

Review

# The Impact of Severe Maternal Morbidity on Perinatal Outcomes in High Income Countries: Systematic Review and Meta-Analysis

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Abstract: While there is clear evidence that severe maternal morbidity (SMM) contributes significantly to poor maternal health outcomes, limited data exist on its impact on perinatal outcomes. We undertook a systematic review and meta-analysis to ascertain the association between SMM and adverse perinatal outcomes in high-income countries (HICs). We searched for full-text publications in PubMed, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Scopus databases. Studies that reported data on the association of SMM and adverse perinatal outcomes, either as a composite or individual outcome, were included. Two authors independently assessed study eligibility, extracted data, and performed quality assessment using the Newcastle–Ottawa Scale. We used random-effects modelling to calculate odds ratios (ORs) with 95% confidence intervals. We also assessed the risk of publication bias and statistical heterogeneity using funnel plots and Higgins I<sup>2</sup>, respectively. We defined sub-groups of SMM as hemorrhagic disorders, hypertensive disorders, cardiovascular disorders, hepatic disorders, renal disorders, and thromboembolic disorders. Adverse perinatal outcome was defined as preterm birth (before 37 weeks gestation), small for gestational age (SGA) (birth weight (BW) < 10th centile for gestation), low birthweight (LBW) (BW < 2.5 kg), Apgar score < 7 at 5 min, neonatal intensive care unit (NICU) admission, stillbirth and perinatal death (stillbirth and neonatal deaths up to 28 days). A total of 35 studies consisting of 38,909,426 women were included in the final analysis. SMMs associated with obstetric hemorrhage (OR 3.42, 95% CI: 2.55–4.58), severe hypertensive disorders (OR 6.79, 95% CI: 6.06–7.60), hepatic (OR 3.19, 95% CI: 2.46–4.13) and thromboembolic disorders (OR 2.40, 95% CI: 1.67–3.46) were significantly associated with preterm birth. SMMs from hypertensive disorders (OR 2.86, 95% CI: 2.51–3.25) or thromboembolic disorders (OR 1.48, 95% CI: 1.09–1.99) were associated with greater odds of having SGA infant. Women with severe hemorrhage had increased odds of LBW infant (OR 2.31, 95% CI: 1.57–3.40). SMMs from obstetric hemorrhage (OR 4.16, 95% CI: 2.54–6.81) or hypertensive disorders (OR 4.61, 95% CI: 1.17–18.20) were associated with an increased odds of low 5-min Apgar score and NICU admission (Severe obstetric hemorrhage: OR 3.34, 95% CI: 2.26-4.94 and hypertensive disorders: OR 3.63, 95% CI: 2.63–5.02, respectively). Overall, women with SMM were 4 times more likely to experience stillbirth (OR 3.98, 95% CI: 3.12–7.60) compared to those without SMM with cardiovascular disease (OR 15.2, 95% CI: 1.29–180.60) and thromboembolic disorders (OR 9.43, 95% CI: 4.38–20.29) conferring greatest risk of this complication. The odds of neonatal death were significantly higher in women with SMM (OR 3.98, 95% CI: 2.44–6.47), with those experiencing hemorrhagic (OR 7.33, 95% CI: 3.06–17.53) and hypertensive complications (OR 3.0, 95% CI: 1.78–5.07) at highest risk. Overall, SMM was also associated with higher odds of perinatal death (OR 4.74, 95% CI: 2.47–9.12)



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mainly driven by the increased risk in women experiencing severe obstetric hemorrhage (OR 6.18, 95% CI: 2.55–14.96). Our results highlight the importance of mitigating the impact of SMM not only to improve maternal health but also to ameliorate its consequences on perinatal outcomes.

Keywords: severe maternal morbidity; adverse perinatal outcomes; high income countries

#### 1. Introduction

Maternal health is a key determinant of perinatal outcomes and an important indicator of a nation's overall socioeconomic progress [1]. However, despite consistent and significant improvements in maternal health over the last century, there remains considerable global inequity in obstetric and neonatal health outcomes. Furthermore, although precipitous declines in maternal mortality rates have occurred in many countries, rates of severe maternal morbidity (SMM) have not shown similar improvements and are increasing in some regions, mainly because of high rates of pre-existing co-morbidities, including diabetes and obesity [2]. The causes of maternal morbidity are varied, complex and inter-related. The Maternal Morbidity Working Group led by the World Health Organization (WHO, Geneva, Switzerland) broadly defines it as "any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing" [1] and has included this definition into the International Classification of Diseases—11 [3]. In contrast, SMM is usually defined as a "near miss" episode characterized as the near death of a woman surviving pregnancy, or a childbirth-related complication, or within 42 days of the termination of pregnancy [4,5]. The true global burden of SMM is not known and thus poorly understood, primarily because of the lack of a standardized definition as well as, crucially, inconsistent recording and reporting of this outcome [1,6-8].

Whilst maternal and perinatal mortality and morbidity are major health issues in low- and middle-income countries, even high-income countries (HICs) are not immune from this issue. In one North American study [9], SMM was approximately 50 times more frequent than maternal mortality, with massive post-partum hemorrhage and complications relating to hypertensive disease in pregnancy common antecedents of severe morbidity [9,10].

Surprisingly, the reduction in maternal mortality rates in HICs is associated with a paradoxical increase in the incidence of SMM which is driven by a combination of factors, including more advanced maternal age at first pregnancy, obesity, chronic medical co-morbidities, and rising rates of operative birth, particularly caesarean section [11]. SMM is now increasingly recognized as an important obstetric care quality indicator for which WHO recommends that HICs should have appropriate surveillance measures in order to identify trends and system failures. SMM is also an important risk factor for adverse perinatal outcomes [10–12], although precise estimates of the magnitude of its contributory risks are unclear, despite both sharing many similar causative pathways [13,14]. Against this background, the aim of this systematic review and meta-analysis was to detail the impact of SMM on perinatal outcomes in HICs.

#### 2. Materials and Methods

This systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42019130933) and conducted in accordance with a previously published protocol [15]. We searched PubMed, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Scopus using different combinations of key terms and search strategies with no restriction by year of publication (Supplementary File 1). The reference lists of included studies were then checked to identify any additional relevant articles. We included only studies published in English, conducted in HICs and meeting the following criteria: (1) original studies of any design, (2) conducted on women with singleton pregnancies > 20 week's gestation,

(3) presented data/results on the association between SMM (as defined by the WHO maternal near-miss criteria) and adverse perinatal outcomes (either as a composite or by individual outcome) and reported sufficient information to calculate risk estimates. The World Bank's definition of HICs was used [16]. We excluded studies of women with multiple pregnancy, pregnancies ending before 20 weeks of gestation, systematic reviews, case series/reports, conference papers/abstracts, proceedings, editorial reviews, letter of communications, commentaries, studies with a small sample size (n < 10) and qualitative studies.

Two reviewers independently assessed the eligibility of studies using the Population/participants, Interventions, Comparisons, Outcomes, and Study design (PICOS) framework [17]. The first reviewer (T.S.M) screened all citations by title, abstract and full text. A second reviewer (J.T) independently reviewed the titles, abstracts, and full text of the screened publications for eligibility. Disagreements on the screening and inclusion of studies were discussed and resolved by consensus with the assistance of a third reviewer (S.K). Findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18].

The methodological quality of the included studies was assessed using the Newcastle–Ottawa scale (NOS) [19]. This tool consists of three domains: selection of study participants, comparability of study groups and reporting and determination of outcomes. Each study was graded out of nine points (separately for case-control and cohort studies) as per the NOS coding manual and summarized in three categories as good (if total score  $\geq$  7), fair (if total score 5–6) or poor (if total score < 5). Studies were deemed to be at high risk of bias if the NOS score was  $\leq$  6 [20].

Two authors (T.S.M. and J.T.) extracted study characteristics, the definition of SMM used in the study, details of adverse perinatal outcomes and other key study findings. We defined sub-groups of SMM as hemorrhagic disorders (postpartum hemorrhage, antepartum hemorrhage, bleeding of unknown origin, abnormally invasive placenta, uterine rupture and hysterectomy), hypertensive disorders (severe gestational hypertension, severe preeclampsia, eclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome), cardiovascular disorders (ischemic or hemorrhagic stroke, cardiac arrhythmia, peripartum cardiomyopathy and cardiac arrest), hepatic disorders, renal disorders and thromboembolic disorders (amniotic fluid embolism, pulmonary embolism, or deep venous thrombosis). We defined adverse perinatal outcome as: preterm birth (before 37 weeks gestation), small for gestational age (SGA) (birth weight (BW) < 10th centile for gestation), low birthweight (LBW) (BW < 2.5 kg), Apgar score < 7 at 5 min, neonatal intensive care unit (NICU) admission, stillbirth and perinatal death (stillbirth and neonatal deaths up to 28 days).

#### Statistical Analysis

We used Review Manager Software (RevMan; Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for data entry and statistical analysis. Heterogeneity between studies was assessed using Higgins I<sup>2</sup> statistics and considered high if I<sup>2</sup>  $\geq$  50% [21]. Because of the heterogeneity of maternal conditions contributing to SMM, as well as the variability within and between studies, we used the random-effects Mantel–Haenszel method to calculate study-specific and pooled odds ratios (ORs) with 95% confidence intervals. As far as possible, we categorized SMM according to the most likely underlying etiology—hemorrhagic, hypertensive, cardiovascular, hepatic, renal or thromboembolic disorders. The effect of publication bias was assessed using funnel plots. Sub-group analyses were performed according to the presumed etiology of SMM. Sensitivity analyses were performed by sequentially removing studies at high risk of bias to evaluate the impact of SMM on different adverse perinatal outcomes.

# 3. Results

# 3.1. Literature Search and Study Selection

The process of study screening, selection and reasons for exclusion are shown in Figure 1. Of the 18,434 studies identified by the initial search, 11,196 (after removing duplicates) were screened by title and 5181 were selected for further abstract screening. Of these, 35 original studies (containing a total of 38,909,426 participants) were eligible for full-text review and used for the final analysis (Table 1).

Etiologic Subgroup of SMM	Country	Definition of SMM
Severe hypertensive disorders		
Buchbinder A et al. 2002	USΔ	Severe gestational hypertension
Buchbinder A. et al., 2002	USA	Severe preeclampsia
Carte E. et al., 2017	USA	Severe preeclampsia
Kim H. et al., 2006	South Korea	HELLP syndrome
Liu S. et al., 2011	Canada	Eclampsia
Hemorrhagic disorders		
Bhandari S. et al., 2014	UK	Antepartum hemorrhage
McCormack et al., 2008	Australia	Antepartum hemorrhage
Yang and Savitz et al., 2001	USA	Antepartum hemorrhage
Baldwin H. et al., 2017	Australia	Hemorrhagic AIP
Jakobsson M. et al. 2015	Finland	Hemorrhagic AIP
jakobboli ivi. et al., 2010	Tinana	Hysterectomy
Patel E et al. 2015	USΔ	Postpartum hemorrhage
Full E. et ul., 2010	UJA	Transfusion
Sheiner E. et al., 2005	Israel	Postpartum hemorrhage
Jakobsson M. et al., 2015	Finland	Uterine rupture
Kaczmarczyk M. et al., 2007	Sweden	Uterine rupture
Ofir K. et al., 2003	Israel	Uterine rupture
Ronel D. et al., 2012	Israel	Uterine rupture
Vilchez G. et al., 2017	USA	Uterine rupture
Cardiovascular disorders		
Patel E. et al., 2015	USA	Acute heart failure
1 ald 21 et all, 2010	0011	Myocardial infarction/Ischemia
Henry D. et al., 2016	USA	Arrhythmia
Kao D. et al., 2013	USA	Peripartum myocardiopathy
Aarnio K. et al., 2017	Finland	Stroke
Kang J. et al., 2010	Taiwan	Stroke
Hepatic disorders		
Brouwers L. et al., 2015	Netherlands	Severe intrahepatic cholestasis
Geenes V. et al., 2014	UK	Severe intrahepatic cholestasis
Herrera C. et al., 2018	USA	Severe intrahepatic cholestasis
Kawakita T. et al., 2015	USA	intrahepatic cholestasis
Rioseco A.J. et al. 1994	USA	Intrahepatic cholestasis
Wikstrom S.E. et al., 2013	Sweden	Intrahepatic cholestasis
Renal discords		
Hildebrand A. et al., 2015	Canada	Acute kidney injury
Patel E. et al., 2015	USA	Acute renal failure

Table 1. Publications included in th	he systematic review.
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Etiologic Subgroup of SMM	Country	Definition of SMM
Thromboembolic disorders		
Kramer M. et al., 2012	Canada	Amniotic fluid embolism
Kramer M. et al., 2013	USA	Amniotic fluid embolism
Roberts C. et al., 2010	Australia	Amniotic fluid embolism
Spiliopoulos et al.2009	USA	Amniotic fluid embolism
Ben-Joseph R. et al., 2009	Israel	Deep venous thrombosis
		Deep venous thrombosis
Patel E. et al., 2015	USA	Pulmonary edema
		Pulmonary embolism
Morris J. et al., 2010	Australia	Pulmonary embolism

Tabl	le 1	. Cont.

