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Severity of pre-eclampsia and the risk of future cardiovascular disease: a systematic review and meta-analysis

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ABSTRACT

Pre-eclampsia (PE) is found in 2-8% of pregnancies and is one of the leading causes of mortality and morbidity. Several studies showed an increased cardiovascular risk of PE in the form of hypertension, heart failure, ischemic heart disease, venous thromboembolism and death. This study aims to evaluate all available evidence on the effect that PE with severe features has on long-term cardiovascular risk compared with PE without severe features. PubMed and ProQuest were searched from January 2000 to December 2019 to identify relevant articles. We estimated the risk by using random effect meta-analysis. Twelve studies involving more than three million women were included. Our study showed the pooled relative risks (RRs) for women with a history of severe PE compared with mild PE were 1.32 (95 % confidence interval [CI] 1.13-1.53) for hypertension, 1.74 (95% CI 0.81-3.72) for heart failure, 1.06 (95% CI 0.78-1.43) for ischemic heart disease, 1.20 (95% CI 0.93-1.54) for thromboembolism, 1.46 (95 % CI 0.92-2.32) for cardiovascular hospitalization, and 1.02 (95 % CI 0.73-1.43) for cardiovascular mortality. Other study on ventricular fibrillation could not be pooled. Severe preeclampsia has an increased risk of hypertension by one- to two-fold compared to mild preeclampsia. Women with a history of preeclampsia should be educated about lifestyle modification as well as regular monitoring to reduce the risk of cardiovascular disease. Further consideration and evaluation should be given to preeclampsia with severe features.

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1. INTRODUCTION

Pregnancy causes significant changes in cardiovascular, hematologic, coagulation, and metabolic function [1], [2]. These cardiovascular changes include activation of the renin angiotensin aldosterone system,

increased cardiac output, heart rate, plasma volume, and decreased systematic vascular resistance [3- 5]. In hypertensive disorders of pregnancy, especially pre-eclampsia these changes occur more significantly [6]. The presence of impaired remodelling of the spiral arteries leads to increased vascular oxidative stress, inflammation, endothelial dysfunction, and decreased vasodilatation mediators [6- 9].

Pre-eclampsia (PE) is found in 2-8% of pregnancies and is one of the leading causes of mortality and morbidity [10], [11]. It is still unclear whether pre-eclampsia is a risk factor that directly affects future cardiovascular disease [10]. However, several studies showed an increased cardiovascular risk of pre-eclampsia in the form of hypertension, heart failure, ischemic heart disease, venous thromboembolism and death [12- 14]. These risk also increases in recurrent pre-eclampsia compared with single episodes, [15], [16] and also increases in early onset pre-eclampsia when compared with late onset pre-eclampsia [17]. The increased risk of pre-eclampsia indicates the importance of a comprehensive and effective management strategy for all pregnancies [17]. Several countries have started implementing education on healthy lifestyles and behaviour, screening for cardiovascular disease and risk factors, and team collaboration between obstetric gynaecology and cardiology in treating patients at risk of cardiovascular disease, by focusing not only on maternal cardiovascular risk but also on foetal risk and outcome [2], [3], [18].

In 2013, the Executive Summary on Hypertension in Pregnancy by the American College of Obstetricians and Gynaecologists (ACOG) modified the diagnosis of pre-eclampsia to emphasize severe features of the disease [17], [19]. This change was made because pre-eclampsia is a dynamic and progressive disease, necessitating repeated monitoring of the presence or absence of severe features [17]. Pre-eclampsia with severe features gives worse maternal and foetal outcomes [20], [21]. Since not all pregnancies with pre-eclampsia showed a future cardiovascular disease, severe features may be an additional indicator that can be used in screening. Although several reviews have been conducted on the relationship between hypertensive disorders and CVD, as far as we know, no systematic review or meta-analysis has been conducted on severity of pre-eclampsia and future lifetime cardiovascular risk. This study aims to evaluate all available evidence on the effect that pre-eclampsia with severe features has on long-term CVD risk compared with pre-eclampsia without severe features.

2. Materials and Methods

2.1 Literature search

This systematic review and meta-analysis was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- analyses) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [22], [23]. PubMed and ProQuest were searched from January 2000 to December 2019 to identify relevant articles. The search terms used were in combination: (1) pre-eclampsia and hypertensive disorder pregnancy; (2) heart failure, coronary artery disease, ischemic heart disease, cardiovascular disease, and cardiovascular risk. For detailed description of search strategy can be found in supplementary material (Appendix S1). In addition, manual search was also conducted by the reviewers to minimize the missing relevant articles from initial search.

2.2 Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) original articles in English language, published from 2000 to 2019; (2) studies that compared women pre-eclampsia with and without severe features, or mild and severe pre-eclampsia, followed by cardiovascular events; (3) hypertension, heart failure, ischemic heart disease, other cardiovascular disease, or cardiovascular death as an outcome; (4) full-text article availability; and (5) inclusion of more than 10 women. Exclusion criteria were studies that including cardiovascular events as an

outcome for women in period of antepartum and six weeks postpartum.

