with a history of preeclampsia in comparison with normotensive pregnancies (MD, 0.84; 95% CI, 0.41–1.27; *P*=0.0001; Figure 4A).[19,22,24,25,29,32,33,36,38,41,42] The E/A ratio was reported in 18 of 27 studies (67%) and was lower in women with a history of preeclampsia in comparison with normotensive pregnancies (MD, −0.08; 95% CI, −0.15 to −0.01; *P*=0.03; Figure 4B).[19–23,25,29,30,32–36,38–41,44] In the 11 studies (41%) that assessed isovolumetric relaxation time, there was no difference in measurements between the preeclampsia and nonpreeclampsia groups (MD, 0.52 ms; 95% CI, −4.30–5.30; *P*=0.83; Figure S2). Similarly, in the 15 studies (56%) that assessed deceleration time, there was no difference in measurements between the preeclampsia and nonpreeclampsia groups (MD, 1.50 ms; 95% CI, −4.56–7.55; *P*=0.63; Figure S3). Funnel plot symmetry revealed no evidence of publication bias across all diastolic indices (Figure S1). However, there was significant heterogeneity between studies in all diastolic indices, with the I^2 statistic ranging from 85% to 95%. Across all diastolic indices, subgroup analysis of sample size, method of data reporting,

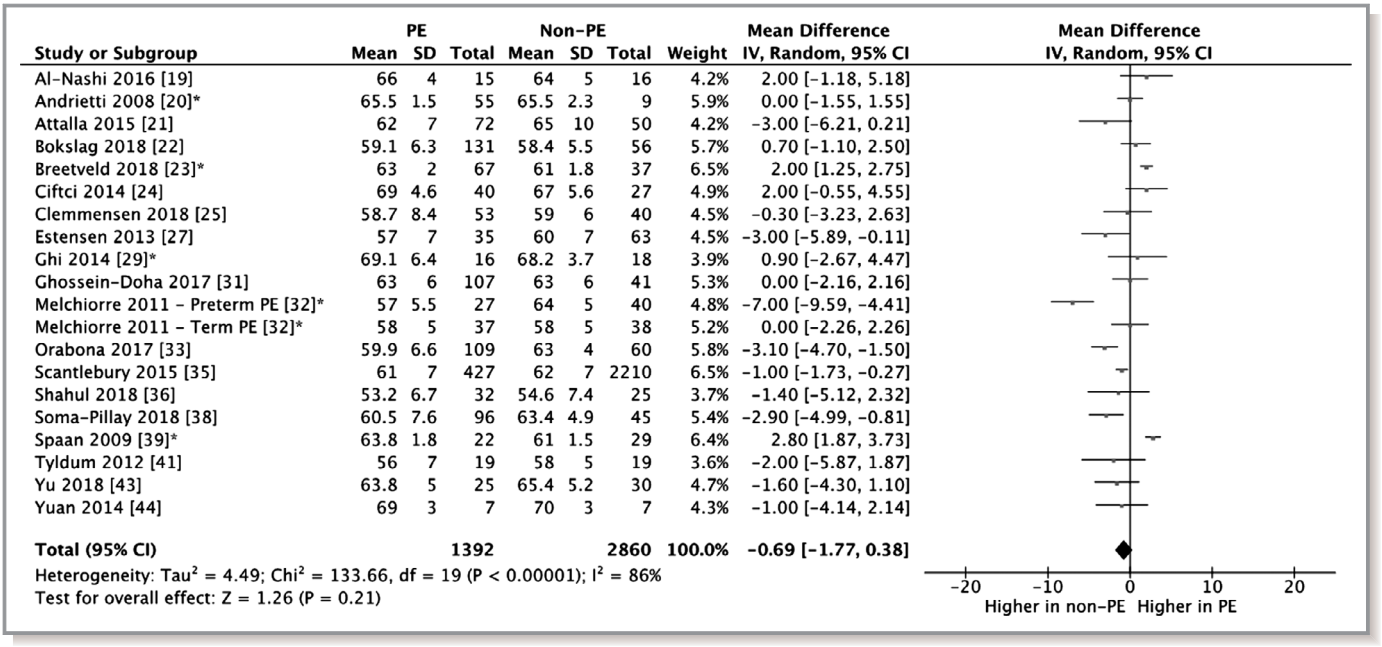

Figure 3. Forest plot illustrating the mean difference in left ventricular ejection fraction (%) in PE and non-PE groups. *Data transformed from median and IQR to mean and SD. IQR indicates interquartile range; PE, preeclampsia.

study quality, mean age at assessment, time from index pregnancy, and BMI did not reduce heterogeneity.