SMM—severe maternal morbidity, HELLP—haemolysis, elevated liver enzymes, low platelet, AIP—abnormally invasive placenta, USA—United States of America, UK—United Kingdom.





## 3.2. Characteristics of Included Studies and Risk of Bias

The characteristics of all included studies and their overall quality score are summarized in Table 2. Of the 35 studies, 26 [22–47] were population-based cohort studies, 8 were case-control studies [48–55] and 1 study [56] was a cross-sectional study. Fifteen studies were conducted in North America [22,27–30,33–35,39,45,47,50,54–56], four each in Australia [23,38,40,42] and Israel [24,41,43,44], three in Canada [31,36,37], two each in Finland [48,51], Sweden [32,46] and the United Kingdom [25,49] and one each in the Netherlands [26], South Korea [53] and Taiwan [52].

Author (Year)	Country	Study Type/Design	Data Source/Setting	Study Population	Participants	SMM Definition	Adverse Perinatal Outcomes	Key Findings (Effect of SMM on Respective Perinatal Outcomes)	Quality Score (Rating)
							Perinatal death	↔ IRR 5.43, (95% CI: 0.80–37.00)	
Aarnio K.	Finland	Retrospective cohort study	Linked data (Medical Birth registry and	Pregnant women	760 women	Ischemic	Small for gestational age	↔ IRR 2.01, (95% CI: 0.87–4.64)	7 (Good)
et al., 2017 [48]	Tinuna	(matched) <sup>a</sup>	Helsinki Young Stroke Registry)	0	700 Wollieli	stroke	Low birth weight	$\leftrightarrow \mathrm{IRR}\ 1.37,\ (95\%\ \mathrm{CI:}\ 0.79{-}2.36)$	
			negionyy				5-min Apgarscore < 7	↔ IRR 0.98, (95% CI: 0.33–2.97)	
Alsulyman O.M. et al. 1 1996 [22]				Women who had antepartum		Intrahepatic	Preterm birth	↑ 2-fold (14% of cases vs. 7.6% of controls)	
	USA	Retrospective cohort study	Medical records over 7 years	intrahepatic cholestasis of	158 patients	cholestasis of pregnancy	Small for gestational age	↑ 2-fold (7.6% for cases vs. 3.8 for controls)	5 (Fair)
				pregnancy			Stillbirth/fetal death	2 cases vs. 0 for controls)	
			Linked data <sup>b</sup>	Women delivered a			Preterm birth	Preterm is higher in AIP (25.5% vs. 7.4)↑ RR 5.8, (95% CI: 4.9–7.0) for < 32 weeks↑ RR 3.2, (95% CI: 2.8–3.8) for 33-36 weeks)	
						Hemorrhagic	Neonatal death	↑ ARR 3.1, (99% CI: 2.7–3.5)	
Baldwin H.	Australia	Retrospective		live born or stillborn infant(s)	922,925	abnormally	Stillbirth/fetal death	↑ RR 5.4, (99% CI: 4.0-7.3)	8 (Cood)
et al., 2017 [23]		cohort study		(>20 weeks of gestation)	deliveries	invasive placenta	5-min Apgarscore < 7	↔ RR 1.3, (99% CI: 0.84–2.077) <sup>d</sup>	0 (0000)
							Small for gestational age	↑ RR 1.24, (99% CI: 1.10–1.40) <sup>d</sup>	-
							NICU admission	↑ RR 1.12, (99% CI: 1.27–5.44) <sup>d</sup>	
				All pregnant			Preterm birth	↑ AOR 1.8, (95%CI: 1.1-2.9)	
Ben-Joseph R. et al., 2009 [24]	Israel	Population-based cohort study	Hospital data	women with and without a history of deep venous	212,086 deliveries	Deep venous thrombosis	5-min Apgarscore < 7	↔ OR 1.31 (95% CI: 0.18-9.41)	7 (Good)
				thrombosis			Perinatal death	↔ OR 1.65, (95% CI: 0.52-5.20)	
							Preterm birth	↑ AOR 2.30, (95% CI: 2.11-2.50)	
				All women who		Abnormal	Stillbirth/fetal death	$\leftrightarrow \text{AOR 0.92, (95\% CI: 0.66-1.30)}$	
Bhandari S.	UK	Population-based	Hospital data	gave singleton birth	75.940 women	bleeding of	Neonatal death	$\leftrightarrow \text{AOR 0.92} \text{ (95\% CI: 0.61-1.38)}$	8 (Good)
et al., 2014 [25]	UK	cohort study	cohort study Hospital data	(≥24 weeks of gestation)	75,240 women	unknown origin	Low birth weight (<2500 g)	↔ AOR 0.90, (95% CI: 0.79–1.03)	
							NICU admission	↔ AOR 1.03: 95% CI: 0.94–1.12)	

# **Table 2.** Detailed characteristics of included studies and quality rating.

Author (Year)	Country	Study Type/Design	Data Source/Setting	Study Population	Participants	SMM Definition	Adverse Perinatal Outcomes	Key Findings (Effect of SMM on Respective Perinatal Outcomes)	Quality Score (Rating)
				Women with			Small for gestational age	$\leftrightarrow \text{OR 1.98, (95\% CI: 0.89-4.43)}^{\text{f}}$	
Brouwers L.	Ni-th color de	Retrospective	Hospital data	singleton pregnancies and diagnosed with	215 women	Intrahepatic cholestasis of	Preterm birth	Higher in ICP cases (19.3% vs. 6.8%)	7 (Good)
et al., 2015 [26]	ivenenancis	cohort study	F	intrahepatic	215 women	pregnancy	NICU admission	$\leftrightarrow$ OR 1.91, (95% CI: 0.54–6.74) $^{\rm f}$	7 (000u)
				cholestasis of pregnancy			Perinatal death	↔ OR 1.88, (95% CI: 0.26–13.56) <sup>f</sup> ↑ AOR 1.26, (95% CI: 1.01–1.57)per 10 micro mol/liter	
							Preterm birth	$\uparrow$ OR 7.18, (95% CI: 4.21–12.25) $^{\rm f}$	
Buchbinder A. et al., 2002 [27]		USA Prospective cohort study	, Hospital data	Women who had preeclampsia for their first birth	598 women	Severe gestational hypertension	Small for gestational age	↑ OR 2.55, (95% CI: 1.19–5.43) <sup>f</sup>	- - 7 (Good)
	LICA						Stillbirth/fetal death	$\leftrightarrow$ OR 2.96, (95% CI: 0.77–11.43) $^{\rm f}$	
	USA						Neonatal death	$\leftrightarrow$ OR 1.93, (95% CI: 0.21–17.52) $^{\rm f}$	
							NICU admission	$\uparrow$ OR 2.78, (95% CI: 1.57–4.91) $^{\rm f}$	
							Intraventricular hemorrhage	↔ OR 1.08, (95% CI: 0.06–21.17) <sup>f</sup>	
					1905 women		5-min Apgarscore < 7	↑ AOR 2.40, (5% CI: 1.58–3.65)	
Carte E. et al.,	USA	Retrospective	Hospital data	labor and delivery		Severe	NICU Admission	↑ AOR 3.38, (95% CI: 2.45–4.67)	- 7 (Cood)
2017 [28]	0011	cohort study	1100phul uuu	unit and gave live	1965 Wollien	preeclampsia	Neonatal death	↔ AOR 0.71, (95% CI: 0.35–1.42)	, (000u)
				bitut			Adverse neonatal outcome	↑ AOR 3.66, (95% CI: 2.71–4.93)	
							Preterm birth	↑ AOR 5.39, (95% CI: 4.17–6.98)	
			UK Obstetric	Women with		Intrahepatic	Small for gestational age	↓ RR 0.70, (95% CI: 0.54–0.91)	-
Geenes V. et al. 2014 [49]	UK	Case-control study	Surveillance System	intrahepatic cholestasis of	669 women	cholestasis of	Stillbirth/fetal death	↑ AOR 2.58, (95% CI: 1.03–6.49)	7 (Good)
et al., 2014 [49]		study	(UKOSS)	pregnancy		pregnancy	5-min Apgarscore < 7	↔ AOR 1.92, (95% CI: 0.92–3.99)	_
							NICU admission	↑ AOR 2.68, (95% CI: 1.97–3.65)	

Table 2. Cont.

Author (Year)	Country	Study Type/Design	Data Source/Setting	Study Population	Participants	SMM Definition	Adverse Perinatal Outcomes	Key Findings (Effect of SMM on Respective Perinatal Outcomes)	Quality Score (Rating)
				Women with		HELLP syndrome	Small for gestational age	↑ OR 3.4, (95% CI: 1.0–11.3)	
Haddad B. et al., 2000 [50]	USA	Case-control study	Hospital data	preeclampsia or without the HELLP syndrome	64 women		Intraventricular hemorrhage	↔ OR 0.5, (95% CI: 0.0–6.1)	8 (Good)
				• )•			Neonatal death	$\leftrightarrow \text{OR 0.6, (95\% CI: 0.1–2.8)}$	
							Stillbirth/fetal death	$\leftrightarrow \text{OR 0.0, (95\% CI: 0.0-5.78)}$	
							Preterm birth	$\leftrightarrow \text{OR 0.79, (95\% CI: 0.32-1.99)}$	
Henry D	USA	Retrospective		Pregnant women		Cardiac	Intrauterine growth restricts	↑ OR 4.08, (95% CI: 1.23–13.54)	
et al., 2016 [29]		cohort study	Hospital data	with cardiac diseases	143 women	arrhythmia	Small for gestational age	↔ OR 0.47, (95% CI: 0.10-2.19)	5 (Fair)
							5-min Apgarscore < 7	↔ OR 1.58, (95% CI: 0.57–4.46))	
							NICU admission	↔ OR 0.86, (95% CI: 0.38–1.97)	
Herrera C.	USA	Retrospective cohort study	Administrative and rospective clinical electronic data nort study (from 22 hospital) administered by	Women with intrahepatic cholestasis of pregnancy based on		Severe intrahepatic	Adverse neonatal outcome	↑ ARR 5.6, (95% CI: 1.3–23.5)	
et al., 2018 [30]					785 mothers	cholestasis of pregnancy	Small for gestational age	↔ ARR 2.19, (95% CI: 0.79–6.05)	0 (Fair)
			Intermountain Healthcare System	serum bile acid test			NICU admission	$\leftrightarrow \text{ARR 0.91, (95\% CI: 0.48-1.74)}$	-
							Low birth weight	↑ RR, 4.66, (95% CI: 3.64–5.96)	
				Women with acute kidney injury			Small for gestational age	↑ RR 3.16, (95% CI: 1.90–5.27)	
			Linked health care	treated with			Preterm birth	↑ RR 2.49, (95% CI: 2.03–3.06)	
Hildebrand A. et al., 2015 [31]	Canada	Retrospectivecohort study	databases (seven databases)	dialysis during pregnancy or postpartum period	1,918,789 deliveries	Acute kidney injury	Stillbirth/fetal death	There were zero cases in AKI and 0.1% in non-AKI group	6 (Fair)
				(≥20 weeks of			Neonatal death	↑ risk (2.7% vs. 0.8)	
				gestation)			Perinatal mortality	↑ risk (2.7% vs. 0.4)	_
							Adverse perinatal outcomes	↑ RR 3.40, (95% CI: 2.52–4.58)	

Table 2. Cont.