2.3 Study selection and data extraction

Three investigators (DY, BF, and SL) independently reviewed the title or abstract meeting the criteria for inclusion. This was followed by screening the full articles. For any disagreement were resolved by discussion and consensus. Data were extracted and cross-checked by three researchers independently, including: first author, year of publication, country, years of data collection, study design, exposure, definition of pre-eclampsia, definition of outcome, number of participants, follow-up period, mean age at follow-up, and outcomes reported.

2.4 Assessment of study quality and bias

Study quality was assessed using the Newcastle–Ottawa Quality Assessment Scale for cohort and case-control by three researchers independently. The Newcastle–Ottawa Scale uses a scoring system of the following categories: selection, comparability and outcome for cohort studies or exposure for case-control studies [24]. For detailed, scoring from each included publication can be found in supplementary material (Table S1).

2.5 Statistics

Raw numbers were extracted from the data reported in each study. Review Manager version 5.4.1 was used to calculate pooled risk ratio with 95% confidence interval (CI) by using Inverse Variance as statistical method. Random effects analysis model was used because the studies were conducted in a wide range of settings in different populations. Separate meta-analyses were performed to measure the six outcomes. One outcome is being excluded from meta-analyses because only one study analysed the association between severity of pre-eclampsia and ventricular fibrillation. The measured risk ratio (RR) was used to know the association between the severity of preeclampsia and a risk of hypertension, ischemic heart disease, heart failure, thromboembolic events, cardiovascular hospitalization, and cardiovascular death. Heterogeneity between the included studies was assessed using I^2 metric.

3. Results

3.1 Characteristics of studies

Initial PUBMED and PROQUEST search produced 3410 titles and abstract, after which 12 studies were included in the analysis (see Figure 1). Table 1 summarize the characteristics of the studies included for cardiovascular morbidity and mortality. The studies examined 3465872 women in total with large variance in sample sizes (140-984865). From 11 studies that reported the number of women in each group, there were 125331 women with mild pre-eclampsia and 43582 women with severe pre-eclampsia. Studies reporting a mean or median age at enrolment ranged from 26.9 to 48 years, whereas follow-up ranged from 3 months postpartum to 15 years. Most studies still use mild and severe pre-eclampsia definitions, but only 2 studies use the 2013 American College of Obstetricians and Gynaecologists (ACOG) definition, namely pre-eclampsia with and without severe features [25], [26]. The definition of cardiovascular morbidity and mortality, the majority of studies used record linkage through International Classification of Disease (ICD) codes and death certificates.

3.2 Quality of evidence

The quality score of the included studies can be found in the Supplementary material (Table S1). One study reached the maximum of stars among the cohort and case-control studies (maximum nine stars) [25], six studies received eight stars, [27- 32] one studies received seven, [33] and three studies obtained six stars.

[26], [34], [35]. The remaining one study received seven out of eight stars for cross sectional study [36].

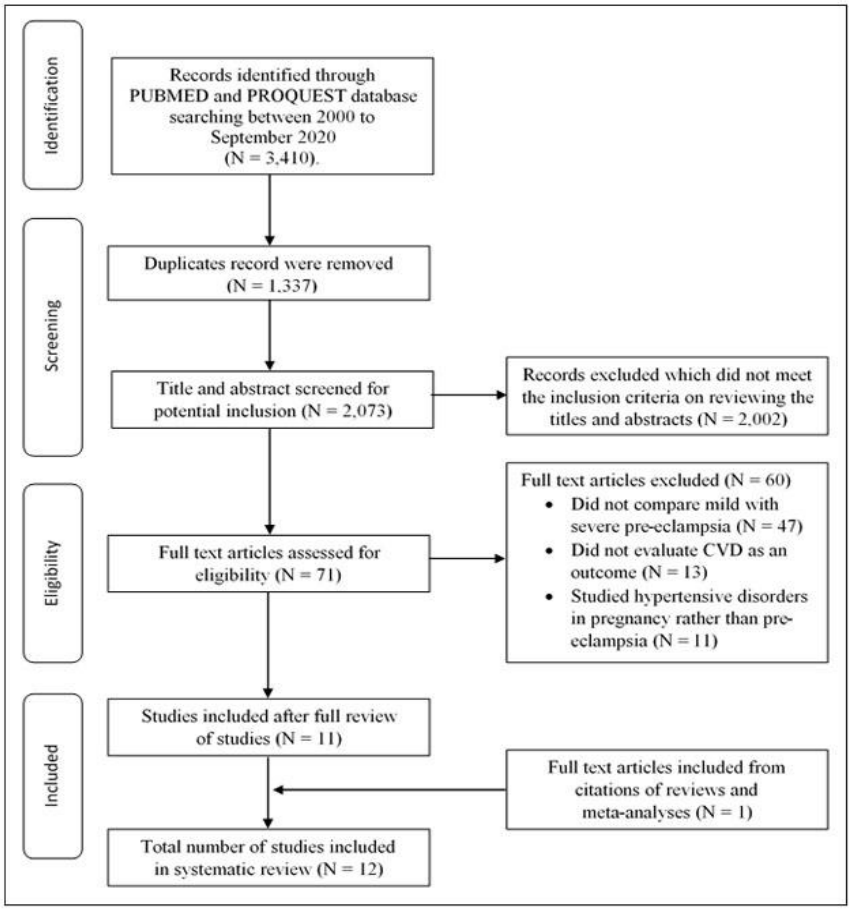

Figure 1. Flow diagram of study selection. CVD indicates cardiovascular disease.