Discussion

Despite epidemiological evidence of increased cardiovascular risk in women with a history of preeclampsia, postpartum evaluation has not been widely implemented. This is in contrast to other pregnancy conditions, such as gestational diabetes mellitus, where because of an increased risk of type 2 diabetes mellitus, it is recommended that women undergo glycemic testing every 1 to 3 years after delivery.[45,46] Unfortunately, widespread implementation of cardiovascular screening in the setting of preeclampsia is limited by an inadequate understanding of the mechanisms that cause cardiovascular disease in this population group. To our knowledge, this systematic review is the first to describe changes to cardiac structure and function in women with a history of preeclampsia. When compared with normotensive pregnancies, women with a history of preeclampsia have a higher LVMI, higher RWT, lower E/A ratio, and higher E/e′ ratio. These findings are highly relevant, in that they add to the body of evidence that preeclampsia is associated with persisting cardiovascular dysfunction and support the need for closer monitoring of this high-risk population group. However, we have also identified a need to study more-robust markers of early cardiac disease, such as myocardial deformation and exercise capacity, to aid in clinical decision making in these high-risk women.[25,47,48]

During pregnancy, women with preeclampsia have evidence of cardiac remodeling and a difference in cardiac function in comparison with those with normotensive pregnancies.[49,50] Systematic reviews by De Haas et al and Castleman et al have shown that antenatally, preeclampsia is associated with increased left ventricular mass and RWT and mild diastolic dysfunction (as demonstrated by a decrease in the E/A ratio and an increase in the E/e′ ratio).[49,50] Long-term epidemiological studies have shown that women with a history of preeclampsia have a 2- to 4-fold increased risk of heart failure and cardiovascular morbidity.[5] Thus, it is assumed that the structural and functional changes observed antenatally persist beyond pregnancy and contribute to the long-term cardiovascular sequelae in this population group. However, while our review supports this hypothesis, the findings suggest that the echocardiogram changes following delivery are perhaps too subtle to explain the longer-term morbidities. This may be attributable to several reasons.

First, a large proportion of the studies excluded women with hypertension, diabetes mellitus, renal disease, and cardiovascular disease. Women with such pre-existing comorbidities are at a greater risk of developing preeclampsia.[51,52] Furthermore, women with a history of preeclampsia are more likely to develop hypertension, metabolic syndrome, renal disease, and diabetes mellitus in the long term.[6,53–56] It is thus plausible that the cardiovascular morbidity associated with preeclampsia is a result of an increased incidence of these cardiovascular risk factors within this population group rather than the preeclampsia per se. Exclusion of these risk