Author (Year)	Country	Study Type/Design	Data Source/Setting	Study Population	Participants	SMM Definition	Adverse Perinatal Outcomes	Key Findings (Effect of SMM on Respective Perinatal Outcomes)	Quality Score (Rating)
							5-min Apgarscore < 7	↑ AOR 3.46, (95% CI:1.37-8.73)	
							Perinatal death	↑ AOR 5.40, (95% CI: 1.30–22.5)	
						Hemorrhagic	Stillbirth/fetal death	↔ OR 5.42, (95% CI: 0.77–38.0)	
						invasive	Preterm birth	↑ OR 7.72, (95% CI: 5.82–10.2	
Jakobsson M. et al., 2015 [51]						placenta	Neonatal death	↑OR 9.87, (95% CI: 1.41–69.2)	
							NICU admission	↑ AOR 2.75, (95% CI:1.54–4.91)	•
							Low birth weight (<2500 g)	↑ AOR 8.30, (95% CI: 4.52–15.2)	
			Nordic Obstetric Surveillance Study (NOSS)	Cases: women developed obstetric near-miss events	145,743		5-min Apgarscore < 7	↑ AOR 3.75, (95% CI: 1.28–11.0)	
				(uterine rupture, abnormally invasive placenta, and emergency peripartum hysterectomy). Controls: all other births			Preterm birth	↑OR 5.99, (95% CI: 3.71–9.68)	
	Finland	Case-control					NICU admission	↑ AOR 11.8, (95% CI: 9.0–15.6)	7 (Good)
	1 111111	study			women	Hysterectomy	Low birth weight (<2500 g)	↔ AOR 1.74, (95% CI: 0.67–4.53)	-
							Stillbirth/fetal death	↑ OR 10.3, (95% CI: 1.50–71.3)	
							Neonatal death	$\leftrightarrow \text{OR 9.2, (95\% CI: 0.56-151.2)}$	
							Perinatal death	↑ AOR 11.8, (95% CI: 5.39–25.8)	-
							Preterm birth	↔ OR 1.33 (95% CI: 0.71–2.49)	
							NICU admission	↑ AOR 1.98 95% CI: 1.28–3.04)	
						Uterine	Neonatal death	↑ OR 10.2, (95% CI: 2.57–40.6)	
						raptare	Stillbirth/fetal death	↑ OR 16.8, (95% CI: 7.67–36.9)	
							Low birth weight (<2500 g)	↔ AOR 1.29, (95% CI: 0.62–2.66)	
							5-min Apgarscore < 7	↑ AOR 10.5, (95% CI: 6.82–16.3)	
Kaczmarczyk		Prospective	Swedish Birth	Women with live	300 200	Uterine	Low birth weight (<2500 g)	↔ AOR 0.58, (95% CI: 0.31–1.08)	) 6 (Fair)
M. et al., 2007	Sweden	Sweden Prospective cohort study	ospective Register (population nort study based)	single births	women	rupture	Preterm birth	↔ AOR 0.34, (95% CI: 0.08–1.45)	
[32]						women rup.	women rupture	Neonatal death	↑ AOR 65.62, (95% CI: 32.60–132.08)

Table 2. Cont.

Author (Year)	Country	Study Type/Design	Data Source/Setting	Study Population	Participants	SMM Definition	Adverse Perinatal Outcomes	Key Findings (Effect of SMM on Respective Perinatal Outcomes)	Quality Score (Rating)
			Linked population-based	Cases: women who have stroke during			Preterm birth	↔ AOR 0.72, (95% CI: 0.35 to 1.50)	
Kang J. et al., 2010 [52]	Taiwan	Case-control study	datasets (Taiwan National Health	their pregnancy period Controls:	1,449 women	Stroke	Low birth weight (<2500 g)	↔ AOR 0.75, (95% CI: 0.36 to 1.54)	7 (Good)
			Insurance Research Dataset (NHIRD) and the national birth certificate registry)	randomly selected women with no history of stroke			Small for gestational age	↔ AOR 0.84, (95% CI: 0.52 to 1.36)	
Kao D. et al., 2013 [33]	USA	Retrospective cohort study	Hospital data	Women who were admitted for delivery	4,003,914 women	Peripartum cardiomyopathy	, Stillbirth/fetal death	↑ OR 3.74, (95% CI: 1.69–5.64)	6 (Fair)
							Adverse perinatal outcome	$\leftrightarrow \text{AOR 4.28, (95\% CI: 0.71-25.83)}$	
				All women			Preterm birth	$\uparrow$ OR 2.49, (95% CI: 1.36–4.57) $^{\rm f}$	-
Kawakita T.	USA	Retrospective	Hospital data	diagnosed with intrahepatic	233 women	Intrahepatic cholestasis of	Stillbirth/fetal death	$\leftrightarrow$ OR 17.71, (0.94–333.16) $^{\rm f}$	_ 8 (Good)
et al., 2015 [34]	0.071	(multicentre)		cholestasis of	255 Wollieft	pregnancy	NICU admission	$\leftrightarrow$ OR 1.37, (95% CI: 0.72–2.58) $^{\rm f}$	0 (000u)
				pregnancy			Low birth weight	$\uparrow$ OR 2.44, (95% CI: 1.07–5.56) $^{\rm f}$	
							Intrauterine growth restricts	↑ OR 1.66, (95% CI: 0.54–5.11) <sup>f</sup>	
				Women with singleton pregnancy	121	HELLP	Neonatal death	↑ OR 11.5, (95% CI: 1.2–110.4)	
Kim H. et al.,	South Korea	Matched case	Hospital data				Intraventricular hemorrhage	↑ OR 39.0, (95% CI: 7.4–206.4)	. 4 (Poor)
2006 [53]	bouurreneu	control study <sup>c</sup>	1	and complicated by HELLP syndrome	pregnancies	syndrome	NICU admission	↑ OR 19.0, (95% CI: 4.8–75.8)	
							5-min Apgarscore < 6 *	↔ OR 0.4, (95% CI: 0.1–1.2)	
		<b>D</b>	Hospital data	All women and			Stillbirth	↑ AOR 5.9, (95% CI: 2.0–17.4)	
Kramer M. et al., 2012 [36]	Canada	Retrospective cohort study	collected by Canadian Institute for Health Information (CIHI)	in Canadian Institute of Health	4,508,462 deliveries	Amniotic fluid embolism	Intrauterine growth restricts	↑ AOR 1.6, (95% CI: 0.7–3.5)	7 (Good)
			Information (CIHI)	Information (CIHI) database		-	Low birth weight	↑ AOR 1.8, (95% CI: 1.8–1.8)	
Kramer M. et al., 2013 [35]	USA	Population-based cohort study	Hospital data (US Nationwide Inpatient Sample)	Women with amniotic fluid embolism	8,571,209 deliveries	Amniotic fluid embolism	Stillbirth	↔ AOR 2.1, (95% CI: 0.8–5.5)	8 (Good)

Table 2. Cont.

Author (Year)	Country	Study Type/Design	Data Source/Setting	Study Population	Participants	SMM Definition	Adverse Perinatal Outcomes	Key Findings (Effect of SMM on Respective Perinatal Outcomes)	Quality Score (Rating)
	Canada						Small for gestational age	↑ AOR 2.6, (95% CI: 2.3–3.0)	8 (Good)
Liu S. et al., 2011 [37]		Population-based	Hospital data	Women with eclampsia and their	1,910,729	Eclampsia	Preterm birth	↑ AOR 4.808, (95% CI: 4.330–5.338) <sup>e</sup>	
2011[07]		conort study		deliveries	women		NICU admission	↑ AOR 2.8, (95% CI: 2.4–3.2)	
							Stillbirth/fetal death	↑ AOR 2.4, (95% CI: 1.5–3.9)	
							Neonatal death	↑ AOR 2.9, (95% CI: 1.6–5.5)	
							Preterm birth	↑ AOR 4.31, (95% CI: 3.84–4.84)	
McCormack et al., 2008 [38]		Retrospective		Women with	28.014	Abnormal bleeding of	Stillbirth/fetal death	Stillbirth is not associated with ABUO and none-ABUO cases (0.90% vs. 0.95%	
	Australia	cohort study	Hospital data	singleton deliveries	deliveries	unknown	5-min Apgar < 7	↔ AOR 1.05, (95% CI: 0.76–1.44)	- 7 (Good) - -
						origin	NICU admission	↑ AOR 1.23, (95% CI: 1.01–1.51)	
							Neonatal death	ABUO is associated with early neonatal death (1.3 versus 0.3%)	
							Perinatal death	↔ AOR 0.67, (95% CI: 0.43–1.08)	
				Women who have			Intrauterine growth restricts	↔ AOR 1.11, (95% CI: 0.82–1.50)	
McPherson J. et al., 2013 [39]	USA	Retrospective cohort study	Hospital data	non-anomalous pregnancies with	47,118 women	Seizure disorder	Intrauterine growth restricts	↔ AOR 0.82, (95% CI: 0.56–1.20)	7 (Good)
				complete outcome			Stillbirth	↑ OR 1.70, (95% CI: 0.55–5.28)	
				uata			Preterm birth	$\leftrightarrow \text{AOR 1.06, (95\% CI: 0.81-1.38)}$	
		<b>D</b>		Women who had			Stillbirth	↑ AOR 5.97, (95% CI: 3.09-11.6)	
Morris J. et al., 2010 [40]	Australia	Retrospective cohort study	Linked dataset	deliveries $\geq 20$	380,459 women	Pulmonary embolism	Preterm birth	↑ AOR 2.18, (95% CI: 1.54–3.09)	8 (Good)
2010 [40] Aus		,		weeks of gestation	women		Small for gestational age	↔ AOR 1.23, (95% CI: 0.84–1.81)	-
		D 1 ( 1 1		All women with		TT	Perinatal death	↑ OR 17.2, (95% CI: 7.3–38.7)	
Ofir K. et al., 2003 [41]	Israel	Population based cohort study	Hospital data	and delivered with	117,685 women	Uterine rupture	Low birth weight	$\uparrow$ OR 1.21, (95% CI: 0.43–3.39) $^{\rm f}$	4 (poor)
		J		and without uterine rupture			5-min Apgarscore < 5	↑ OR 42.8, (95% CI: 12.8–126.8) <sup>f</sup>	

## Table 2. Cont.

Author (Year)	Country	Study Type/Design	Data Source/Setting	Study Population	Participants	SMM Definition	Adverse Perinatal Outcomes	Key Findings (Effect of SMM on Respective Perinatal Outcomes)	Quality Score (Rating)
						Cardiac arrest	Stillbirth	↑ OR 14.84, (95% CI: 10.97–20.07)	
Patel E. et al., 2015 [56]						Pulmonary edema	Stillbirth	↑ OR 7.66, (95% CI: 5.94–9.89)	
						Acute respiratory distress	Stillbirth	↑ OR 12.25, (95% CI: 10.30–14.57)	- 8 (Good)
	USA	Cross-sectional study	Hospital data (>1000	All delivery records containing of	12,524,119	Pulmonary embolism	Stillbirth	↑ OR 5.06, (95% CI: 4.00–6.42)	
		(Prospective)	nospitaisj	stillbirth	denveries	Deep venous thrombosis	Stillbirth	↑ OR 2.89, (95% CI: 2.29–3.64)	
						Sepsis	Stillbirth	↑ OR 12.29, (95% CI: 10.94–13.80)	
						Acute renal failure	Stillbirth	↑ OR 20.00, (95% CI: 18.28–21.88)	-
						Postpartum hemorrhage	Stillbirth	↑ OR 1.65, (95% CI: 1.58–1.72)	
						Chorioamnionit	is Stillbirth	↑ OR 2.74, (95% CI: 2.65–2.84)	
					640 motionto		Preterm birth	↑ 3-fold, (19.3% vs. 6.8%)	
							5-min Apgarscore < 7	↑1.3-fold, (2.2% vs. 1.3%)	
Rioseco, A.J.	LISA	Case control		Women with		Intrahepatic cholestasis of	Small for gestational age	↑1.4-fold, (6.3% vs. 4.4%)	6 (Fair)
et al. 1994 [54]	USA	study	weatcal record	cholestasis	o io puterito	pregnancy	Stillbirths	Higher in ICP cohort (12 vs.9 per 1000 births)	0 (i uii)
							Neonatal deaths	Higher in ICP cohort (6 vs. 3 per 1000 births)	
							Perinatal death	Higher in ICP cohort (18 vs.612 per 1000 births)	-
							Preterm birth	↔ RR 1.9, (95% CI: 0.4–8.6)	6 (Fair)
Roberts C. et al., 2010 [42]	Australia	Population-based cohort study	ased Linked data (birth, hospital, and death dy data)	All women and deliveries	606,393 deliveries	Amniotic fluid embolism	Perinatal death	Perinatal death rate was 32% (95% CI: 12–56)	
							Stillbirth/fetal death	Stillbirth was higher in AFE group (26% vs. 0%)	

Table 2. Cont.

