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Complete List of Authors:	Celaya, Martín; Arizona Department of Health Services, Bureau of Assessment and Evaluation; The University of Arizona Mel and Enid Zuckerman College of Public Health, Health Promotion Sciences Zahlan, Alaa I; The University of Arizona Mel and Enid Zuckerman College of Public Health Rock, Chelsea; Arizona State University Nathan, Akshay ; Boston University Acharya, Aishwarya; The University of Arizona Mel and Enid Zuckerman College of Public Health Madhivanan, Purnima ; The University of Arizona Mel and Enid Zuckerman College of Public Health Ehiri, John; The University of Arizona Mel and Enid Zuckerman College of Public Health Hu, Chengcheng; The University of Arizona Mel and Enid Zuckerman College of Public Health Pettygrove, Sydney ; The University of Arizona Mel and Enid Zuckerman College of Public Health McClelland, D. Jean ; The University of Arizona, Health Sciences Library Nuño, Velia Leybas; The University of Arizona Mel and Enid Zuckerman College of Public Health Bellucci, Laura; Arizona Department of Health Services, Bureau of Women's and Children's Health
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TITLE

Individual and community level risk factors for maternal morbidity and mortality among Native American women in the United States: A systematic review

AUTHORS AND AFFILIATION

Martín F. Celaya[1,2], Alaa I. Zahlan[2], Chelsea Rock[3], Akshay Nathan[4], Aishwarya Acharya[2], Purnima Madhivanan[2], John Ehiri[2], Chengcheng Hu[2], Sydney Pettygrove[2], Jean McClelland[5], Velia Leybas Nuño[2], Laura Luna Bellucci[1]

1. Arizona Department of Health Services, Phoenix, Arizona, United States

2. Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona, United States

3. College of Health Solutions, Arizona State University, Phoenix, Arizona, United States

4. Boston University, Boston, Massachusetts, United States

5. Health Sciences Library, The University of Arizona, Tucson, Arizona, United States

AUTHORS' E-MAIL ADDRESSES

Martín F. Celaya, martin.celaya@azdhs.gov; Alaa I Zahlan, azahlan@arizona.edu; Chelsea Rock, chelsea.rock@azdhs.gov; Akshay Nathan, shayaknathan@gmail.com; Aishwarya Acharya, aishwaryaacharya@arizona.edu; Purnima Madhivanan, pmadhivanan@arizona.edu; John Ehiri, jehiri@arizona.edu; Chengcheng Hu, hucc@arizona.edu; Sydney Pettygrove, sydneyp@arizona.edu; Jean McClelland, jmcc@arizona.edu, Velia Leybas Nuño, vleybas@arizona.edu

SUBMITTING AND CORRESPONDING AUTHOR

Martín F. Celaya, martin.celaya@azdhs.gov

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KEYWORDS: American Indian or Alaska Native, Mothers, Morbidity

ABSTRACT

Introduction and objective

Maternal morbidity and mortality (MMM) is a public health concern in the US, with Native American (NA) women experiencing higher rates than non-Hispanic White women. However, research examining specific risk factors (RF) for MMM outcomes experienced by NA women is limited. This systematic review comprehensively synthesizes and critically appraises the literature on individual and community risk factors for MMM.

Methods and analysis

A systematic search was performed in PubMed, Embase, CINAHL, and Scopus for articles published since 2012 using database-specific controlled vocabulary for MMM and NA. Selection criteria included studies with an observational study design, set in the US, including NA women in the perinatal period, and examining the relationship between an RF and an MMM outcome. Three reviewers screened and extracted data from the included studies. Risk of bias was assessed using the NIH's quality assessment tools for cohort, cross-sectional, and case-control studies. The data were analyzed using a descriptive approach.

Results

Fifteen studies were analyzed. NA women were the primary study population in 7 studies. All studies used administrative databases. The study settings were nationwide (7 studies), statewide (4 studies), and on Indian reservations (4 studies). Nine MMM outcomes were identified (e.g., postpartum hemorrhage and disseminated intravascular coagulation). Most studies examined hypertensive disorders of pregnancy (8 studies) and composite MMM (4 studies) as outcomes. Twenty-six RFs were identified. Twenty-four were individual-level RFs, and two were

community-level. Being of NA race (6 studies), rural maternal residency (4 studies), overweight/obese BMI (2 studies), maternal age (2 studies), nulliparity (2 studies), and preexisting medical conditions (1 study) demonstrated increased risk with an MMM outcome.

Conclusion

These findings underscore the scarcity of research on the role of RFs and MMM outcomes for NA women. This scarcity confines the ability of healthcare and public health organizations to design and implement tailored approaches to reduce disparities.

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ARTICLE SUMMARY

Strenghts and limitations of this study

- The review searched a variety of databses to identify a wide range of studies on maternal morbidity and mortality in Native American women in the United States.
- The review incorporated studies conducted on Indian reservations and within specific tribal health systems, providing insights tailored to the unique contexts and experiences of Native American women.
- The review synthesizes and critically appraises the limited existing literature on risk factors for maternal morbidity and mortality specifically among Native American women in the United States.
- Many included studies had small sample sizes or low percentages of Native American women, limiting the generalizability of the findings to this specific population.
- Included studies relied on administrative databases, which introduce potential reporting biases and misclassification issues, especially concerning the racial categorization of Native American participants.

INTRODUCTION

Maternal morbidity and mortality (MMM) are alarming public health problems in the United States. The Centers for Disease Control and Prevention (CDC) defines maternal mortality as the death of a woman during pregnancy, at delivery, or soon after delivery. [1] Severe maternal morbidity (SMM) refers to complications during labor and delivery with short- and long-term health consequences (e.g., sepsis, blood transfusion, preeclampsia, or hysterectomy). [2,3] The US has one of the highest maternal mortality ratios of any high-income country, reporting 26.4 maternal deaths per 100,000 live births. In contrast, Finland has the lowest maternal mortality ratio of 3.8 maternal deaths per 100,000 live births, a value nearly seven times lower than the US. [4] The causes behind the rising MMM rates are not fully understood but involve complex interactions of factors at patients and families, providers or facilities, overall systems, and within the community at various points in the reproductive life cylce. [5]

Significant racial and ethnic health inequities persist in maternal health. [6–9] Native American women are three to four times more likely to die than non-Hispanic White women from pregnancy-related complications in the US and are three to five times more likely to experience SMM than non-Hispanic White women. [6,10,11] Historical trauma, racism, colonization, genocide, forced migration, reproductive coercion, and cultural erasure contribute to these adverse outcomes. [12–14] Native American women experience unique prolonged systemic barriers that create inequitable social conditions compared to other groups. [14–16] Some systemic barriers affecting include limited access to providers and birthing facilities. [14,17,18] In addition, a history of forced sterilization and forced infant and child separations has led to a strong distrust of the healthcare systems and providers, including the Indian Health Service. [19–21]

Rationale

Despite these concerns, only a sparse amount of research supports the presence MMM risk factors specific to Native American women. A recent scoping review on Native American women and the leading causes of maternal mortality in the US identified risk factors like historical trauma, inequities in healthcare availability, access and utilization, preexisting health conditions, and rurality. [22] A separate review of social determinants of pregnancy-related mortality and morbidity identified that race was a significant factor for MMM. [3] However, the review did not provide a list of risk factors specific to Native American women, nor did it include a study that evaluated maternal deaths among Native American women. [3] There is a need to explore further and assess the quality of research specific to MMM risk factors experienced by Native American women. Identifying this information can help identify areas for prevention focused on Native American communities. Therefore, this systematic review aims to comprehensively synthesize and critically appraise the literature on MMM risk factors experienced by Native American women.

Objective

To assess and critically appraise individual and community-level risk factors for pregnancy-related morbidity and mortality experienced by Native American women in the US.

METHODS

Eligibility criteria

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Mata-Analyses (PRISMA) guidelines. [23] Inclusion criteria for studies were: 1) observational study design; 2) study set in the United States; 3) population was Native American women in the

perinatal or puerperium period; 4) outcomes focused on measures of pregnancy-related mortality and morbidity; 5) examined the relationship between a risk factor/exposure and stated outcomes. Studies focusing on a different population were included if they offered a stratified analysis by race and contained a racial category for Native Americans. Studies were excluded if: 1) studies focused only on birth, neonatal, or infant outcomes; 2) studies that did not examine the relationship between a risk factor/exposure and stated outcomes; 3) studies with settings outside of the United States; 4) studies that did not include findings for Native American women; and 5) studies that focus on the preconception or postpartum phases.

Information sources and search strategy

The review searched databases (PubMed, Embase, CINAHL, and Scopus) from 1 January 2012 to 10 October 2022. This timeframe was chosen because the CDC released a new standard for monitoring severe maternal morbidity on 12 November 2012. [2] With technical assistance from a specialized health sciences librarian, the team used search tools and strategies, including shortening keywords where appropriate, using thesaurus terms, and using database-specific controlled vocabulary (e.g., Medical Subject Headings, MeSH). The search strategy combined terms and search strings with the appropriate Boolean operators.

Selection process

Two independent reviewers screened the titles and abstracts based on the eligibility criteria to. If any disagreement occurred, a third reviewer helped arbitrate. After the title and abstract were screened, two independent reviewers screened full-text article. Each excluded article's reason for exclusion was noted at each stage.

Data collection process

Two independent reviewers extracted data using Covidence. [24] The data collected included study details such as location, study design, and eligibility criteria, methods, year of the article, year(s) of study, data source, objectives, sample size and population, independent (risk factors) and dependent (outcomes) variables, key findings, measures of effect/association with p-values and confidence intervals, and limitations. If there were disagreements between the reviewers, a third reviewer arbitrated. For any missing information, the lead author contacted corresponding authors to request for information. Authors were contacted three times via email or phone. Any discrepancies within data extraction were reviewed and discussed in a team setting.

Data items

Primary outcomes of interest were maternal morbidity and mortality, including severe maternal morbidity (SMM) based on the CDC's list of 21 diagnoses and procedures (Table 1). [25]

Table 1 Outcomes of interest

Mortality and near-misses	
Severe maternal morbidity diagnostic or procedural outcomes	Acute myocardial infarction Acute renal failure Adult respiratory Distress Syndrome Amniotic fluid embolism Aneurysm Cardiac arrest Disseminated intravascular coagulation Eclampsia Heart failure Puerperal cerebrovascular disorders Pulmonary edema Sepsis Severe anesthesia complications Shock Sickle cell anemia with crisis Thrombotic embolism Blood transfusion Conversion of cardiac rhythm Hysterectomy

	Temporary tracheostomy Ventilation
Additional morbidity outcomes	Postpartum hemorrhage Ectopic pregnancy Placental abruption Uterine atony

This list was used to identify additional articles that did not utilize a composite outcome of severe maternal morbidity or mortality and instead had a more focused outcome in their investigation. Given the scope of this review, the terms "pregnancy complications," "obstetric complications," "labor complications," and "near-miss" were added to the list of outcomes to increase the sensitivity of the review. Pregnancy, labor, and obstetric complications all refer to conditions or pathological processes associated with pregnancy. [26] They can occur during or after pregnancy, ranging from minor discomforts to severe diseases requiring medical interventions. These include diseases in pregnant women, and pregnancies in women with diseases. Near-miss refers to an event that presented a risk but did not result in death. Maternal mortality refers to the death of a woman while pregnant or within one year of the end of a pregnancy, regardless of the outcome, duration or site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.[27]

The search strategy was pilot tested in PubMed, finalized, and adapted to other databases. The complete search strategy is available in Appendix 1. The results from each database-specific search strategy were downloaded from the respective databases and uploaded to the EndNote version 20 reference manager software. [28] After removing the duplicates, the citations were imported into Covidence.

Study risk of bias assessment and certainty assessment

Risk of bias was assessed using the NIH's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, and Case-Control Studies to examine critical concepts for each study's validity. [29] Two independent reviewers used the tool criteria and rated articles as "good," "fair," or "poor" quality. A rating of "good" meant that there was the least risk of bias, and the results were considered valid. [29] A "fair" rating indicated susceptibility to some bias but was still insufficient to invalidate its results and would vary in their strengths and weaknesses. [29] A "poor" rating indicated a significant risk of bias and invalidated its results. [29] When the ratings differed, a third reviewer arbitrated the article's rating to reach a consensus.

Effect measures

Measures of effect such as risk and odds ratios with 95% confidence intervals were extracted. Descriptive statistics like prevalence and incidence were also included.

Synthesis methods

A description of the findings for each study included in the review is provided in Appendix 2. This table includes the risk factors and outcomes of interest and study characteristics. A descriptive synthesis of the results was the most appropriate for this review since there was a large diversity of study designs, risk factors, and outcomes. The variety of the studies included in this review hindered any quantitative synthesis of the identified risk factors' effect sizes. The identified risk factors are also organized into socioecological levels (i.e., individual, family, community, society, or systems). Risk factors were grouped by outcome examined. The information that was reported for each risk factor included 1) the number of studies that analyzed the risk factor, 2) the number of studies that had a measure of effect for a risk factor and was

reported to be statistically significant, and 3) the number of studies that had a measure of effect for a risk factor, and was not statistically significant. Ratings and descriptive information for each article are provided in a tabular format.

[INSERT FIGURE 1]

RESULTS

Study Selection and study characteristics

A total of 8,220 articles were identified, of which 357 duplicates were removed, resulting in 7,863 articles for screening (Figure 1). During the screening process, there were 6,967 agreements for inclusion and 896 conflicts resolved by an arbitrator, for an overall percent agreement of 88.6%. The selection process yielded a total of 145 articles, of which 15 were included in the review. [10,11,30–39] The most common reasons for study exclusion were: wrong patient population (41 studies), wrong setting (22 studies), and wrong type of publication (21 studies). Most (80.0%) studies used secondary data to examine associations between risk factors and outcomes. There was an equal number of studies across three study designs (5 studies each). The sample size across all studies ranged from 196 to 51,685,525 with a mean sample size of 4,479,962, a median of 72,697, a standard deviation of 12,732,821.6, and an interquartile range of 2,123,375.0. Seven studies focused primarily on Native American women (i.e., the study sample made up mainly of Native American women).[32–34,36–38,40] The remaining eight studies included Native American women as a subgroup in their sample.[10,11,30,31,35,39,41,42] Of these eight studies, the percentage of Native American women that were part of the overall sample ranged from 0.41% to 10.1%, and six of these studies had a proportion of Native American women in their sample that was ≤ 1.35%. The total number

of Native American participants across all studies ranged from 196 to 492,771 with a mean of 57,266.5, a median of 7,107, a standard deviation of 129,234.2, and an interquartile range of 26,817.0. Study settings included nationwide (7/15 studies) [10,11,35,36,39,41,42] , statewide (4/15 studies) [30,31,37,38], and on Indian reservations (4/15 studies) [32–34,40]. All studies used administrative databases such as birth vital records or hospital medical/discharge records.

Risk of bias in studies

Thirteen studies were rated as "good" and two were rated as "fair" according to the NIH's Study Quality Assessment Tools. See Appendix 3 for individual assessments of quality. Amongst the cohort and cross-sectional studies, fourteen were rated "good," [11,30,31,35,39–43] while one was rated "fair." [36] Most studies did not assess the exposure more than once over time (7/10 studies). [30,31,35,39–41,43] A smaller proportion were unable to demonstrate that the exposure of interest was measured before the outcome being measured (5/10 studies) [11,36,39,42,43] or did not adjust models to include potential confounders to assess their impact on the relationship between exposure(s) and outcome(s) (3/10 studies).[36,40,42] The reviewers were unable to find evidence in some studies if the outcome assessors were blinded to the exposure status of participants (3/10 studies) [11,36,42] or whether there was a loss to follow-up amongst the cohort studies (3/5 studies). [30,35,40] Amongst the case-control studies, four were rated as "good" [32–34,37] while one was rated as "fair." [38] The reviewers ascertained that some studies failed to provide a sample size justification (3/5 studies) [32–34] or did not randomly select cases and/or controls from the eligible study population (2/5 studies). [33,38]

Results of individual studies and syntheses

Nine outcomes were identified in the studies: hypertensive disorders of pregnancy (preeclampsia, severe preeclampsia, gestational hypertension, and hypertensive disorders of pregnancy), blood transfusions, postpartum hemorrhage, disseminated intravascular coagulation (DIC), hysterectomy, ectopic pregnancy, uterine atony, placental abruption, and SMM and/or mortality as a composite outcome. Twenty-six risk factors were identified, 24 of these were individual risk factors while two were community risk factors. No studies examined interpersonal/relationship (e.g. marital status or social support) or societal levels (e.g. historical trauma, structural racism, or discrimination) risk factors.

