

ORIGINAL ARTICLES

Evaluating the effect of maternal health conditions on severe maternal morbidity adjusting for emergent cesarean delivery: A mediation analysis approach

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ABSTRACT

The prevalence of pre-existing and gestational maternal health conditions is rising; affected women are at increased risk for both cesarean delivery (CD) and severe maternal morbidity (SMM). We estimated the increased risk of SMM associated with key maternal health conditions, and determined the extent to which it was directly associated with these conditions versus indirectly associated because of an increased risk of CD. Nulliparous, term, singleton, vertex (NTSV) gestations were identified among laboring women in California 2008-2010 hospital discharge datasets. Logistic regression models (stratified by younger vs. older women [≥ 35 years]) were constructed for each condition: chronic/gestational diabetes mellitus (DM), chronic/gestational hypertension, obesity, heart disease, and mental health diagnoses. Using mediation analysis, the potential effect associated with each condition (exposure) on SMM (outcome) consisted of a direct effect and an indirect effect caused by modification of the risk of an emergent CD (mediator). Of 502,654 deliveries, 24.3% had an emergent CD; 1.7% had SMM, which was present in 1.6% of younger vs. 2.2% of older mothers. The modeled odds ratios (ORs) for the direct effect on SMM were 2.00-2.67 for any hypertension, 0.78 for obesity in younger women, 6.57-7.97 for heart disease, and 1.43-1.58 for mental health diagnoses. No direct effect was identified for DM or obesity in older women. The ORs for the indirect effect were low, ranging from 0.94-1.11 for all models. For women laboring with NTSV gestations where key maternal health conditions were present, the risk of SMM mediated by an emergent CD was low, relative to the direct risk.

Key Words: Emergent cesarean delivery, Severe maternal morbidity, Mediation analysis

1. INTRODUCTION

The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine

(SMFM) recently published a joint statement proposing the development of standards for maternal risk-appropriate care.^[1] This proposal comes amid documentation of con-

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tinuing national increases in maternal mortality and severe maternal morbidity (e.g., renal failure, adult respiratory distress syndrome, and shock).^[2-6] The premise of the proposed regionalization infrastructure is that women who are most at risk for experiencing severe maternal morbidity should receive antenatal referrals to facilities with the optimal resources and personnel for their care. Chronic disease (e.g., chronic hypertension, diabetes mellitus [DM], heart disease), and gestational disease (e.g., gestational DM [GDM] and preeclampsia) put women at risk for severe maternal morbidity.^[5-8] With the exception of the declining trend in heart disease, the prevalence of these pre-existing and gestational conditions has been increasing.^[9,10] Obesity, which has also been increasing,^[9,11] is often associated with these conditions and is also a risk factor for severe maternal morbidity.^[8,12,13] Furthermore, mental health diagnoses are now reported more frequently during childbirth admissions,^[10] and appear to put women at risk for severe maternal morbidity.^[8] These pre-existing and gestational conditions have been studied in various combinations, yet because they are potential candidates for triggering antenatal transfer to sophisticated childbirth facilities, it is important to quantify the risk associated with each of them. Although the potential to avoid severe maternal morbidity may be limited^[14] there may still be opportunities for primary and secondary prevention, particularly if these conditions are recognized early and women have access to risk-appropriate care.

Estimates of the association of severe maternal morbidity and these pre-existing and gestational conditions have generally not taken the route of delivery into account. Women undergoing cesarean delivery (CD) are at increased risk for intra-operative and postpartum complications, and these risks are greater if a CD is performed after labor has occurred (e.g., failed vaginal birth or emergent CD).^[15-17] Emergent CD (hereafter referred to as CD for simplicity) itself has been associated with increased rates of severe maternal morbidity,^[7,12,18] and the degree to which the risk of severe maternal morbidity is affected by CD in the presence of key maternal health conditions is unknown.

The estimation of the risk of these pre-existing and gestational conditions is complicated because CD not only is associated with them but also because CD is itself a causal factor for severe maternal morbidity. Treating CD as an independent risk factor would introduce collinearity resulting in underestimation of the effect of pre-existing and gestational conditions.^[19] Rather, there exists both a direct effect of the conditions themselves, and an indirect effect of the conditions that is mediated through the performance of a CD (see Figure 1). Most studies correctly ignore the role of CD and report the total effect of these conditions, which

is the product of the direct effect and the indirect effect. If the indirect effect of these conditions through CD does not contribute greatly to the total effect, then this distinction may be negligible, and reporting of the total risk, adequate. However, if the indirect effect were large, this could impact clinical decision-making regarding the use of CD in affected patients.

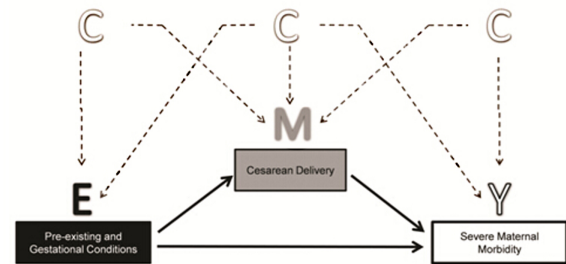


Figure 1. Conceptual model for the risk of severe maternal complication from childbirth. Pre-existing and Gestational Conditions = E (Exposure), Cesarean Delivery = M (Mediator), Severe Maternal Morbidity = Y (Outcome), Confounders = C (Vector of Covariates)*

*The same set of potential confounders were used in the equations for both the direct and indirect effects; it includes: control variables: maternal age, race/ethnicity, education, insurance status, prenatal care status, year of delivery; obstetrical conditions: placenta previa, premature rupture of membranes (PROM), postterm pregnancy, cord prolapse, cord entanglement, antepartum bleeding/abruption, isoimmune disease, soft tissue conditions (i.e., disorders of the organs and soft tissue of the pelvis); fetal conditions: polyhydramnios, oligohydramnios, intrauterine growth restriction, excessive fetal growth; and intrapartum conditions: fetal distress and dystocia; other pre-existing conditions were: Herpes virus infection, and presence of hepatic or renal disease.

Here, using a population of laboring women, our objective was to estimate the total effect (TE) of several key pre-existing and gestational conditions on severe maternal morbidity, and determine the direct effect (DE) of the condition itself, and the indirect effect (IE) of the condition as mediated through CD, where $TE = DE \times IE$.

2. METHODS

2.1 Data

The study was approved by the California Health and Human Services Agency Committee for the Protection of Human Subjects (protocol 12-08-0596) and by the Cedars-Sinai Medical Center Institutional Review Board (protocol 00029744). Data obtained from California 2008-2010 linked maternal and neonatal hospital discharge datasets were aggregated. These datasets are linked to vital statistics data and include over 97% of California births.^[20] For improved interpretability

ity of the analyses, we selected a study population of nulliparous, term (≥ 37 weeks), singleton, vertex (NTSV) inborn, liveborn gestations. The NTSV population is a commonly used denominator for the assessment of the quality of child-birth services as it controls for key risk factors associated with maternal outcomes and use of CD.^[21] Because many women in the NTSV population undergo elective (*i.e.*, non-laboring) CD for other obstetrical, fetal or maternal complications, or upon maternal request, this population was further limited to women undergoing labor. The presence of labor was defined by a previously validated algorithm using ICD-9-CM codes,^[22] with some minor modifications (see Table 1).