Author (Year)	Country	Study Type/Design	Data Source/Setting	Study Population	Participants	SMM Definition	Adverse Perinatal Outcomes	Key Findings (Effect of SMM on Respective Perinatal Outcomes)	Quality Score (Rating)
							Preterm birth	↑ AOR 2.48, (95% CI: 1.49–4.12)	
Ronel D. et al., 2012 [43]	Israel	Population-based cohort study	Perinatal database	All singleton births	240,189 deliveries	Uterine rupture	5-min ApgarScore < 5 *	↑ OR 9.59, (95% CI: 6.45–14.24)	6 (Fair)
							Perinatal death	↑ AOR 17.4, (95% CI: 9.87–23.88)	
							Small for gestational age	↔ OR 1.19, (95% CI: 0.89–1.58) <sup>f</sup>	
Sheiner E. et al., 2005 [44]	Israel	Population-based	Hospital data	Deliveries complicated by	154,311	Postpartum	5-min Apgarscore < 7	$\leftrightarrow$ OR 0.75, (95% CI: 0.24–2.330) $^{\rm f}$	7 (Good)
	151801	cohort study	1100prini unu	postpartum hemorrhage	deliveries	hemorrhage	Preterm birth	$\leftrightarrow$ OR 1.51, (95% CI: 0.89-2.57) $^{\rm f}$	7 (0000)
				nemormage			Low birth weight	$\leftrightarrow \text{OR 0.94, (95\% CI: 0.72, 1.23)}^{f}$	
							Perinatal death	↑ by 3.5%	
Spiliopoulos		Population-based	Perinatal linked data	All births from 1997	1.004.116	Amniotic fluid	NICU admission	6-fold, (48.6% vs. 8.1%)	
et al., 2009 [45]	USA	cohort study	set	to 2005	births	embolism	5-min Apgarscore < 7	Low Apgar score is higher in AFE cases (22.2% vs. 0.5.6%	6 (Fair)
Vilchez G.	USA	USA Cases-control USA study (Prospective)	CDC and National Centre for Health	Cases: women with uterine rupture. Controls: Women with no uterine	5690 women	Uterine	NICU admission	↑ AOR 3.88, (95% CI: 3.28–4.60)	7 (Good)
et al., 2017 [55]			Statistics (NCHS) birth database		3070 women	rupture	Low birth weight	↑ OR 9.2, (95% CI: 7.2–11.6)	7 (300a)
				raptare			Preterm birth	↑ OR 2.93, (95% CI: 2.71–3.17) <sup>f</sup>	
			Linked data (Hospital				Stillbirth	↔ AOR 0.92, (95% CI: 0.52–1.62)	
Wikstrom Shemer E.	Sweden	Population-based cohort study	data plus Swedish Medical Birth Register	Women with singleton deliveries	1,213,668 deliveries	Intrahepatic cholestasis of	5-min Apgarscore < 7	↑ AOR 1.45, (95% CI: 1.14–1.85)	6 (Fair)
et al., 2013 [40]			(MBR))			pregnancy	Neonatal death	↔ AOR 0.45, (95% CI: 0.15–1.40)	
							Small for gestational age	↓ AOR 0.44, (95% CI: 0.32–0.60)	
Yang and	USA	Population-based	d US Maternal and	Women with	9953 hirths	hs Antepartum hemorrhage	Preterm birth	$\uparrow$ OR 2.81, (95% CI: 2.48–3.18) $^{\rm f}$	4 (Poor)
Savitz 2001 [47]	0011	cohort study	Infant Health Survey	vaginal bleeding during pregnancy	2700 bit ulb		Small for gestational age	↑ OR 1.25, (95% CI: 1.07–1.46) <sup>f</sup>	

Table 2. Cont.

<sup>a</sup> Matched by maternal age, year of delivery, parity, residence and number of newborns; <sup>b</sup> Data link is from NSW Register of Births, Deaths and Marriages (2003–2013) (death data), NSW Perinatal Death Review Database (2003–2009) (stillbirth data) and classification resources; <sup>c</sup> Samples were matched by gestational age, race, infant gender, and mode of delivery; <sup>d</sup> pooled estimates (using fixed effect model) from stratified data presented for pre-term and term births neonates; <sup>e</sup> pooled estimate (fixed effect model) from stratified; data presented for very preterm (22–31 weeks) and mild preterm (32–36 weeks) estimates; <sup>f</sup> effect estimate computed from available data in the study; ↑ Significant positive association; ↓ Significant negative association; ↔ No significant association. Abbreviations: RR—relative risk, IRR—incidence risk ratio, AIP—abnormally invasive placenta, HELLP—hemolysis, elevated liver enzymes, low platelet, OR—odds ratio, AOR—adjusted odds ratio, NICU—neonatal intensive care unit, USA—United States of America, UK—United Kingdom.

The methodological quality of the studies were rated as: good (21 studies) [23–28,34–40,44,48–52,55,56], fair (11 studies) [22,29–33,42,43,45,46,54] and poor (3 studies) [41,47,53]. Five studies had a NOS score < 6 [22,29,41,47,53] and were deemed to have high risk of bias. Most of the included studies scored high in the participant selection and outcome assessment categories, while most of the variability between studies was in the comparability category shown in Table 2. The pooled global effect, citations and Higgins I<sup>2</sup> values for each sub-group of SMM and adverse perinatal outcomes are shown in Table 3.

	Effect Estimate (Odds Ratio (M-H, Random, 95% CI))	Citations	Heterogeneity (I <sup>2</sup> ), %
Preterm birth	3.11 (2.56–3.78)	[22–27,29,31,32,34,37,38, 40,42,46,47,49,51,52,54]	95
Hemorrhagic disorders	3.42 (2.55–4.58)	[23,25,32,38,47,51]	96
Hypertensive disorders	6.79 (6.06–7.60)	[27,37]	0
Cardiovascular disorders	0.78 (0.44–1.37)	[29,52]	0
Hepatic disorders	3.19 (2.46–4.13)	[22,26,34,46,49,54]	64
Thromboembolic disorders	2.40 (1.67–3.46)	[24,40,42]	30
Acute kidney disorders	3.31 (2.44-4.50	[31]	NA
Test for sub-group differences			<b>95.5</b> ( $X^2 = 110.30$ , $p < 0.0001$ )
Small for gestational age (SGA)	1.33 (0.98–1.81)	[22–24,26,27,29–31,37,40, 44,46–50,52,54]	93
Hemorrhagic disorders	1.09 (0.83–1.42)	[23,44,47]	83
Hypertensive disorders	2.86 (2.51–3.25)	[27,37,50]	0
Cardiovascular disorders	1.01 (0.53–1.90)	[29,48,52]	53
Hepatic disorders	0.95 (0.51, 1.77)	[22,26,30,46,49,54]	86
Acute renal disorders	3.52 (2.08–5.97)	[31]	NA
Thromboembolic disorders	1.48 (1.09–1.99)	[24,40]	0
Test for sub-group differences			<b>92.3</b> ( $X^2 = 65.20$ , $p < 0.0001$ )
Low birth weight (<2500 g)	2.20 (1.56–3.09)	[23,31,34,38,41,43,44,48, 51,52,55]	94
Hemorrhagic disorders	2.31 (1.57–3.40)	[23,38,41,43,44,51,55]	95
Cardiovascular disorders	0.91 (0.61–1.38)	[48,52]	0
Acute renal disorders	6.39 (4.62–8.83)	[31]	NA
Hepatic disorders	2.44 (1.07-5.56)	[34]	NA
Test for sub-group differences			<b>94.5</b> ( $X^2 = 54.50$ , $p < 0.0001$ )
5-min Apgar score < 7	3.66 (2.41–5.56)	[23,24,28,29,38,41,43–46, 48,49,51,53,54]	93
Hemorrhagic disorders	4.16 (2.54–6.81)	[23,38,41,43,44,51]	92
Hypertensive disorders	4.61 (1.17–18.20)	[28,53]	80
Cardiovascular disorders	1.26 (0.63–2.52)	[29,48]	0
Hepatic disorders	1.97 (0.95–4.05)	[46,49,54]	74
Thromboembolic disorders	8.93 (0.07–1086.45)	[24,45]	95
Test for sub-group differences			56.5 ( $X^2 = 9.20, p = 0.06$ )

 Table 3. Adverse perinatal outcomes, number of reports from studies, effect estimate, citations, and heterogeneity.

	Effect Estimate (Odds Ratio (M-H, Random, 95% CI))	Citations	Heterogeneity (I <sup>2</sup> ), %
NICU admission	3.22 (2.45–4.25)	[23,25–29,34,37,38,45,49, 51,53,55]	97
Hemorrhagic disorders	3.34 (2.26–4.94)	[23,25,38,51,55]	98
Hypertensive disorders	3.63 (2.63–5.02)	[27,28,37,53]	64
Cardiovascular disorders	0.86 (0.37-1.99)	[29]	NA
Hepatic disorders	1.89 (1.11–3.20)	[26,34,49]	45
Thromboembolic disorders	10.81 (6.02–19.39)	[45]	NA
Test for sub-group differences			86.8 ( $X^2 = 30.30$ , p < 0.0001)
Stillbirth	4.87 (2.63–69.01)	[22,23,25,27,29,31,33,34, 37,38,40,42,46,49,51,53, 54,56]	99
Hemorrhagic disorders	3.40 (1.88-6.15)	[23,25,38,51,56]	96
Hypertensive disorders	2.74 (1.73-4.34)	[27,37,53]	0
Cardiovascular disorders	15.24 (1.29–180.60)	[29,33,56]	98
Hepatic disorders	1.95 (0.82–4.67)	[22,34,46,49,54]	58
Acute renal disorders	15.16 (4.41–52.14)	[31,56]	32
Thromboembolic disorders	5.07 (3.12-8.24)	[40,42,56]	91
Test for sub-group differences			<b>68.3</b> ( $X^2 = 15.70$ , $p < 0.008$ )
Neonatal death	4.02 (2.45–6.59)	[23,25,27,28,31,32,37,38, 46,50,51,53,54]	89
Hemorrhagic disorders	7.33 (3.06–17.53)	[23,25,32,38,51]	94
Hypertensive disorders	3.00 (1.78–5.07)	[27,28,37,50,53]	39
Hepatic disorders	0.92 [0.47–1.79]	[46,54]	0
Acute renal disorders	3.28 (1.35–7.97)	[31]	NA
Test for sub-group differences			<b>80.4</b> ( $X^2 = 15.30$ , $p = 0.002$ )
Perinatal death	4.74 (2.47–9.12)	[24,26,31,38,41,43,44,48, 51,54]	89
Hemorrhagic disorders	6.18 (2.55–14.96)	[38,41,43,44,51]	93
Cardiovascular disorders	3.92 (0.79–19.57)	[48]	NA
Hepatic disorders	1.63 (0.81–3.28)	[26,54]	0
Acute renal disorders	7.13 (2.93–17.35)	[31]	NA
Thromboembolic disorders	1.66 (0.53–5.21)	[24]	NA
Test for sub-group differences			<b>60.6</b> ( $X^2 = 10.20, p = 0.04$ )

Table 3. Cont.