3.3 Hypertension

Overall, there are six articles (five cohort studies [26- 28], [30], [34], and one case-control study [33]) reported hypertension as an outcome of pre-eclampsia. Four studies only showed mean blood pressure after variable length of follow up [26], [27], [33], [34]. Three studies showed higher risk for developing hypertension in women with severe pre-eclampsia [28], [30], [34]. There was an increasing risk ratio when comparing mild and severe pre-eclampsia in women with persistent hypertension at three months after delivery [34]. Study by [30] showed an increasing 10 year cumulative incidences of post pregnancy hypertension in women with severe pre-eclampsia [28] also reported a significant increased hazard ratio in women with mild PE (HR 3.87 95% CI 3.70-4.05) and severe PE (HR 7.58 95% CI 7.05-8.14). Two other studies reported approximately equal results between women with mild and severe pre-eclampsia [26], [27]. One study found a lower mean blood pressure in women with severe pre-eclampsia [33].

3.3.1 Meta-analysis

Due to the difference in outcome measures, only the data from two studies were comparable [28], [30]. In total, 14519 women who experienced severe pre-eclampsia are at higher risk of developing hypertension (pooled RR 1.32, 95 % CI 1.13-1.53; Figure 2.1.1). There was a high degree of heterogeneity between two studies (I^2 = 89 %).

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Table 1. Characteristics and outcomes of studies.

Author, year published	Country, baseline years study	Study Design	Exposure	Definition of preeclampsia		No. of partici-pants in study	Follow-up time (median, years)	Age at follow-up (median, years)	Definition of Outcome	Outcome
				SBP,DBP (mmHg)	Proteinuria					
Kestenbaum, 2003	United States, 1978-1998	PCS	mild PE 15508 , severe PE 5044	ICD 9-CM: mild 642.4, severe 642.5 or positive response on the birth certificate		124.148	7.8	36.1	IHD: ICD9-CM 410. or revascularization procedure: 36.x	mild PE 24/15508, HR 2.2 (1.3-3.6) severe PE 11/5044, HR 3.3 (1.7-6.5)
									VTE: ICD9-CM: 451.1, 453.x, 415.1	mild PE 30/15508,HR 1.4 (0.9-2.2) severe PE 15/5044, HR 2.3 (1.3-4.2)
Arnadottir, 2004	Iceland, 1931-1947	CCS	mild PE 70 , severe PE 96	mild >=140/90 severe >= 160/110	Esbach method	954	50	NS	CV mortality: death certificate ICD9 410-414.9 or coronary artery sclerosis	mild PE 18/70, 26% severe PE 26/96, 27%
Wikstrom, 2005	Sweden, 1973-1982	CS	mild PE 9718 , severe PE 2815	mid >=140/90 severe DBP >=110	mild >=300 mg/24h severe >=5g/24h	403.550	15	48	IHD ICD10: i20-i25	mild PE 123/9718, IRR 1.90 (1.60-2.20) severe PE 53/2815, IRR 2.80 (2.20-3.70)
Lykke, 2009	Denmark, 1978-2007	RCS	mild PE 26810 , severe PE 7016	ICD 10 mild PE: O140, O149 severe PE: O141, O142, O150-152, O159		643.935	14.6	26.9	HTN ICD 10: i10-i13	mild PE 2126/26810, HR 3.87 (3.70-4.05) severe PE 793/7016, HR 7.58 (7.05-8.14)
									IHD ICD10: i20-i25	mild PE 530/26810, HR 1.76 (1.61-1.92) severe PE 121/7016, HR 2.11 (1.76-2.52)
									HF ICD10: i50, i51.3, i51.9	mild PE 151/26810, HR 1.90 (1.61-2.24) severe PE 36/7016, HR 2.24 (1.61-3.12)
									VTE: ICD 10: i26, i74, i82	mild PE 212/26810, HR 1.54 (1.34-1.77) severe PE 63/7016, HR 2.18 (1.7-2.80)
Smith, 2009	Canada, NS	PCS	mild PE 34 , severe PE 36	mild >=140/90 severe >= 160/110	mild >=300 mg/24h or >=2+ on dipstick severe >=5g/24h	140	1	NS	HTN: Mean BP (mmHg)	NS
Lykke, 2010	Denmark, 1978-2007	RCS	mild PE 26810 , severe PE 7016	mild PE: O140, O149 severe PE: O141, O142, or O150-152, O159		643.935	14.6	26.9	CV mortality: cause of death registry or a first cardiovascular diagnosis	mild PE 92/26810, HR 1.99 (1.61-2.47) severe PE 24/7016, HR 2.89 (1.93-4.33)