Table 1. Administrative codes used to identify the presence of labor (in addition to vaginal delivery)

ICD-9-CM [#] Diagnostic Code	ICD-9-CM Code Description
659.7	Abnormality in fetal heart rate or rhythm
661	Abnormality of forces of labor
652.1	Breech or other malpresentation successfully converted to cephalic presentation
658.2	Delayed delivery after spontaneous or unspecified rupture of membranes
653	Disproportion in pregnancy labor and delivery
644.2	Early onset of delivery
659.0	Failed mechanical induction of labor
659.1	Failed medical or unspecified induction of labor
656.3	Fetal distress affecting management of mother
659.3	Generalized infection during labor
658.4	Infection of amniotic cavity
662	Long labor
659.2	Maternal pyrexia during labor unspecified
660	Obstructed labor
658.1	Premature rupture of membranes
663.0	Pro lapse of cord complicating labor and delivery
ICD-9-CM Procedure Code	
73.01	Induction of labor by artificial rupture of membranes
73.4	Medical induction of labor
96.49	Other genitourinary instillation
73.1	Other surgical induction of labor

[#]International Classification of Diseases, Ninth Revision, Clinical Modification.

We used vital statistics data to identify parity, gestational age, and maternal body mass index (BMI). Preterm deliveries, defined based on obstetrical estimates of gestational age between 24 and 36 completed weeks, were excluded. Last menstrual period estimates were used if obstetrical estimates were missing. We used hospital discharge data to identify all other clinical conditions. Multiple gestations were identified based on International Classification of Diseases, Version 9, Clinical Modification (ICD-9-CM) codes V272, V273, V274, V275, V276, V277, or 651.xx; malpresentation was based on code 652.xx (except 652.1x or 652.5x).

2.2 Outcome, mediator and exposures

This analysis focused on the effects of key pre-existing and gestational conditions on severe maternal morbidity. Severe maternal morbidity is a composite measure of morbidity, and includes maternal mortality, life-threatening conditions, and the use of life-saving procedures at the time of labor and delivery. Methods for classifying severe maternal morbidity from hospital discharge data have been documented in the obstetrical literature,^[3] including a severe maternal morbidity definition that we have published previously^[22] and modified slightly for purposes of this analysis. For the ICD-9-CM codes used in the definition, please see Table 2.

Table 2. Administrative codes used to define severe maternal morbidity

Severe maternal morbidity	ICD-9-CM [#] codes
Anesthesia complication	668.0, 668.1, 668.2
Cerebral hemorrhage	348.5, 430-434, 436, 437.2, 671.5, 674.0, 780.01, 780.03
Hysterectomy (procedure codes)	68.3-68.7, 68.9
Maternal infection (All codes must be associated with length of stay ≥ 4 days)	038, 785.52, 995.91, 995.92
Maternal death	Maternal death variable
Obstetrical Shock	669.1, 669.2
Other maternal morbidity	286.6, 669.4, 997.1, 570, 584, 586, 669.3, 669.4, 671.4, 674.8, 997.1, 998.0, 998.1, 998.2, 998.3, 998.4, 998.5, 998.6, 998.7, 998.81, 998.83, 998.89, 998.9
Pulmonary embolism	415.11, 415.19, 673.0, 673.1, 673.2, 673.3, 673.8
Transfusion (procedure codes)	99.00, 99.03, 99.04
Uterine rupture	665.1
Additional potential maternal intensive care unit admission	518, 674.5
Additional potential maternal intensive care unit admission (procedure codes)	31.1, 38.86, 38.88, 39.95, 54.11, 54.12, 54.19, 89.6, 96.70, 96.71, 96.73, 93.90, 93.91, 93.93, 99.60, 99.61, 99.62, 99.63, 99.69

[#]International Classification of Diseases, Ninth Revision, Clinical Modification: diagnosis codes unless otherwise noted.

The key pre-existing and gestational conditions studied were: chronic and gestational DM, chronic and gestational hypertension, obesity, heart disease, and mental health diagnoses. These conditions were defined based on the presence of ICD-9-CM diagnosis or procedure codes in the maternal discharge record and are included in Table 3. DM was defined as GDM or chronic DM. Hypertension was defined as gestational (includes preeclampsia), and chronic/superimposed preeclampsia hypertension. Unspecified hypertension was included in the general hypertension definition (“any”) but not in the specific sub-classification. Obesity was defined as BMI ≥ 30 kg/m² based on the birth certificate maternal height and pre-pregnancy weight; in cases with missing height or weight, obesity was defined by the presence of ICD-9-CM code 278.xx in the maternal discharge record. CD was identified by ICD-9-CM codes 669.70, 669.71 or procedure codes 74.0x, 74.1x, 74.2x, 74.4x, or 74.99.

Table 3. Administrative codes used to define maternal pre-existing and gestational health conditions

Health Condition	ICD-9-CM Diagnostic Code [*]	Code definition	
Diabetes	648.8x	Gestational diabetes	
	250.0x-250.9x; 648.80	Chronic diabetes	
Hypertension	642.3x-642.6x	Gestational hypertension	
	401.xx-405.xx; 642.0x-652.2x, 642.7x	Chronic hypertension	
	642.9x	Unspecified hypertension	
Heart disease	648.5x; 645.xx-747.xx	Congenital heart disease	
	414.xx, 416.xx, 417.xx, 424.xx, 429.xx	Other heart disease	
	410.xx + POA [#] , 411.xx + POA	Acute myocardial infarction (MI)	
	413.xx + POA	Angina	
	415.xx + POA	Acute pulmonary heart disease	
	420.xx+ POA	Acute pericarditis	
	421.xx + POA	Acute/subacute pericarditis	
	422.xx+ POA	Acute myocarditis	
	423.xx + POA	Other pericardial	
	425.xx + POA	Cardiomyopathy	
	426.xx + POA	Conduction disorders	
	427.xx + POA	Dysrhythmias	
	428.xx + POA	Heart failure	
	35.xx-37.xx; 39.xx	Operations on heart and pericardium (procedure codes)	
	Mental health diagnoses	296.0x, 296.2x- 296.8x, 298.0x, 300.4x, 311.xx	Mood disorders
		300.0x, 300.2x, 300.3x, 308.0x, 309.81	Anxiety disorders:
309.xx		Adjustment disorders	
291.xx, 292.xx, 303.xx-305.xx, 648.3x		Substance use disorders	
295.xx, 297.xx		Psychotic disorders	
293.0x, 293.1x		Cognitive disorders	
307.1x, 307.50-307.54		Eating disorders	
Obesity	Body mass index (BMI) ≥ 30 kg/m ² (as noted on birth certificate) or 278.xx		

^{*}International Classification of Diseases, Ninth Revision, Clinical Modification; [#]Present on admission.