Funnel plots for each adverse perinatal outcome to assess the effect of publication bias are presented in Supplementary File 2. Sensitivity analyses were also performed for each adverse outcome after the exclusion of low-quality studies [22,29,41,47,53] but they did not affect the significance of any of the outcomes of interest.

# 3.3. Meta-Analysis: Effect of SMM on Adverse Perinatal Outcomes

#### 3.3.1. Preterm Birth

This outcome was reported in 20 studies [22–27,29,31,32,34,37,38,40,42,46,47,49,51,52,54]. Overall, women who had SMM were three times more likely to experience preterm birth (OR 3.11; 95% CI: 2.56–3.78). However, the risk of preterm birth was variably influenced depending on the underlying etiology of SMM (Chi<sup>2</sup> = 110.58, p < 0.0001, I<sup>2</sup> = 95.50%). Obstetric hemorrhage (OR 3.42, 95%)

CI: 2.55–4.58), hypertensive (OR 6.79, 95% CI: 6.06–7.60), hepatic (OR 3.19, 95% CI: 2.46–4.13) and thromboembolic disorders (OR 2.40, 95% CI: 1.67–3.46) were all associated with increased odds of preterm birth. There was, however, no significant association between SMM and preterm birth for cardiovascular disorders (Figure 2).

	Cas	e	Con	trol		Odds Ratio		Od	ds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ra	ndom, 95% Cl	
1.1.1 Haemorrhagic disorders										
Kaczmarczyk M et al. 2007 (UR)	3	9288	274	300200	2.0%	0.35 [0.11, 1.10]	-	· · ·	+	
Jakobsson M et al. 2015 (UR)	9	118	8464	147551	3.7%	1.36 [0.69, 2.68]				
Bhandari S et al. 2014 (APH)	1060	7517	4397	68423	6.5%	2.39 [2.22, 2.57]			•	
Yang and Savitz et al. 2001 (APH)	589	1272	1501	6386	6.4%	2.81 [2.48, 3.18]			-	
McCormack et al. 2008 (APH)	567	1431	3897	26583	6.4%	3.82 [3.42, 4.27]			+	
Baldwin H et al. 2017 (AIP)	583	2285	68259	920643	6.5%	4.28 [3.89, 4.70]			+	
Jakobsson M et al. 2015 (Hyst)	11	32	8464	147551	3.4%	8.61 [4.15, 17.86]				
Jakobsson M et al. 2015 (AIP)	27	61	8464	147551	4.6%	13.05 [7.87, 21.64]			-	-
Subtotal (95% CI)		22004		1764888	39.5%	3.42 [2.55, 4.58]			•	
Total events	2849		103720							
Heterogeneity: Tau² = 0.13; Chi² = ^ Test for overall effect: Z = 8.25 (P <	171.25, df 0.00001)	= 7 (P <	0.00001);	l² = 96%						
1.1.2 Hypertensive disorders										
Liu S et al. 2011	124	1225	116105	1707471	6 4 96	6 77 16 02 7 601			+	
Duchhinder & et al. 2002	424	1323	110100	1/0/4/1 520	4 4 90	7 10 14 21 12 261				
Subtotal (95% CI)	43	1304	33	1788000	4.4 %	6 70 [6 06 7 60]				
Tatal avente	407	1354	446004	1700000	10.0%	0.79 [0.00, 7.00]			•	
Total events	407	(D) 0 (	110284	,						
Heterogeneity: Tau* = 0.00; Chi* = 0 Test for overall effect: Z = 33.23 (P	2.05, df = 1 < 0.00001	(P = 0.8 )	33); 1* = 09	6						
1.1.3 Cardiovascular disorders										
Kang J 2010	9	161	92	1288	3.5%	0.77 [0.38, 1.56]		·	•	
Henry D et al. 2016	7	36	25	107	2.6%	0.79 [0.31, 2.02]				
Subtotal (95% CI)		197	20	1395	6.1%	0.78 [0.44, 1.37]				
Total events	16		117						-	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0 Test for overall effect: Z = 0.87 (P =	0.00, df = 1 0.38)	(P = 0.9	96); I² = 09	6						
1.1.4 Henotic disorders	,									
1.1.4 Hepauc disorders										
Alsulyman OM et al 1996	11	79	6	79	2.3%	1.97 [0.69, 5.61]				
Brouwers L et al. 2015	19	107	9	108	3.0%	2.38 [1.02, 5.52]				
Kawakita T et al. 2015	30	81	29	152	4.0%	2.49 [1.36, 4.57]				
Wikstrom SE et al. 2013	721	5477	59430	1213668	6.5%	2.94 [2.72, 3.19]				
Rioseco, AJ et al. 1994	62	320	22	320	4.5%	3.26 [1.95, 5.44]				
Geenes V et al. 2014 Subtotal (95% CI)	164	669 6733	144	2205 1216532	6.0% 26.2%	4.65 [3.64, 5.93] 3.19 [2.46, 4.13]			•	
Total events	1007		59640							
Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup> = 1 Test for overall effect: Z = 8.80 (P <	13.76, df = 0.00001)	5 (P = 0	.02); I <sup>2</sup> = 6	4%						
115 Thromboombolic disorders										
Deborte C et al. 2010	2	10	20445	606202	1 400	1 60 10 20 7 221				
Roberts Clet al. 2010	2	19	39415	000393	1.4%	1.09 [0.39, 7.33]				
Ben-Joseph R et al. 2009	20	122	20349	211964	4.7%	1.85 [1.14, 2.98]				
Morris J et al. 2010 Subtotal (05% CI)	47	230	40814	510177	5.6%	2.95 [2.14, 4.07]				
Subtotal (95% CI)		3/1		1328534	11.7%	2.40 [1.67, 3.46]			-	
Total events Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 2 Test for overall effect: $Z = 4.73$ (P <	69 2.86, df = 2 0.00001)	? (P = 0.2	100578 24); I² = 30	1%						
1.1.6 Acute kidney disorders										
Hildebrand A et al. 2015 Subtotal (95% CI)	61	188	242844	1918601	5.7%	3.31 [2.44, 4.50]			-	
Total events	61	100	242044	1010001	5.1 /0	0.01 [2.44, 4.00]			-	
Heterogeneity: Not applicable Test for overall effect: Z = 7.69 (P <	0.00001)		242044							
Total (95% CI)		30887		8017950	100.0%	3 11 [2 56 3 79]			•	
	1100	30007	6004.00	0011930	100.0%	J.11 [2.30, 3.70]			•	
Total events	4469	- 24 /5	023183	12-050			_	1		
Heterogeneity: Tau* = 0.15; Chi* = 3	587.57, df	= 21 (P ·	× 0.00001	), in= 95%			0.05	0.2	1 5	20
Test for overall effect: Z = 11.39 (P Test for subgroup differences: Chi <sup>a</sup>	< 0.00001) = 110.33	) df=5(F	P < 0.0000	)1), I² = 95.	5%					

**Figure 2.** Forest plot of studies assessing association of Severe maternal morbidity (SMM) and preterm birth.

#### 3.3.2. Small for Gestational Age Infant

SGA as an outcome was reported in 18 studies [22–24,26,27,29–31,37,40,44,46–50,52,54]. Although the pooled effect of SMM for SGA was not significant (OR 1.33, 95% CI: 0.98–1.81), women who had SMM associated with hypertensive disorders (OR 2.86, 95% CI: 2.51–3.25) or thromboembolic disorders (OR 1.48, 95% CI: 1.09–1.99) had greater odds of having a SGA infant. The effect of SMM on SGA also showed significant sub-group differences (Chi<sup>2</sup> = 65.16, p < 0.0001, I<sup>2</sup> = 92.30%) (Figure 3).

04. d 0. b	Cas	e	Con	trol	Malake	Odds Ratio	Odds Ratio
Study of Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.2.1 Haemornagic disorders	20		0000	450045	7.00	0.0000000000	
Sheiner Elet al. 2005 (PPH)	28	1000	9833	153645	7.0%	0.64 [0.44, 0.94]	
rang and Savizetal. 2001 (APH)	240	1272	1020	0380	7.0%	1.25 [1.07, 1.46]	+
Subtotal (95% CI)	204	4223	91435	920043 1080674	22 3%	1.29 [1.14, 1.40]	L
Fotal events	559	1220	102204	1000014	221070	100 [0.00, 1142]	Ť
Jotarogeneity: Tou? = 0.04: Chi? = 1	1 02 df-	2 /0 - 0	002234	0.000			
Fest for overall effect: Z = 0.61 (P = 1	0.54)	20 -0	.003),1 =	05%			
1.2.2 Hypertensive disorders							
Buchbinder A et al. 2002	10	69	33	529	5.3%	2.55 [1.19, 5.43]	<b>-</b> _
Haddad B et al. 2000	10	27	5	29	3.4%	2.82 [0.82, 9.76]	
Liu S et al. 2011	273	1325	148360	1787471	7.7%	2.87 [2.51, 3.28]	+
Subtotal (95% CI)		1421		1788029	16.3%	2.86 [2.51, 3.25]	•
Fotal events	293		148398				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0	.09, df = 2	(P = 0.9)	96); I <sup>2</sup> = 09	6			
Test for overall effect: Z = 15.77 (P <	0.00001)	2					
1.2.3 Cardiovascular disorders							
Henry D et al. 2016	2	36	12	107	2.6%	0.47 [0.10, 2.19]	
<ang 2010<="" j="" td=""><td>23</td><td>161</td><td>218</td><td>1288</td><td>6.6%</td><td>0.82 [0.51, 1.30]</td><td>-++</td></ang>	23	161	218	1288	6.6%	0.82 [0.51, 1.30]	-++
Aarnio K et al. 2017	13	207	30	803	5.7%	1.73 [0.88, 3.37]	±
Subtotal (95% CI)		404		2198	14.9%	1.01 [0.53, 1.90]	-
Fotal events	38		260				
Heterogeneity: Tau² = 0.16; Chi² = 4 Fest for overall effect: Z = 0.02 (P = 1	24, df = 2 0.98)	(P = 0.1	2); I <sup>2</sup> = 53	3%			
I.2.4 Hepatic disorders							
Herrera C et al. 2018	0	0	0	0		Not estimable	
Nikstrom SE et al. 2013	59	5477	26948	1213668	7.4%	0.48 [0.37, 0.62]	-
Brouwers L et al. 2015	5	107	8	108	3.7%	0.61 [0.19, 1.94]	
Geenes V et al. 2014	70	669	193	2205	7.3%	1.22 [0.91, 1.63]	+
Rioseco, AJ et al. 1994	20	320	14	320	5.5%	1.46 [0.72, 2.94]	
Alsulyman OM et al 1996	6	79	3	79	2.9%	2.08 [0.50, 8.64]	
Subtotal (95% CI)	400	0052	07400	1210300	20.0%	0.95[0.51, 1.77]	
Heterogeneity: Tau <sup>2</sup> = 0.36; Chi <sup>2</sup> = 2 Test for overall effect: Z = 0.17 (P = 1	8.85, df = 0.87)	4 (P < 0	27166 .00001); I	<b>=</b> 86%			
1.2.5 Acute renal disorders							
Hildebrand A et al. 2015 Subtotal (95% CI)	15	188 <b>188</b>	46080	1918601 1918601	6.3% 6.3%	3.52 [2.08, 5.97] 3.52 [2.08, 5.97]	•
Fotal events	15		46080				
Heterogeneity: Not applicable Fest for overall effect: Z = 4.68 (P < 1	0.00001)						
2.6 Thromboembolic disorders	,						
Apric Latal 2010	22	220	62029	610177	7.0%	1 42 00 00 2 071	L
Noms Jetal. 2010 Pop. Jocoph Piotol. 2000	32	230	20004	211064	6.49	1.42 [0.98, 2.07]	
Subtotal (95% CI)	18	352	20964	722141	13.4%	1.48 [1.09, 1.99]	•
Fotal events	50		73022				-
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0 Fest for overall effect: Z = 2.55 (P = 1	1.10, df = 1 0.01)	(P = 0.7	'5); I <sup>2</sup> = 09	б			
Fotal (95% CI)		13240		6728023	100.0%	1.33 [0.98, 1.81]	•
Fotal events	1114		397220				
Heterogeneity: Tau <sup>2</sup> = 0.31: Chi <sup>2</sup> = 2	32.40, df=	= 16 (P <	0.00001	); I <sup>z</sup> = 93%			
	0.07	×.					0.05 0.2 1 5 20

**Figure 3.** Forest plot of studies assessing association between SMM and infants being small for gestational age.

# 3.3.3. Low Birth Weight

The association between SMM and LBW was assessed in 11 studies [23,31,34,38,41,43,44,48,51,52,55]. There was substantial heterogeneity in the results. The pooled effect demonstrated higher odds of LBW in women with SMM (OR 2.20, 95% CI: 1.56–3.09), with only severe hemorrhage exhibiting increased odds of this outcome (OR 2.31, 95% CI: 1.57–3.40) (Figure 4).