Author, year published	Country, baseline years study	Study Design	Exposure	Definition of preeclampsia		No. of participants in study	Follow-up time (median, years)	Age at follow-up (median, years)	Definition of Outcome	Outcome
				SBP,DBP (mmHg)	Proteinuria					
Nakimuli, 2013	Uganda, 2009-2011	PCS	mild PE, severe PE	mild <160/110 severe >=160/110	mild dipstick +2 severe >=3+	188	0.25	NS	BP >=140/90 mmHg or required antihypertensive medication	NS
Alsnes, 2014	Norway, 1993-1995	CCS	mild PE 164 , severe PE 54	ICD 10 mild PE: O.14.0 or O.14.9 severe PE: O.14.1, O.14.2, or O.15.0-15.9		611	11	27.0	HTN: Mean BP (mmHg)	NS
Kessous, 2015	Israel, 1988-2012	RCS	mild PE 6018 , severe PE 1719	NS	NS	96.370	11.2	28.3	IHD: simple CV events	mild PE 108/6018, 1.8% severe PE 25/1719, 1.5%
									HF: complex CV events	mild PE 168/6018, 2.8% severe PE 58/1719, 3.4%
									CV morbidity: ICD9 codes hospitalization	mild PE 270/6018, 4.5% severe PE 89/1719 , 5.2%
Behrens, 2017	Denmark, 1995-2012	PCS	mild PE 24057 , severe PE 7503	ICD 10 mild PE: O.14.0 or O.14.9, severe PE: O.14.1, O.14.2, or O.15.0-15.9		984.865	10	NS	HTN: second prescription (ATC C02-03 or C07-09)	mild PE 2780/24057 severe PE 1056/7503
Hromadnikova, 2019	Czech Republic	PCS	mild PE 25 , severe PE 77	ACOG criteria		276	7	38.0	HTN: Mean BP (mmHg)	NS
Ackerman, 2019	United States, 2008-2012	RCS	mild PE 16117 , severe PE 12206	ICD 9-CM without severe features: 642.4, 642.9, with severe features: 642.5x		569.900	4.9	NS	IHD ICD9-CM: 410.x	mild PE 2/16117, 0.12 (>0.0-<0.3) severe 1/12206, 0.08 (>0.0-<0.2)
									HF IC9-CM: 428.x	mild PE 5/16117, 0.3 (0.1-0.7) severe 30/12206, 2.5 (1.6-3.3)
									Vfib ICD9-CM: 427.41, 427.5	mild PE 2/16117, 0.1 (>0.0-<0.4) severe 9/12206, 0.7 (0.3-1.2)
									CV morbidity: ICD9 hospitalization	mild PE 153/16117, aOR 1.96 (1.66-2.32) severe 214/12206, aOR 3.46 (2.99-4.00)

BP, blood pressure; CCS, case-control study; CS, cross-sectional; CV, cardiovascular; DBP, diastolic blood pressure; HF, heart failure; HTN, hypertension; IHD, Ischemic Heart Disease; PE, pre-eclampsia; PCS,

prospective cohort study; RCS, retrospective cohort study; SBP, systolic blood pressure; VTE, venous thromboembolism. NS: data not shown or specified

3.4 Heart Failure

Three record-linkage studies described the development of heart failure, all of them were cohort studies [25], [28], [29]. [28] reported an increasing hazard ratio in more severe pre-eclampsia (HR 2.24; 95% CI 1.61-3.12 in severe pre-eclampsia and HR 1.90; 95% CI 1.61-2.24 in mild pre-eclampsia) compared with no hypertensive disorder. The other two studies showed a similar increase in hazard ratio when comparing women with mild or severe pre-eclampsia with women without hypertensive disorder [25], [29].

3.4.1 Meta-analysis

With all studies combined, 20941 women who had severe pre-eclampsia contributed to the meta-analysis on heart failure. When data were combine, a pooled risk ratio of 1.74 (95% CI 0.81-3.72; Figure 2.1.2) was found [25], [28], [29]. Heterogeneity between three studies was considerable (I^2 = 89%), so a sensitivity analysis was performed. When excluding the study by [25] from the pooled analysis, heterogeneity tested was lower (I^2 = 29%) and the pooled RR decreased to 1.07 (95% CI 0.81-1.41).

3.5 Ischemic Heart Disease

Five studies reported ischemic heart disease (IHD) as an outcome of pre-eclampsia, four cohort studies and one cross sectional study [25], [28], [29], [31], [36] performed a cross-sectional population based study reporting on fatal or non-fatal ischemic heart disease. The risk of being hospitalized for, or dying from IHD, was found increased on severe pre-eclampsia (IRR 3.1; 95% CI 2.4-4.1) and mild pre-eclampsia (IRR 2.1; 95% CI 1.8-2.5) compared with non-hypertensive women. [36] This result was also found in the other two studies [28], [31]. Contrary, the remaining studies reported different result. [29] showed a decrease in the incidence of ischemic heart disease in a population based retrospective study. Latter study also showed lower rate in women with severe pre-eclampsia (0.08 per 1000 deliveries, 95% CI 0.0-0.2) compared with mild pre-eclampsia (0.12 per 1000 deliveries, 95% CI 0.0-0.3) [25].

3.5.1 Meta-analysis

In total, 28800 women had severe pre-eclampsia and did not show a statistically significant increased risk of ischemic heart disease (pooled RR 1.06; 95% CI 0.78-1.43; Figure 2.1.3) [25], [28], [29], [31], [36]. Heterogeneity between five studies was considerable (I^2 = 59%). The pooled risk ratio was found to be decreasing after a sensitivity analysis was carried out (pooled RR 0.89; 95% CI 0.75-1.05). After excluding the study by [36] from the pooled analysis, there was no more heterogeneity between the four remaining studies (I^2 = 0%).