2.3 Confounders

Socio-demographic characteristics (*i.e.*, maternal age, race/ethnicity, mother's highest education level, Medicaid insurance, prenatal care [PNC] status), year of delivery, obstetrical conditions (placenta previa, premature rupture of membranes [PROM], postterm pregnancy, cord prolapse with compression, cord entanglement with compression, antepartum bleeding/abruption, isoimmune disease, soft tissue conditions [*i.e.*, disorders of the organs and soft tissue of the pelvis]), fetal conditions (polyhydramnios, oligohydramnios, intrauterine growth restriction [IUGR], excessive fetal growth), intrapartum conditions (fetal distress and dystocia), and other pre-existing conditions (Herpes virus infection, presence of renal or hepatic disease) were also used as controls in all models. PNC status was defined as inadequate, adequate, or adequate plus based on the Adequacy of PNC Index.^[24] These characteristics, including race/ethnicity, are known to have a potential effect on severe maternal morbidity and CD (outcomes), and were considered as possible confounders for the effect of maternal conditions on both of these outcomes.

Missing values for maternal race/ethnicity, highest education

level and PNC index ranged from 1.6% to 5.1% of the sample. Given the relatively low rate of missing values, these observations were kept in the analyses by defining 'unknown' as a separate level for these variables.

Other potential control variables that were tested and eliminated due to insignificant differences in their association with the route of delivery and/or severe morbidity were: human immunodeficiency virus (HIV) infection, vasa previa, chorioamnionitis, fetal central nervous system abnormality, and idiopathic hydrops or hemolytic disease due to isoimmunization.

2.4 Statistical analysis

The specification of the mediation models and decomposition of the risk associated with the key maternal health conditions was based on the publication by Valeri and VanderWeele.^[24] The two pathways for the potential effect associated with each health condition (exposure) on severe maternal morbidity (outcome) are (1) a direct effect, and (2) an indirect effect by modifying the risk of CD (mediator) that in turn is associated with the risk of severe maternal morbidity (see Figure 1). In our case, all three variables of interest are binary. Of

concern is that the effects of the maternal health condition and CD on complications may interact, and this is taken into consideration by using the following models.

The decomposition is based on fitting two multiple logistic regression models:

$$\ln[p(M)/(1-p(M))] = \beta_0 + \beta_1 E + \beta_2' C \quad (1)$$

$$\ln[p(Y)/(1-p(Y))] = \theta_0 + \theta_1 E + \theta_2 M + \theta_3 EM + \theta_4' C \quad (2)$$

where Y is the outcome, M the mediator, E the exposure and C is a vector of covariates. The natural direct effect (NDE) and natural indirect effect (NIE) are calculated from the estimated model parameters and are given by

$$NDE = \theta_1 + \theta_3(\beta_0 + \beta_2' C); NIE = \theta_2\beta_1 + \theta_3\beta_1$$

The NDE expresses how much the risk of severe maternal morbidity would change in the presence versus the absence of the pre-existing or gestational condition of interest, and for each delivery, the measure of risk of CD is based on other covariates in the absence of the maternal health condition. The NIE expresses how much the risk of severe maternal morbidity would change in the presence of the maternal health condition and considers the risk of CD measured in the presence and in the absence of the maternal health condition. The risk of CD in the absence of the maternal health condition is referred to as the “natural” CD risk and is used here as a counterfactual construct. The TE expresses how much the risk of severe maternal morbidity would change overall for a change in the presence versus absence of the maternal health condition (irrespective of CD). The TE is calculated based on the average values for the rest of the model covariates, and for our binary outcome models, the TE equals the product of the NDE and NIE (even in the presence of interactions and non-linearity).

Analyses were performed separately for each of the maternal health conditions, and separate models were constructed for younger versus older women (aged ≥ 35 years) due to substantial differences in measured and potentially unmeasured characteristics. All variable rates were compared by route of delivery and by severe maternal morbidity status and tested with chi-square tests for categorical variables and two-sided two-sample *t*-test for continuous variables. When estimating the risk associated with each specific pre-existing or gestational condition, all other conditions were entered in the model as controls along with the confounders. Given the large sample used multicollinearity was not a concern; therefore all control variables were retained in all models.

Multiple logistic regression models, as described in equations (1) and (2) above, were fitted to severe maternal morbidity status for each of the pre-existing and gestational conditions:

chronic DM, GDM, chronic hypertension, gestational hypertension, obesity, heart disease, and mental health diagnoses using the SAS code provided by Valeri and VanderWeele.^[25] The interaction between the pre-existing and gestational conditions and CD was tested for each model and retained if significant. Hosmer and Lemeshow^[26] goodness-of-fit test was used to assess adequacy of model fit. Odds ratios (ORs) for natural direct, natural indirect, and total effects are reported with 95% confidence intervals using the delta method. *P*-values less than .05 were considered statistically significant. Analyses were performed using SAS, version 9.3.

2.5 Model assumptions

We determined whether CD functioned as a mediator between pre-existing and gestational conditions and severe maternal morbidity, if any of the following conditions were met after controlling for confounders: 1) variation in maternal conditions significantly accounted for variation in CD; 2) variation in CD significantly accounted for variation in severe maternal morbidity; 3) variation in maternal conditions significantly accounted for variation in severe maternal morbidity; and 4) variation in maternal conditions accounted for less of the variation in severe maternal morbidity when controlling for CD. In order to allow for causal interpretation of the effects, it is necessary to assume that there are no unmeasured confounders in the relationships between (1) the exposure and outcome, (2) the mediator and outcome, (3) the exposure and mediator, and (4) no mediator-outcome confounder that is affected by the exposure. We have included socio-demographic characteristics, year of delivery, obstetrical, fetal and intrapartum conditions, and other pre-existing conditions as potential confounders and conducted separate analyses by age group in an attempt to meet these conditions as best as the data permitted.

Of the four assumptions concerning no unmeasured confounders, assumption (2) above regarding the mediator-outcome relationship has been considered as the most likely to be violated.^[25,26] That is, that there are common causes of CD and severe maternal morbidity for which we have not adjusted. We estimated the potential bias in the NIE estimates due to this form of unmeasured confounding. To accomplish this, unmediated total effects were obtained from logistic models on each of the outcomes, with the same specification as in the mediated models but ignoring the mediator (CD), and modified NIEs were calculated from dividing these unmediated total effects by the corresponding NDEs from the mediated models. Comparison of the modified NIEs to the original NIEs can assess the potential bias, since the unmediated total effects obtained from the models of exposure on outcome are unconfounded.^[27]

Table 4. Distribution of risk factors by route of delivery and age group among laboring women with nulliparous term singleton vertex (NTSV) gestations