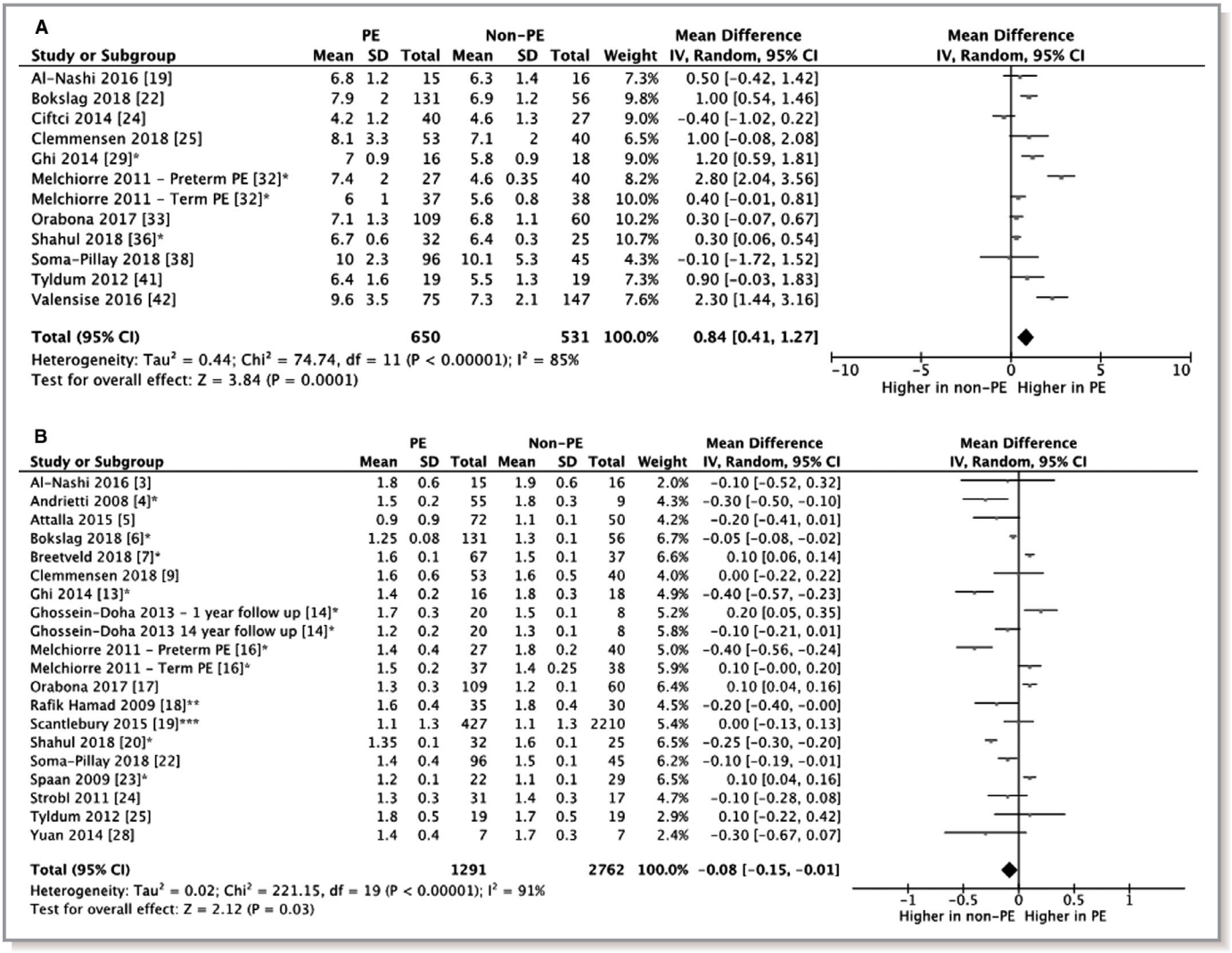

Figure 4. Forest plot illustrating the mean difference in indices of diastolic function. **A**, Mean difference in E/e′ ratio between PE and non-PE groups; **B**, Mean difference in E/A ratio between PE and non-PE groups. *Data transformed from median and IQR to mean and SD. **Data originally reported as mean and standard error. ***Data originally reported as geometric mean and SD. IQR indicates interquartile range; PE, preeclampsia.

factors may have contributed to selection bias and may have influenced the results of the constituent trials included in this review. It is also plausible that the cardiovascular sequelae observed in those with a history of preeclampsia are a result of shared risk factors between preeclampsia and cardiovascular disease.[57] Therefore, when women with cardiovascular risk factors are excluded, the effect of preeclampsia on cardiac structure, function, and morbidity may be clinically insignificant. Further studies which compare pre-eclamptic women with and without cardiovascular risk factors are required in order to answer this clinical question.

Second, the available studies included in this review are of small sample size and significant heterogeneity. It is likely that the heterogeneity stems from the inherent limitations of cohort studies which cannot control for all demographic factors within the population assessed. While a random-effects model and subgroup analyses were performed in order to account for such differences, this did not significantly improve heterogeneity measures. Potential methods of addressing this in future research would include larger sample sizes and consistent reporting of patient demographics and echocardiogram measures. Limitations to performing large studies in women with a history of preeclampsia include the low incidence of disease and significant loss to follow-up. Thus, international collaboration is essential. Standardization and consistent reporting of echocardiogram measurements is also vital. The American Society of Echocardiography and the European Association of Cardiovascular Imaging provide clear guidelines on methods of measurement of cardiovascular indices to assess chamber size, systolic function, and diastolic

function.[11,12] These guidelines now include the use of 4 markers to catagorize diastolic dysfunction—average E/e′, septal e′ velocity, lateral e′ velocity, tricuspid regurgitation velocity, and left atrial volume index.[58] This increases the sensitivity for prediction of left ventricular filling pressures over using markers in isolation.[58] The studies included in this review did not evaluate the newly included tricuspid regurgitation maximum velocity, and very few assessed volumetric measures of left atrial size. Unfortunately, this limits our ability to apply the new guidelines in this cohort. Adopting these guidelines may reduce heterogeneity and allow for easier comparison between different cohort studies examining cardiac function in women with a history of preeclampsia.