Table 2 lists the frequency by which each risk factor and outcome was studied in the literature. A majority of studies examined "hypertensive disorders of pregnancy" (8/15 studies) [30–35,37,42] and "severe maternal morbidity and/or mortality" (4/15 studies) [10,11,39,41] as outcomes. Fewer studies examined the remaining outcomes. A majority of studies examined body mass index (BMI) (6/15 studies) [30–34,38], maternal age (6/15 studies) [32–36,40] , maternal race (5/15 studies) [10,31,39–41], and parity (5/15 studies) [32–34,38,40] as risk factors for various outcomes. Table 3 is a summary table that reports the number of studies grouped by outcome, the risk factors examined for associations, and the direction of those associations. Appendix 2 summarizes additional details on study design, sample size, and data sources; exposures and outcome variables; covariates; key findings including the measures of effect and study quality ratings.

Table 2. Risk factors and outcomes by volume of studies

Risk Factor	Outcome*

	SMMM	HDP†	BT	PPH	DIC	Hyst	EP	UA	PA	No. of Studies Examining Each Risk Factor
Body mass index	0	5	0	1	0	0	1	1	0	7
Age	0	4	0	1	0	0	1	1	0	6
Maternal race	3	1	2	1	1	1	0	1	0	5
Parity	0	3	0	1	0	0	0	1	0	5
Maternal residence	2	1	2	0	1	1	0	0	0	3
Gene expressions	0	3	0	0	0	0	0	0	0	3
Tobacco use	0	2	0	0	0	0	0	0	1	2
Birth primary payer type	1	0	1	0	0	0	0	0	0	1
Mag Sulfate Use	0	0	0	2	0	0	0	1	0	2
Inpatient induction	0	0	0	2	0	0	0	1	0	2
Augmentation	0	0	0	1	0	0	0	1	0	1
Birthweight	0	0	0	1	0	0	0	1	0	1
Physical health/ chronic health status	1	0	0	0	0	0	0	0	0	1
Gestational diabetes	0	1	0	0	0	0	0	0	0	1
Behavioral health status	1	0	0	0	0	0	0	0	0	1
Indian Health Service region	0	0	0	0	0	0	1	0	0	1
Gravidity	0	0	0	0	1	0	0	1	0	1
Routine aspirin use	0	0	0	1	0	0	0	0	0	1
Prior uterine incision or VBAC	0	0	0	1	0	0	0	0	0	1
Macrosomia	0	0	0	1	0	0	0	0	0	1
Antepartum Bleeding	0	0	0	1	0	0	0	0	0	1
Previous PPH	0	0	0	1	0	0	0	0	0	1

Length of labor	0	0	0	1	0	0	0	0	0	1
Oxytocin use	0	0	0	1	0	0	0	0	0	1
Chorioamnionitis	0	0	0	1	0	0	0	1	0	1
Retained placenta	0	0	0	1	0	0	0	1	0	1
No. of Studies Examining Each Outcome	4	8	2	2	2	1	1	1	1	15

*Acronyms: severe maternal morbidity and mortality (SMM), hypertensive disorders of pregnancy (HDP), blood transfusion (BT), postpartum hemorrhage (PPH), disseminated intravascular coagulation (DIC), hysterectomy (Hyst), ectopic pregnancy (EP), uterine atony (UA), and placental abruption (PA)
† The HDP category includes pre-eclampsia, severe pre-eclampsia, gestational hypertension, and hypertensive disorders of pregnancy.

Table 3. Summary of risk factors and outcomes by risk/association category*

Outcome	↑Increased risk or positive association	—No association	↓Decreased risk or negative association
Hypertensive disorders of pregnancy (8 studies)			
Pregnancy induced hypertension	***Rural maternal residency***[1178] Maternal age 35 years or older and smoked during pregnancy[1371]	***Continuous smokeless tobacco use***[2230] ***Continuous cigarette smoking***[2230]	***Maternal age<35 years and smoked during pregnancy***[1371]
Pre-eclampsia	Native American maternal race[8141] ***Overweight/obese BMI***[7372, 835, 836, 837] ***Age at delivery***[835,836] ***Nulliparity***[835, 836, 837] Gestational diabetes[837] Genetic factors CRP_A, rs3093077, (T allele additive)[836] MBL2, rs1800451, (T allele dominant)[836] IL1A, rs3273550, (T allele dominant)[836] CTLA4, rs21775, (A allele dominant)[836] CRP, rs3093068, (G allele additive)[837] CRP, rs3093068, (G allele dominant)[837] CRP, rs876538, (C allele additive)[837] CRP, rs876538, (C allele recessive)[837]	***Continuous smokeless tobacco use***[2230] ***Continuous cigarette smoking***[2230] Age at delivery [837] ***BMI***[8141]	Genetic factors CRP_B, rs1205, (A allele dom)[836] CRP_C, rs1130864, (T allele dom)[836] CRP, rs876538, (C allele dominant)[837]

Severe pre-eclampsia	***Nulliparity[836, 837]*** ***Obese BMI[836,837]*** Age at delivery[836] Gestational diabetes[837] Genetic factors MBL2, rs1800451, (T allele dominant)[836] IL1A, rs3273550, (T allele dominant)[836] CTLA4, rs21775, (A allele dominant)[836] CRP, rs3093068, (G allele additive)[837] ***CRP, rs3093068, (G allele dominant)[837]*** CRP, rs876538, (C allele additive)[837] CRP, rs876538, (C allele recessive)[837]	Age at delivery[837]	Genetic factors CRP_A, rs3093077, (T allele additive)[836] ***CRP_B, rs1205, (A allele dom)[836]*** CRP_C, rs1130864, (T allele dom)[836] CRP, rs876538, (C allele dominant)[837]
Severe Maternal Morbidity and/or Mortality (4 studies)			
Severe maternal morbidity (SMM) with transfusions	***Native American maternal race[119]*** ***Any physical health condition[119]*** Any behavioral health condition[119] Multiple chronic conditions[119]	***Native American maternal race[952]***	
Severe maternal morbidity without transfusions		***Rural maternal residency[4010]***	
Severe maternal morbidity and mortality (SMMM)	***Rural maternal residency[3421]*** ***Native American race[4010]*** ***Medicaid funded births[3421]***	***Urban maternal residency[3421]***	
Blood Transfusions (2 studies)			
	Rural maternal residency[3421, 4010] ***Medicaid-funded births[3421]***		
	Native American maternal race[4010]		
Postpartum Hemorrhage (2 studies)			

	Native American ***Maternal race[1331]*** ***Gravidity<5[1131]*** ***Birthweight>4500g[1131]*** ***Retained placenta[1131]*** ***Magnesium sulfate use[1131, 2944]*** ***Antepartum bleeding[2944]*** ***Previous postpartum hemorrhage[2944]*** ***Third stage of labor≥20m[2944]*** ***Maternal rural residence[2944]*** ***Fetal macrosomia[2944]*** ***Oxytocin use>12h[2944]*** Routine aspirin use[2944] Prior uterine incision and vaginal delivery[2944] Pre-eclampsia without severe features without use of magnesium sulfate[2944] Parity≥5[2944] Length of second stage of labor≥ 1h[2944] Inpatient induction length≥ to 36h[2944]	***Prior uterine incision[2944]***	
Uterine Atony (1 study)			
	Native American maternal race[1331] ***Birthweight>4500g[1331]***	***Gravidity<5[1331]*** ***Induction augmentation[1331]*** ***Chorioamnionitis[1331]***	
Ectopic Pregnancy (1 study)			
	Maternal age>19 years[1861] ***IHS region[1861]***		
Placental Abruption (1 study)			
	Continuous use of smokeless tobacco[2230] Continuous cigarette smoking[2230]		
Disseminated Intravascular Coagulation (1 study)			
	Native American race[4010]	***Rural maternal residency[4010]***	
Hysterectomy (1 study)			

	Native American race[4010] Rural maternal residency[4010]		

*BMI, body mass index; h, hours; m, minutes; significant associations are italicized and bolded, significant association in the same direction as categorized

Specific to hypertensive disorders of pregnancy as an outcome having a rural residency (1/1 studies), an overweight or obese BMI (4/5 studies), age above 35 years also referred to as "advanced maternal age" (1/4 studies), and nulliparity (3/3 studies) were significantly associated with increased risk. [30,32–34,42] Genetic predispositions to hypertensive disorders of pregnancy were not significantly associated with increased risk (3/3 studies). [32–34] Studies that focused on severe maternal morbidity and/or mortality as a distinct composite outcome identified being a Native American race (2/3 studies), having a physical health condition (1/1 study), a rural residency (1/2 studies), and Medicaid funded births (1/1 study) as significantly associated with increased risk. The risk of blood transfusions was significantly associated with Native American race (1/1 study), rural residency (2/2 studies), and Medicaid-funded births (1/1 study). [10,11,39] Postpartum hemorrhage risk was significantly associated with being of Native American race when compared to other racial/ethnic groups, a gravidity ≤5, a birthweight of 4500g, having a retained placenta, magnesium sulfate use (2/2 studies), antepartum bleeding, previous postpartum hemorrhage, being in third stage labor greater than 20 minutes, maternal rural residency, fetal macrosomia, and oxytocin use for longer than 12 hours. [38,40] Other outcomes, such as uterine atony, ectopic pregnancy, hysterectomy, and positively associated risk factors, are further described in Appendix 2. This systematic review did not identify risk factors significantly associated with placental abruptions.

This systematic review also identified factors that demonstrated no association or a reduction of risk for Native American women. For pregnancy-induced hypertension, one study identified that

continuous smokeless tobacco use and cigarette smoking had no association. [37] A separate study determined that an age younger than 35 had a decreased risk of hypertensive disorders of pregnancy compared to those older than 35. [40] One study found no association between hypertensive disorders of pregnancy (e.g., preeclampsia) and BMI. [31] While one of the three studies that focused on genetic predisposition identified that having CRP_B, rs1205, (A allele dominant) decreased risk. [32] Native American race and rural residency were found to have no risk of severe maternal morbidity and/or mortality in three distinct studies. [10,39,41]. One study did not find an association between having a prior uterine incision and postpartum hemorrhage. [38] Another study found no association between uterine atony and having a gravidity greater than 5, induction augmentation, or chorioamnionitis. In contrast, a separate study found no association between disseminated intravascular coagulation and a rural residency. [10,40].

Reporting biases and certainty of evidence

All studies had a reliance on administrative data sources to assess outcomes and exposures simultaneously. All studies noted this to be a considerable limitation in their study design. Four studies noted concerns with small sample sizes, missing exposure and outcome data, and critical demographic information that may have led to misclassification bias. Two studies considered reporting bias in their study designs, while almost all studies (14/15 studies) referred to the misidentification of Native American women based on predetermined guidelines for race designation.

DISCUSSION

This systematic review synthesized the current literature by conducting a broad search of outcomes associated with maternal morbidity and mortality and identifying their associated risk factors for Native American women in the US. A large number of studies identified risk factors at the individual level concerning maternal outcomes; of these, the majority suggested that an overweight or obese BMI, advanced maternal age, parity, and rural maternal residency are associated with Native American maternal morbidity or mortality. Few studies contradicted these findings and demonstrated no association with Native American race, rural maternal residency, or advanced maternal age. One study found no association with hypertensive disorders of pregnancy, including pregnancy-induced hypertension, preeclampsia, and severe preeclampsia with continuous smokeless tobacco use or continuous cigarette smoking. [37]

Studies assessing the relationship between genetic factors and preeclampsia or severe preeclampsia were completed in an Indian Reservation within a specific tribal health system. [32–34] This ensured that the findings were specific to supporting community initiatives with tribal support. These studies uncovered that there may not be evidence of an association between genetic expression and preeclampsia for Native American women. However, all these studies concurred that many of the risk factors, such as maternal age, nulliparity, and obesity, that are associated with preeclampsia and severe preeclampsia in other populations were also operative in Native American communities. [32–34]

Unfortunately, we identified a small number of risk factors at the community level of the socioecological model (i.e., maternal residency and Indian Health Service region). This limitation further indicates the need to expand research to identify and understand the role of community and society-level risk factors on maternal health among Native American women in the United States. Determinants of health such as access to behavioral and primary care services,

housing, crime and violence, and health policies have been demonstrated to contribute directly to maternal mortality and morbidity in more extensive population studies. [44]

In addition, this review was only able to identify a minimal number of studies that examined risk factors for maternal morbidities. This low number of studies further limits our ability to correctly identify any level of agreement for these findings on the outcomes. Surprisingly, this review could not find any information on prenatal care utilization patterns and their association with maternal mortality or morbidity despite strong evidence supporting adequate prenatal care utilization in culturally informed healthcare institutions. Early and adequate prenatal care is thought to promote healthy pregnancies through screening and managing a woman's risk factors and health conditions and promote healthy behaviors during pregnancy. [6]

This study focused on a very clinical outcome in Native American women; however, it's critical to note that there were other risk factors and outcomes that did not necessarily manifest themselves during the delivery event that can also lead to morbidity and mortality, such as postpartum depression, substance use behavior, or exposure to infectious diseases. There continues to be a gap in the literature exploring the relationship between depression and maternal morbidity and mortality in Native American women. [45] In addition, the effects of historical trauma, discrimination, and racism were not considered in this study despite it being a significant determinant of health in the lives of Native American peoples. [17] These experiences have played a role in the weathering of health status for Native American women. The weathering hypothesis suggests that cumulative stress from racism and socioeconomically disadvantaged communities produce a weathering effect on health that can explain disparate outcomes. [13]

Appraisal

Most of the included studies were rated as "good" (13/15 studies), while two were rated as "fair" based. Despite this, we were able to highlight the methodological shortcomings of some of the studies, such as the failure to assess the exposure more than once over time, the inability to demonstrate that exposure was measured before outcome measurement, or not adjusting models to include potential confounders. Additionally, some studies failed to provide sample size justification or did not randomly select cases or controls from the eligible study population, posing bias risks.

We identified additional shortcomings in the available evidence. Racial/ethnic misclassification on administrative databases leads to challenges with underreporting and further affects the selection of study participants. Given that the total population of Native American women of reproductive age (15-44 years) in the United States is 0.8%, small errors in misclassification can greatly affect data analyses [46]. Multiple studies in this review reported small sample sizes, making it difficult to determine if a particular outcome was a true finding, possibly allowing for type II errors. Among studies that included samples that were not fully Native American, the majority reported a Native American sample size of ≤ 1.35%. This is a long-standing concern in research with Native American communities. This lack of research in these communities, primarily inhibited by concerns about low sample sizes, prevents additional risk factors for morbidity and mortality that are particular to Native American women from being discovered. Measurement of maternal morbidity and mortality varied across the studies. The review used a broader definition of the outcomes and included others not listed by CDC as severe maternal morbidity such as postpartum hemorrhage, uterine atony, placental abruption, and ectopic pregnancy. Lastly, a heavy reliance on administrative data poses unique challenges in identifying risk factors not traditionally included in these datasets, given that their purpose is not always

aligned with the study hypothesis. Improvements in the collection of social determinants of health in administrative databases have demonstrated a promising approach to further study the effects of these determinants on population health. [47] Studies also mentioned the lack of consistency in data quality, such as the accuracy of self-reported data or the level of detail collected, including missing data.

Strengths and limitations

Our systematic review face some limitations. The search terms in MeSH and other standardized language posed a unique challenge as the terms "maternal morbidity" and "maternal mortality" were non-existent. Therefore, this systematic review adopted an expansive search strategy informed by other published literature. [3,48] There is a possibility of missing articles, given that an adopted search strategy was used. Addiitonally not all MesH terms in PubMed translated into other standardized languages for other databases. There is a risk of publication bias and selective reporting of significant findings in the studies. Using NIH's quality assessment tools which are not independently published nor standardized may introduce bias due to the qualitative nature of the review. Despite this, other systematic reviews have built the evidence supporting the utility and practicality of utilizing this tool in critical review of published evidence. [3] Furthermore, the diverse methodologies prevented us from conducting a meta-analysis, so our findings are descriptive and guide future research on risk factors for maternal morbidity and mortality in Native American women.

Despite these limitations, this systematic review is one of the few that identifies risk factors for various outcomes indicating severe maternal morbidity and mortality among Native American women in the US. We comprehensively reviewed the current literature using multiple search strategies followed the CDC's list of procedural and diagnoses for SMM. This systematic review

utilized recommended language to identify research in Native American communities following the National Library of Medicine guidance. [49]

Implications for practice, policy, and future research

Our review demonstrates the lack of attention reflected in the scarcity of evidence available to understand this maternal and child health crisis among a population that is often ignored. The limited type of risk factors studied, the study designs, settings, and outcomes limit the ability of healthcare and public health organizations to properly design and implement tailored approaches to reduce disparities in this community further. More needs to be done to expand the research to reduce these inequities among Native American women in the US.

OTHER INFORMATION

Registration and protocol: The registration and protocol information for this review can be accessed at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=363405, identifier: CRD42022363405. No amendments were submitted during implementation of the protocol.

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Patient consent for publication: Not required

Contributorship statement: MC and PM: developed the protocol objectives and design. MC wrote the protocol and is the submitting author unders supervision of PM and JM. MC and JM developed the search strategy. AZ, CR, AN, and AA reviewed abstrats and full-text articles, extracted data from included studies, and critically appraised the literature. AZ and AN co-wrote the introduction, CR and AA co-wrote the methods, and MC wrote the remaining sections

including results and discussion. PM, JE, CH, SP, VN, and LB reviewed and made corrections to the manuscript on multiple occasions that led to the final written manuscript.