Variable	Younger women (< 35)			Older women (≥ 35)		
	Vaginal (N = 351,528)	CD ^{#1} (N = 104,888)	P Value*	Vaginal (N = 28,925)	CD (N = 17,313)	P Value*
Socio-demographic						
Age category, n (%)			< .001			< .001
0-19	84,281 (24.0%)	17,367 (16.6%)				
20-24	110,940 (31.6%)	31,448 (30.0%)				
25-29	91,631 (26.1%)	30,476 (29.1%)				
30-34	64,676 (18.4%)	25,597 (24.4%)				
35-39				24,282 (83.9%)	13,542 (78.2%)	
40-44				4,428 (15.3%)	3,469 (20.0%)	
45+				215 (0.7%)	302 (1.7%)	
Age of mother ^{#2} , Mean (SD ^{#3})	24.0 (5.1)	25.1 (5.1)	< .001	37.3 (2.2)	37.7 (2.5)	< .001
Race/Ethnicity, n (%)			< .001			< .001
Hispanic	174,592 (49.7%)	52,274 (49.8%)		5,593 (19.3%)	4,053 (23.4%)	
Multiple race	7,819 (2.2%)	2,390 (2.3%)		662 (2.3%)	410 (2.4%)	
Black, non-Hispanic	18,847 (5.4%)	7,266 (6.9%)		740 (2.6%)	626 (3.6%)	
American Indian	1,110 (0.3%)	361 (0.3%)		29 (0.1%)	26 (0.2%)	
Asian	44,190 (12.6%)	13,333 (12.7%)		7,353 (25.4%)	4,330 (25.0%)	
Pacific Islander	1,347 (0.4%)	443 (0.4%)		76 (0.3%)	42 (0.2%)	
White, non-Hispanic	97,740 (27.8%)	26,905 (25.7%)		13,601 (47.0%)	7,297 (42.1%)	
Other	221 (0.1%)	71 (0.1%)		20 (0.1%)	12 (0.1%)	
Unknown	5,662 (1.6%)	1,845 (1.8%)		851 (2.9%)	517 (3.0%)	
Highest education level, n (%)			< .001			< .001
Less than high school	76,102 (21.6%)	20,259 (19.3%)		1,366 (4.7%)	1,061 (6.1%)	
High school	96,095 (27.3%)	28,359 (27.0%)		2,541 (8.8%)	1,838 (10.6%)	
College or more	166,626 (47.4%)	52,559 (50.1%)		23,548 (81.4%)	13,550 (78.3%)	
Missing/Unknown	12,705 (3.6%)	3,711 (3.5%)		1,470 (5.1%)	864 (5.0%)	
MediCaid, n (%)	169,083 (48.1%)	50,293 (47.9%)	< .001	3,631 (12.6%)	2,757 (15.9%)	< .001
Prenatal care index, n (%)			< .001			< .001
Inadequate	36,305 (10.3%)	9,419 (9.0%)		1,074 (3.7%)	709 (4.1%)	
Intermediate	32,688 (9.3%)	9,721 (9.3%)		2,570 (8.9%)	1,428 (8.2%)	
Adequate	161,522 (45.9%)	49,532 (47.2%)		13,293 (46.0%)	7,976 (46.1%)	
Adequate plus	108,062 (30.7%)	32,727 (31.2%)		10,839 (37.5%)	6,663 (38.5%)	
Missing information	12,951 (3.7%)	3,489 (3.3%)		1,149 (4.0%)	537 (3.1%)	
Year, n (%)			.008			.330
2008	122,601 (34.9%)	36,256 (34.6%)		9,833 (34.0%)	5,811 (33.6%)	
2009	116,107 (33.0%)	35,180 (33.5%)		9,459 (32.7%)	5,776 (33.4%)	
2010	112,820 (32.1%)	33,452 (31.9%)		9,633 (33.3%)	5,726 (33.1%)	
Pre-existing or gestational conditions						
DM ^{#4} (any), n (%)	14,738 (4.2%)	7,573 (7.2%)	< .001	3,029 (10.5%)	2,428 (14.0%)	< .001
DM category, n (%)			< .001			< .001
None	336,790 (95.8%)	97,315 (92.8%)		25,896 (89.5%)	14,885 (86.0%)	
Chronic +/- gestational DM	905 (0.3%)	1,037 (1.0%)		161 (0.6%)	276 (1.6%)	
Gestational DM only	13,833 (3.9%)	6,536 (6.2%)		2,868 (9.9%)	2,152 (12.4%)	
HTN ^{#5} (any), n (%)	21,062 (6.0%)	13,085 (12.5%)	< .001	2,173 (7.5%)	2,343 (13.5%)	< .001
HTN category, n (%)			< .001			< .001
None	330,466 (94.0%)	91,803 (87.5%)		26,752 (92.5%)	14,970 (86.5%)	
Chronic/Superimposed HTN	2,111 (0.6%)	1,512 (1.4%)		543 (1.9%)	585 (3.4%)	
Gestational HTN only	17,869 (5.1%)	10,974 (10.5%)		1,496 (5.2%)	1,615 (9.3%)	
Unspecified HTN	1,082 (0.3%)	599 (0.6%)		134 (0.5%)	143 (0.8%)	
Obesity, n (%)	41,056 (11.7%)	23,064 (22.0%)	< .001	2,719 (9.4%)	2,889 (16.7%)	< .001
Heart disease, n (%)	1,219 (0.3%)	537 (0.5%)	< .001	212 (0.7%)	142 (0.8%)	.300
Mental health condition, n (%)	8,189 (2.3%)	2,916 (2.8%)	< .001	874 (3.0%)	583 (3.4%)	.039
Renal disease, n (%)	499 (0.1%)	221 (0.2%)	< .001	40 (0.1%)	30 (0.2%)	.350
Liver disease, n (%)	191 (0.1%)	83 (0.1%)	0.004	39 (0.1%)	34 (0.2%)	.110
Herpes, n (%)	4,762 (1.4%)	1,586 (1.5%)	< .001	758 (2.6%)	470 (2.7%)	.540
Obstetrical conditions						
Placenta previa, n (%)	738 (0.2%)	563 (0.5%)	< .001	109 (0.4%)	237 (1.4%)	< .001
Abruption PROM ^{#6} , n (%)	840 (0.2%)	1,127 (1.1%)	< .001	136 (0.5%)	237 (1.4%)	< .001
PROM, n (%)	16,731 (4.8%)	6,736 (6.4%)	< .001	2,175 (7.5%)	1,407 (8.1%)	.018
Postterm, n (%)	66,616 (19.0%)	31,549 (30.1%)	< .001	6,149 (21.3%)	5,245 (30.3%)	< .001
Cord prolapse with compression, n (%)	198 (0.1%)	529 (0.5%)	< .001	17 (0.1%)	73 (0.4%)	< .001
Cord entanglement + compression, n (%)	21,762 (6.2%)	5,754 (5.5%)	< .001	2,064 (7.1%)	965 (5.6%)	< .001
Antepartum bleed, n (%)	1,670 (0.5%)	1,725 (1.6%)	< .001	264 (0.9%)	482 (2.8%)	< .001
Isoimmune disease, n (%)	5,566 (1.6%)	1,504 (1.4%)	< .001	523 (1.8%)	263 (1.5%)	.020
Soft tissue condition, n (%)	129,032 (36.7%)	48,245 (46.0%)	< .001	13,383 (46.3%)	9,870 (57.0%)	< .001
Fetal conditions						
Polyhydramnios, n (%)	521 (0.1%)	606 (0.6%)	< .001	77 (0.3%)	157 (0.9%)	< .001
Oligohydramnios, n (%)	10,000 (2.8%)	5,756 (5.5%)	< .001	1,016 (3.5%)	1,060 (6.1%)	< .001
IUGR ^{#7} , n (%)	4,537 (1.3%)	1,814 (1.7%)	< .001	433 (1.5%)	326 (1.9%)	.002
Excessive fetal growth, n (%)	3,042 (0.9%)	5,599 (5.3%)	< .001	320 (1.1%)	896 (5.2%)	< .001
Intra-partum conditions						
Fetal distress, n (%)	56,785 (16.2%)	47,723 (45.5%)	< .001	5,899 (20.4%)	8,023 (46.3%)	< .001
Dystocia, n (%)	24,362 (6.9%)	77,411 (73.8%)	< .001	3,290 (11.4%)	12,403 (71.6%)	< .001