It is also important to note that many of the included studies performed poorly with regard to quality assessment. Primary issues included a lack of blinding for outcome, controlling for confounding factors, and loss to follow-up. These quality issues make it difficult to draw meaningful conclusions. As a result, it is essential that while also addressing heterogeneity, future research efforts focus on robust methodology with adequate blinding of echocardiogram assessors and reporting of loss to follow-up. Furthermore, it is necessary that confounding factors, such as age, BMI, smoking, and other cardiovascular risk factors, are reported and considered in analysis. Although out of the scope of this review, there is also a need for an individual patient data meta-analysis. This may help address issues with heterogeneity and confounding. Furthermore, an individual patient data would enable a detailed review of the echocardiogram markers and allow for both categorical and continuous analysis of cardiac indices. This would shed light on whether the differences between preeclampsia and nonpreeclampsia groups are within the variation of normal or a true reflection of a higher incidence of abnormal results.

Last, it is also plausible that grading of diastolic dysfunction may not be the ideal method of risk stratification in women with a history of preeclampsia. Invasive studies have shown only modest correlations of E/e′ ratio and invasive filling pressures.[59] The measurement of global myocardial deformation using speckle tracking imaging is a novel marker that can be performed during routine echocardiographic assessment. It has been demonstrated that global longitudinal strain is a robust marker of cardiac outcomes and incremental to other echocardiogram parameters for prediction of outcomes in stage B heart failure.[47] A small number of studies have used global longitudinal strain in preeclampsia cohorts and observed reduced strain in preeclampsia as compared with normotensive pregnancies.[25,48] Furthermore, the differences between women with and without a history of preeclampsia in this systematic review are analogous to hypertensive heart disease and are relatively subtle. Global longitudinal strain has proved to be an important prognostic marker of cardiovascular events in the general population and in hypertensive cohorts,[60,61] suggesting that this may be a logical investigative tool for future research. An overlooked, but essential, parameter is a clear definition of exercise capacity. When combined with echocardiography, cardiopulmonary exercise testing can aid in the identification of stage B heart failure,[62] and reduced exercise capacity has been shown to be one of the strongest predictors of heart failure and premature mortality.[63–65] Further research is required to delineate whether a combination of structural evaluation of cardiac function and exercise capacity is necessary to determine risk of cardiovascular sequelae in pre-eclamptic women.

Nonetheless, the findings of this study support that women with a history of preeclampsia have persisting cardiac dysfunction, and further efforts should be directed at identifying the most appropriate method of monitoring these high-risk women. Furthermore, it is important to investigate whether, once identified, intervention within this high-risk group improves outcomes. It is plausible that early detection and treatment of hypertension, diabetes mellitus, and renal disease with lifestyle and pharmacological measures will alter cardiovascular risk in women with a history of preeclampsia. This, however, has not been investigated. Interestingly, studies have demonstrated that an awareness of the probability of developing cardiovascular disease influences behavior modification in those with a history of preeclampsia.[66] Thus, empowering patients with such information may, on its own, trigger the necessary lifestyle changes to improve cardiovascular outcomes. There is also considerable evidence to demonstrate that progression from asymptomatic to symptomatic heart failure is associated with a 5-fold increase in mortality.[67] Early identification of asymptomatic heart failure and implementation of lipid management and blood pressure control have been shown to reduce the risk of progression to symptomatic disease.[67] There are no studies to date that have addressed the role of monitoring and early intervention in women with a history of preeclampsia, and it is certainly an important area of future research.

Conclusions

Women with a history of preeclampsia demonstrate altered cardiac structure and evidence of diastolic function, which may then translate to an increased risk of long-term cardiovascular sequelae. However, the ideal method of monitoring and risk stratification in this high-risk group remains elusive. Further research with larger sample sizes, consistent reporting, and assessment of sensitive preclinical markers, such as myocardial deformation, are required in order to clarify these findings.

Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Study methodology in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[1].

Reporting criteria	Reported (Yes/No)	Location Reported (pages/section)
Reporting of Background		
Problem definition	Yes	5-6
Hypothesis statement	Yes	6
Description of Study Outcomes	Yes	9
Type of exposure or intervention used	Yes	7
Study population	Yes	7
Reporting of search strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	7
Search strategy, including time period included in the synthesis and keywords	Yes	6-7, Suppl. Table 2
Effort to include all available studies, including contact with authors	Yes	7-8
Databases and registries searched Search software used, name and version, including special features used (eg, explosion)	Yes	6
Use of hand searching (eg, reference lists of obtained articles)	Yes	7
List of citations located and those excluded, including justification	Yes	Figure 1
Method for addressing articles published in languages other than English	N/A	N/A
Method of handling abstracts and unpublished studies	Yes	7
Description of any contact with authors	Yes	N/A
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	7
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	7

Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	7-8
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	Page 9-10, Table 1 Suppl. Table 2
Reporting criteria		
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	8-9, 10-11, Suppl. Table 2
Assessment of heterogeneity	Yes	9-10
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	9-10
Provision of appropriate tables and graphics	Yes	All tables and figures
Reporting of Results		
Table giving descriptive information for each study included	Yes	Table 2
Results of sensitivity testing (eg, subgroup analysis)	Yes	Results
Indication of statistical uncertainty of findings	Yes	Results, Discussion
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	Results, Discussion
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	7
Assessment of quality of included studies	Yes	Results, Suppl Table 2, Discussion
Reporting of conclusions		
Consideration of alternative explanations for observed results	Yes	Discussion

Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	Discussion, Conclusion
Guidelines for future research	Yes	Discussion
Disclosure of funding source	Yes	21

Table S2. Search strategy used for each database.

Database	Search Strategy
MEDLINE	exp Hypertension, Pregnancy-Induced/ OR (preeclampsia or pre-eclampsia).mp. OR . gestation* hypertension.mp. OR (pregnancy adj2 hypertension). OR . ("eclampsia" or "HELLP syndrome").mp. AND exp Echocardiography/ OR exp Ventricular Function/ OR exp Heart Ventricles/ OR exp Ventricular Dysfunction/ ORexp Heart Failure/ OR echocardiogra*.mp. OR ("systolic function*" or "diastolic function*").mp. OR ("diastolic dysfunction" or "systolic dysfunction").mp. OR ("ventricular remodelling" or "ventricular remodeling").mp. *[mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]*
EMBASE	exp preeclampsia/ or exp "eclampsia and preeclampsia"/ OR exp maternal hypertension/ OR (preeclampsia or pre-eclampsia) OR gestation* hypertension.mp. OR (pregnancy adj2 hypertension).mp. OR ("eclampsia" or "HELLP syndrome").mp. AND

	exp echocardiography/ OR exp heart function/ IR exp heart failure/ OR echocardiogra*.mp. OR ("systolic function*" or "diastolic function*") OR ("diastolic dysfunction" or "systolic dysfunction").mp. OR ("ventricular remodelling" or "ventricular remodeling").mp. *[mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]*
CINAHL	(MW preeclampsia OR pre-eclampsia OR eclampsia OR hypertension in pregnancy OR gestational hypertension OR pregnancy induced hypertension OR maternal hypertension) OR (preeclampsia OR pre-eclampsia OR gestation* hypertension OR pregnancy adj2 hypertension OR eclampsia OR "HELLP syndrome") AND (MW echocardiography OR ventricular function OR ventricular dysfunction OR heart failure) OR (echocardiog* OR "systolic function" OR "diastolic function" OR "systolic dysfunction" OR "diastolic dysfunction" OR "ventricular remodelling" OR "ventricular remodeling"

Table S3. Quality assessment using the Newcastle Ottawa Scale.