3.6 Thromboembolism

Thromboembolism events were reported on two cohort studies. [28], [31] showed an increasing risk of deep vein thrombosis or pulmonary embolism in women with mild pre-eclampsia (HR 1.5; 95% CI 1.0-2.2) and severe pre-eclampsia (HR 2.6; 95% CI 1.5-4.5) compared with normotensive pregnancy [31]. The other study also showed a risk gradient of subsequent thromboembolism, mild pre-eclampsia increased the risk 1.54 fold and severe pre-eclampsia increased the risk 2.18 fold [28].

3.6.1 Meta-analysis

When results of both studies were combined a pooled risk ratio of 1.20 (95% CI 0.93-1.54; Figure 2.1.4) was found without any heterogeneity (I2 = 0%) between two studies [28], [31].

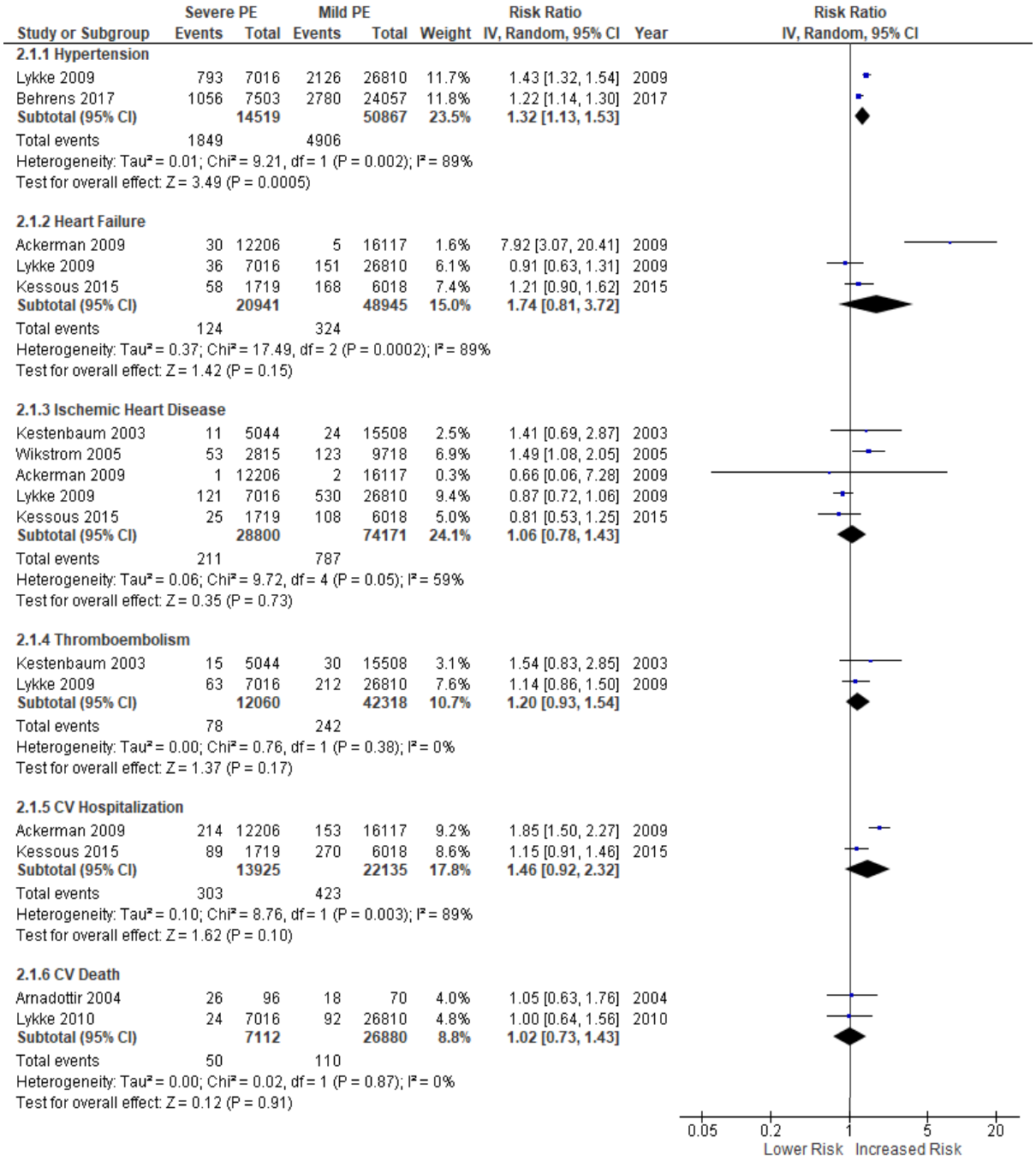

Figure 2. Forest plot of studies reporting the risk of hypertension (2.1.1), heart failure (2.1.2), ischemic heart disease (2.1.3), thromboembolism (2.1.4), cardiovascular hospitalization (2.1.5), and cardiovascular death (2.1.6) in women with severe pre-eclampsia when compared with women with mild pre-eclampsia. Incidence data were extracted from original studies using available tables and figures.