^{#1}CD = Cesarean delivery; ^{#2}Women with missing age (n = 55) excluded; ^{#3}SD = Standard deviation; ^{#4}DM = Diabetes mellitus; ^{#5}HTN = Hypertension; ^{#6}PROM = Premature rupture of membranes; ^{#7}IUGR = Intrauterine growth restriction; *Chi-square and two-sided two-sample t tests for categorical and continuous variables, respectively.

3. RESULTS

3.1 Descriptive summaries

The dataset included 529,645 California NTSV deliveries that occurred between 2008-2010 and were linked to the birth certificate. Of these, 26,936 CD with no codes to indicate labor and 55 deliveries missing maternal age were excluded. The remaining 502,654 deliveries (94.95%) were included in this analysis. The overall maternal mean age was 25.5 (6.2) years with a range of 11-54 years; most deliveries, 456,416 (90.8%), were to younger mothers, with the following racial/ethnic distribution: 47.1% of Hispanic origin, 29.0% White, 13.8% Asian, 5.5% African-American, and the remainder were of other or unknown race/ethnicity. Medicaid was the principal insurance payer for 44.9% of women. The most prevalent pre-existing conditions were obesity (13.9%), hypertension (7.7% of which 6.4% was classified as gestational hypertension) and DM (5.5% of which 5.1% was GDM).

Table 4 presents the distribution of risk factors for women by

delivery route and maternal age group. There were 122,201 (24.3%) CD reported. Older women were more likely to undergo CD compared to younger women (37.4% vs. 23.0%). For both younger and older mothers, the presence of most obstetrical, fetal and intrapartum conditions listed was associated with a CD ($p < .01$). With respect to the key pre-existing health conditions, the prevalence of DM, hypertension, and obesity was specifically noted to be higher among older women and women undergoing CD.

Women experienced severe maternal morbidity in 1.7% of deliveries; this proportion was 1.6% for younger and 2.2% for older women. Table 5 presents the distribution of risk factors for women with and without severe maternal morbidity by maternal age group. Rates of CD associated with severe maternal morbidity were higher in both younger (44.7% vs. 22.6%) and older women (53.4% vs. 37.1%) ($p < .001$). The presence of most maternal health, fetal, and intrapartum conditions studied was also associated with severe maternal morbidity for both younger and older women ($p < .01$).

Table 5. Distribution of risk factors by presence of severe maternal complications and age group among laboring women with nulliparous term singleton vertex (NTSV) gestations

Variable	Younger women (< 35 years)			Older women (≥ 35 years)		
	No Severe Complications (N = 448,927)	Severe Complications (N = 7,489)	P Value*	No Severe Complications (N = 45,231)	Severe Complications (N = 1,007)	P Value*
Cesarean delivery						
CD ^{#1} , n (%)	101,541 (22.6%)	3,347 (44.7%)	< .001	16,775 (37.1%)	538 (53.4%)	< .001
Socio-demographic						
Age category, n (%)			.031			.120
0-19	99,931 (22.3%)	1,717 (22.9%)				
20-24	140,091 (31.2%)	2,297 (30.7%)				
25-29	120,184 (26.8%)	1,923 (25.7%)				
30-34	88,721 (19.8%)	1,552 (20.7%)				
35-39				37,018 (81.8%)	806 (80.0%)	
40-44				7,713 (17.1%)	184 (18.3%)	
45+				500 (1.1%)	17 (1.7%)	
Age of mother ^{#2} , Mean(SD ^{#3})	24.3 (5.1)	24.3 (5.2)	.71	37.4 (2.4)	37.7 (2.5)	.001
Race/Ethnicity, n (%)			< .001			< .001
Hispanic	222,878 (49.6%)	3,988 (53.3%)		9,423 (20.8%)	223 (22.1%)	
Multiple race	10,068 (2.2%)	141 (1.9%)		1,048 (2.3%)	24 (2.4%)	
Black, non-Hispanic	25,644 (5.7%)	469 (6.3%)		1,329 (2.9%)	37 (3.7%)	
American Indian	1,451 (0.3%)	20 (0.3%)		50 (0.1%)	5 (0.5%)	
Asian	56,459 (12.6%)	1,064 (14.2%)		11,386 (25.2%)	297 (29.5%)	
Pacific Islander	1,756 (0.4%)	34 (0.5%)		116 (0.3%)	2 (0.2%)	
White, non-Hispanic	123,000 (27.4%)	1,645 (22.0%)		20,509 (45.3%)	389 (38.6%)	
Other	287 (0.1%)	5 (0.1%)		31 (0.1%)	1 (0.1%)	
Unknown	7,384 (1.6%)	123 (1.6%)		1,339 (3.0%)	29 (2.9%)	
Highest education level, n (%)			< .001			.200
Less than high school	94,547 (21.1%)	1,814 (24.2%)		2,373 (5.2%)	54 (5.4%)	
High school	122,478 (27.3%)	1,976 (26.4%)		4,264 (9.4%)	115 (11.4%)	
College or more	215,775 (48.1%)	3,410 (45.5%)		36,309 (80.3%)	789 (78.4%)	
Missing/Unknown	16,127 (3.6%)	289 (3.9%)		2,285 (5.1%)	49 (4.9%)	
Medicaid insurance, n (%)	215,656 (48.0%)	3,720 (49.7%)	< .001	6,239 (13.8%)	149 (14.8%)	.160

(Table 5 continued on page 43)

Table 5. (continued.)