Study	*Selection (Total score - 4)*	*Comparability (Total score - 2)*	*Outcome (Total score - 3)*	*Total*	*Quality*
Abdel Wahab (2018)[2]	3	1	1	5	Poor
Al-Nashi (2016)[3]	4	1	2	7	High
Andrietti (2008)[4]	1	0	1	2	Poor
Atalla (2015)[5]	4	1	2	7	High
Bokslag (2018)[6]	4	1	2	7	High
Breetveld (2018)[7]	4	0	1	5	Poor
Ciftci (2014)[8]	1	2	2	5	Poor
Clemmensen (2018)[9]	3	1	2	6	High
Collen (2013)[10]	2	1	2	5	Fair
Estensen (2013)[11]	1	0	2	3	Poor
Evans (2011)[12]	3	0	2	5	Poor
Ghi (2014)[13]	3	1	1	5	Poor
Ghossein-Doha (2013)[14]	1	0	1	2	Poor
Ghossein-Doha (2017)[15]	2	0	2	4	Poor
Melchiorre (2011)[16]	3	1	2	6	High
Orabona (2017)[17]	4	1	2	7	High
Rafik Hamad (2009)[18]	4	1	1	6	Poor
Scantlebury (2015)[19]	1	0	3	4	Poor
Shahul (2018)[20]	4	1	3	8	High
Simmons (2002)[21]	4	1	2	7	High

Soma-Pillay (2018)[22]	3	0	2	5	Poor
Spaan (2009)[23]	3	1	1	5	Poor
Strobl (2011)[24]	3	0	2	5	Poor
Tyldum (2012)[25]	4	0	1	5	Poor
Valensise (2016)[26]	3	1	2	6	High
Yu (2018)[27]	3	0	1	4	Poor
Yuan (2014)[28]	4	1	1	6	Poor

Table S4. Assessment of cardiovascular risk factors in included studies. NR = not reported.

	Hypertension (%)		Current/Past Smoking (%)		Diabetes (%)		Renal Disease (%)		Cardiovascular or cerebrovascular events (%)	
	PE	**No-PE**	**PE**	**No-PE**	**PE**	**No-PE**	**PE**	**No-PE**	**PE**	**No-PE**
Abdel Wahab (2018)[2]	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Al-Nashi (2016)[3]	1 (7)	0(0)	0(0)	1 (6)	0(0)	0(0)	NR	NR	0(0)	0(0)
Andrietti (2008)[4]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Atalla (2015)[5]*	Excluded	Excluded	NR	NR	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Bokslag (2018)[6]	50 (38)	8 (14)	23 (18)	9 (16)	NR	NR	NR	NR	NR	NR
Breetveld (2018)[7]	10 (15)	1 (3)	5 (7)	3 (8)	3 (4)	0 (0)	NR	NR	NR	NR
Ciftci (2014)[8]	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Clemmensen (2018)[9]	13 (25)	6 (15)	19 (36)	17 (43)	3 (6)	1 (3)	NR	NR	NR	NR
Collen (2013)[10]	25 (50)	17 (31)	NR	NR	3 (12)	0 (0)	NR	NR	NR	NR
Estensen (2013)[11]*	NR	Excluded	6 (8)	0 (0)	NR	Excluded	NR	Excluded	NR	Excluded
Evans (2011)[12]	NR	NR	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded

Ghi (2014)[13]	Excluded	Excluded	Excluded	Excluded	NR	NR	NR	NR	Excluded	Excluded
Ghossein-Doha (2013) - 1year[14]	3 (15)	0 (0)	2 (10)	1 (13)	NR	NR	NR	NR	NR	NR
Ghossein-Doha (2013) – 14 years[14]	7 (35)	1 (13)	1 (5)	3 (38)	NR	NR	NR	NR	NR	NR
Ghossein-Doha (2017)[15]	25 (23)	1 (2)	8 (7)	5 (12)	1 (1)	0 (0)	NR	NR	NR	NR
Melchiorre (2011)[16]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Orabona (2017)[17]	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	NR	NR	Excluded	Excluded
Rafik Hamad (2009)[18]	NR	NR	Excluded	Excluded	NR	NR	NR	NR	NR	NR
Scantlebury (2015)[19]	294 (69)	1164 (53)	111 (26)	631 (29)	151 (35)	614 (28)	NR	NR	NR	NR
Shahul (2018)[20]*	7 (22)	1 (4)	NR	NR	Excluded	Excluded	NR	NR	Excluded	Excluded
Simmons (2002)[21]*	Excluded	Excluded	NR	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Soma-Pillay (2018)[22]	52 (54)	2 (4)	NR	NR	6 (6)	0 (0)	NR	NR	NR	NR
Spaan (2009)[23]	12 (55)	2 (7)	3 (14)	10 (35)	Excluded	Excluded	Excluded	Excluded	2 (9)	1 (3)
Strobl (2011)[24]	Excluded	Excluded	5 (16)	3 (17)	Excluded	Excluded	NR	NR	Excluded	Excluded