3.7 Ventricular Fibrillation

Ventricular fibrillation is a rare developed presentation after preeclampsia. Only one study reported the number of events in mild and severe preeclampsia on ventricular fibrillation. There is a higher rate of ventricular fibrillation in women with severe preeclampsia (0.7 per 1000 deliveries; 95% CI 0.3-1.2) compared with mild preeclampsia (0.1 per 1000 deliveries; 95% CI 0.0-0.4) [25].

3.8 Cardiovascular Morbidity and Hospitalization

Cardiovascular (CV) morbidity and hospitalization was reported by 2 studies. All of which were cohort studies [25], [29]. These two studies showed an increasing risk for CV hospitalization linearly with the severity of the disease (mild and severe PE). The author of the study reported a higher incidence of CV hospitalization in women with severe PE, compared with mild PE (5.2% versus 4.5%; P = 0.001) [29]. Among women with pre-eclampsia, there was a statistically significant and progressively increased risk of CV morbidity with mild PE (OR 1.96; 95% CI, 1.66-2.32) and severe PE (OR 3.46; 95% CI, 2.99-4.00) [25].

3.8.1 Meta-analysis

Incidence data on 13925 women with severe pre-eclampsia could be extracted from two studies to perform a meta-analysis [25], [29]. CV morbidity and hospitalization showed a pooled risk ratio 1.46 (95 % CI 0.92-2.32, Figure 2.1.5). There was a high degree of heterogeneity between two studies (I2 = 89 %).

3.9 Cardiovascular Mortality

Two record-linkage studies (one case-control study and one cohort study) reported on CV mortality after the event of pre-eclampsia [32], [35]. One study showed approximately equal result of CV deaths from ischemic heart disease between mild and severe pre-eclampsia (26% versus 27%) [35]. Another study reported an increased hazard ratio in women with mild PE (HR 1.99 95% CI 1.61-2.47) and severe PE (HR 2.89 95% CI 1.93-4.33) [32].

3.9.1 Meta-analysis

When data were pooled for cardiovascular mortality, the severity of pre-eclampsia were not found to be statistically significant in increasing CV death (pooled RR = 1.02, 95 % CI 0.73-1.43, Figure 2.1.6) [32], [35]. There was not any heterogeneity between two studies (I^2 = 0%).

4. Discussion

4.1 Main Findings

In this systematic review and meta-analysis, we investigate the correlation between the severity of preeclampsia in pregnant women and cardiovascular disease risk. The results of this study indicate that severe preeclampsia has an increased risk of hypertension by one- to two-fold compared to mild preeclampsia. In contrast, severity of preeclampsia did not show an increased risk of the other cardiovascular outcome such as heart failure, ischemic heart disease, thromboembolism, cardiovascular hospitalization, and death. Although the results of pooled risk ratio were not statistically significant, almost all of the studies included in this review reported an increased number of cardiovascular disease in accordance with the severity of preeclampsia.

4.2 Strengths and Limitations

We conducted a systematic review and meta-analysis by collecting all available studies from January 2000 to December 2019. There has been no evidence that shows the relationship between the severity of preeclampsia and the risk of developing cardiovascular disease, therefore a meta-analysis is performed. This study collected a large sample of 3465872 women. A sufficiently large sample is expected to provide a more precise estimate of the effect size and more represents the overall results of the study. Data extraction and analysis was carried out by three reviewers independently. We only include studies that clearly define and compare mild and severe preeclampsia, which can provide more accurate results.

The main limitation of this review lies in the different definitions of mild and severe preeclampsia in each included study. The 2013 ACOG revised the definition of preeclampsia, with and without severe features, but

only 2 studies [25], [26] used this definition. One study did not define preeclampsia clearly, [29] another study defined preeclampsia based on the ICD 10, [30] and the last study defined mild and severe preeclampsia based on diastolic blood pressure and proteinuria. The remaining seven studies were conducted before 2013 and thus used the old definition of preeclampsia [27], [28], [31], [32], [34- 36]. This difference in definition could result in an over or underestimated diagnosis in women with preeclampsia.

Another limitation is the lack of studies assessing the risk of cardiovascular disease in mild and severe preeclampsia. We believe that if more studies discuss the severity of preeclampsia, there may be an increase in the pooled risk ratio. In addition, the large variance in population of studies and different research methodology leads to high degree in heterogeneity. The varying duration of follow-up in each study led to the possibility of other risk factors that could contribute to the development of the cardiovascular disease. Not all studies have adequately adjusted the relevant risk factor. We used Newcastle-Ottawa scoring to assess the quality of each included studies, yet only one study had a maximum score [25]. Seven other studies scored only one point less than the maximum score [27- 32], [36]. A publication bias can also be found, where studies with positive results have a higher probability of publication than studies with neutral or negative results. Furthermore, searching was carried out only for studies in English and may have missed any potential studies in other languages.

4.3 Interpretation

Women have specific risk factors for cardiovascular disease that differentiate them from men [18], [37]. Higher risk of developing autoimmune diseases such as rheumatoid arthritis, systematic lupus erythematous, scleroderma, and breast cancer leads to an increased risk of developing cardiovascular disease [38- 40]. Moreover, pregnancy which only occurs in women, is essentially a ‘stress test’. Any outcome that occurs during pregnancy up to birth can be used to assess whether these women have an increased risk for cardiovascular disease or not [15], [18].