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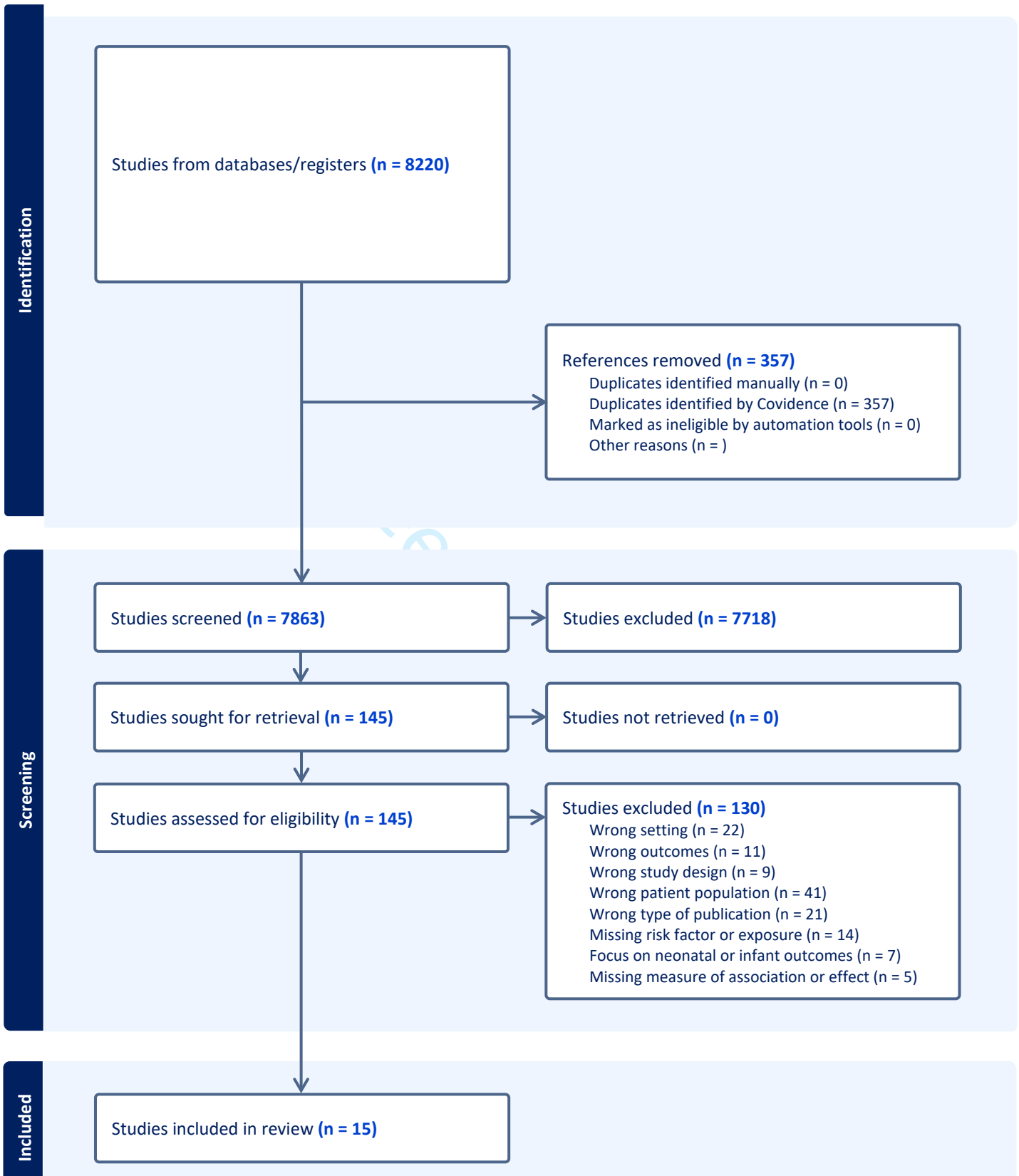
Individual and community level risk factors for maternal morbidity and mortality among Native American women in the United States



Appendix 1. Search Strategy by Database

PubMed Search Strategy

#1 birth[tiab] OR labor[tiab] OR delivery[tiab] OR mothers[tiab] OR maternal[tiab] OR "peripartum period"[mesh] OR peripartum[tiab] OR "labor, obstetric"[mesh] OR "obstetric*"[mesh] OR "obstetric*"[tiab] OR "pregnancy"[mesh] OR "pregnan*"[tiab] OR "perinatal"[tiab] OR "prenatal"[tiab] OR "parturition"[mesh] OR "parturition"[tiab]

#2 "tribal" OR "tribe" OR "first nations" OR "indigenous peoples"[mesh] OR indigenous OR "health services, indigenous"[mesh] OR "american indians or alaska natives"[mesh] OR "american indian*" OR "indians, north american"[mesh] OR "native American" OR "alaska native"

#3 "severe maternal morbidity" OR "near miss" OR "adverse maternal outcomes" OR "maternal mortality" OR "Near Miss, Healthcare"[Mesh] OR "Pregnancy/Adverse Effects"[Mesh] OR "Pregnancy/Injuries"[Mesh] OR "Pregnancy/Mortality"[Mesh] OR "Pregnancy/complications"[Mesh] OR "Obstetric Labor Complications"[Mesh] OR "Delivery, Obstetric/adverse effects"[Mesh] OR "Delivery, Obstetric/complications"[Mesh] OR "Delivery, Obstetric/mortality"[Mesh] OR "Maternal Mortality"[Mesh] OR "mortality"[mesh] OR "morbidity"[mesh] OR "pregnancy complications" OR mortality OR morbidity OR "labor complications" OR "delivery complications"

#4 Search (#1 AND #2 AND #3)

EMBASE Search Strategy

('delivery:ab,ti' OR 'birth:ab,ti' OR 'labor:ab,ti' OR 'mothers':ab,ti OR 'maternal':ab,ti OR 'peripartum':ab,ti OR 'obstetric':ab,ti OR 'pregnancy':ab,ti OR 'perinatal':ab,ti OR 'prenatal':ab,ti OR 'parturition':ab,ti OR 'perinatal period'/exp OR 'labor'/exp OR 'pregnancy'/exp OR 'birth'/exp)

AND

(tribe OR 'indian health service' OR indigenous OR tribal OR 'first nations' OR 'american indian' OR 'native american' OR 'alaska native' OR 'indigenous people'/exp OR 'indigenous health care'/exp OR 'american indian'/exp)

AND

('severe maternal morbidity' OR 'adverse maternal outcomes' OR 'maternal mortality' OR 'pregnancy complications' OR 'mortality' OR 'morbidity' OR 'labor complications' OR 'delivery complications' OR 'near miss (health care)'/exp OR 'near miss' OR 'pregnancy complication'/exp OR 'maternal mortality'/exp OR 'labor complication'/exp OR 'maternal outcome'/exp OR 'delivery complications'/exp OR 'maternal morbidity'/exp OR 'morbidity'/exp OR 'mortality'/exp)

CINAHL Search Strategy

((TI delivery OR AB delivery) OR (TI birth OR AB birth) OR (TI labor OR AB labor) OR (TI mothers OR AB mothers) OR (TI maternal OR AB maternal) OR (TI peripartum OR AB peripartum) OR (TI obstetrics OR AB obstetrics) OR (TI pregnancy OR AB pregnancy) OR (TI perinatal OR AB perinatal) OR (TI prenatal OR AB prenatal) OR (TI parturition OR AB parturition) OR (TI delivery OR AB delivery) OR MM "Perinatal Period" OR MM "Obstetric Patients" OR MM "Delivery, Obstetric+" OR MM "Pregnancy+" OR MM "Labor+" OR MM "Obstetrics+" OR MM "Childbirth+")

AND

(tribe OR "indian health service" OR Indigenous OR "native american" OR "american indian" OR Tribal OR "first nations people" OR "alaska native" OR MM "Indigenous Peoples+" OR MM "Health Services, Indigenous" OR MM "Native Americans+")

AND

("severe maternal morbidity" OR "near miss" OR "pregnancy complications" OR "obstetric complications" OR mortality OR morbidity OR "maternal mortality" OR "maternal morbidity" OR "delivery complications" OR MM "near-death experiences" OR MM "maternal mortality" OR MM "obstetric emergencies" OR MM "Pregnancy Complications+" OR MM "labor complications" OR MM "maternal mortality" OR MM "morbidity+" OR MM "mortality+")

SCOPUS Search Strategy

("severe maternal morbidity" OR "near miss" OR "pregnancy complications" OR mortality OR morbidity OR "labor complications" OR "delivery complications" OR "maternal mortality" OR "maternal morbidity" OR "obstetric complications")

AND

(indigenous OR "native american" OR "american indian" OR tribal OR "alaska native" OR "first nations" OR tribe OR "indian health service")

AND

(TITLE-ABS (mother) OR TITLE-ABS (maternal) OR TITLE-ABS (peripartum) OR TITLE-ABS (obstetric) OR TITLE-ABS (pregnancy) OR TITLE-ABS (perinatal) OR TITLE-ABS (prenatal) OR TITLE-ABS (parturition) OR TITLE-ABS (labor) OR TITLE-ABS (birth) OR TITLE-ABS (delivery))

Appendix 2. Table of included studies

Study #	Authors	Year	Study Design	Location	Sample Size, Data Source	Native American subsample size (% of total sample)	Risk Factor (Social ecological level)	Outcome(s)	Covariates	Quality Rating	Key Findings ([95% Confidence Intervals] unless otherwise stated
Hypertensive Disorders of Pregnancy (8)											
1178	Cameron, N et al.	2022	Cross Sectional	Nationwide	51,685,525 all live births in the US to individuals aged 15-44 years, birth vital records	492,771 (9.3%)	Maternal residence (C)	Pregnancy induced hypertension	None	Good	-The incidence of hypertensive disorders of pregnancy differed by racial and ethnic identity within both rural and urban areas. The highest age-adjusted incidence of hypertensive disorders of pregnancy was observed among individuals who identify as American Indian/ Alaskan Native. -Significant increase in the incidence of hypertension disorders of pregnancy among Native American women in rural areas compared to those in urban areas in 2007 and 2014 (2017 RR=1.21, [1.11-1.33] and 2014 RR=1.17, [1.08-1.13]) -No significant increase in the incidence of hypertension disorders of pregnancy among

										Native American women living in rural areas compared to those in urban areas was observed in 2019 (2019 RR=1.03, [0.96-1.11])
2230	England, L et al.	2013	Case Control	Anchorage, AK	1,123 singleton deliveries from 1997-2005 to AN women residing in western Alaska, hospital administrative database / 503 cases and 502 controls	1,123 (100%)	Continuous smokeless tobacco use (I) and continuous cigarette smoking (I)	Pregnancy associated hypertension, pre-eclampsia, and gestational hypertension	Parity, pre-pregnancy BMI, maternal age	Good	-No significant associations were observed between smokeless tobacco use and pregnancy-associated hypertension (aOR 0.92, [0.56–1.51]). -No significant associations were observed between smokeless tobacco use and pre-eclampsia (aOR 0.90, [0.52–1.56]). -No significant associations were observed between smokeless tobacco use and gestational hypertension (aOR 0.93, [0.42–2.03). -No significant associations were observed between continuous cigarette smoking and pregnancy-associated hypertension (aOR 0.65, [0.31–1.37]). -No significant associations were observed between

										continuous cigarette smoking and pre-eclampsia (aOR 0.69, [0.30–1.58]). -No significant associations were observed between continuous cigarette smoking and gestational hypertension (aOR 0.52, [0.14–1.90).
8141	Zamora-Kapoor, A et al.	2016	Cohort	Washington State	71,080 singleton live births from 2003-2013 to Whit and AI/AN women, linked birth-hospital discharge records	7,189 (10.1%)	Maternal race (I), BMI (I)	Pre-eclampsia	Birth year, maternal age, educational attainment, marital status, Medicaid insurance, WIC participation, prenatal smoking, BMI	Good	-AI/ANs had an increased risk of pre-eclampsia compared to Whites after controlling for all covariates except BMI (OR 1.17 [1.06–1.29]). After further adjustment for BMI, the racial disparity in pre-eclampsia risk was greatly attenuated (aOR 1.05, [0.95–1.16]). -AI/ANs who were underweight (OR 1.39, [0.64-3.02]), normal weight (OR 1.02, [0.83-1.22]), overweight (OR 1.23, [0.93, 1.36]), or obese (OR 1.00, [0.86, 1.17]) generally had relative risks of pre-eclampsia comparable, or slightly (but not statistically significantly) greater than those of their White counterparts.

1371	Chang, J et al.	2014	Cohort	Nationwide	3,113,164 singleton births between 20-44 weeks gestation without major fetal anomalies in 2010, US natality file	34,348 (1.10%)	Cigarette use during pregnancy (I), maternal age (I)	Pregnancy induced hypertension (inclusive of pre-eclampsia and eclampsia)	Prenatal care adequacy, weight gain, parity, diabetes, marital status, chronic hypertension, preeclampsia, eclampsia, tobacco use	Good	-The odds of pregnancy induced hypertension was greater in non-Hispanic American Indian women 35 years or older who smoked during pregnancy (aOR 1.29, [0.88-1.89]). -A reduced odds of PIH was evident in non-Hispanic American Indian women younger than 35 years old who smoked during pregnancy based (aOR 0.76, [0.66-0.87]).
7372	Tiwari, R et al.	2021	Cohort	Washington State	105,466 singleton live births from 22 facilities from 2018-2018, hospital administrative database	978 (0.92%)	Pre-pregnancy BMI (I)	Pre-eclampsia	Maternal age, parity, delivery hospital, government health insurance, substance abuse, nicotine use, and alcohol use	Good	-The strength of the association of overweight/obesity with preeclampsia was much greater among NH AI/AN women (aRR 5.24; [1.92–14.30]) and NH Native Hawaiian/Other Pacific Islander women than among other race/ethnicities (aRR 5.88, [1.30-36.51]).
835	Best, L et al.	2012	Case Control	Belcourt, ND	299 women tribal members of the Turtle Mountain Band of Chippewa who sought care in an IHS	299 (100%)	Age at delivery (I), nulliparity (I), BMI (I), Single nucleotide polymorphisms [NOS3, rs1799983	Pre-eclampsia	Nulliparity, BMI, age at delivery	Good	-Age at delivery (aOR 1.0823, [p=0.0185]) , nulliparity (aOR 6.8628, [p<0.001]), and obesity (aOR 1.0951, [p<0.001]) show robust independent effects associated with preeclampsia.

					hospital or clinic from 2004-2009, electronic medical records / 101 cases and 198 matched controls		(G allele recess), NOS3, rs3918227 (A allele dom), GNB3, rs5442 (A allele dom), DDAH1, rs10158674 (C allele recess), DDAH1, rs233115 (A allele recess)] (I)			-There was no significant association between any of single nucleotide polymorphisms studied and pre-eclampsia. -NOS3, rs1799983 (G allele recess) (aOR 1.4087, [p=0.2354]) -NOS3, rs3918227 (A allele dom) (aOR 0.7356, [p=0.4611]) -GNB3, rs5442 (A allele dom) (aOR 0.9147, [p=0.8655]) -DDAH1, rs10158674 (C allele recess) (aOR 1.0165, [p=0.9898]) -DDAH1, rs233115 (A allele recess) (aOR 2.2227. [p=0.1578])
836	Best, L et al.	2012	Case Control	Belcourt, ND	196 women tribal members of the Turtle Mountain Band of Chippewa who sought care in an IHS hospital or clinic from 2004-2009, electronic medical records / 66 cases and	196 (100%)	Age at delivery (I), nulliparity (I), BMI (I), single nucleotide polymorphisms [CRP_A rs3093077 (T allele additive), CRP_B rs1205 (A allele dom), CRP_C rs1130864	Pre-eclampsia, severe pre-eclampsia	Nulliparity, weight at first prenatal visit, BMI, birthweight of infant, gestational diabetes, age at delivery	Good	-Age at delivery did not show a significant association with pre-eclampsia (aOR 1.036, [p=0.398]) and severe preeclampsia (aOR 1.027, [p=0.586]). -Nulliparity (aOR 4.274, [p=0.003] and aOR 4.520, [p=0.009])) and obesity (aOR 1.093, [p=0.002] and aOR 1.094, [p=0.007]) show robust independent associations with