Tyldum (2012)[25]*	Excluded	Excluded	1(5)	2 (10)	Excluded	Excluded	NR	NR	Excluded	Excluded
Valensise (2016)[26]	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Yu (2018)[27]*	Excluded	Excluded	Excluded	Excluded	NR	NR	NR	NR	Excluded	Excluded
Yuan (2014)[28]*	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	NR	NR	NR	NR

*** These studies are longitudinal studies which reported cardiovascular risk factors at time of antenatal assessment**

Figure S1. Funnel plots as an assessment of publication bias.

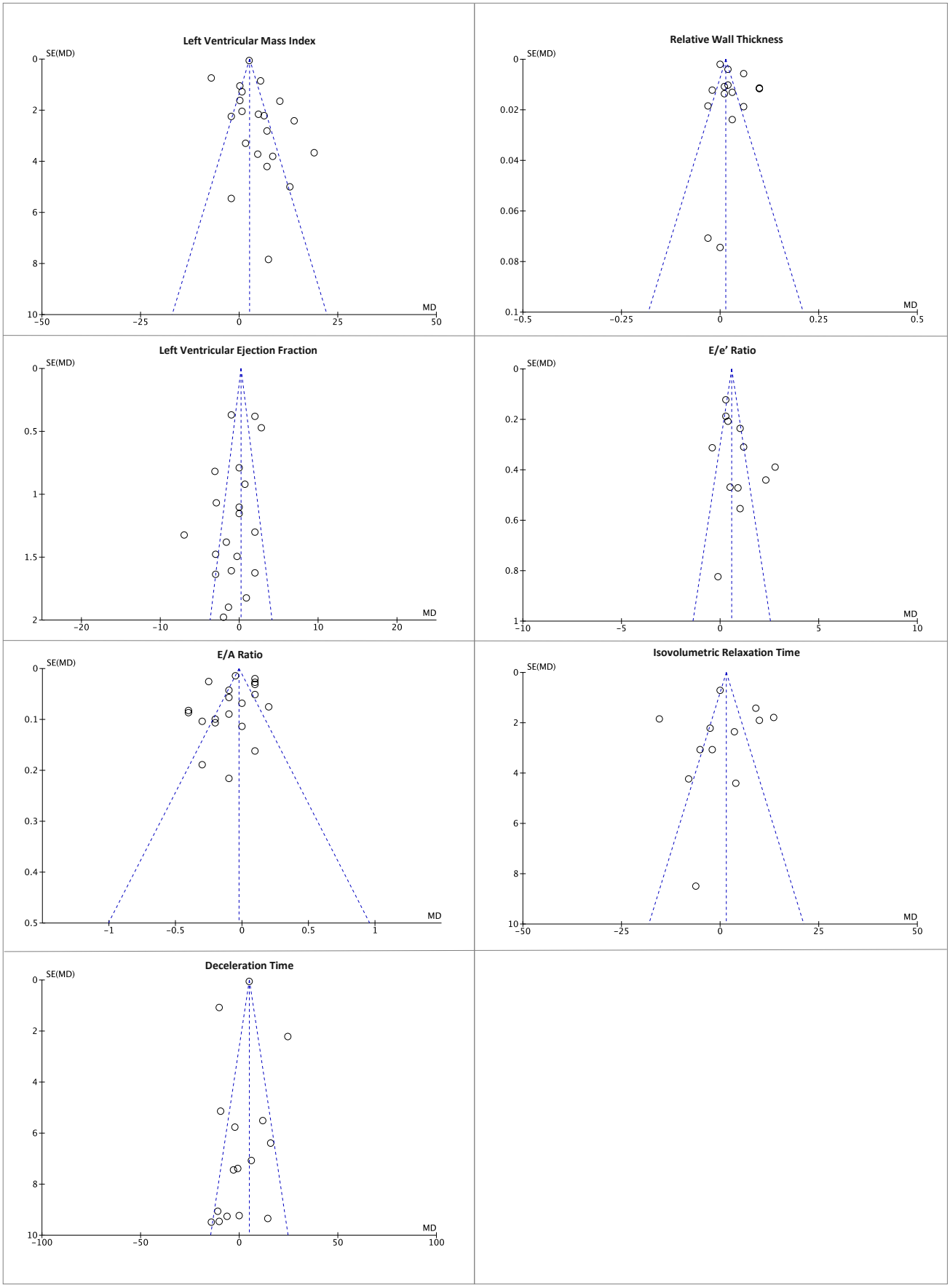
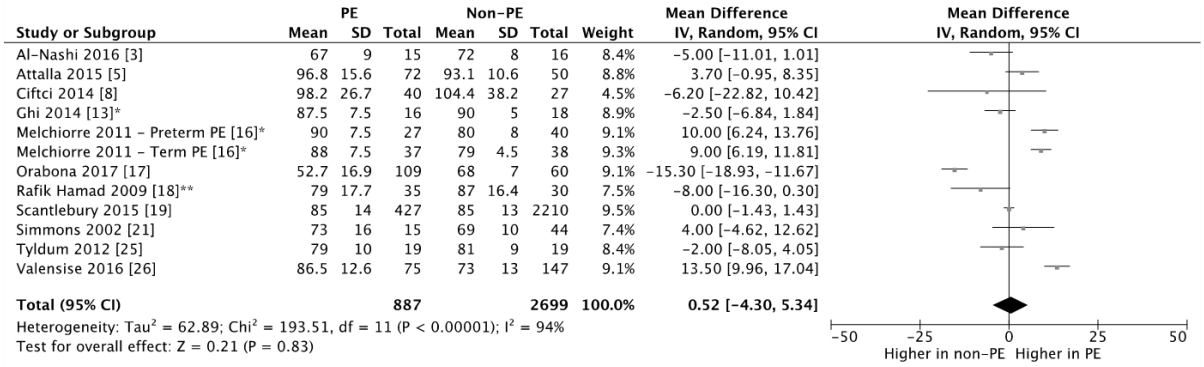