Several systematic reviews and meta-analyses have shown an association between pre-eclampsia and increased risk of cardiovascular disease [12- 16]. Only a few studies have compared between mild and severe pre-eclampsia, with several studies suggesting an increased risk in CVD for women with more severe pre-eclampsia [25], [36]. During pregnancy, there are changes in the maternal body system, one of which is vascular remodelling. These changes can sometimes persist after delivery, as in preeclampsia. This condition will show a difference in total vascular resistance between women with early preeclampsia and late preeclampsia. Increased vascular resistance will interfere with systolic and diastolic functions, which in turn will lead to chronic hypertension and other cardiovascular disease. It means that the more severe the preeclampsia, the more severe the level of vascular damage. If the vascular damage persists, it may contribute to the formation of cardiovascular disease later in life [41], [42]. However, it is not certain whether the severity of pre-eclampsia causes direct changes in the metabolic and cardiovascular systems or is it simply a stronger predisposition for cardiovascular disease.

A possible mechanism that could explain is severe pre-eclampsia shows an increase in augmentation index (AIx) and pulse wave velocity (PWV) compared to mild pre-eclampsia, indicating decreased vascular compliance and increased arterial stiffness [43], [44]. Arterial stiffness alone can be used to assessing cardiovascular risk in the future [45]. The progression and dynamic nature of preeclampsia cause severe features to appear at any time. Early onset pre-eclampsia, a condition in which pre-eclampsia occurs under 34 weeks, carries a much higher risk of cardiovascular disease than late onset pre-eclampsia [46], [47]. This can be associated with a longer exposure and an increased severity of pre-eclampsia in early onset [48]. It is also known that severe pre-eclampsia has a higher risk of causing recurrent pre-eclampsia in subsequent

pregnancy, leads to an increased risk of cardiovascular disease [16], [49], [50].

Severe preeclampsia is also known to have a worse outcome in offspring compared with mild preeclampsia, either an increase in the incidence of intrauterine growth restriction, foetal complications or stillbirth [51], [52]. [28] demonstrated that preeclampsia with preterm delivery and/or small for gestational age have an increased cardiovascular risk compared to normal delivery. These findings indicate the need for closer monitoring in women with severe preeclampsia.

Increased risk of cardiovascular disease may also be caused by other factors, such as age, body mass index, family history of cardiovascular disease, hypercholesterolemia, hypertension, diabetes mellitus and smoking. Unfortunately, only a few studies have adjusted for these factors. Preeclampsia and cardiovascular disease are believed to share risk factors [2], [18]. These factors can overlap, making it difficult to identify whether preeclampsia increases cardiovascular risk in a specific pathway or through other cardiovascular risk factors, such as hypertension and dyslipidaemia, which can lead to cardiovascular disease. The American Heart Association has included a history of preeclampsia and gestational hypertension as an additional risk factor in routine examination of pregnant women [38]. Risk stratification is essential for early identification of women at high risk with the aim of optimizing prevention and management.

5. Conclusions

Our meta-analysis found an increased risk between the severity of preeclampsia and hypertension. Despite the severity of preeclampsia did not show any increased risk of other cardiovascular disease, preeclampsia with severe features may still play an important role in developing future cardiovascular risk. Nonetheless, women with a history of preeclampsia should be educated about lifestyle modification as well as regular monitoring to reduce the risk of cardiovascular disease. Further consideration and evaluation should be given to preeclampsia with severe features.

Conflicts of Interest

The authors have no conflict of interest to declare.

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6. References

[1] American College of Obstetricians and Gynecologist. ACOG practice bulletin no 212: pregnancy and heart disease. Obstet Gynecol 2019;133:320-56.

[2] Zagrosek VR, Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines on cardiovascular disease during pregnancy: The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2018;39:3165–241.

[3] Mehta LS, Warnes CA, Bradley E, et al. Cardiovascular considerations in caring for pregnant patients: a scientific statement from the american heart association. Circulation 2020;141:884-903.

[4] Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation 2014;130:1003-8.

[5] Pillay PS, Catherine NS, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr 2016;27:89-94.

[6] Goulopoulou S. Maternal vascular physiology in preeclampsia. Hypertension 2017;70:1066-73.

[7] Ali SM, Khalil RA. Genetic, immune, and vasoactive factors in the vascular dysfunction associated with hypertension in pregnancy. Epub 2015;19:1495-515.

[8] Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia pathophysiology, challenges, and perspective. Circulation 2019;124:1094-112.

[9] Gathiram P, Moodley J. Preeclampsia: its pathogenesis and pathophysiology. Cardiovasc J Afr 2016;27:71-8.

[10] Elkayam U, Goland S, Pieper PG, Silversides CK. High risk cardiac disease in pregnancy. J Am Coll Cardiol 2016;68:396-410.

[11] Say L, Chou D, Gemmill A, Tuncalp O, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2:323-33.

[12] 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.

[13] Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2017;10(2):e003497.

[14] Wu R, Wang T, Gu R, et al. Hypertensive disorders of pregnancy and risk of cardiovascular disease-related morbidity and mortality: a systematic review and meta-analysis. Cardiology 2020;145(10):633-47.

[15] Auger N, Fraser WD, Schnitzer M, Leduc L, Healy-Profitós J, Paradis G. Recurrent preeclampsia and subsequent cardiovascular risk. Heart 2017;103(3):235–43.