					130 matched controls		(T allele dom), MBL2 rs1800451 (T allele dom, IL1A rs3783550 (T allele dom), CTLA4 rs231775 (A allele dom)](I)			preeclampsia and severe pre-eclampsia. -There was no significant association between any of single nucleotide polymorphisms studied with pre-eclampsia and severe pre-eclampsia except CRP_B, rs1205, (A allele dom). -CRP_B, rs1205, (A allele dom) was the only single nucleotide polymorphism that showed a significant association with severe pre-eclampsia (aOR 0.259, [p=0.020]).
837	Best, L et al.	2013	Case Control	Belcourt, ND	410 women tribal members of the Turtle Mountain Band of Chippewa who sought care at an IHS hospital or clinic from 2004-2012, electronic medical records / 140 cases and 270 matched controls	410 (100%)	Age at delivery (I), nulliparity (I), BMI (I), gestational diabetes (I), single nucleotide polymorphisms [CRP rs3093068 (G allele add), CRP rs3093068 (G allele recess, CRP rs3093068 (G allele dom), CRP	Pre-eclampsia, severe pre-eclampsia	Nulliparity, weight at first prenatal visit, BMI, birthweight of infant, gestational diabetes	Good	-Age at delivery did not show a significant association with pre-eclampsia (aOR 1.053, [p=0.076]) and severe preeclampsia (aOR 1.052, [p=0.166]). -Gestational diabetes did not show a significant association with pre-eclampsia (aOR 1.684, [p=0.278]) and severe pre-eclampsia (aOR 2.241, [p=0.166]). -Independent effects of nulliparity (aOR 5.6, [p=0.001] and aOR 4.17, [p=0.001]) and

							rs876538 (C allele add), CRP , rs876538 (C allele recess), CRP rs876538 (C allele dom), rs3093068 (G dom) and rs876538 (C recess) add risk score] (I)			obesity (aOR 1.061, [p=0.002] and aOR 1.059, [p=0.001]) on pre-eclampsia and severe pre-eclampsia were observed. -There was no significant association between any of single nucleotide polymorphisms studied with pre-eclampsia and severe pre-eclampsia except CRP rs3093068 (G allele add) and CRP rs3093068 (G allele dom) with severe pre-eclampsia (aOR 2.587, [p=0.05] and aOR 2.587, [p=0.050]) -The rs3093068 (G dom) and rs876538 (C recess) additive risk score showed significant association with pre-eclampsia (aOR 1.779, [p=0.016]) and severe pre-eclampsia (aOR 2.035, [p=0.013]).
	Severe Maternal Morbidity and Mortality (4)									
119	Admon, L et al.	2018	Cross Sectional	Nationwide	2,523,528 all hospital deliveries that occurred between 2012-2015,	20,447 (0.810%)	No chronic conditions, any physical health condition (I), any	SMM	Age, income, payer, rural vs. urban residence, and	Good	-The incidence of severe maternal morbidity was significantly higher among deliveries to women in every racial and ethnic minatory

					National Inpatient Sample		behavioral health condition (I), multiple chronic conditions (I), maternal race (I)		hospital region.	category compared with deliveries among non-Hispanic white women. -American Indian/Alaska Native women are at increased risk of severe maternal morbidity compared to non-Hispanic white women (aRR 1.5, [1.3-1.7]) . This is not significant when blood transfusions are not included in severe maternal morbidity (aRR 0.90, [0.68-1.2]). -Among deliveries to women with comorbid physical and behavioral health conditions, significant differences in severe maternal morbidity were identified among racial and ethnic minority compared with non-Hispanic white women and the largest disparities were identified among women with multiple chronic conditions. -In comparing deliveries among American Indian/Alaskan Native women with non-Hispanic white women, the rate difference for severe maternal

										morbidity incidence increased from 66.6 [95% CI 39.9-93.3] to 101.3 [95% CI -41.0-243.5] per 10,000 delivery hospitalizations, respectively, in comparing deliveries in which no and multiple chronic conditions were identified. -American Indian/Alaskan Native women compared to non-Hispanic white women are at increased risk for severe maternal morbidity when any physical health condition is present (aRR 1.5, [1.3-1.7]), any behavioral health condition is present (aRR 1.2, [0.90-1.6]), and having multiple (2 or more) chronic conditions (aRR 1.4, [0.93-2.20]).
3421	Interrante, J et al.	2022	Cross Sectional	Nationwide	6,357,796 maternal records from childbirth hospitalizations from 2007-2015, National Inpatient Sample	43,929 (0.691%)	Primary payer type (I), maternal residence (C), maternal race (I)	SMM and Mortality (SMMM)	Maternal race and ethnicity, maternal residence, maternal age, childbirth year, bottom quartile of	Good	-Rural Indigenous Medicaid-funded births had the highest adjusted predicted rate of SMMM (224.9 per 10,000 births, [187.0-262.9]). -Among rural residents, births by Indigenous people had the greatest differences in rates

									income, hospital region, cesarean birth, substance use disorder, depression, HIV or AIDS, pulmonary hypertension, systemic lupus erythematosus, chronic kidney disease, chronic heart disease, diabetes, chronic hypertension, and chronic respiratory disease	between Medicaid-funded and privately insured births (aRD, 97.8, [50.4–145.3]). -When examining the intersection of rurality and race and ethnicity, births among Indigenous rural residents had significant additive interaction, with 40% (aAP 0.40, [0.11-0.69]) of SMMM cases in that population owing to the interaction. -When examining the intersection of urban status and race and ethnicity, births among Indigenous urban residents did not have an additive interaction (aAP 0.06, [-0.20-0.32]). -If the excess risk of SMMM associated with Medicaid could be mitigated (i.e., if the risk of SMMM among Medicaid-funded births could be decreased to the risk among the privately insured), this would not only prevent the 23 cases per 10,000 births that occur among white urban residents, but an additional 98 cases per 10,000 births

										among Indigenous rural residents.
952	Booker, W et al.	2018	Cohort	Nationwide	1,724,694 delivery hospitalizations from women aged 40-54 years between 1998-2014, National Inpatient Sample	7,107 (0.412%)	Maternal race (I)	SMM, SMM excluding blood transfusions	Year, bed size, insurance status, hospital location, income quartile, hospital region, hospital teaching status, and race	Good	-The incidence of SMM was greater among Native American women but not significant compared to Non-Hispanic white women (aRR 1.08, [0.93-1.25]). -Risk for severe morbidity excluding transfusion among Native Americans is not demonstrated because of small denominators.
4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (I)	SMMM, SMMM excluding blood transfusion	Age, insurance payer, income, hospital region	Good	-The incidence of SMMM was greater among indigenous women compared with white women (aRR 1.8, [1.6–2.0]). -Within each racial group, incidence of SMMM was higher among rural compared with urban residents (2.3% for rural indigenous women vs 1.8% for urban indigenous women) (a RR 1.3, [1.0–1.6]); (1.3% for rural white women vs 1.2% for urban white women) (aRR 1.1, [1.1–1.2]). -Within indigenous women, the incidence

										of SMM (excluding transfusions) among rural compared to urban residents was not significant (aRR 0.7, [0.4-1.0)].
	Blood Transfusions (2)									
3421	Interrante, J et al.	2022	Cross Sectional	Nationwide	6,357,796 maternal records from childbirth hospitalizations from 2007-2015, National Inpatient Sample	43,929 (0.691%)	Primary payer type (I), maternal residence (C), maternal race (I)	Blood transfusions	Maternal race and ethnicity, maternal residence, maternal age, childbirth year, bottom quartile of income, hospital region, cesarean birth, substance use disorder, depression, HIV or AIDS, pulmonary hypertension, systemic lupus erythematosus, chronic kidney disease, chronic	Good	-Rural residents had greater odds of blood transfusion for both Medicaid-funded (aOR 1.15, [1.06-1.25]) and privately insured (aOR 1.20, [1.11-1.31]) hospital births compared to urban residents. -Medicaid-funded (aOR 1.71, [1.39-2.11]) and privately insured hospital (aOR 1.42, [1.05-1.92]) indigenous births had the second highest odds of blood transfusions compared to other racial/ethnic groups. This yielded an additive interaction p-value of 0.006.

									heart disease, diabetes, chronic hypertension, and chronic respiratory disease		
4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (I)	Blood transfusions	Age, insurance payer, income, hospital region	Good	-The incidence of blood transfusions was greater among indigenous women compared with white women (aRR 1.8, [1.5–2.0]). -The incidence of blood transfusion among rural indigenous women compared to urban indigenous women was statistically greater (aRR 1.6, [1.2-2.0]).
	Postpartum Hemorrhage (PPH) (2)										
1331	Chalouhi, S et al	2015	Cohort	Gallup, NM	1,062 women who delivered vaginally at the Rehoboth McKinley Hospital, medical records	751 (70.7%)	Maternal race (I), age (I), parity (I), gravidity (I), birthweight (I), retained placenta (I), magnesium sulfate use (I), induction augmentation (I),	Postpartum hemorrhage	None	Good	-A significantly higher proportion of Native Americans than non-native women developed PPH (11.6% vs 7.0%, [p= 0.02]). -In multivariable logistic regression analysis, the significant predictors of PPH were Native American ethnic origin (OR 1.8, [1.1-3.0]), decreased gravidity of fewer than

							chorioamnionitis (I)				5 (OR 1.2, [1.1-1.4]), increased birth weight greater than 4500 grams (OR 1.1, [1.0-1.0]), retained placenta (OR 51.0, [9.8-288.2]), and use of magnesium sulfate (OR 3.5, [1.4-9.0]).
2944	Hadley, M et al	2021	Case Control	Anchorage, AK	384 deliveries between 2018-2019 at the Alaska Native Medical Center, medical records / 128 cases and 256 controls	384 (100%)	BMI (I), antepartum bleeding (I), routine aspirin used prescribed (I), prior uterine incision (I), prior uterine incision and vaginal delivery (I), parity (I), macrosomia, pre-eclampsia without severe features with magnesium sulfate during labor (I), pre-eclampsia with severe features and use of	Postpartum hemorrhage	Not reported	Fair	-In the bivariate analysis, the following risk factors were significantly associated with a higher likelihood of postpartum hemorrhage: BMI of 40 or more (OR 2.6, [1.4-4.5]), antepartum bleeding (OR 6.3, [1.2-31.6]), previous postpartum hemorrhage (OR 5.0, [2.6-9.8]), suspected macrosomia with estimated fetal weight of 4000 g or more (OR 2.7, [1.4-5.3]), pre-eclampsia with severe features and use of magnesium sulfate during labor (OR 4.7, [2.4-9.2], length of third stage labor longer than 20 min (OR 2.2, [1.1-4.4]), and use of oxytocin for more than 12 h (OR 5.0, [2.3-10.6]). -Residence in a rural community (OR 2.2, [1.4-3.6]) and vitamin

							magnesium sulfate (I), previous postpartum hemorrhage (I), length of 2nd stage of labor (I), length of 3rd stage of labor (I), rural residence (C), and oxytocin (I), and inpatient induction length (I)			D supplementation (OR 1.7, [1.1-2.6]) were also significantly associated with postpartum hemorrhage. -Multivariate condition logistic regression analyses found that antepartum bleeding (OR 8.8, [1.6-48.5]) , pre-eclampsia with severe features and use of magnesium sulfate (OR 5.3, [2.4-11.9]), previous postpartum hemorrhage (OR 2.7, [1.2-6.1]), third stage of labor of 20min or more (OR 2.9, [1.2-6.9]), rural residence (OR 2.0, [1.2-3.5]), fetal macrosomia (OR 4.0, [2.1-7.5]), and oxytocin use for more than 12h (OR 3.0, [1.1-8.0]) all remained significantly associated with an increased risk of hemorrhage in Native American women. -Routine aspirin use (OR 1.7, [0.9-3.4]), prior uterine incision (OR 1.0, [0.52-2.1]), prior uterine incision and vaginal delivery (OR 1.6, [0.58-4.4]), a parity of 5 or more (OR 1.8, [0.87-3.9]), pre-eclampsia without severe features without

											use of magnesium sulfate (OR 2.1, [0.98-4.4]), length of second stage of labor grater or equal to 1 hour (OR 1.6, [0.88-3.0]), and an inpatient induction length of greater or equal to 36 hours (OR 2.3, [0.4-12.8]) were not significantly associated with a higher likelihood of postpartum hemorrhage.
	Misc. Outcomes (5)										
1331	Chalouhi, S et al	2015	Cohort	Gallup, NM	1,062 women who delivered vaginally at the Rehoboth McKinley Hospital, medical records	751 (70.7%)	Maternal race (I), age (I), parity (I), gravidity (I), birthweight (I), retained placenta (I), magnesium sulfate use (I), induction augmentation (I), chorioamnionitis (I)	Uterine atony	None	Good	-Uterine atony was recorded in a significantly higher proportion of Native Americans than non-native patients (9.6% vs 4.8%; [p=0.01]). -In univariate analysis, factors predicting uterine atony were native race (p=0.01), decreasing gravidity (p=0.02), induction augmentation (p=0.1), increasing birthweight (p=0.07), and chorioamnionitis (p=0.08). -In multivariable logistic regression analysis, Native American ethnic origin

											(OR 2.0, [1.1–3.7]) and increasing birthweight (OR 1.0, [1.0 1.0]) were significant predictors of uterine atony.
1861	deRavello, L et al	2015	Cross Sectional	Nationwide	229,986 American Indian and Alaska Native (AI/AN) women aged 15–44 years seeking care at Indian Health Service (IHS), Tribal, and urban Indian health facilities during 2002–2009, Indian Health Service National Patient Information Reporting System	229,986 (100%)	Maternal age (I), IHS region (C)	Ectopic pregnancy	None	Fair	-The ectopic pregnancy (EP) rate among AI/AN women was lowest in the 15–19 years age group (5.5 EPs per 1,000 pregnancies) and highest among 35–39 year old (18.7 EPs per 1,000 pregnancies). -Compared to AI/AN women aged 15-18 years, women aged 35-39 years were 3.4 times more likely to have an EP (RR 3.4, [2.90-4.03]). Compared to AI/AN women aged 15-18 years, the risk of an EP increased with age from 1.56-3.42, except in women aged 40-44 years were the risk was less at 2.62 times (RR 2.62, [2.02-3.36]). -EP rates varied by geographic region, ranging between 6.9 and 24.4 per 1,000 pregnancies in the Northern Plains East and the East region, respectively. -Compared to AI/AN women who received

											care in the Northern Plains East region, women who received care in the East region were 3.55 times more likely to have an EP (RR 3.55, [2.75-4.57]), in the Alaska region the risk was 2.17 times (RR 2.17, [1.73-2.72]), in the Southern plains region the risk was 1.56 times (RR 1.57, [1.25-1.95]), in the West region the risk was 1.39 times (RR 1.39, [1.09-1.77]), in the Norther Plains West region the risk was 1.36 times (1.36, [1.08-1.71]), and in the Southwest region the risk was lowest at 1.33 times (RR 1.33, [1.07-1.65]). -We found relatively stable annual rates of EP among AI/AN women receiving care at IHS-affiliated facilities during 2002–2009, but considerable variation by age group and geographic region.
2230	England, L et al.	2013	Case Control	Anchorage, AK	1,123 singleton deliveries from 1997-2005 to AN women residing in	1,123 (100%)	Continuous smokeless tobacco use (I) and continuous cigarette smoking (I)	Placental abruption, placental abruption expanded definition	Parity, pre-pregnancy BMI, maternal age	Good	-Thirty-nine percent of case deliveries were also preterm (compared with 7% of controls, [p<0.001]), and 9.8% were also complicated by pregnancy

					western Alaska, hospital administrative database					associated hypertension (compared with 7% of controls. [p=0.38]). -There were no significant associations between placental abruption and continuous smokeless tobacco use (aOR 1.11, [0.53-2.33] and continuous cigarette smoking (aOR 1.19, [0.43-3.29). -An expanded definition of abruption did not change this finding. There were no significant associations between continuous smokeless tobacco use (OR 1.07, [0.63-1.83]) or continuous cigarette smoking (aOR 1.04, [0.48-2.23]).

4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (C)	Disseminated intravascular coagulation (DIC), hysterectomy	Age, insurance payer, income, hospital region	Good	DIC -The incidence of DIC was greater but not significant among indigenous woman compared with white women (1.6% vs 0.9%, respectively) (aRR 1.1, [0.8-1.5]). -Within indigenous women, there was no difference between rural women and urban women (0.2% vs 0.2%, respectively) (aRR 0.8, [0.3-1.3]). Hysterectomy -The incidence of a hysterectomy was greater among indigenous woman compared with white women (0.1% vs 0.1%, respectively) (aRR 1.8, [1.0-2.6]). -Within indigenous women, there was a marginal increased risk but not significant of hysterectomy among rural women (aRR 1.3, [0.3-2.3]).