Figure S2. Forest plot illustrating the mean difference in isovolumetric relaxation time (ms) between PE and non-PE groups.

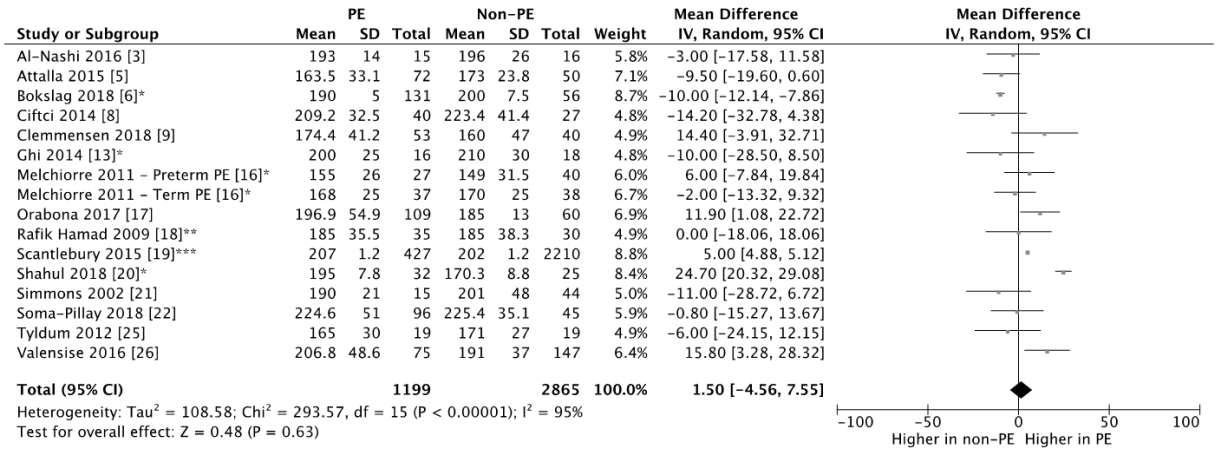


C) Mean difference in isovolumetric relaxation time (ms) between PE and non-PE groups

** Data transformed from median and IQR to mean and SD*

*** Data originally reported as mean and standard error*

Figure S3. Forest plot illustrating the mean difference in deceleration time (ms) between PE and non-PE groups.



** Data transformed from median and IQR to mean and SD*

*** Data originally reported as mean and standard error*

**** Data originally reported as geometric mean and SD*

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