Variable	Younger women (< 35)			Older women (≥ 35)		
	No Severe Complications (N = 448,927)	Severe Complications (N = 7,489)	P Value*	No Severe Complications (N = 45,231)	Severe Complications (N = 1,007)	P Value*
Prenatal care index, n (%)			< .001			.003
Inadequate	44,940 (10.0%)	784 (10.5%)		1,736 (3.8%)	47 (4.7%)	
Intermediate	41,632 (9.3%)	777 (10.4%)		3,880 (8.6%)	118 (11.7%)	
Adequate	207,776 (46.3%)	3,278 (43.8%)		20,837 (46.1%)	432 (42.9%)	
Adequate plus	138,468 (30.8%)	2,321 (31.0%)		17,133 (37.9%)	369 (36.6%)	
Missing info	16,111 (3.6%)	329 (4.4%)		1,645 (3.6%)	41 (4.1%)	
Year, n (%)			< .001			.570
2008	156,426 (34.8%)	2,431 (32.5%)		15,319 (33.9%)	325 (32.3%)	
2009	148,701 (33.1%)	2,586 (34.5%)		14,897 (32.9%)	338 (33.6%)	
2010	143,800 (32.0%)	2,472 (33.0%)		15,015 (33.2%)	344 (34.2%)	
Pre-existing or pregnancy-related conditions						
DM ^{#4} (any), n (%)	21,869 (4.9%)	442 (5.9%)	< .001	5,309 (11.7%)	148 (14.7%)	.004
DM category, n (%)			< .001			.015
None	427,058 (95.1%)	7,047 (94.1%)		39,922 (88.3%)	859 (85.3%)	
Chronic +/- gestational DM	1,890 (0.4%)	52 (0.7%)		426 (0.9%)	11 (1.1%)	
Gestational DM only	19,979 (4.5%)	390 (5.2%)		4,883 (10.8%)	137 (13.6%)	
HTN ^{#5} (any), n (%)	32,831 (7.3%)	1,316 (17.6%)	< .001	4,332 (9.6%)	184 (18.3%)	< .001
HTN category, n (%)			< .001			< .001
None	416,096 (92.7%)	6,173 (82.4%)		40,899 (90.4%)	823 (81.7%)	
Chronic/Superimposed HTN	3,527 (0.8%)	96 (1.3%)		1,089 (2.4%)	39 (3.9%)	
Gestational HTN only	27,669 (6.2%)	1,174 (15.7%)		2,980 (6.6%)	131 (13.0%)	
Unspecified HTN	1,635 (0.4%)	46 (0.6%)		263 (0.6%)	14 (1.4%)	
Obesity, n (%)	63,040 (14.0%)	1,080 (14.4%)	.35	5,478 (12.1%)	130 (12.9%)	.440
Heart disease, n (%)	1,531 (0.3%)	225 (3.0%)	< .001	310 (0.7%)	44 (4.4%)	< .001
Mental health diagnosis, n (%)	10,792 (2.4%)	313 (4.2%)	< .001	1,407 (3.1%)	50 (5.0%)	< .001
Renal disease, n (%)	686 (0.2%)	34 (0.5%)	< .001	65 (0.1%)	5 (0.5%)	.004
Liver disease, n (%)	253 (0.1%)	21 (0.3%)	< .001	68 (0.2%)	5 (0.5%)	.006
Herpes, n (%)	6,209 (1.4%)	139 (1.9%)	< .001	1,193 (2.6%)	35 (3.5%)	.100
Obstetrical conditions						
Placenta previa, n (%)	1,247 (0.3%)	54 (0.7%)	< .001	323 (0.7%)	23 (2.3%)	< .001
Abruptio PROM ^{#6} , n (%)	1,854 (0.4%)	113 (1.5%)	< .001	351 (0.8%)	22 (2.2%)	< .001
PROM, n (%)	23,008 (5.1%)	459 (6.1%)	< .001	3,496 (7.7%)	86 (8.5%)	.340
Postterm, n (%)	96,214 (21.4%)	1,951 (26.1%)	< .001	11,134 (24.6%)	260 (25.8%)	.380
Cord prolapse with compression, n (%)	704 (0.2%)	23 (0.3%)	0.001	85 (0.2%)	5 (0.5%)	.028
Cord entanglement + compression, n (%)	27,136 (6.0%)	380 (5.1%)	< .001	2,963 (6.6%)	66 (6.6%)	1.000
Antepartum bleed, n (%)	3,218 (0.7%)	177 (2.4%)	< .001	699 (1.5%)	47 (4.7%)	< .001
Isoimmune disease, n (%)	6,950 (1.5%)	120 (1.6%)	.71	776 (1.7%)	10 (1.0%)	.080
Soft tissue condition, n (%)	174,006 (38.8%)	3,271 (43.7%)	< .001	22,685 (50.2%)	568 (56.4%)	< .001
Fetal conditions						
Polyhydramnios, n (%)	1,078 (0.2%)	49 (0.7%)	< .001	225 (0.5%)	9 (0.9%)	.080
Oligohydramnios, n (%)	15,456 (3.4%)	300 (4.0%)	0.008	2,031 (4.5%)	45 (4.5%)	.970
IUGR ^{#7} , n (%)	6,262 (1.4%)	89 (1.2%)	.13	738 (1.6%)	21 (2.1%)	.260
Excessive fetal growth, n (%)	8,396 (1.9%)	245 (3.3%)	< .001	1,177 (2.6%)	39 (3.9%)	.013
Intra-partum conditions						
Fetal distress, n (%)	102,188 (22.8%)	2,320 (31.0%)	< .001	13,551 (30.0%)	371 (36.8%)	< .001
Dystocia, n (%)	98,795 (22.0%)	2,978 (39.8%)	< .001	15,265 (33.7%)	428 (42.5%)	< .001

^{#1}CD = Cesarean delivery; ^{#2}Women with missing age (n = 55) excluded; ^{#3}SD = Standard deviation; ^{#4}DM = Diabetes mellitus; ^{#5}HTN = Hypertension; ^{#6}PROM = Premature rupture of membranes; ^{#7}IUGR = Intrauterine growth restriction; *Chi-square and two-sided two-sample t tests for categorical and continuous variables, respectively.

3.2 Modeling results

Heart disease and hypertension had the highest total effects on severe maternal morbidity in both age groups (see Table 6). For younger and older women, the adjusted odds ratios (95% CI) for heart disease were 8.38 (7.16, 9.81) and 6.48 (4.65, 9.03), respectively. For any hypertension, the total effects were 2.77 (2.59, 2.97) and 2.11 (1.79, 2.52).

Decomposition of these total effects showed that most of the impact of these comorbid conditions on severe mater-

nal morbidity was direct, and not through the increased risk of CD. The direct effects of heart disease for younger and older women were 7.97 (6.79, 9.36) and 6.57 (4.73, 9.14), respectively. In younger women the indirect risk of severe maternal morbidity due to heart disease was increased by 5% (indirect effect OR 1.05, 1.01, 1.10) as a result of the increased risk of CD. There was no significant indirect effect in older women. The direct effects of any hypertension for younger and older women were 2.67 (2.47, 2.88) and 2.00 (1.68, 2.37), respectively. In younger women, the in-

direct risk of severe maternal morbidity from hypertension was increased by 4% (indirect effect OR 1.04 [1.03, 1.06]) and by 6% (indirect effect OR 1.06 [1.04, 1.09]) in older women. Separate examination of chronic/superimposed and gestational hypertension showed similar risk decomposition

and that the direct effect from gestational hypertension was higher: the OR was 2.84 in younger and 2.09 in older women compared to the chronic/superimposed hypertension OR of 1.59 and 1.64 in younger and older age groups, respectively.