	Cas	e	Con	trol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.3.1 Haemorrhagic disorders							
McCormack et al. 2008 (APH)	3	5042	274	300200	4.8%	0.65 [0.21, 2.03]	
Vilchez G et al. 2017	60	666	14596	153645	9.4%	0.94 [0.72, 1.23]	-
Ronel D et al. 2012 (UR)	4	42	9411	117643	5.3%	1.21 [0.43, 3.39]	
Jakobsson M et al. 2015 (UR)	9	118	6569	147551	7.2%	1.77 [0.90, 3.50]	<b>—</b>
Sheiner E et al. 2005 (PPH)	20	138	19204	240051	8.4%	1.95 [1.21, 3.13]	
Baldwin H et al. 2017 (AIP)	935	7517	4537	68423	9.9%	2.00 [1.86, 2.16]	•
Ofir K et al. 2003 (UR)	487	1431	3294	26583	9.9%	3.65 [3.25, 4.09]	+
Jakobsson M et al. 2015 (AIP)	16	61	6569	147551	7.8%	7.63 [4.31, 13.51]	
Jakobsson M et al. 2015 (Hyst)	9	32	6569	147551	6.6%	8.40 [3.88, 18.16]	
Subtotal (95% CI)		15047		1349198	69.3%	2.31 [1.57, 3.40]	•
Total events	1543		71023				
Heterogeneity: Tau <sup>2</sup> = 0.26; Chi <sup>2</sup>	= 154.38,	df = 8 (P	< 0.0000	1); I <sup>2</sup> = 95%			
Test for overall effect: Z = 4.25 (F	< 0.0001	1					
1.3.2 Cardiovascular disorders							
Kang J 2010	9	161	91	1288	7.0%	0.78 [0.38, 1.58]	
Aarnio K et al. 2017	21	207	82	803	8.2%	0.99 [0.60, 1.65]	
Subtotal (95% CI)		368		2091	15.2%	0.91 [0.61, 1.38]	•
Total events	30		173				
Heterogeneity: Tau² = 0.00; Chi²	= 0.30, df	= 1 (P = 1	0.58); I² =	0%			
Test for overall effect: Z = 0.43 (F	'= 0.67)						
4.2.2 Acute repel disorders							
1.3.3 Acute renardisorders					0.00		
Hildebrand A et al. 2015	50	188	102958	1918601	9.2%	6.39 [4.62, 8.83]	
Subtotal (95% CI)	60	100	400050	1910001	9.270	0.39 [4.02, 0.03]	•
l otal events	50		102958				
Heterogeneity: Not applicable	n - 0 000	243					
Test for overall effect: $Z = 11.23$ (	P < 0.000	01)					
1.3.4 Hepatic disorders							
Kawakita Tiet al. 2015	14	81	12	152	63%	2 44 [1 07 5 56]	
Subtotal (95% CI)	14	81	12	152	6.3%	2.44 [1.07, 5.56]	
Total events	14		12				-
Heterogeneity: Not applicable	14		12				
Test for overall effect: 7 = 2.12 (P	= 0.03						
1001101 070101 01001. 2 = 2.12 (I	= 0.00)						
Total (95% CI)		15684		3270042	100.0%	2.20 [1.56, 3.09]	◆
Total events	1637		174166				
Heterogeneity: Tau <sup>2</sup> = 0.31; Chi <sup>2</sup>	= 213.66,	df = 12 (l	P < 0.000	01); <b>i<sup>2</sup> =</b> 949	%		
Test for overall effect: Z = 4.49 (F	< 0.0000	1) .					0.05 0.2 1 5 20
Test for subgroup differences: C	hi² = 54.5;	2. df = 3 (	P < 0.000	101), I <sup>2</sup> = 94	.5%		

**Figure 4.** Forest plot of studies assessing association between Severe maternal morbidity (SMM) and low birth weight.

# 3.3.4. Five-Minute Apgar Score < 7

Fifteen studies [23,24,28,29,38,41,43–46,48,49,51,53,54] reported this outcome. Pooled analysis showed higher odds of low 5-min Apgar score (OR 3.66, 95% CI: 2.41–5.56), albeit with considerable study variability (Chi<sup>2</sup> = 228.26; I<sup>2</sup> = 93%). Based on sub-group analysis, severe obstetric hemorrhage (OR 4.16, 95% CI: 2.54–6.81) and hypertensive disorders (OR 4.61, 95% CI: 1.17–18.20) were associated with increased odds of low 5-min Apgar score (Figure 5).

	Case	е	Cor	ntrol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.4.1 Haemorrhagic disorders							
Sheiner E et al. 2005 (PPH)	3	666	922	153645	4.9%	0.75 [0.24, 2.33]	
Jakobsson M et al. 2015 (AIP)	4	61	6137	147551	5.3%	1.62 [0.59, 4.46]	_ <b>-</b>
McCormack et al. 2008 (APH)	131	1431	1183	26583	7.5%	2.16 [1.79, 2.61]	-
Baldwin H et al. 2017 (AIP)	181	2285	19306	920643	7.6%	4.02 [3.45, 4.68]	-
Jakobsson M et al. 2015 (Hyst)	5	32	6137	147551	5.5%	4.27 [1.64, 11.08]	
Jakobsson M et al. 2015 (UR)	21	118	6137	147551	7.0%	4.99 [3.11, 8.00]	
Ronel D et al. 2012 (UR)	32	138	7442	240051	7.1%	9.44 [6.35, 14.02]	-
Dfir K et al. 2003 (UR)	4	42	353	117643	5.2%	34.98 [12.42, 98.51]	
Subtotal (95% CI)		4773		1901218	49.9%	4.16 [2.54, 6.81]	•
Fotal events	381		47617				
Heterogeneity: Tau² = 0.38; Chi² =	= 86.26, df	= 7 (P <	0.00001	l); I² = 92%			
Fest for overall effect: Z = 5.68 (P	< 0.00001	)					
1.4.2 Hypertensive disorders							
Carte Ellet al. 2017	80	902	37	1003	7.1%	2.54 [1.70, 3.79]	-
<im 2006<="" al.="" et="" h="" td=""><td>14</td><td>21</td><td>8</td><td>50</td><td>4.7%</td><td>10.50 [3.22, 34.21]</td><td></td></im>	14	21	8	50	4.7%	10.50 [3.22, 34.21]	
Subtotal (95% CI)		923		1053	11.9%	4.61 [1.17, 18.20]	
"otal events	94		45				
Heterogeneity: Tau² = 0.80; Chi² =	= 4.97, df =	1 (P = 1	0.03); l² =	: 80%			
Fest for overall effect: Z = 2.18 (P	= 0.03)						
.4.3 Cardiac disorders							
arnio K et al. 2017	6	207	22	803	5.6%	1.06 [0.42, 2.65]	
lenry D et al. 2016	6	36	12	107	5.1%	1.58 [0.55, 4.58]	
Subtotal (95% CI)		243		910	10.7%	1.26 [0.63, 2.52]	-
Fotal events	12		34				
leterogeneity: Tau² = 0.00; Chi² =	= 0.32, df =	: 1 (P = I	0.57); l² =	:0%			
est for overall effect: Z = 0.65 (P	= 0.52)						
.4.4 Hepatic disorders							
Vikstrom SE et al. 2013	77	5477	12925	1213668	7.5%	1.32 [1.06, 1.66]	-
Rioseco, AJ et al. 1994	7	320	4	320	4.6%	1.77 [0.51, 6.10]	
}eenes V et al. 2014	18	669	17	2205	6.4%	3.56 [1.82, 6.94]	
Subtotal (95% CI)		6466		1216193	18.4%	1.97 [0.95, 4.05]	-
otal events	102		12946				
leterogeneity: Tau² = 0.28; Chi² =	= 7.62, df =	2 (P = 1	0.02); I² =	: 74%			
est for overall effect: Z = 1.83 (P	= 0.07)						
.4.5 Thromboembolic disorders	S						
en-Joseph R et al. 2009	1	122	1272	211964	2.8%	1.37 [0.19, 9.80]	
Spiliopoulos et al.2009	10	45	5591	1004071	6.3%	51.02 [25.26, 103.09]	
Subtotal (95% CI)		167		1216035	9.1%	8.93 [0.07, 1086.45]	
otal events	11		6863				
leterogeneity: Tau <sup>2</sup> = 11.45; Chi <sup>2</sup> est for overall effect: Z = 0.89 (P	² = 21.12, d = 0.37)	if=1 (P	< 0.0000	01); I² = 95%	6		
	,	40570		1225400	400.05	2 66 12 44 5 503	
otal (95% CI)		125/2		4335409	100.0%	3.00 [2.41, 5.56]	
otal events	600		67505				
teterogeneity: Tau* = 0.59; Chi* =	= 228.26, d	រា= 16 (l	P < 0.000	JU1); I* = 93	96		0.005 0.1 1 10 20/
est for overall effect: Z = 6.10 (P	< 0.00001	)	0.00				
l est for subgroup differences: Ch	ni≝ = 9.19, d	at = 4 (P	' = 0.06),	I*= 56.5%			

Figure 5. Forest plot of studies assessing association between SMM and 5-min Apgar score < 7.

## 3.3.5. Admission to Neonatal Intensive Care Unit

The association between SMM and NICU admission was reported in 14 studies [23,25–29,34,37, 38,45,49,51,53,55]. SMM was associated with increased odds of admission to NICU (OR 3.22, 95% CI: 2.45–4.25). There was, however, significant heterogeneity (Chi<sup>2</sup> = 340.61; I<sup>2</sup> = 97%) and sub-group differences (Chi<sup>2</sup> = 30.30, I<sup>2</sup> = 86.80%) within the eligible studies. Severe obstetric hemorrhage (OR 3.34, 95% CI: 2.26–4.94), hypertensive (OR 3.63, 95% CI: 2.63–5.02) and hepatic disorders (OR 1.89, 95% CI: 1.11–3.20) were associated with increased odds of NICU admission (Figure 6).