[16] Brouwers L, Roest AJ, Savelkoul C, et al. Reccurence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. BJOG 2018;125(13):1642-54.

[17] American College of of Gynecologists, Task Force on Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on hypertension in pregnancy. Obstet Gynecol 2013;122:1122–31.

[18] Brown HL, Warner JJ, Gianos E, et all. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists. Circulation 2018;137:843-52.

[19] Sabol B, Burwick R. Preeclampsia with severe features: evaluation of the new ACOG criteria in a contemporary cohort. AJOG 2016;214:622

[20] Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test. Ther Adv Cardiovasc Dis 2008;2(4):249-59.

[21] Benschop L, Duvekot JJ, Lennep JE. Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy. Heart 2019;105:1273-8.

[22] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339:2535.

[23] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12

[24] Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. 2000. Available from: www. ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 10 October 2020.

[25] Ackerman CM, Platner MH, Spatz ES, et al. Severe cardiovascular morbidity in women with hypertensive disease during delivery hospitalization. AJOG 2019;220(6):582.

[26] Hromadnikova I, Kotlabova K, Dvorakova L, Krofta L. Maternal cardiovascular risk assessment 3-to-11 years postpartum in relation to previous occurrence of pregnancy-related complications. .J Clin Med 2019;8(4):544.

[27] Smith GN, Walker MC, Liu A, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol 2009;200:58.e1-8.

[28] Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension 2009;53:944-51.

[29] Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Sheiner E. Long term maternal atherosclerotic morbidity in women with pre-eclampsia. Heart 2015;101(6):442-6.

[30] Behrens I, Basit S, Melbye M, et al. Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. BMJ 2017;358:j3078.

[31] Kestenbaum B, Seliger SL, Easterling TR, et al. Cardiovascular and thromboembolic events following pregnancy. AJKD 2003;42(5):982-89.

[32] Lykke JA, Langhoff-Roos J, Lockwood CJ, Triche EW, Paidas MJ. Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery. Paediatr Perinat Epidemiol 2010;24:323–30.

[33] Alsnes, IV, Janszky, I, Forman, MR A population-based study of associations between preeclampsia and later cardiovascular risk factors. Am J Obstet Gynecol 2014;211:657.

[34] Nakimuli A, Elliott AM, Kaleebu P, Moffett A, Mirembe F. Hypertension persisting after pre-eclampsia: a prospective cohort Study at mulago hospital, Uganda. PLoS ONE 2013;8(12):e85273.

[35] Arnadottir GA, Geirsson RT, Arngrimsson R, Jonsdottir LS, Olafsson O. Cardiovascular death in women who had hypertension in pregnancy: a case-control study. BJOG 2005;112:286–92.

[36] Wikstrom A, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. BJOG 2005;112:1486-91.

[37] Gulati M. Improving the cardiovascular health of women in the nation. Circulation 2017;135:495-8.

[38] Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update. Circulation 2011;123:1243-62.

[39] Salmon JE, Roman MJ. Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. Am J Med 2008;121:3-8.

[40] Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. Epidemiology 2016;27(1):6-13.

[41] Stergiotou I, Crispi F, Valenzuela-Alcaraz B, Bijnens B, Gratacos E. Patterns of maternal vascular remodeling and responsiveness in early- versus late-onset preeclampsia. Am J Obstet Gynecol 2013;209:558.

[42] Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension 2008;52:873–80.

[43] Enkhmaa D, Wall D, Mehta PK, Rich-Edwards JW, Merz CN, Shufelt C. Preeclampsia and vascular function: a window to future cardiovascular disease risk. J Women Health 2016;25(3):284-91.

[44] Oylumlu M, Oylumlu M, Yuksel M, et al. A simple method for the assessment of arterial stiffness in pre-eclamptic patients. Clin Exp Hypertens 2014;36(8):531-7.

[45] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. JACC 2010;55(33):1318-27.

[46] Bokslag A, Teunissen PW, Franssen C, et al. Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life. AJOG 2017;216(5):523.

[47] Veerbeek JH, Hermes W, Breimer AY, et al. Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension. Hypertension 2015;65:600-6.

[48] Wojtowicz A, Zembala-Szczerba M, Babczyk D, Kolodziejczyk-Pietruszka M, Lewaczynska O, Huras H. Early- and late-onset preeclampsia: a comprehensive cohort study of laboratory and clinical findings according to the new ISHHP criteria. International Journal of Hypertension 2019;4108271.

[49] Sibai BM, Ramadan MK, Friedman SA. Pregnancies complicated by HELLP syndrome: subsequent pregnancy outcome and long-term prognosis. Am J Obstet Gynecol 1995;172:125-9.

[50] Sibai BM, Mercer B, Sarinoglu C. Severe preeclampsia in the second trimester: recurrence risk and long term prognosis. Am J Obstet Gynecol 1991;165:1408-12.

[51] Backes CH, Markham K, Moorehead P, et al. Maternal preeclampsia and neonatal outcomes. J Pregnancy 2011;214365.

[52] Bose C, Marter LJ, Laughon M, et al. Fetal growth restriction and risk of chronic lung disease among infants born before the 28th week of gestation. Pediatrics 2009;124(3):450-8.