Appendix 3. Results of NIH Quality Assessments for Included Studies

For observational cohort and cross-sectional studies:

ID#	Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q13	Rating
119	Admon L, et al.	2018	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	NA	Yes	NR	NA	Yes	Good
952	Booker W, et al.	2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good
1178	Cameron, N. et al.	2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NA	No	Good
1331	Chalouhi, S. et al.	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	No	Good
1371	Chang, J et al	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Good
1861	deRavello, L. et al.	2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NA	No	Fair
3421	Interrante, J. et al.	2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Good
4010	Kozhimannil, K et al.	2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	NA	Yes	Good
7372	Tiwari, R. et al	2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Good
8141	Zamora-Kapoor A., et al	2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Good

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Q1. Was the research question or objective in this paper clearly stated?
Q2. Was the study population clearly specified and defined?
Q3. Was the participation rate of eligible persons at least 50%?
Q4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
Q5. Was a sample size justification, power description, or variance and effect estimates provided?
Q6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
Q7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q10. Was the exposure(s) assessed more than once over time?
Q11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q12. Were the outcome assessors blinded to the exposure status of participants?
Q13. Was loss to follow-up after baseline 20% or less?
Q14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

For case-control studies:

ID#	Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Rating
835	Best, L. et al	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
836	Best, L. et al.	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
837	Best, L et al.	2013	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
2230	England L, et al	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
2944	Hadley, M et al	2021	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Fair

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment of Case-Control Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools):

Q1. Was the research question or objective in this paper clearly stated and appropriate?
Q2. Was the study population clearly specified and defined?
Q3. Did the authors include a sample size justification?
Q4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
Q5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?
Q6. Were the cases clearly defined and differentiated from controls?
Q7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
Q8. Was there use of concurrent controls?
Q9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
Q10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
Q11. Were the assessors of exposure/risk blinded to the case or control status of participants?
Q12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Q, question; CD, cannot be determined; NA, not applicable; NR, not reported; N, no; Y, yes.

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Complete List of Authors:	Celaya, Martín; Arizona Department of Health Services, Bureau of Assessment and Evaluation; The University of Arizona Mel and Enid Zuckerman College of Public Health, Health Promotion Sciences Zahlan, Alaa I; The University of Arizona Mel and Enid Zuckerman College of Public Health Rock, Chelsea; Arizona State University Nathan, Akshay ; Boston University Acharya, Aishwarya; The University of Arizona Mel and Enid Zuckerman College of Public Health Madhivanan, Purnima ; The University of Arizona Mel and Enid Zuckerman College of Public Health Ehiri, John; The University of Arizona Mel and Enid Zuckerman College of Public Health Hu, Chengcheng; The University of Arizona Mel and Enid Zuckerman College of Public Health Pettygrove, Sydney ; The University of Arizona Mel and Enid Zuckerman College of Public Health Nuño, Velia Leybas; The University of Arizona Mel and Enid Zuckerman College of Public Health
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TITLE

Individual and community level risk factors for maternal morbidity and mortality among Native American women in the United States: A systematic review

AUTHORS AND AFFILIATION

Martín F. Celaya[1,2], Alaa I. Zahlan[2], Chelsea Rock[3], Akshay Nathan[4], Aishwarya Acharya[2], Purnima Madhivanan[2], John Ehiri[2], Chengcheng Hu[2], Sydney Pettygrove[2], Velia Leybas Nuño[2]

1. Arizona Department of Health Services, Phoenix, Arizona, United States

2. Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona, United States

3. College of Health Solutions, Arizona State University, Phoenix, Arizona, United States

4. Boston University, Boston, Massachusetts, United States

AUTHORS' E-MAIL ADDRESSES

Martín F. Celaya, martin.celaya@azdhs.gov; Alaa I Zahlan, azahlan@arizona.edu; Chelsea Rock, chelsea.rock@azdhs.gov; Akshay Nathan, shayaknathan@gmail.com; Aishwarya Acharya, aishwaryaacharya@arizona.edu; Purnima Madhivanan, pmadhivanan@arizona.edu; John Ehiri, jehiri@arizona.edu; Chengcheng Hu, hucc@arizona.edu; Sydney Pettygrove, sydneyp@arizona.edu; Velia Leybas Nuño, vleybas@arizona.edu

SUBMITTING AND CORRESPONDING AUTHOR

Martín F. Celaya, martin.celaya@azdhs.gov

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Table 2. PubMed search strategy

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Figure 1. PRISMA flow diagram

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Appendix 1. Search strategy by database

Appendix 2. Risk factors and outcomes by volument of studies

Appendix 3. Table of included studies

Appendix 4. Results of NIH Quality Assessments for included studies

KEYWORDS: American Indian or Alaska Native, Mothers, Morbidity

ABSTRACT

Introduction and objective

Maternal morbidity and mortality (MMM) is a public health concern in the US, with Native American women experiencing higher rates than non-Hispanic White women. However, research on risk factors for MMM outcomes among Native American women is limited. This systematic review comprehensively synthesizes and critically appraises the literature on risk factors for MMM experienced by Native American women.

Methods and analysis

A systematic search was conducted on 10 October 2022 in PubMed, Embase, CINAHL, and Scopus for articles published since 2012. Selection criteria included observational studies set in the US, involving Native American women in the perinatal period, and examining the relationship between risk factors and MMM outcomes. Three reviewers screened and extracted data from the included studies, with risk of bias assessed using National Institutes of Health quality assessment tools. Data were analyzed descriptively.

Results

Fifteen studies were analyzed, with Native American women as the primary study population in seven studies. All studies utilized administrative databases, with settings including nationwide (7 studies), statewide (4 studies), and Indian reservations (4 studies). Nine MMM outcomes were identified. The majority of studies focused on hypertensive disorders of pregnancy (8 studies) and severe maternal morbidity (SMM) (4 studies). Twenty-six risk factors were identified at the individual level (24 factors) and community level (2 factors). Key risk factors included Native American race (6 studies), rural maternal residency (4 studies), overweight/obese body mass

index (2 studies), maternal age (2 studies), nulliparity (2 studies), and preexisting medical conditions (1 study).

Conclusion

The findings highlight the scarcity of research on MMM risk factors for Native American women, limiting the ability of healthcare and public health organizations to develop and implement tailored approaches to reduce disparities. More focused research is needed to better understand and address these risk factors.

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ARTICLE SUMMARY

Strengths and limitations of this study

- The review searched a variety of scientific databses to identify a wide range of studies on maternal morbidity and mortality in Native American women in the United States.
- The review incorporated studies conducted on Indian reservations and within specific tribal health systems, providing insights tailored to the unique contexts and experiences of Native American women.
- The review synthesizes and critically appraises the limited existing literature on risk factors for maternal morbidity and mortality specifically among Native American women in the United States.
- Many included studies had small sample sizes or low percentages of Native American women, limiting the generalizability of the findings to this specific population.
- Included studies relied on administrative databases (i.e., hospital discharge database, vital recods registries, or electronic health records), which introduce potential reporting biases and misclassification issues, especially concerning the racial categorization of Native American participants.

INTRODUCTION

Maternal morbidity and mortality (MMM) are alarming public health problems in the United States (US). The Centers for Disease Control and Prevention (CDC) defines maternal mortality as the death of a woman during pregnancy, at delivery, or soon after delivery. [1] Severe maternal morbidity (SMM) refers to complications during labor and delivery with short- and long-term health consequences (e.g., sepsis, blood transfusion, preeclampsia, or hysterectomy). [2,3] The US has one of the highest maternal mortality ratios of any high-income country, reporting 26.4 maternal deaths per 100,000 live births.[4] The SMM rate surged 75% from 1998-1999 to 129 per 10,000 delivery hospitalizations in 2008-2009.[2] Rising rates of blood transfusions, acute renal failure, shock, and other adverse outcomes primarily drove this increase.[2] The rising MMM rates involve complex interactions of factors at patients and families, providers or facilities, overall systems, and within the community at various points in a woman's reproductive life cylce. [5]

Significant racial and ethnic health inequities persist in maternal health. [6–9] Native American women are three to four times more likely to die than non-Hispanic White women from pregnancy-related complications and are three to five times more likely to experience SMM than non-Hispanic White women. [6,10,11] Historical trauma, racism, colonization, genocide, forced migration, reproductive coercion, and cultural erasure contribute to these adverse outcomes. [12–14] Native American women experience unique prolonged systemic barriers that create inequitable social conditions compared to other groups. [14–16] Some systemic barriers include limited access to providers and birthing facilities. [14,17,18] In addition, a history of forced sterilization and forced infant and child separations has led to a strong distrust of the healthcare systems and providers, including the Indian Health Service. [19–21]

Rationale

A scoping review on Native American women and the leading causes of maternal mortality in the US identified risk factors like historical trauma, inequities in healthcare availability, access and utilization, preexisting health conditions, and rurality. [22] A separate review of social determinants on pregnancy-related mortality and morbidity identified that race was a significant factor. [3] However, the review did not provide a list of risk factors specific to Native American women, nor did it identify a study that evaluated maternal deaths among Native American women. [3] There is a need to explore further and assess the quality of research specific to MMM risk factors experienced by Native American women. Identifying this information can help identify areas for prevention focused on Native American communities.

Objective

To assess and critically appraise individual and community-level risk factors for pregnancy-related morbidity and mortality experienced by Native American women in the US.

METHODS

This systematic review follows a protocol previously published, which provides a comprehensive framework for examining pregnancy-related mortality and morbidity among Native American women. [23] Adhering to this pre-established protocol ensures methodological rigor and transparency, facilitating reproducibility and reliability in the findings presented.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination of this research.

Eligibility criteria

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Mata-Analyses (PRISMA) guidelines. [24] Inclusion criteria for studies were: 1) observational study design; 2) study set in the United States; 3) population was Native American women in the perinatal (i.e., the time surrounding childbirth) or puerperium period (i.e., the time after childbirth up to 6 weeks); 4) outcomes focused on measures of pregnancy-related mortality and morbidity; 5) examined the relationship between a risk factor/exposure and stated outcomes. Studies focusing on a different population were included if they offered a stratified analysis by race and contained a racial category for Native Americans. Studies were excluded if: 1) studies focused only on birth, neonatal, or infant outcomes; 2) studies that did not examine the relationship between a risk factor/exposure and stated outcomes; 3) studies with settings outside of the United States; 4) studies that did not include findings for Native American women; and 5) studies that focus on the preconception or postpartum phases.

Information sources and search strategy

The search was carried out on 10 October 2022. The review searched scientific databases (PubMed, Embase, CINAHL, and Scopus) from 1 January 2012 to 10 October 2022. This timeframe was chosen to align with a new standard for identifiying severe maternal morbidity published on 12 November 2012. [2] With technical assistance from a health sciences librarian, the team used search tools and strategies, including shortening keywords where appropriate, using thesaurus terms, and using database-specific controlled vocabulary (e.g., Medical Subject Headings, MeSH). The search strategy combined terms and search strings with the appropriate Boolean operators. The complete search strategy is available in Appendix 1. Covidence was used

to manage every stage of the systematic review, including screenings, data extractions, and risk of bias assessments. [25]

Selection process

Two independent reviewers screened titles and abstracts based on the eligibility criteria. If any disagreement occurred, a third reviewer arbitrated. After the titles and abstracts were screened, two independent reviewers screened full-text articles. The reasons for exclusion were noted at the full-text article stage.

Data collection process

Two independent reviewers extracted study details such as location, study design, eligibility criteria, methods, year of the article, year(s) of study, data source, objectives, sample size and population, independent (risk factors) and dependent (outcomes) variables, key findings, measures of effect/association with p-values and confidence intervals, and limitations. If there were disagreements between the reviewers, a third reviewer arbitrated. For any missing information, the lead author contacted the corresponding authors thrice via email or phone to request information. Any discrepancies within data extraction were reviewed and discussed in a team setting.

Data items

Primary outcomes of interest were maternal morbidity and mortality, including severe maternal morbidity (SMM) based on the CDC's list of 21 diagnoses and procedures (Table 1). [26]

Table 1	**Outcomes of interest**
Mortality and near-misses	

Severe maternal morbidity diagnostic or procedural outcomes	Acute myocardial infarction Acute renal failure Adult respiratory Distress Syndrome Amniotic fluid embolism Aneurysm Cardiac arrest Disseminated intravascular coagulation Eclampsia Heart failure Puerperal cerebrovascular disorders Pulmonary edema Sepsis Severe anesthesia complications Shock Sickle cell anemia with crisis Thrombotic embolism Blood transfusion Conversion of cardiac rhythm Hysterectomy Temporary tracheostomy Ventilation
Additional morbidity outcomes	Postpartum hemorrhage Ectopic pregnancy Placental abruption Uterine atony

This list was used to identify additional articles that did not utilize a composite outcome of severe maternal morbidity or mortality. Given the scope of this review, the terms "pregnancy complications," "obstetric complications," "labor complications," and "near-miss" were added to the list of outcomes to increase the sensitivity of the review. The search strategy was pilot-tested in PubMed, finalized, and adapted to other databases (Table 2). The complete search strategy is available in Appendix 1. The results from each database-specific search strategy were downloaded from the respective databases and uploaded to the EndNote version 20 reference manager software. [27] After removing the duplicates, the citations were imported into Covidence.

Table 2	**PubMed search strategy**
#1 birth[tiab] OR labor[tiab] OR delivery[tiab] OR mothers[tiab] OR maternal[tiab] OR "peripartum period"[mesh] OR peripartum[tiab] OR "labor, obstetric"[mesh] OR "obstetric*"[mesh] OR "obstetric*"[tiab] OR "pregnancy"[mesh] OR "pregnan*"[tiab] OR "perinatal"[tiab] OR "prenatal"[tiab] OR "parturition"[mesh] OR "parturition"[tiab]
#2 "tribal" OR "tribe" OR "first nations" OR "indigenous peoples"[mesh] OR indigenous OR "health services, indigenous"[mesh] OR "american indians or alaska natives"[mesh] OR "american indian*" OR "indians, north american"[mesh] OR "native American" OR "alaska native"
#3 "severe maternal morbidity" OR "near miss" OR "adverse maternal outcomes" OR "maternal mortality" OR "Near Miss, Healthcare"[Mesh] OR "Pregnancy/Adverse Effects"[Mesh] OR "Pregnancy/Injuries"[Mesh] OR "Pregnancy/Mortality"[Mesh] OR "Pregnancy/complications"[Mesh] OR "Obstetric Labor Complications"[Mesh] OR "Delivery, Obstetric/adverse effects"[Mesh] OR "Delivery, Obstetric/complications"[Mesh] OR "Delivery, Obstetric/mortality"[Mesh] OR "Maternal Mortality"[Mesh] OR "mortality"[mesh] OR "morbidity"[mesh] OR "pregnancy complications" OR mortality OR morbidity OR "labor complications" OR "delivery complications"
#4 Search (#1 AND #2 AND #3)

Study risk of bias assessment and certainty assessment

Risk of bias was assessed using the NIH's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case-Control Studies to examine critical concepts for each study's validity. [28] Two independent reviewers assessed articles using the tool's criteria and

rated them as "good," "fair," or "poor" quality. This rating was based on the percentage of "Yes" responses out of the total applicable questions in each tool. A study will be rated as “good” if it receives a “Yes" response for ≥80% of the applicable NIH critical appraisal questions, “fair” for 50%-79%, and “poor” for ≤49%. A “good” rating meant there was the least risk of bias, and the results were considered valid. [28] A "fair" rating indicated susceptibility to some bias but was insufficient to invalidate its results and would vary in their strengths and weaknesses. [28] A "poor" rating indicated a significant risk of bias and invalidated its results. [28] When the ratings differed, a third reviewer arbitrated an article's rating.

Effect measures

Measures of effect such as risk and odds ratios with 95% confidence intervals were extracted. Descriptive statistics like prevalence and incidence were also included.

Potential overlap in cohorts

Given the research scarcity on the population of interest and topic mentioned in this article, we attempted to manage for potential overlap in populations across different cohorts in the included studies. Several strategies were used to manage any potential overlap and ensure the integrity and accuracy of the findings: 1) data sources for cohorts were meticulously documented, including specific populations covered by each study; 2) cohorts were often segmented by geographic regions and demographic characteristics relevant to Native American women and; 3) assessed study periods to identify and address any potential overlap in cohorts.

Synthesis methods

A description of the findings for each study included in the review is provided in Appendix 2. This table includes the risk factors, outcomes of interest, and study characteristics. A descriptive

synthesis of the results was the most appropriate for this review since there was a large diversity of study designs, risk factors, and outcomes. The heterogeneity of the studies in this review hindered any quantitative synthesis of the identified risk factors' effect sizes. The identified risk factors are also organized into socioecological levels (i.e., individual, family, community, society, or systems).[29] Risk factors were grouped by outcome examined. The information that was reported for each risk factor included 1) the number of studies that analyzed the risk factor, 2) the number of studies that had a measure of effect for a risk factor and was reported to be statistically significant, and 3) the number of studies that had a measure of effect for a risk factor, and was not statistically significant.