Table 6. Natural direct effect (NDE), natural indirect effect (NIE) and total effect (TE) of pre-existing and gestational conditions (comorbid conditions) on severe maternal morbidity mediated by cesarean delivery (CD) among laboring women with nulliparous term singleton vertex (NTSV) gestations^{#1}

	Younger women (< 35 years)						Older women (≥ 35 years)					
	NDE		NIE		TE		NDE		NIE		TE	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Any diabetes	Comorbid cases n = 22,311 (4.9%) ^{#3, #4}						Comorbid cases n = 5,457 (11.8%) ^{#3, #4}					
	0.981	0.884-1.090	1.030	1.024-1.037	1.011	0.910-1.123	1.093	0.894-1.338	1.001	0.990-1.012	1.094	0.894-1.339
	Any diabetes was not significant in the outcome model						Any diabetes was not significant in the outcome and CD models					
Chronic diabetes (± gestational diabetes)	Comorbid cases n = 1,942 (0.4%) ^{#3, #4}						Comorbid cases n = 437 (0.9%) ^{#3, #4}					
	0.995	0.749-1.322	1.111	1.086-1.137	1.106	0.832-1.470	0.792	0.424-1.479	1.061	1.020-1.103	0.841	0.450-1.571
	Chronic diabetes was not significant in the outcome model						Chronic diabetes was not significant in the outcome model					
Gestational diabetes only	Comorbid cases n = 20,369 (4.5%) ^{#2, #4}						Comorbid cases n = 5,020 (10.9%) ^{#2, #4}					
	0.907	0.794-1.037	1.033	1.021-1.046	0.937	0.824-1.066	1.124	0.915-1.381	0.996	0.985-1.007	1.119	0.911-1.376
	Gestational diabetes was not significant in the outcome model						Gestational diabetes was not significant in the outcome and CD models					
Any hypertension	Comorbid cases n = 34,147 (7.5%) ^{#2}						Comorbid cases n = 4,516 (9.8%) ^{#3}					
	2.667	2.473-2.876	1.040	1.026-1.055	2.774	2.587-2.974	1.996	1.680-2.371	1.063	1.039-1.088	2.112	1.786-2.522
Chronic/ Superimposed hypertension	Comorbid cases n = 3,623 (0.8%) ^{#3}						Comorbid cases n = 1,128 (2.4%) ^{#3}					
	1.587	1.285-1.958	1.067	1.051-1.083	1.693	1.371-2.090	1.644	1.168-2.313	1.055	1.026-1.084	1.734	1.231-2.441
Gestational hypertension only	Comorbid cases n = 28,843 (6.3%) ^{#2}						Comorbid cases n = 3,111 (6.7%) ^{#3}					
	2.842	2.627-3.074	1.038	1.023-1.053	2.949	2.743-3.170	2.090	1.721-2.537	1.068	1.041-1.095	2.231	1.837-2.710
Obesity	Comorbid cases n = 64,120 (14.0%) ^{#3}						Comorbid cases n = 5,608 (12.1%) ^{#3, #4}					
	0.778	0.726-0.833	0.966	0.962-0.969	0.751	0.701-0.804	0.857	0.702-1.047	0.939	0.921-0.958	0.805	0.658-0.985
	Obesity was not significant in the outcome model											
Heart disease	Comorbid cases n = 1,756 (0.4%) ^{#2}						Comorbid cases n = 354 (0.8%) ^{#3, #4}					
	7.972	6.795-9.362	1.051	1.009-1.097	8.379	7.164-9.805	6.570	4.725-9.136	0.987	0.956-1.019	6.483	4.655-9.029
	Heart disease was not significant in the CD model											
Mental health diagnosis	Comorbid cases n = 11,105 (2.4%) ^{#3, #4}						Comorbid cases n = 1,457 (3.2%) ^{#3}					
	1.581	1.400-1.785	0.998	0.992-1.003	1.577	1.397-1.781	1.433	1.058-1.940	0.981	0.963-0.999	1.405	1.038-1.904
	Mental health diagnosis was not significant in the CD model											

^{#1}Outcome and mediator logistic regression models adjusted for: Race/ethnicity, mother's education level, Medicaid insurance, PNC index, year of delivery, placenta previa, abruption with premature rupture of membranes (PROM), PROM, postterm, cord prolapse with compression, cord entanglement with compression, antepartum bleed, isoimmune disease, soft tissue condition, polyhydramnios, oligohydramnios, intrauterine growth restriction, excessive fetal growth, renal disease, liver disease, herpes, fetal distress, dystocia and comorbid conditions other than the specific one under consideration. Interaction between comorbid condition of interest (exposure) and cesarean delivery (CD) (mediator) tested for each model and included in outcome logistic regression if significant.

^{#2}Significant interaction between comorbid condition of interest (exposure) and CD (mediator) included in the outcome logistic regression model.

^{#3}Insignificant interaction between comorbid condition of interest (exposure) and CD (mediator) not included in the outcome logistic regression model.

^{#4}Conditions not met due to insignificance of the adjusted effect of maternal condition (exposure) and/or CD (mediator). Specifics indicated in footnote under model results for each maternal condition.

The total effects of any DM, chronic, and gestational DM on severe maternal morbidity were insignificant in both age groups. However, for the younger women, there were significant indirect effects of 1.03 (1.03, 1.04) for any DM, 1.11 (1.09, 1.14) for chronic DM, and 1.03 (1.02, 1.05) for GDM as a result of the increased risk of an CD. For older women, only a significant indirect effect of 1.06 (1.02, 1.10) in women with chronic DM was observed.

Obesity had a total effect of 0.75 (0.70, 0.80) for younger women, driven primarily by a direct effect of 0.78 (0.73, 0.83). Similar results were observed in older women. For

both younger and older women, there was a significant indirect effect slightly below “1”.

Mental health diagnoses had a total effect on severe maternal morbidity of 1.58 (1.40, 1.79) and 1.43 (1.06, 1.94) in younger and older women, respectively. The indirect effects were close to “1” for both age groups and insignificant for the younger women. Therefore, almost all the increased risk of severe maternal morbidity appeared attributable directly to the mental health diagnoses.

Assessment of potential bias in the NIE estimates due to violation of the assumption of no unmeasured confounding

of the exposure-outcome relationship showed mostly small estimate biases of less than 5% absolute change, with the exception of 10%, 9%, and 7% change in younger women's gestational hypertension, any hypertension, and gestational DM, respectively.

4. DISCUSSION

This study took a mediation approach to evaluate the impact of key pre-existing and gestational conditions on severe maternal morbidity and the risk mediated through an emergent CD. We focused on laboring, NTSV women to obtain a more homogeneous sample and built separate models for each health condition and for younger versus older women.