	Cas	e	Con	trol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.5.1 Haemorrhagic disorders							
Bhandari S et al. 2014 (APH)	1054	7517	6585	68423	8.1%	1.53 [1.43, 1.64]	•
McCormack et al. 2008 (APH)	611	1431	5925	26583	8.1%	2.60 [2.33, 2.90]	+
Baldwin H et al. 2017 (AIP)	738	2285	142060	920643	8.1%	2.61 [2.39, 2.85]	•
Jakobsson M et al. 2015 (UR)	32	118	14693	147551	6.9%	3.36 [2.24, 5.05]	
Jakobsson M et al. 2015 (AIP)	21	61	14693	147551	6.3%	4.75 [2.80, 8.05]	
Vilchez G et al. 2017	663	1925	298	3765	8.0%	6.11 [5.25, 7.11]	+
Jakobsson M et al. 2015 (Hyst)	13	32	14693	147551	5.3%	6.19 [3.05, 12.53]	
Subtotal (95% CI)		13369		1462067	50.8%	3.34 [2.26, 4.94]	•
Total events	3132		198947				
Heterogeneity: Tau <sup>2</sup> = 0.25; Chi <sup>2</sup> :	= 321.57,	df = 6 (P	< 0.0000	1); I <sup>2</sup> = 98%			
Test for overall effect: Z = 6.05 (P	< 0.0000	1)					
1.5.2 Hypertensive disorders							
Buchbinder A et al. 2002	21	69	72	529	6.1%	2.78 [1.57, 4.91]	
Carte E et al. 2017	149	902	61	1003	7.4%	3.06 [2.23, 4.18]	
Liu S et al. 2011	330	1325	141210	1787471	8.0%	3.87 [3.41, 4.38]	-
Kim H et al. 2006	18	21	12	50	2.7%	19.00 [4.76, 75.82]	
Subtotal (95% CI)		2317		1789053	24.2%	3.63 [2.63, 5.02]	•
Total events	518		141355				
Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup> :	= 8.26, df	= 3 (P = 1	0.04); I <sup>2</sup> =	64%			
Test for overall effect: Z = 7.85 (P	< 0.0000	1)					
1.5.3 Cardiovascular disorders							
Henry D et al. 2016	10	36	33	107	4.7%	0.86 [0.37, 1.99]	
Subtotal (95% CI)		36		107	4.7%	0.86 [0.37, 1.99]	-
Total events	10		33				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.35 (P	= 0.73)						
1.5.4 Hepatic disorders							
Kawakita T et al. 2015	19	81	31	152	5.6%	1.20 [0.63, 2.29]	
Geenes V et al. 2014	80	669	123	2205	7.5%	2.30 [1.71, 3.09]	
Brouwers L et al. 2015	4	107	1	108	1.3%	4.16 [0.46, 37.80]	
Subtotal (95% CI)		857		2465	14.4%	1.89 [1.11, 3.20]	-
Total events	103		155				
Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> :	= 3.62, df	= 2 (P = 1	0.16); I <sup>2</sup> =	45%			
Test for overall effect: Z = 2.36 (P	= 0.02)						
1.5.5 Thromboembolic disorder	s						
Spiliopoulos et al 2009	22	45	81629	1004071	6.0%	10.81 (6.02, 19.39)	
Subtotal (95% CI)		45		1004071	6.0%	10.81 [6.02, 19.39]	•
Total events	22		81629				-
Heterogeneity: Not applicable							
Test for overall effect: Z = 7.98 (P	< 0.0000	1)					
Total (95% CI)		16624		4257763	100.0%	3.22 [2.45. 4.25]	
Total evente	3705	10024	422110	4251105	100.0%	J.22 [2.40, 4.20]	•
Heteregeneity Tev3 - 0.24: Chi2	3785	46-15 1	422119	043-12-07	r.		
Toot for everall effect: 7 = 0.24; Chi*s	- 430.01,	ui= 15 (i 1)	r ≺ 0.000	01); F= 97	70		0.05 0.2 1 5 20
Test for overall effect: $z = 8.31$ (P	< 0.0000°	1) Date 1	(n - 0 000	043 12 - 00	000		
rescior subgroup amerences: C	nr= 30.3t	J, a⊺ = 4 (	(r ≤ 0.00L	iui), i* = 86	.0%0		

**Figure 6.** Forest plot of studies assessing association between Severe maternal morbidity (SMM) and neonatal intensive care unit (NICU) admission.

# 3.3.6. Stillbirth

Eighteen studies [22,23,25,27,29,31,33,34,37,38,40,42,46,49,51,53,54,56] reported the association between SMM and stillbirth. Women with SMM were about five times more likely to experience stillbirth (OR 4.87, 95% CI: 2.63–9.01) compared to those without SMM. Those with cardiovascular disease (OR 15.24, 95% CI: 1.29–180.60) or acute renal (OR 15.16, 95% CI: 4.41–52.12) or thromboembolic disorders (OR 5.07, 95% CI: 3.12–8.24) had significantly higher odds of this complication (Figure 7).

	Cas	se	Co	ntrol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI
1.6.1 Haemorrhagic disorders								
McCormack et al. 2008 (APH)	13	1431	253	26583	4.9%	0.95 [0.55, 1.67]		-
Patel E et al. 2015	2106	51075	317357	12473044	5.1%	1.65 [1.58, 1.72]		•
Bhandari S et al. 2014 (APH)	99	7517	418	68423	5.0%	2.17 [1.74, 2.71]		-
Jakobsson M et al. 2015 (AIP)	1	61	446	147551	3.3%	5.50 [0.76, 39.75]		
Baldwin H et al. 2017 (AIP)	80	2285	5662	920643	5.0%	5.86 [4.68, 7.34]		-
Jakobsson M et al. 2015 (Hyst)	1	32	446	147551	3.3%	10.64 [1.45, 78.11]		
Jakobsson M et al. 2015 (UR)	6	118	446	147551	4.6%	17.67 [7.73, 40.38]		
Subtotal (95% CI)		62519		13931346	31.3%	3.40 [1.88, 6.15]		-
Total events	2306		325028					
Test for overall effect: Z = 4.03 (P	< 0.0001)	at= 6 (P ·	< 0.00001	); 1= 96%				
1.6.2 Hypertensive disorders								
Liu S et al. 2011	16	1481	7720	1882957	4.9%	2.65 [1.62, 4.34]		
Buchbinder A et al. 2002	3	69	8	529	4.1%	2.96 [0.77, 11.43]		
Kim H et al. 2006	1	21	0	50	2.1%	7.39 [0.29, 188.98]		
Subtotal (95% CI)		1571		1883536	11.1%	2.74 [1.73, 4.34]		•
Total events	20		7728					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> : Test for overall effect: Z = 4.31 (P	= 0.39, df= < 0.0001)	= 2 (P = 0	.82); I² = 0	%				
1.6.3 Cardiovascular disorders								
Henry D et al. 2016	0	36	2	107	2.2%	0.58 [0.03, 12.32]	_	
Patel E et al. 2015	234	51075	5462	12473044	5.1%	10.51 [9.21, 11.98]		-
Kao D et al. 2013	11	535	458	4003379	4.8%	183.47 [100.28, 335.69]		→ →
Subtotal (95% CI)		51646		16476530	12.1%	15.24 [1.29, 180.60]		
Total events	245		5922					
Heterogeneity: Tau <sup>2</sup> = 4.15; Chi <sup>2</sup> : Test for overall effect: Z = 2.16 (P	= 88.64, df = 0.03)	í=2(P <	0.00001);	I <sup>2</sup> = 98%				
1.6.4 Hepatic disorders								
Wikstrom SE et al. 2013	16	5477	3870	1213668	4.9%	0.92 [0.56, 1.50]		
Rioseco, AJ et al. 1994	4	328	3	319	3.9%	1.30 [0.29, 5.86]		
Geenes V et al. 2014	10	669	11	2205	4.6%	3.03 [1.28, 7.16]		
Alsulyman OM et al 1996	2	79	0	79	2.3%	5.13 [0.24, 108.57]		
Kawakita T et al. 2015	4	81	0	152	2.4%	17.71 [0.94, 333.16]		
Subtotal (95% CI)		6634		1216423	18.0%	1.95 [0.82, 4.67]		-
Total events	36		3884					
Heterogeneity: Tau <sup>2</sup> = 0.47; Chi <sup>2</sup> : Test for overall effect: 7 = 1.50 (P	= 9.47, df =	= 4 (P = 0	.05); I² = 5	8%				
	- 0.13)							
1.0.5 Acute renai disorders	~	100	1.110	1010601	2.50	2 50 10 22 57 51		
Hildebrand A et al. 2015	0	188	1416	1918601	2.5%	3.59 [U.22, 57.64]		
Patel E et al. 2015 Subtotal (95% CI)	517	51075	6386	1/4/3044	5.1% 7.6%	19.90 [18.24, 21.84] 15 16 [4 41, 52 14]		
Total evente	617	51205	7002	14331043	1.0%	15.10 [4.41, 52.14]		
Hotorogonoity Tours = 0.47: Chill	017 - 1 47 df -	- 1 /P - 0	780Z	200				
Test for overall effect: Z = 4.31 (P	< 0.0001)	- 1 (F = 0	.23),1 = 3	2 %				
1.6.6 Thromboembolic disorder	s							
Patel E et al. 2015 (Pul.Emb)	72	51075	6113	12473044	5.0%	2.88 [2.28, 3.63]		-
Patel E et al. 2015 (Pul.Edem)	69	51075	3371	12473044	5.0%	5.00 [3.94, 6.35]		-
Morris J et al. 2010 (Pul.Emb)	10	230	3571	510177	4.8%	6.45 [3.42, 12.16]		
Patel E et al. 2015 (DVT)	61	51075	1946	12473044	5.0%	7.66 [5.94, 9.89]		-
Roberts C et al. 2010	5	19	0	606393	0.0%	460022.66 [24308.27, 8705713.00]		-
Subtotal (95% CI)		153455		37929309	19.9%	5.07 [3.12, 8.24]		◆
Total events	212		15001					
Heterogeneity: Tau <sup>2</sup> = 0.21; Chi <sup>2</sup> : Test for overall effect: 7 = 6.55 /P	= 33.56, df < 0.00001	f=3(P <	0.00001);	l² = 91%				
	0.00001	/						
Total (95% CI)		327088		85828789	100.0%	4.87 [2.63, 9.01]		
Total events	3336		365365					
Heterogeneity: Tau* = 1.94; Chi*:	= 3442.43	, af = 23 (	P < 0.000	U1); I* = 99%	, ,		0.01	0.1 1 10 100
Test for subgroup differences: $O$	≤ 0.00001 5i2 - 11 67	) df = 6 /2	2-0.04	2-571%				
reactor subgroup unterences. Cl		, ui – 0 (i	- 0.04/, 1	- 07.170				

**Figure 7.** Forest plot of studies assessing association between Severe maternal morbidity (SMM) and stillbirth.

# 3.3.7. Neonatal Death

Thirteen studies [23,25,27,28,31,32,37,38,46,50,51,53,54] reported this outcome. The odds of neonatal death were significantly higher in women with SMM (OR 4.02, 95% CI: 2.45–6.59). There was, however, significant study variability (Chi<sup>2</sup> = 125.28; I<sup>2</sup> = 89%). We also found that the odds of this adverse outcome were greater in women with hemorrhagic (OR 7.33, 95% CI: 3.06–17.53) and hypertensive disorders (OR 3.00, 95% CI: 1.78–5.07). The overall test of sub-group difference was also significant with substantial heterogeneity (Chi<sup>2</sup> = 15.33, p = 0.002, I<sup>2</sup> = 80.4%) (Figure 8).