[INSERT FIGURE 1]

RESULTS

Study Selection and study characteristics

A total of 8,220 articles were identified, of which 357 duplicates were removed, resulting in 7,863 articles for screening (Figure 1). During the screening process, there were 6,967 agreements for inclusion and 896 conflicts resolved by an arbitrator, for an overall percent agreement of 88.6%. The selection process yielded 145 articles, of which 15 were included in the review. [10,11,30–39] The most common reasons for study exclusion were: the wrong patient population (41 studies), the wrong setting (22 studies), and the wrong type of publication (21 studies). Most (80.0%) studies used secondary data sources (i.e. hospital discharge records, vital records, as such) to examine associations between risk factors and outcomes. There was an equal number of studies across three study designs (5 studies each). The sample size across all studies ranged from 196 to 51,685,525 with a mean sample size of 4,479,962, a median of 72,697, a

standard deviation of 12,732,821.6, and an interquartile range of 2,123,375.0. Seven studies focused primarily on Native American women (i.e., the study sample comprised mainly of Native American women).[32–34,36–38,40] The remaining eight studies included Native American women as a subgroup in their sample.[10,11,30,31,35,39,41,42] Of these eight studies, the percentage of Native American women that were part of the overall sample ranged from 0.4% to 10.1%, and six of these studies had a proportion of Native American women in their sample that was ≤ 1.4%. The total number of Native American participants across all studies ranged from 196 to 492,771 with a mean of 57,266.5, a median of 7,107, a standard deviation of 129,234.2, and an interquartile range of 26,817.0. Study settings included nationwide (7/15 studies) [10,11,35,36,39,41,42] , statewide (4/15 studies) [30,31,37,38], and on Indian reservations (4/15 studies) [32–34,40].

Risk of bias in studies

Fourteen studies were rated as "good" and one was rated as "fair" according to the NIH's Study Quality Assessment Tools. See Appendix 4 for individual assessments of quality. All cohort and cross-sectional studies were rated "good." [11,30,31,35,36,39–43] Most studies did not assess the exposure more than once over time (7/10 studies). [30,31,35,39–41,43] A smaller proportion were unable to demonstrate that the exposure of interest was measured before the outcome being measured (5/10 studies) [11,36,39,42,43] or did not adjust models to include potential confounders to assess their impact on the relationship between exposure(s) and outcome(s) (3/10 studies).[36,40,42] The reviewers were unable to find evidence in some studies if the outcome assessors were blinded to the exposure status of participants (3/10 studies) [11,36,42] or whether there was a loss to follow-up amongst the cohort studies (3/5 studies). [30,35,40] Amongst the case-control studies, four were rated as "good" [32–34,37] while one was rated as "fair." [38]

The reviewers ascertained that some studies failed to provide a sample size justification (3/5 studies) [32–34] or did not randomly select cases and/or controls from the eligible study population (2/5 studies). [33,38]

Results of individual studies and syntheses

Nine outcomes were identified in the studies: hypertensive disorders of pregnancy (preeclampsia, severe preeclampsia, gestational hypertension, and hypertensive disorders of pregnancy), blood transfusions, postpartum hemorrhage, disseminated intravascular coagulation (DIC), hysterectomy, ectopic pregnancy, uterine atony, placental abruption, and SMM with mortality as a composite outcome. Twenty-six risk factors were identified, 24 of these were individual risk factors while two were community risk factors. No studies examined interpersonal/relationship or societal levels risk factors.

Appendix 2 lists the frequency by which each risk factor and outcome was studied in the literature. A majority of studies examined "hypertensive disorders of pregnancy" (8/15 studies) [30–35,37,42] and "severe maternal morbidity and/or mortality" (4/15 studies) [10,11,39,41] as outcomes. A majority of studies examined body mass index (BMI) (6/15 studies) [30–34,38], maternal age (6/15 studies) [32–36,40] , maternal race (5/15 studies) [10,31,39–41], and parity (5/15 studies) [32–34,38,40] as risk factors for various outcomes. Table 3 is a summary table that reports the number of studies grouped by outcome, the risk factors examined for associations, and the direction of those associations. Appendix 3 summarizes additional details on study design, sample size, and data sources, exposures and outcome variables, covariates, key findings, including the measures of effect and study quality ratings.

Table 3. Summary of risk factors and outcomes by risk/association category*

Outcome	↑Increased risk or positive association	—No association	↓Decreased risk or negative association
Hypertensive disorders of pregnancy (8 studies)			
Pregnancy-induced hypertension	***Rural maternal residency***[1178] Maternal age 35 years or older and smoked during pregnancy[1371]	***Continuous smokeless tobacco use***[2230] ***Continuous cigarette smoking***[2230]	***Maternal age<35 years and smoked during pregnancy***[1371]
Pre-eclampsia	Native American maternal race[8141] ***Overweight/obese BMI***[7372, 835, 836, 837] ***Age at delivery***[835,836] ***Nulliparity***[835, 836, 837] Gestational diabetes[837] Genetic factors CRP_A, rs3093077, (T allele additive)[836] MBL2, rs1800451, (T allele dominant)[836] IL1A, rs3273550, (T allele dominant)[836] CTLA4, rs21775, (A allele dominant)[836] CRP, rs3093068, (G allele additive)[837] CRP, rs3093068, (G allele dominant)[837] CRP, rs876538, (C allele additive)[837] CRP, rs876538, (C allele recessive)[837]	***Continuous smokeless tobacco use***[2230] ***Continuous cigarette smoking***[2230] Age at delivery[837] ***BMI***[8141]	Genetic factors CRP_B, rs1205, (A allele dom)[836] CRP_C, rs1130864, (T allele dom)[836] CRP, rs876538, (C allele dominant)[837]
Severe pre-eclampsia	***Nulliparity***[836, 837] ***Obese BMI***[836,837] Age at delivery[836] Gestational diabetes[837] Genetic factors MBL2, rs1800451, (T allele dominant)[836] IL1A, rs3273550, (T allele dominant)[836] CTLA4, rs21775, (A allele dominant)[836] CRP, rs3093068, (G allele additive)[837] ***CRP, rs3093068, (G allele dominant)***[837] CRP, rs876538, (C allele additive)[837] CRP, rs876538, (C allele recessive)[837]	Age at delivery[837]	Genetic factors CRP_A, rs3093077, (T allele additive)[836] ***CRP_B, rs1205, (A allele dom)***[836] CRP_C, rs1130864, (T allele dom)[836] CRP, rs876538, (C allele dominant)[837]

Severe Maternal Morbidity and/or Mortality (4 studies)			
Severe maternal morbidity (SMM) with transfusions	***Native American maternal race[119]*** ***Any physical health condition[119]*** Any behavioral health condition[119] Multiple chronic conditions[119]	***Native American maternal race[952]***	
Severe maternal morbidity without transfusions		***Rural maternal residency[4010]***	
Severe maternal morbidity and mortality (SMMM)	***Rural maternal residency[3421]*** ***Native American race[4010]*** ***Medicaid funded births[3421]***	***Urban maternal residency[3421]***	
Blood Transfusions (2 studies)			
Blood transfusions	***Rural maternal residency[3421, 4010]*** ***Medicaid-funded births[3421]*** ***Native American maternal race[4010]***		
Postpartum Hemorrhage (2 studies)			
Postpartum hemorrhagePostpartum hemorrhage	***Native American Maternal race[1331]*** ***Gravidity<5[1131]*** ***Birthweight>4500g[1131]*** ***Retained placenta[1131]*** ***Magnesium sulfate use[1131, 2944]*** ***Antepartum bleeding[2944]*** ***Previous postpartum hemorrhage[2944]*** ***Third stage of labor≥20m[2944]*** ***Maternal rural residence[2944]*** ***Fetal macrosomia[2944]*** ***Oxytocin use>12h[2944]*** Routine aspirin use[2944] Prior uterine incision and vaginal delivery[2944] Pre-eclampsia without severe features without use of magnesium sulfate[2944] Parity≥5[2944] Length of second stage of labor≥ 1h[2944] Inpatient induction length≥ to 36h[2944]	***Prior uterine incision[2944]***	
Other Outcomes (4 studies)			
Uterine atony	***Native American maternal race[1331]*** ***Birthweight>4500g[1331]***	***Gravidity<5[1331]*** ***Induction augmentation[1331]*** ***Chorioamnionitis[1331]***	
Ectopic pregnancy	***Maternal age>19 years[1861]*** ***IHS region[1861]***		
Placental abruption	Continuous use of smokeless tobacco[2230] Continuous cigarette smoking[2230]		
Disseminated intravascular coagulation	Native American race[4010]	***Rural maternal residency[4010]***	
Hysterectomy	***Native American race[4010]*** Rural maternal residency[4010]		

*BMI, body mass index; h, hours; m, minutes; significant associations are italicized and bolded, significant association in the same direction as categorized

Specific to hypertensive disorders of pregnancy, having a rural residency (1/1 studies), an overweight or obese BMI (4/5 studies), age above 35 years also referred to as "advanced maternal age" (1/4 studies), and nulliparity (3/3 studies) were significantly associated with increased risk. [30,32–34,42] Genetic predispositions to hypertensive disorders of pregnancy were not significantly associated with increased risk (3/3 studies). [32–34] Studies that focused on SMMM identified being of Native American race (2/3 studies), having a physical health condition (1/1 study), a rural residency (1/2 studies), and births primarly paid by Medicaid (i.e., public government insurance) (1/1 study) as significantly associated with increased risk. The risk of blood transfusions was significantly associated with Native American race (1/1 study), rural residency (2/2 studies), and Medicaid-funded births (1/1 study). [10,11,39] Postpartum hemorrhage risk was significantly associated with being of Native American race when compared to other racial/ethnic groups, a gravidity ≤5, a birthweight of 4500g, having a retained placenta, magnesium sulfate use (2/2 studies), antepartum bleeding, previous postpartum hemorrhage, being in third stage labor greater than 20 minutes, maternal rural residency, fetal macrosomia, and oxytocin use for longer than 12 hours. [38,40] Other outcomes are further described in Appendix 3.

This systematic review identified factors that demonstrated no association or a reduction of risk for Native American women. For pregnancy-induced hypertension, one study identified that continuous smokeless tobacco use and cigarette smoking had no association. [37] A separate study determined that those younger than 35 had a decreased risk of hypertensive disorders of pregnancy compared to those older than 35. [40] One study found no association between hypertensive disorders of pregnancy (e.g., preeclampsia) and BMI. [31] One of the three studies that focused on genetic predisposition identified that having CRP_B, rs1205, (A allele dominant)

decreased risk. [32] Native American race and rural residency were found to have no risk of severe maternal morbidity and/or mortality in three distinct studies. [10,39,41]. One study did not find an association between having a prior uterine incision and postpartum hemorrhage. [38] Another study found no association between uterine atony and having a gravidity greater than 5, induction augmentation, or chorioamnionitis. In contrast, a separate study found no association between disseminated intravascular coagulation and a rural residency. [10,40].

Reporting biases and certainty of evidence

All studies relied on administrative data sources to assess outcomes and exposures simultaneously, and all noted this as a considerable limitation in their study design. Four studies noted concerns with small sample sizes, missing exposure and outcome data, and critical demographic information that may have led to misclassification bias. Two studies considered reporting bias in their study designs, while almost all studies (14/15 studies) referred to the misidentification of Native American women based on predetermined guidelines for race designation.

DISCUSSION

This systematic review synthesized the current literature by conducting a broad search of outcomes associated with maternal morbidity and mortality and identifying their associated risk factors for Native American women in the US. Despite the importance of understanding these outcomes for this population, we found a limited number of studies addressing these critical issues. All fifteen studies identified risk factors at the individual level, suggesting that an overweight or obese BMI, advanced maternal age, parity, and rural maternal residency are associated with Native American maternal morbidity or mortality. Few studies contradicted these

findings and demonstrated no association with Native American race, rural maternal residency, or advanced maternal age. One study found no association with hypertensive disorders of pregnancy, including pregnancy-induced hypertension, preeclampsia, and severe preeclampsia with continuous smokeless tobacco use or continuous cigarette smoking. [37]

One notable finding is that age does not appear to be a substantial risk factor, contrasting with findings in other populations where advanced maternal age is often linked to higher risks.[44] This could be attributed to potential protective factors or differences in health profiles among Native American women that merit further investigation. Two studies found no significant association between age at delivery and preeclampsia among Native American women.[33,34] Conversely, the higher risk of morbidities among public governmental health insurance (i.e., Medicare or Medicaid) recipients is concerning and suggests a need for targeted interventions within this subgroup. Studies showed that rural Native American Medicaid-funded births had the highest adjusted rate of severe maternal morbidity and mortality, indicating potential disparities in healthcare quality and access.[39,45]

Studies assessing the relationship between genetic factors and preeclampsia or severe preeclampsia were completed in an Indian Reservation within a specific tribal health system.[32–34] These studies uncovered that there is no association between genetic expression and preeclampsia for Native American women. However, all these studies concurred that many of the risk factors, such as maternal age, nulliparity, and obesity, that are associated with preeclampsia and severe preeclampsia in other populations were also operative in Native American communities.[32–34]

At the community level, our review identified four studies that included risk factors such as maternal residency and the Indian Health Service Region. This limitation further indicates the

need to expand research to identify and understand the role of community and society-level risk factors. Social determinants of health, such as access to behavioral and primary care services, housing, crime and violence, and health policies, have been demonstrated to contribute directly to maternal mortality and morbidity in more extensive population studies.[46] Studies highlighted the higher incidence of SMM and mortality among rural Native American women compared to their urban counterparts, emphasizing the critical impact of geographic and systemic disparities. [38,40,43]

This review did not find any information on prenatal care utilization and its association with maternal morbidity or mortality despite strong evidence supporting adequate prenatal care utilization in culturally competent healthcare institutions.[15,47,48] Early and adequate prenatal care is thought to promote healthy pregnancies through screening and managing a woman's risk factors and health conditions and promote healthy behaviors during pregnancy.[6]

It's important to recognize that other risk factors, like postpartum depression, substance use, and behavioral health challenges, can also lead to morbidity and mortality, even if they don't occur during delivery.[49] This study didn't consider the effects of historical trauma, discrimination, and racism, which are significant health determinants for Native Americans.[17] These experiences contribute to health deterioration over time, as explained by the weathering hypothesis, which suggests that cumulative stress from racism and socioeconomic disadvantages leads to worse health outcomes.[13]

Appraisal

Most studies were rated as "good" (14/15 studies), while one was rated as "fair." Despite this, we were able to highlight the methodological shortcomings of some of the studies, such as the

failure to assess the exposure more than once over time, the inability to demonstrate that exposure was measured before outcome measurement, or not adjusting models to include potential confounders. Additionally, some studies failed to provide sample size justification or did not randomly select cases or controls from the eligible study population, posing bias risks.

We identified additional shortcomings in the available evidence. Racial/ethnic misclassification on administrative databases leads to challenges with underreporting and further affects the selection of study participants. Given the small percentage of Native American births in the United States, which is only 0.7%, minor errors in misclassification can significantly impact data analysis.[50] Multiple studies in this review reported small sample sizes, making it difficult to determine if a particular outcome was a true finding, possibly allowing for type II errors. Among studies that included samples that were not fully Native American, most reported a Native American sample size of ≤ 1.4%. The limited research in these communities hinders the identification of additional risk factors for morbidity and mortality specific to Native American women.[51] The measurement of maternal morbidity and mortality varied across the studies. This review used a broader definition of these outcomes, including conditions not listed by the CDC as severe maternal morbidity. This approach aimed to provide a complete understanding of the risk factors and health outcomes specific to Native American women. Lastly, relying heavily on administrative data presents unique challenges in identifying risk factors not traditionally included in these datasets, as their primary purpose may not align with the study's hypothesis.[52]

Strengths and limitations

Our systematic review faced some limitations despite our use of an expansive search strategy informed by other published reviews.[3,53] We were unable to translate all MesH terms from

PubMed into indexed language for other databases. There is also a risk of publication bias and selective reporting of significant findings in the studies. Using NIH's quality assessment tools, which are not independently published nor standardized may introduce bias due to the qualitative nature of the review. Despite this, other systematic reviews have built the evidence supporting the utility and practicality of utilizing this tool. [3] Furthermore, the review revealed significant variation in the risk factors and outcomes across different studies. This highlights the complexity and heterogeneity of maternal health issues among Native American women. This variation presents a challenge in drawing definitive conclusions.

Despite these limitations, this systematic review is one of the few that identifies risk factors for various outcomes indicating severe maternal morbidity and mortality among Native American women in the US. The review addresses a critical gap in the literature by focusing on this historically marginalized and underserved population, providing valuable insights for targeted public health interventions and policies. Including various study designs allows for a more comprehensive understanding of the associated risk factors and outcomes. We comprehensively reviewed the current literature using multiple search strategies incorporating the CDC's list of procedural and diagnoses for SMM. This systematic review utilized recommended language to identify research in Native American communities following the National Library of Medicine guidance. [54] Rigorous quality assessment tools were employed to evaluate the methodological quality of the included studies, ensuring that the findings are based on reliable and valid evidence. Additionally, organizing the identified risk factors into socioecological levels provides a structured approach to understanding the complex interplay of factors influencing maternal health in Native American communities.

Implications for practice, policy, and future research

Our review demonstrates the lack of attention reflected in the scarcity of evidence available to understand this public health crisis among a population that is often ignored. The limited type of risk factors studied, the study designs, settings, and outcomes limit the ability of healthcare and public health organizations to properly design and implement tailored approaches to reduce disparities in this community further. Public health initiatives must prioritize culturally competent care and address the unique challenges faced by Native American women to mitigate the risks of maternal morbidity and mortality. By acknowledging and addressing these gaps in the literature, public health can better inform policy, enhance clinical practices, and ultimately improve health outcomes for Native American mothers and their families.