Most studies that address the question of the total effect of pre-existing conditions on severe maternal morbidity consider composite pre-existing condition measures^[6,8,31,32] with varying degree of adjustment for confounders. Definitions of the pre-existing condition composite also vary, but all include diabetes and hypertension as the conditions with the highest prevalence, heart disease as the condition with highest risk, and some include mental disease.^[8,32] In a Washington State population-based study, Gray *et al.*^[8] reported an OR of 2.1-fold increased risk of severe maternal morbidity for women with at least one pre-existing condition, with older women at higher risk of severe maternal morbidity. Two other large population-based studies from Australia/Ireland^[7] and from Canada^[6] found ORs of 2.6 and 5.8, respectively. Goffman *et al.*^[31] found an OR of 2.7 in a matched case-control US study on chronic conditions. In another recent population-based study from Australia, Lindquist *et al.*^[32] found an OR of 1.4. Collectively, these ORs are comparable to our findings in a broad sense, both in terms of direction and magnitude of effect.

As in the current study, some authors separately examined specific pre-existing conditions. Grobman *et al.*^[5] examined the total effect of specific pre-existing conditions in a large study of deliveries in the US. These included diabetes, hypertension and antenatal anticoagulant use as an indication of heart disease; ORs were 1.6 (borderline significant) for chronic and 2.1 for gestational diabetes, 3.4 for hypertension and 5.2 for anticoagulant use, adjusting for socio-demographic, parity, gestational age and obstetrical complication factors. A prospective Canadian study found 13% severe maternal morbidity or mortality in women with pre-existing heart disease,^[33] which is an 8 to 10-fold higher risk than that found in the general delivery population. Palasmaa *et al.*^[17] studied severe maternal morbidity in all Finnish singleton deliveries with labor (*i.e.*, attempted vaginal delivery) between 2007-2011 and found adjusted ORs of 2.0 for pre-eclampsia and non-significant effects for

DM. Compared to our non-significant total effects for diabetes, "any" hypertension effects of 2.7 and 2.0 and heart disease effects of 8.0 and 6.6 for older and younger women, respectively, there is considerable variation in these effect sizes. The OR estimates of Palasmaa *et al.*^[17] study are closer to our findings, and this is probably due to the greater similarity between the studies (*i.e.*, specifically focusing on singleton deliveries undergoing labor). It is also possible that the elevated ORs associated with chronic and gestational hypertension may be due to the inclusion of women who underwent cesarean without labor; such non-laboring women are generally sicker and at increased risk for experiencing severe maternal morbidity. This population was not captured in our model and their exclusion may explain the decreased the magnitude of our effect sizes for these conditions. Still, the substantially largest effect of heart disease, and the larger effect of hypertension compared to diabetes was evident in all studies.

With regard to obesity, two studies found a moderate (OR = 1.2) increased risk of severe maternal morbidity,^[8,17] and another study found a non-significant effect.^[31] All defined obesity as BMI ≥ 30 kg/m², but there were many variations in study design (*e.g.*, use of clinical registries or case-control methods) and definitions of severe maternal morbidity, with some studies including wound infections or separations, and longer postpartum follow up (*i.e.*, periods ranged from 6 weeks to 1 year for maternal mortality). In contrast to other studies, we found a seemingly "protective" effect of obesity. Possible reasons for the reversal in the obesity effect may be that our results were limited to events reported to happen within the hospital during the delivery admission that were recorded in an administrative database. Further, we limited the population of interest to NTSV laboring women, stratifying by age group and adjusting for a comprehensive set of pre-existing, obstetrical, fetal, and intra-partum conditions. Further research is needed to confirm the direction and magnitude of impact of obesity on a standardized definition of severe maternal morbidity. We are not aware of studies that examined the separate effect of mental health on severe maternal morbidity. Our total effect showed moderate increased risks of OR = 1.6 and 1.4 for younger and older women, respectively.

While our age-stratified analyses generally found similar or lower effects for older women, other studies that adjusted for age generally found a non-significant age ≥ 35 effect^[7,17] or a higher risk (ORs from 1.06 to 1.7) of severe maternal morbidity for older women.^[5,8,30] However, these studies did not consider potential interactions of age with the risk factors of interest and did not consider non-linear relationships with age. For example, why were younger women with

hypertension and heart disease found to be at higher risk than older women? It may be that they have more severe disease, but disease severity could not be established with ICD-9-CM codes alone. Furthermore, younger women with heart disease in pregnancy may be receiving the diagnosis and treatment for the first time, especially when considering that half of all cardiac disease in pregnancy is congenital.^[34]

Our attempt at decomposing the effect of several pre-existing and gestational maternal conditions is an original contribution to the literature that estimates the degree to which the severe maternal morbidity risk for NTSV laboring women is directly attributable to the conditions and how much of that risk is mediated by increasing the risk of CD. We generally found low indirect effects for the pre-existing and gestational conditions ranging from 0.94-1.11 (-6% to 11%) for all models, indicating that, for these women, the presence of the condition was the main driver for the higher severe maternal morbidity risk; exceptions were found for DM and obesity. The quantification of the direct and indirect risks for severe maternal morbidity will require further exploration to better understand the clinical implication of these findings. Explanations for these findings remain speculative because they have not been well-examined in the obstetrical literature.

The strengths of this study include the use of a large population-based sample and a linked dataset that allowed for the inclusion of multiple covariates potentially related to the maternal outcome. The definition of the study population (*i.e.*, laboring women with NTSV gestations), and the stratification by age, facilitated the interpretation of the results by removing potentially strong confounders and interactions. Limitations of this study include the use of administrative data, which rely on ICD-9-CM codes that may not distinguish the severity or acuity of the condition, and although highly specific, are likely to be under-reported. Although this particular database undergoes routine validity checks, and has been found to be reliable regarding method of delivery, routine quality checks of the key maternal clinical conditions evaluated and the severe maternal morbidity outcomes are not done. The prevalence of the conditions studied in this investigation likely reflects a minimum baseline for the state of California. We also note that the findings are limited to California, although with approximately 500,000 births each

year, this represents 12.6% of all births in the United States (US), more than any other US state.^[35]

The benefits of working with a large sample come with the difficulty in interpreting statistical significance, as even small differences are statistically significant with large samples. Therefore, we emphasized the results with the largest effects that are likely to also be clinically meaningful.

Several assumptions related to unmeasured confounders are required for the unbiasedness of the natural direct and indirect effects estimates. We focused on the assumption most likely to be violated of no unmeasured confounders of the mediator-outcome relationship and showed that our findings were stable. Although it is difficult to rule out violation of all other assumptions, the inclusion of model controls for socio-demographic characteristics, year of delivery, obstetrical conditions, fetal conditions, intrapartum conditions, and other pre-existing conditions may have reduced the possibility of unmeasured confounding.

Lastly, while we attempted to identify women in labor, we did not have primary data to account for a patient's length of time in labor or clinical events during labor that might have contributed to the development of severe morbidity. For example, induction of labor was not included as a covariate, yet it is associated with increased rates of maternal sepsis and hemorrhage, both of which can be classified as severe maternal morbidity.^[16]

In summary, we used a mediation approach to estimate the risk of severe maternal morbidity associated with key maternal health conditions, finding that the conditions with the largest ORs were heart disease and hypertension, and that generally the increased risk mediated by NTSV CD in laboring women was low. These findings direct attention to the identification of antepartum opportunities for both primary and secondary prevention efforts in these at-risk populations.

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