	Cas	е	Cor	trol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.7.1 Haemorrhagic disorders							
Bhandari S et al. 2014 (APH)	49	7517	208	68423	9.9%	2.15 [1.57, 2.94]	
McCormack et al. 2008 (APH)	21	1431	94	26583	9.4%	4.20 [2.61, 6.76]	
Baldwin H et al. 2017 (AIP)	45	2285	3489	920643	9.9%	5.28 [3.92, 7.11]	+
Jakobsson M et al. 2015 (Hyst)	0	32	245	147551	2.4%	9.23 [0.56, 151.18]	
Jakobsson M et al. 2015 (AIP)	1	61	245	147551	3.9%	10.02 [1.38, 72.59]	
Jakobsson M et al. 2015 (UR)	2	118	245	147551	5.6%	10.37 [2.55, 42.18]	
Kaczmarczyk M et al. 2007 (UR) Subtotal (95% CI)	14	274 11718	407	299926 1758228	9.1% 50.2%	39.63 [22.94, 68.44] 7.33 [3.06, 17.53]	★ <sup>-</sup>
Total events	132		4933				
Heterogeneity: Tau <sup>2</sup> = 1.06; Chi <sup>2</sup> :	= 93.66, df	= 6 (P <	0.00001	); I <sup>2</sup> = 94%			
Test for overall effect: Z = 4.48 (P	< 0.00001	)					
		, ,					
1.7.2 Hypertensive disorders							
Haddad B et al. 2000	3	27	5	29	5.2%	0.60 [0.13, 2.80]	
Buchbinder A et al. 2002	1	69	4	529	3.4%	1.93 [0.21, 17.52]	
Carte E et al. 2017	31	902	11	1003	8.6%	3.21 [1.60, 6.42]	
Liu S et al. 2011	99	1325	39324	1787471	10.1%	3.59 [2.92, 4.41]	+
Kim H et al. 2006	4	21	1	50	3.3%	11.53 [1.20, 110.45]	
Subtotal (95% CI)		2344		1789082	30.5%	3.00 [1.78, 5.07]	•
Total events	138		39345				
Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> :	= 6.57, df =	4 (P = 0	1.16); I <sup>2</sup> =	39%			
Test for overall effect: Z = 4.12 (P	< 0.0001)						
1.7.4 Hepatic disorders							
Wikstrom SE et al. 2013	8	5477	2058	1213668	8.6%	0.86 [0.43, 1.73]	
Rioseco, AJ et al. 1994	2	328	1	319	3.0%	1.95 [0.18, 21.62]	
Subtotal (95% CI)		5805		1213987	11.6%	0.92 [0.47, 1.79]	<b>•</b>
Total events	10		2059				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> :	= 0.41, df =	1 (P = 0	).52); I <sup>2</sup> =	0%			
Test for overall effect: Z = 0.25 (P	= 0.80)						
1.7.5 Acute renal disorders							
Hildebrand A et al. 2015	5	188	15858	1918601	7.7%	3.28 [1.35, 7.97]	
Subtotal (95% CI)		188		1918601	7.7%	3.28 [1.35, 7.97]	-
Total events	5		15858				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.62 (P	= 0.009)						
Total (95% CI)		20055		6679898	100.0%	4.02 [2.45, 6.59]	•
Total events	285		62195				
Heterogeneity: Tau <sup>2</sup> = 0.62; Chi <sup>2</sup> :	= 125.28, 0	if = 14 (F	< 0.000	01); I <sup>2</sup> = 89	%		
Test for overall effect: Z = 5.50 (P	< 0.00001	)					0.01 0.1 1 10 100
Test for subgroup differences: C	hi² = 15.33	df = 3 (	P = 0.002	?), l² = 80.4	%		

**Figure 8.** Forest plot of studies assessing association between Severe maternal morbidity (SMM) and neonatal death.

# 3.3.8. Perinatal Death

Ten studies [24,26,31,38,41,43,44,48,51,54] reported perinatal death. SMM was associated with higher odds of perinatal death (OR 4.74, 95% CI: 2.47–9.12). There was, however, significant sub-group difference (Chi<sup>2</sup> = 10.16, p = 0.04, I<sup>2</sup> = 60.60%), as well as substantial heterogeneity (Chi<sup>2</sup> = 1.04; Chi<sup>2</sup> = 98.75, p < 0.0001); I<sup>2</sup> = 89%). Sub-group analysis confirmed that only obstetric hemorrhage was associated with greater odds of perinatal death (OR 6.18, 95% CI: 2.55–14.96) (Figure 9).

	Cas	е	Con	trol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
1.8.1 Haemorrhagic disorders							
Sheiner E et al. 2005 (PPH)	15	666	2151	153645	10.0%	1.62 [0.97, 2.71]	
McCormack et al. 2008 (APH)	32	1431	330	26583	10.3%	1.82 [1.26, 2.63]	-
Jakobsson M et al. 2015 (AIP)	2	61	843	147551	7.1%	5.90 [1.44, 24.18]	
Ronel D et al. 2012 (UR)	24	138	7201	240051	10.2%	6.81 [4.38, 10.58]	
Jakobsson M et al. 2015 (Hyst)	2	32	843	147551	7.1%	11.60 [2.77, 48.62]	
Ofir K et al. 2003 (UR)	8	42	1647	117643	9.3%	16.57 [7.66, 35.85]	
Jakobsson M et al. 2015 (UR) Subtotal (95% CI)	12	118 2488	843	147551 980575	9.8% 63.9%	19.70 [10.80, 35.93] 6.18 [2.55, 14.96]	
Total events	95		13858				
Heterogeneity: Tau <sup>2</sup> = 1.24: Chi <sup>2</sup> =	86.70 d	f = 6 (P	< 0.0000	(1): $I^2 = 939$	6		
Test for overall effect: Z = 4.04 (P	< 0.0001)			.,,			
1.8.3 Cardiovascular disorders							
Aarnio K et al. 2017	3	207	3	803	6.5%	3.92 [0.79, 19.57]	
Subtotal (95% CI)		207	2.12	803	6.5%	3.92 [0.79, 19.57]	
Total events	3		3				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 1.67$ (P =	= 0.10)						
1.8.4 Hepatic disorders							
Rioseco, AJ et al. 1994	20	328	13	320	9.5%	1.53 [0.75, 3.14]	<b>—</b>
Brouwers L et al. 2015 Subtotal (95% CI)	2	107 435	0	108 428	3.2% 12.7%	5.14 [0.24, 108.38] 1.63 [0.81, 3.28]	
Total events	22		13				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =	0.58, df =	= 1 (P =	: 0.45); I <sup>2</sup>	= 0%			
Test for overall effect: Z = 1.38 (P =	= 0.17)						
1.8.5 Acute renal disorders							
Hildebrand A et al. 2015	5	188	7320	1918601	8.9%	7.13 [2.93, 17.35]	
Subtotal (95% CI)		188		1918601	8.9%	7.13 [2.93, 17.35]	
Total events	5		7320				
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.33 (P	< 0.0001)						
1.8.6 Thromboembolic disorders							
Ben-Joseph R et al. 2009	3	122	3179	211964	8.0%	1.66 [0.53, 5.21]	
Subtotal (95% CI)		122		211964	8.0%	1.66 [0.53, 5.21]	
Total events	3		3179				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.86 (P =	= 0.39)						
Total (95% CI)		3440		3112371	100.0%	4.74 [2.47, 9.12]	•
Total events	128		24373				
Heterogeneity: Tau <sup>2</sup> = 1.04; Chi <sup>2</sup> =	98.75, d	f=11 (	P < 0.000	01); l² = 89	9%		
Test for overall effect: Z = 4.67 (P	< 0.0000°	1)					0.02 0.1 1 10 50
Test for subgroup differences: Ch	i <sup>2</sup> = 10.18	6, df = 4	(P = 0.0-	4), I <sup>2</sup> = 60.6	i%		

**Figure 9.** Forest plot of studies assessing association between Severe maternal morbidity (SMM) and perinatal death.

### 4. Discussion

The results of this systematic review and meta-analysis clearly show the strong and consistent association between SMM and adverse perinatal outcomes in women with singleton pregnancies in HICs. We found that women who experienced SMM were at significantly greater risk for preterm birth, SGA and LBW infants, low 5-min Apgar score, NICU admission, stillbirth, neonatal death, and overall perinatal death. Although we were unable to compare SMM by country due to the heterogeneity of definitions for SMM, our results are in concordance with other data showing that the association between SMM and adverse perinatal outcome does not appear to be influenced by differences in healthcare systems in these countries [11]. Our results highlight the crucial importance of mitigating SMM through high quality care given its impact not only on maternal health but also its consequences on perinatal outcomes.

Our findings related to the compelling relationship between SMM and stillbirth (OR 4.87, 95% CI: 2.63–9.01) are consistent with another large study from North America [57] which showed that SMM was associated with a significantly higher odds of stillbirth after 23 weeks' gestation (aOR 7.05, 95% CI: 6.27–7.93), particularly among women with other co-morbidities. There is also evidence that SMM is an independent risk factor for infant mortality (RR 1.39, 95% CI: 1.14–1.70) in very preterm infants, particularly in the first year of life [58].

Our broader results are consistent with other evidence [11] linking maternal morbidity and reproductive outcomes [59], thus highlighting the crucial importance of primary prevention and reducing the burden of SMM to mitigating the burden of SNM [2,60] and its associated consequences [10,12]. It is an imperative that transcends the socioeconomic status of a country. Whilst in many cases, SMM can rapidly develop and escalate, it is vital that healthcare professionals are aware of risk factors that predispose to poor outcomes, particularly in susceptible women. The perinatal risks we highlight are likely to be even more marked and impactful in low- and middle-income countries, and efforts should continue for effective surveillance of SMM rates as a measure of maternal health and perinatal outcome regardless of a nation's socioeconomic development status. Our results highlight specific perinatal risks associated with a variety of maternal obstetric complications causing SMM and should be of benefit for clinicians. Indeed, there is evidence that almost 40% of cases of SMM are preventable [11].

To ascertain the impact of SMM, robust and ascertainable data are required. The WHO [11] and the American College of Obstetricians and Gynecologists [61] recommend careful surveillance using real-time data, which are sometimes lacking, even in HICs. However, despite these recommendations, there remains uncertainty as to the optimum surrogate indicators for SMM. Some HICs [62,63] have maternity outcome surveillance systems which use regular data updates to identify trends and adverse outcomes associated with SMM. However, although there is acknowledgement of rising rates of SMM [60] and the limitations of current surveillance systems [64], only a few HICs have instituted specific monitoring systems for SMM [62,63]. Developing a universally accepted classification system for SMM [61,65–69] would help in the standardized collection and reporting of important clinical data. In Europe, using hospital discharge data from eight countries, Chantry et al. found that diagnosis codes indicating obstetric hemorrhage, hysterectomy and red cell transfusion were all good candidates for the surveillance of maternal morbidity [70].

#### Strengths and Limitations

One of the limitations of this review is the use of the WHO near miss criteria to define SMM, as these criteria are not consistently used by all HICs. Furthermore, we limited our analysis to only women with singleton pregnancies, cognizant that multiple pregnancy is an additional risk factor for adverse outcomes. Although the WHO near miss definition is widely accepted, not all HICs use this definition. The EURO-PERISTAT collaboration of 15 European countries defined SMM as a composite of the rates of eclampsia, hysterectomy for postpartum hemorrhage, ICU admission, blood transfusion, and uterine artery embolization [66], whilst the French EPIMOMS study group recommended 17 indicators (some which overlap with the EURO-PERISTAT indicators) specifically for use in HICs [65]. In the United States, a broadly similar list of 18 indicators is used [67,69].

In our systematic review, five studies were at high risk of publication bias, mainly because of a lack of confounder adjustment and comparison group ascertainment [22,29,41,47,53]. We also observed evidence of funnel plot asymmetry in some of the funnel plots. Interpretation of possible publication bias using funnel plots should take into account that funnel plots are crude and subjective [71], and are inaccurate measures [72] of publication bias, where its asymmetry does not necessarily indicate publication bias, and give misleading interpretations [73]. Our sensitivity analyses also demonstrate that the results were not significantly influenced by studies with high a risk of publication bias. We were unable to perform subgroup analysis based on study designs because of data limitations. Additionally, we chose to use odds ratios for our analyses, which may not always reflect the true risks at the population level. However, Viera et al., recommends that either odds ratios or relative risks are equally reliable when assessing rare events such as adverse perinatal outcomes [74].

Sample size variation between studies (64 women [50] to 12,524,119 women [56]) and study design, the use of heterogeneous SMM definitions, differences in participant characteristics and sampling procedures would also have introduced high heterogeneity into our analysis. However, our use of random-effects modeling [75] as well as the use of components within a widely accepted and standard SMM definition mitigates this limitation.

## 5. Conclusions

This systematic review and meta-analysis provide data demonstrating the robust association between SMM and adverse perinatal outcomes as well as highlighting specific maternal conditions that are risk factors for SMM and adverse perinatal outcomes. Our results also highlight an obvious research gap and emphasize the need for ongoing surveillance in all countries, regardless of socio-economic development status.

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