OTHER INFORMATION

Registration and protocol: The registration and protocol information for this review can be accessed at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=363405, identifier: CRD42022363405. No amendments were submitted during implementation of the protocol.

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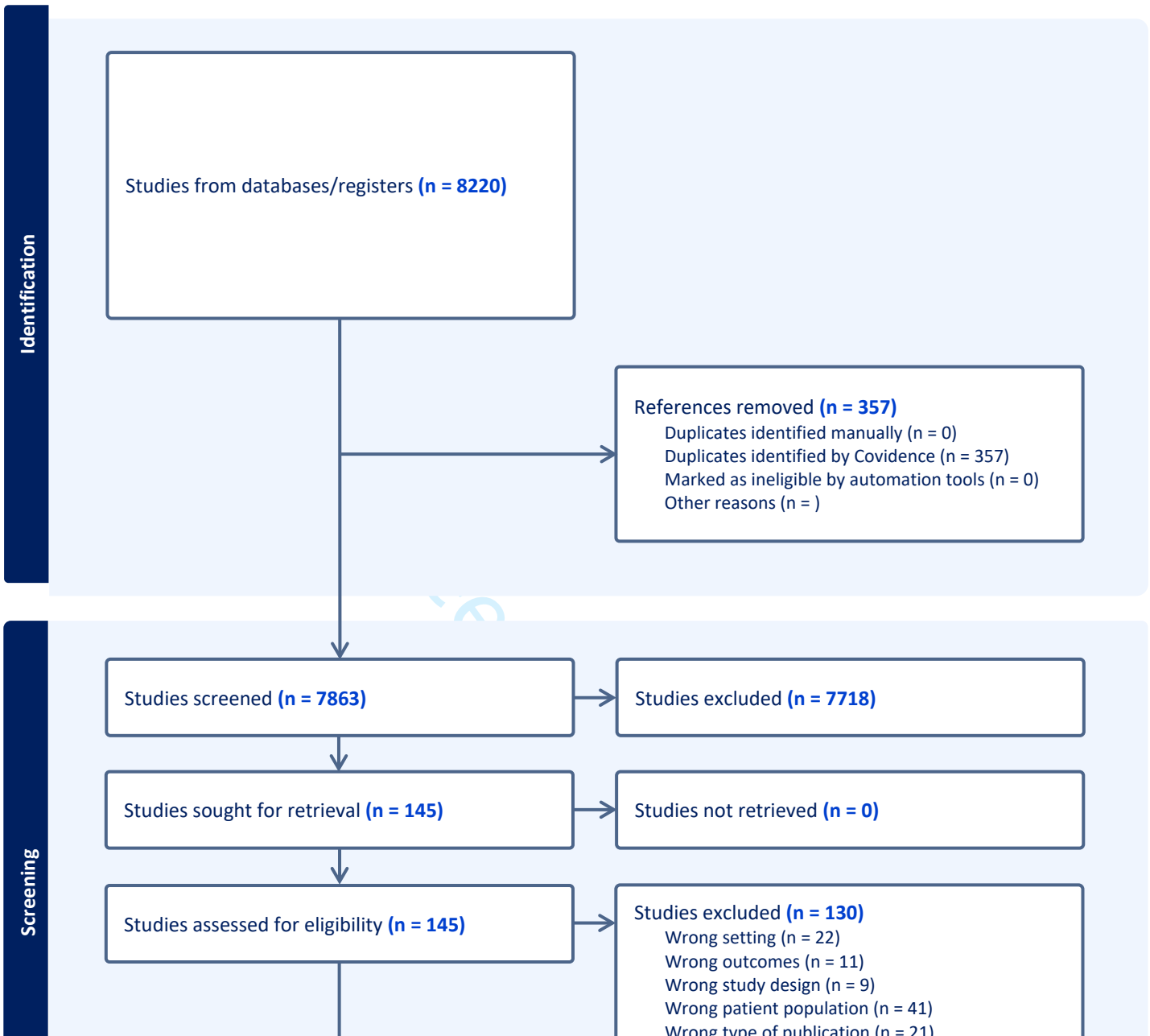
Figure Legend:

Figure 1 - PRISMA flow diagram

Individual and community level risk factors for maternal morbidity and mortality among Native American women in the United States



Appendix 1. Search strategy by database

PubMed Search Strategy

#1 birth[tiab] OR labor[tiab] OR delivery[tiab] OR mothers[tiab] OR maternal[tiab] OR "peripartum period"[mesh] OR peripartum[tiab] OR "labor, obstetric"[mesh] OR "obstetric*"[mesh] OR "obstetric*"[tiab] OR "pregnancy"[mesh] OR "pregnan*"[tiab] OR "perinatal"[tiab] OR "prenatal"[tiab] OR "parturition"[mesh] OR "parturition"[tiab]

#2 "tribal" OR "tribe" OR "first nations" OR "indigenous peoples"[mesh] OR indigenous OR "health services, indigenous"[mesh] OR "american indians or alaska natives"[mesh] OR "american indian*" OR "indians, north american"[mesh] OR "native American" OR "alaska native"

#3 "severe maternal morbidity" OR "near miss" OR "adverse maternal outcomes" OR "maternal mortality" OR "Near Miss, Healthcare"[Mesh] OR "Pregnancy/Adverse Effects"[Mesh] OR "Pregnancy/Injuries"[Mesh] OR "Pregnancy/Mortality"[Mesh] OR "Pregnancy/complications"[Mesh] OR "Obstetric Labor Complications"[Mesh] OR "Delivery, Obstetric/adverse effects"[Mesh] OR "Delivery, Obstetric/complications"[Mesh] OR "Delivery, Obstetric/mortality"[Mesh] OR "Maternal Mortality"[Mesh] OR "mortality"[mesh] OR "morbidity"[mesh] OR "pregnancy complications" OR mortality OR morbidity OR "labor complications" OR "delivery complications"

#4 Search (#1 AND #2 AND #3)

EMBASE Search Strategy

('delivery:ab,ti' OR 'birth:ab,ti' OR 'labor:ab,ti' OR 'mothers':ab,ti OR 'maternal':ab,ti OR 'peripartum':ab,ti OR 'obstetric':ab,ti OR 'pregnancy':ab,ti OR 'perinatal':ab,ti OR 'prenatal':ab,ti OR 'parturition':ab,ti OR 'perinatal period'/exp OR 'labor'/exp OR 'pregnancy'/exp OR 'birth'/exp)

AND

(tribe OR 'indian health service' OR indigenous OR tribal OR 'first nations' OR 'american indian' OR 'native american' OR 'alaska native' OR 'indigenous people'/exp OR 'indigenous health care'/exp OR 'american indian'/exp)

AND

('severe maternal morbidity' OR 'adverse maternal outcomes' OR 'maternal mortality' OR 'pregnancy complications' OR 'mortality' OR 'morbidity' OR 'labor complications' OR 'delivery complications' OR 'near miss (health care)'/exp OR 'near miss' OR 'pregnancy complication'/exp OR 'maternal mortality'/exp OR 'labor complication'/exp OR 'maternal outcome'/exp OR 'delivery complications'/exp OR 'maternal morbidity'/exp OR 'morbidity'/exp OR 'mortality'/exp)

CINAHL Search Strategy

((TI delivery OR AB delivery) OR (TI birth OR AB birth) OR (TI labor OR AB labor) OR (TI mothers OR AB mothers) OR (TI maternal OR AB maternal) OR (TI peripartum OR AB peripartum) OR (TI obstetrics OR AB obstetrics) OR (TI pregnancy OR AB pregnancy) OR (TI perinatal OR AB perinatal) OR (TI prenatal OR AB prenatal) OR (TI parturition OR AB parturition) OR (TI delivery OR AB delivery) OR MM "Perinatal Period" OR MM "Obstetric Patients" OR MM "Delivery, Obstetric+" OR MM "Pregnancy+" OR MM "Labor+" OR MM "Obstetrics+" OR MM "Childbirth+")

AND

(tribe OR "indian health service" OR Indigenous OR "native american" OR "american indian" OR Tribal OR "first nations people" OR "alaska native" OR MM "Indigenous Peoples+" OR MM "Health Services, Indigenous" OR MM "Native Americans+")

AND

("severe maternal morbidity" OR "near miss" OR "pregnancy complications" OR "obstetric complications" OR mortality OR morbidity OR "maternal mortality" OR "maternal morbidity" OR "delivery complications" OR MM "near-death experiences" OR MM "maternal mortality" OR MM "obstetric emergencies" OR MM "Pregnancy Complications+" OR MM "labor complications" OR MM "maternal mortality" OR MM "morbidity+" OR MM "mortality+")

SCOPUS Search Strategy

("severe maternal morbidity" OR "near miss" OR "pregnancy complications" OR mortality OR morbidity OR "labor complications" OR "delivery complications" OR "maternal mortality" OR "maternal morbidity" OR "obstetric complications")

AND

(indigenous OR "native american" OR "american indian" OR tribal OR "alaska native" OR "first nations" OR tribe OR "indian health service")

AND

(TITLE-ABS (mother) OR TITLE-ABS (maternal) OR TITLE-ABS (peripartum) OR TITLE-ABS (obstetric) OR TITLE-ABS (pregnancy) OR TITLE-ABS (perinatal) OR TITLE-ABS (prenatal) OR TITLE-ABS (parturition) OR TITLE-ABS (labor) OR TITLE-ABS (birth) OR TITLE-ABS (delivery))

Appendix 2. Risk Factors and Outcomes by Volume of Studies

	Outcome*									
Risk Factor	**SMMM**	**HDP†**	**BT**	**PPH**	**DIC**	**Hyst**	**EP**	**UA**	**PA**	**No. of Studies Examining Each Risk Factor$^{\alpha}$**
Body mass index		5		1			1	1		7
Age		4		1			1	1		6
Maternal race	3	1	2	1	1	1		1		5
Parity		3		1				1		5
Maternal residence	2	1	2		1	1				3
Gene expressions		3								3
Tobacco use		2							1	2
Birth primary payer type	1		1							1
Magnesium Sulfate use				2				1		2
Inpatient induction				2				1		2
Augmentation				1				1		1
Birthweight				1				1		1
Physical health/ chronic health status	1									1
Gestational diabetes		1								1
Behavioral health status (depression or substance use disorder)	1									1
Indian Health Service region							1			1
Gravidity					1			1		1
Routine aspirin use				1						1
Prior uterine incision or vaginal birth after cesarean				1						1
Macrosomia				1						1
Antepartum Bleeding				1						1
Previous PPH				1						1
Length of labor				1						1
Oxytocin use				1						1
Chorioamnionitis				1				1		1
Retained placenta				1				1		1
No. of Studies Examining Each Outcome$^{\alpha}$	4	8	2	2	2	1	1	1	1	15

*Severe maternal morbidity and mortality (SMMM), hypertensive disorders of pregnancy (HDP), blood transfusion (BT), postpartum hemorrhage (PPH), disseminated intravascular coagulation (DIC), hysterectomy (Hyst), ectopic pregnancy (EP), uterine atony (UA), and placental abruption (PA), blank cells represent no studies found. † The HDP category includes pre-eclampsia, severe pre-eclampsia, gestational hypertension, and hypertensive disorders of pregnancy. α Row and column figures do not represent totals since a study can include multiple risk factors or outcomes.

Appendix 3. Table of included studies

Study #	Authors	Year	Study Design	Location	Sample Size, Data Source	Native American subsample size (% of total sample)	Risk Factor (Social ecological level)	Outcome(s)	Covariates	Quality Rating	Key Findings ([95% Confidence Intervals] unless otherwise stated
Hypertensive Disorders of Pregnancy (8)											
1178	Cameron, N et al.	2022	Cross Sectional	Nationwide	51,685,525 all live births in the US to individuals aged 15-44 years, birth vital records	492,771 (9.3%)	Maternal residence (C)	Pregnancy induced hypertension	None	Good	-The incidence of hypertensive disorders of pregnancy differed by racial and ethnic identity within both rural and urban areas. The highest age-adjusted incidence of hypertensive disorders of pregnancy was observed among individuals who identify as American Indian/ Alaskan Native. -Significant increase in the incidence of hypertension disorders of pregnancy among Native American women in rural areas compared to those in urban areas in 2007 and 2014 (2017 RR=1.21, [1.11-1.33] and 2014 RR=1.17, [1.08-1.13]) -No significant increase in the incidence of hypertension disorders of pregnancy among

										Native American women living in rural areas compared to those in urban areas was observed in 2019 (2019 RR=1.03, [0.96-1.11])
2230	England, L et al.	2013	Case Control	Anchorage, AK	1,123 singleton deliveries from 1997-2005 to AN women residing in western Alaska, hospital administrative database / 503 cases and 502 controls	1,123 (100%)	Continuous smokeless tobacco use (I) and continuous cigarette smoking (I)	Pregnancy associated hypertension, pre-eclampsia, and gestational hypertension	Parity, pre-pregnancy BMI, maternal age	Good	-No significant associations were observed between smokeless tobacco use and pregnancy-associated hypertension (aOR 0.92, [0.56–1.51]). -No significant associations were observed between smokeless tobacco use and pre-eclampsia (aOR 0.90, [0.52–1.56]). -No significant associations were observed between smokeless tobacco use and gestational hypertension (aOR 0.93, [0.42–2.03). -No significant associations were observed between continuous cigarette smoking and pregnancy-associated hypertension (aOR 0.65, [0.31–1.37]). -No significant associations were observed between

										continuous cigarette smoking and pre-eclampsia (aOR 0.69, [0.30–1.58]). -No significant associations were observed between continuous cigarette smoking and gestational hypertension (aOR 0.52, [0.14–1.90).
8141	Zamora-Kapoor, A et al.	2016	Cohort	Washington State	71,080 singleton live births from 2003-2013 to Whit and AI/AN women, linked birth-hospital discharge records	7,189 (10.1%)	Maternal race (I), BMI (I)	Pre-eclampsia	Birth year, maternal age, educational attainment, marital status, Medicaid insurance, WIC participation, prenatal smoking, BMI	Good	-AI/ANs had an increased risk of pre-eclampsia compared to Whites after controlling for all covariates except BMI (OR 1.17 [1.06–1.29]). After further adjustment for BMI, the racial disparity in pre-eclampsia risk was greatly attenuated (aOR 1.05, [0.95–1.16]). -AI/ANs who were underweight (OR 1.39, [0.64-3.02]), normal weight (OR 1.02, [0.83-1.22]), overweight (OR 1.23, [0.93, 1.36]), or obese (OR 1.00, [0.86, 1.17]) generally had relative risks of pre-eclampsia comparable, or slightly (but not statistically significantly) greater than those of their White counterparts.

1371	Chang, J et al.	2014	Cohort	Nationwide	3,113,164 singleton births between 20-44 weeks gestation without major fetal anomalies in 2010, US natality file	34,348 (1.10%)	Cigarette use during pregnancy (I), maternal age (I)	Pregnancy induced hypertension (inclusive of pre-eclampsia and eclampsia)	Prenatal care adequacy, weight gain, parity, diabetes, marital status, chronic hypertension, preeclampsia, eclampsia, tobacco use	Good	-The odds of pregnancy induced hypertension was greater in non-Hispanic American Indian women 35 years or older who smoked during pregnancy (aOR 1.29, [0.88-1.89]). -A reduced odds of PIH was evident in non-Hispanic American Indian women younger than 35 years old who smoked during pregnancy based (aOR 0.76, [0.66-0.87]).
7372	Tiwari, R et al.	2021	Cohort	Washington State	105,466 singleton live births from 22 facilities from 2018-2018, hospital administrative database	978 (0.92%)	Pre-pregnancy BMI (I)	Pre-eclampsia	Maternal age, parity, delivery hospital, government health insurance, substance abuse, nicotine use, and alcohol use	Good	-The strength of the association of overweight/obesity with preeclampsia was much greater among NH AI/AN women (aRR 5.24; [1.92–14.30]) and NH Native Hawaiian/Other Pacific Islander women than among other race/ethnicities (aRR 5.88, [1.30-36.51]).
835	Best, L et al.	2012	Case Control	Belcourt, ND	299 women tribal members of the Turtle Mountain Band of Chippewa who sought care in an IHS	299 (100%)	Age at delivery (I), nulliparity (I), BMI (I), Single nucleotide polymorphisms [NOS3, rs1799983	Pre-eclampsia	Nulliparity, BMI, age at delivery	Good	-Age at delivery (aOR 1.0823, [p=0.0185]) , nulliparity (aOR 6.8628, [p<0.001]), and obesity (aOR 1.0951, [p<0.001]) show robust independent effects associated with preeclampsia.

					hospital or clinic from 2004-2009, electronic medical records / 101 cases and 198 matched controls		(G allele recess), NOS3, rs3918227 (A allele dom), GNB3, rs5442 (A allele dom), DDAH1, rs10158674 (C allele recess), DDAH1, rs233115 (A allele recess)] (I)			-There was no significant association between any of single nucleotide polymorphisms studied and pre-eclampsia. -NOS3, rs1799983 (G allele recess) (aOR 1.4087, [p=0.2354]) -NOS3, rs3918227 (A allele dom) (aOR 0.7356, [p=0.4611]) -GNB3, rs5442 (A allele dom) (aOR 0.9147, [p=0.8655]) -DDAH1, rs10158674 (C allele recess) (aOR 1.0165, [p=0.9898]) -DDAH1, rs233115 (A allele recess) (aOR 2.2227. [p=0.1578])
836	Best, L et al.	2012	Case Control	Belcourt, ND	196 women tribal members of the Turtle Mountain Band of Chippewa who sought care in an IHS hospital or clinic from 2004-2009, electronic medical records / 66 cases and	196 (100%)	Age at delivery (I), nulliparity (I), BMI (I), single nucleotide polymorphisms [CRP_A rs3093077 (T allele additive), CRP_B rs1205 (A allele dom), CRP_C rs1130864	Pre-eclampsia, severe pre-eclampsia	Nulliparity, weight at first prenatal visit, BMI, birthweight of infant, gestational diabetes, age at delivery	Good	-Age at delivery did not show a significant association with pre-eclampsia (aOR 1.036, [p=0.398]) and severe preeclampsia (aOR 1.027, [p=0.586]). -Nulliparity (aOR 4.274, [p=0.003] and aOR 4.520, [p=0.009])) and obesity (aOR 1.093, [p=0.002] and aOR 1.094, [p=0.007]) show robust independent associations with

					130 matched controls		(T allele dom), MBL2 rs1800451 (T allele dom, IL1A rs3783550 (T allele dom), CTLA4 rs231775 (A allele dom)](I)				preeclampsia and severe pre-eclampsia. -There was no significant association between any of single nucleotide polymorphisms studied with pre-eclampsia and severe pre-eclampsia except CRP_B, rs1205, (A allele dom). -CRP_B, rs1205, (A allele dom) was the only single nucleotide polymorphism that showed a significant association with severe pre-eclampsia (aOR 0.259, [p=0.020]).
837	Best, L et al.	2013	Case Control	Belcourt, ND	410 women tribal members of the Turtle Mountain Band of Chippewa who sought care at an IHS hospital or clinic from 2004-2012, electronic medical records / 140 cases and 270 matched controls	410 (100%)	Age at delivery (I), nulliparity (I), BMI (I), gestational diabetes (I), single nucleotide polymorphisms [CRP rs3093068 (G allele add), CRP rs3093068 (G allele recess, CRP rs3093068 (G allele dom), CRP	Pre-eclampsia, severe pre-eclampsia	Nulliparity, weight at first prenatal visit, BMI, birthweight of infant, gestational diabetes	Good	-Age at delivery did not show a significant association with pre-eclampsia (aOR 1.053, [p=0.076]) and severe preeclampsia (aOR 1.052, [p=0.166]). -Gestational diabetes did not show a significant association with pre-eclampsia (aOR 1.684, [p=0.278]) and severe pre-eclampsia (aOR 2.241, [p=0.166]). -Independent effects of nulliparity (aOR 5.6, [p=0.001] and aOR 4.17, [p=0.001]) and

							rs876538 (C allele add), CRP , rs876538 (C allele recess), CRP rs876538 (C allele dom), rs3093068 (G dom) and rs876538 (C recess) add risk score] (I)			obesity (aOR 1.061, [p=0.002] and aOR 1.059, [p=0.001]) on pre-eclampsia and severe pre-eclampsia were observed. -There was no significant association between any of single nucleotide polymorphisms studied with pre-eclampsia and severe pre-eclampsia except CRP rs3093068 (G allele add) and CRP rs3093068 (G allele dom) with severe pre-eclampsia (aOR 2.587, [p=0.05] and aOR 2.587, [p=0.050]) -The rs3093068 (G dom) and rs876538 (C recess) additive risk score showed significant association with pre-eclampsia (aOR 1.779, [p=0.016]) and severe pre-eclampsia (aOR 2.035, [p=0.013]).
Severe Maternal Morbidity and Mortality (4)										
119	Admon, L et al.	2018	Cross Sectional	Nationwide	2,523,528 all hospital deliveries that occurred between 2012-2015,	20,447 (0.810%)	No chronic conditions, any physical health condition (I), any	SMM	Age, income, payer, rural vs. urban residence, and	Good	-The incidence of severe maternal morbidity was significantly higher among deliveries to women in every racial and ethnic minatory

					National Inpatient Sample		behavioral health condition (I), multiple chronic conditions (I), maternal race (I)		hospital region.	category compared with deliveries among non-Hispanic white women. -American Indian/Alaska Native women are at increased risk of severe maternal morbidity compared to non-Hispanic white women (aRR 1.5, [1.3-1.7]) . This is not significant when blood transfusions are not included in severe maternal morbidity (aRR 0.90, [0.68-1.2]). -Among deliveries to women with comorbid physical and behavioral health conditions, significant differences in severe maternal morbidity were identified among racial and ethnic minority compared with non-Hispanic white women and the largest disparities were identified among women with multiple chronic conditions. -In comparing deliveries among American Indian/Alaskan Native women with non-Hispanic white women, the rate difference for severe maternal

											morbidity incidence increased from 66.6 [95% CI 39.9-93.3] to 101.3 [95% CI -41.0-243.5] per 10,000 delivery hospitalizations, respectively, in comparing deliveries in which no and multiple chronic conditions were identified. -American Indian/Alaskan Native women compared to non-Hispanic white women are at increased risk for severe maternal morbidity when any physical health condition is present (aRR 1.5, [1.3-1.7]), any behavioral health condition is present (aRR 1.2, [0.90-1.6]), and having multiple (2 or more) chronic conditions (aRR 1.4, [0.93-2.20]).
3421	Interrante, J et al.	2022	Cross Sectional	Nationwide	6,357,796 maternal records from childbirth hospitalizations from 2007-2015, National Inpatient Sample	43,929 (0.691%)	Primary payer type (I), maternal residence (C), maternal race (I)	SMM and Mortality (SMMM)	Maternal race and ethnicity, maternal residence, maternal age, childbirth year, bottom quartile of	Good	-Rural Indigenous Medicaid-funded births had the highest adjusted predicted rate of SMMM (224.9 per 10,000 births, [187.0-262.9]). -Among rural residents, births by Indigenous people had the greatest differences in rates

									income, hospital region, cesarean birth, substance use disorder, depression, HIV or AIDS, pulmonary hypertension, systemic lupus erythematosus, chronic kidney disease, chronic heart disease, diabetes, chronic hypertension, and chronic respiratory disease	between Medicaid-funded and privately insured births (aRD, 97.8, [50.4–145.3]). -When examining the intersection of rurality and race and ethnicity, births among Indigenous rural residents had significant additive interaction, with 40% (aAP 0.40, [0.11-0.69]) of SMMM cases in that population owing to the interaction. -When examining the intersection of urban status and race and ethnicity, births among Indigenous urban residents did not have an additive interaction (aAP 0.06, [-0.20-0.32]). -If the excess risk of SMMM associated with Medicaid could be mitigated (i.e., if the risk of SMMM among Medicaid-funded births could be decreased to the risk among the privately insured), this would not only prevent the 23 cases per 10,000 births that occur among white urban residents, but an additional 98 cases per 10,000 births

											among Indigenous rural residents.
952	Booker, W et al.	2018	Cohort	Nationwide	1,724,694 delivery hospitalizations from women aged 40-54 years between 1998-2014, National Inpatient Sample	7,107 (0.412%)	Maternal race (I)	SMM, SMM excluding blood transfusions	Year, bed size, insurance status, hospital location, income quartile, hospital region, hospital teaching status, and race	Good	-The incidence of SMM was greater among Native American women but not significant compared to Non-Hispanic white women (aRR 1.08, [0.93-1.25]). -Risk for severe morbidity excluding transfusion among Native Americans is not demonstrated because of small denominators.
4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (I)	SMMM, SMMM excluding blood transfusion	Age, insurance payer, income, hospital region	Good	-The incidence of SMMM was greater among indigenous women compared with white women (aRR 1.8, [1.6–2.0]). -Within each racial group, incidence of SMMM was higher among rural compared with urban residents (2.3% for rural indigenous women vs 1.8% for urban indigenous women) (a RR 1.3, [1.0–1.6]); (1.3% for rural white women vs 1.2% for urban white women) (aRR 1.1, [1.1–1.2]). -Within indigenous women, the incidence

											of SMM (excluding transfusions) among rural compared to urban residents was not significant (aRR 0.7, [0.4-1.0)].
	Blood Transfusions (2)										
3421	Interrante, J et al.	2022	Cross Sectional	Nationwide	6,357,796 maternal records from childbirth hospitalizations from 2007-2015, National Inpatient Sample	43,929 (0.691%)	Primary payer type (I), maternal residence (C), maternal race (I)	Blood transfusions	Maternal race and ethnicity, maternal residence, maternal age, childbirth year, bottom quartile of income, hospital region, cesarean birth, substance use disorder, depression, HIV or AIDS, pulmonary hypertension, systemic lupus erythematosus, chronic kidney disease, chronic	Good	-Rural residents had greater odds of blood transfusion for both Medicaid-funded (aOR 1.15, [1.06-1.25]) and privately insured (aOR 1.20, [1.11-1.31]) hospital births compared to urban residents. -Medicaid-funded (aOR 1.71, [1.39-2.11]) and privately insured hospital (aOR 1.42, [1.05-1.92]) indigenous births had the second highest odds of blood transfusions compared to other racial/ethnic groups. This yielded an additive interaction p-value of 0.006.

									heart disease, diabetes, chronic hypertension, and chronic respiratory disease		
4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (I)	Blood transfusions	Age, insurance payer, income, hospital region	Good	-The incidence of blood transfusions was greater among indigenous women compared with white women (aRR 1.8, [1.5–2.0]). -The incidence of blood transfusion among rural indigenous women compared to urban indigenous women was statistically greater (aRR 1.6, [1.2-2.0]).
Postpartum Hemorrhage (PPH) (2)											
1331	Chalouhi, S et al	2015	Cohort	Gallup, NM	1,062 women who delivered vaginally at the Rehoboth McKinley Hospital, medical records	751 (70.7%)	Maternal race (I), age (I), parity (I), gravidity (I), birthweight (I), retained placenta (I), magnesium sulfate use (I), induction augmentation (I),	Postpartum hemorrhage	None	Good	-A significantly higher proportion of Native Americans than non-native women developed PPH (11.6% vs 7.0%, [p= 0.02]). -In multivariable logistic regression analysis, the significant predictors of PPH were Native American ethnic origin (OR 1.8, [1.1-3.0]), decreased gravidity of fewer than

							chorioamnionitis (I)			5 (OR 1.2, [1.1-1.4]), increased birth weight greater than 4500 grams (OR 1.1, [1.0-1.0]), retained placenta (OR 51.0, [9.8-288.2]), and use of magnesium sulfate (OR 3.5, [1.4-9.0]).
2944	Hadley, M et al	2021	Case Control	Anchorage, AK	384 deliveries between 2018-2019 at the Alaska Native Medical Center, medical records / 128 cases and 256 controls	384 (100%)	BMI (I), antepartum bleeding (I), routine aspirin used prescribed (I), prior uterine incision (I), prior uterine incision and vaginal delivery (I), parity (I), macrosomia, pre-eclampsia without severe features with magnesium sulfate during labor (I), pre-eclampsia with severe features and use of	Postpartum hemorrhage	Not reported	Fair	-In the bivariate analysis, the following risk factors were significantly associated with a higher likelihood of postpartum hemorrhage: BMI of 40 or more (OR 2.6, [1.4-4.5]), antepartum bleeding (OR 6.3, [1.2-31.6]), previous postpartum hemorrhage (OR 5.0, [2.6-9.8]), suspected macrosomia with estimated fetal weight of 4000 g or more (OR 2.7, [1.4-5.3]), pre-eclampsia with severe features and use of magnesium sulfate during labor (OR 4.7, [2.4-9.2], length of third stage labor longer than 20 min (OR 2.2, [1.1-4.4]), and use of oxytocin for more than 12 h (OR 5.0, [2.3-10.6]). -Residence in a rural community (OR 2.2, [1.4-3.6]) and vitamin

							magnesium sulfate (I), previous postpartum hemorrhage (I), length of 2nd stage of labor (I), length of 3rd stage of labor (I), rural residence (C), and oxytocin (I), and inpatient induction length (I)			D supplementation (OR 1.7, [1.1-2.6]) were also significantly associated with postpartum hemorrhage. -Multivariate condition logistic regression analyses found that antepartum bleeding (OR 8.8, [1.6-48.5]) , pre-eclampsia with severe features and use of magnesium sulfate (OR 5.3, [2.4-11.9]), previous postpartum hemorrhage (OR 2.7, [1.2-6.1]), third stage of labor of 20min or more (OR 2.9, [1.2-6.9]), rural residence (OR 2.0, [1.2-3.5]), fetal macrosomia (OR 4.0, [2.1-7.5]), and oxytocin use for more than 12h (OR 3.0, [1.1-8.0]) all remained significantly associated with an increased risk of hemorrhage in Native American women. -Routine aspirin use (OR 1.7, [0.9-3.4]), prior uterine incision (OR 1.0, [0.52-2.1]), prior uterine incision and vaginal delivery (OR 1.6, [0.58-4.4]), a parity of 5 or more (OR 1.8, [0.87-3.9]), pre-eclampsia without severe features without

											use of magnesium sulfate (OR 2.1, [0.98-4.4]), length of second stage of labor grater or equal to 1 hour (OR 1.6, [0.88-3.0]), and an inpatient induction length of greater or equal to 36 hours (OR 2.3, [0.4-12.8]) were not significantly associated with a higher likelihood of postpartum hemorrhage.
Misc. Outcomes (5)											
1331	Chalouhi, S et al	2015	Cohort	Gallup, NM	1,062 women who delivered vaginally at the Rehoboth McKinley Hospital, medical records	751 (70.7%)	Maternal race (I), age (I), parity (I), gravidity (I), birthweight (I), retained placenta (I), magnesium sulfate use (I), induction augmentation (I), chorioamnionitis (I)	Uterine atony	None	Good	-Uterine atony was recorded in a significantly higher proportion of Native Americans than non-native patients (9.6% vs 4.8%; [p=0.01]). -In univariate analysis, factors predicting uterine atony were native race (p=0.01), decreasing gravidity (p=0.02), induction augmentation (p=0.1), increasing birthweight (p=0.07), and chorioamnionitis (p=0.08). -In multivariable logistic regression analysis, Native American ethnic origin

											(OR 2.0, [1.1–3.7]) and increasing birthweight (OR 1.0, [1.0 1.0]) were significant predictors of uterine atony.
1861	deRavello, L et al	2015	Cross Sectional	Nationwide	229,986 American Indian and Alaska Native (AI/AN) women aged 15–44 years seeking care at Indian Health Service (IHS), Tribal, and urban Indian health facilities during 2002–2009, Indian Health Service National Patient Information Reporting System	229,986 (100%)	Maternal age (I), IHS region (C)	Ectopic pregnancy	None	Fair	-The ectopic pregnancy (EP) rate among AI/AN women was lowest in the 15–19 years age group (5.5 EPs per 1,000 pregnancies) and highest among 35–39 year old (18.7 EPs per 1,000 pregnancies). -Compared to AI/AN women aged 15-18 years, women aged 35-39 years were 3.4 times more likely to have an EP (RR 3.4, [2.90-4.03]). Compared to AI/AN women aged 15-18 years, the risk of an EP increased with age from 1.56-3.42, except in women aged 40-44 years were the risk was less at 2.62 times (RR 2.62, [2.02-3.36]). -EP rates varied by geographic region, ranging between 6.9 and 24.4 per 1,000 pregnancies in the Northern Plains East and the East region, respectively. -Compared to AI/AN women who received

										care in the Northern Plains East region, women who received care in the East region were 3.55 times more likely to have an EP (RR 3.55, [2.75-4.57]), in the Alaska region the risk was 2.17 times (RR 2.17, [1.73-2.72]), in the Southern plains region the risk was 1.56 times (RR 1.57, [1.25-1.95]), in the West region the risk was 1.39 times (RR 1.39, [1.09-1.77]), in the Norther Plains West region the risk was 1.36 times (1.36, [1.08-1.71]), and in the Southwest region the risk was lowest at 1.33 times (RR 1.33, [1.07-1.65]). -We found relatively stable annual rates of EP among AI/AN women receiving care at IHS-affiliated facilities during 2002–2009, but considerable variation by age group and geographic region.
2230	England, L et al.	2013	Case Control	Anchorage, AK	1,123 singleton deliveries from 1997-2005 to AN women residing in	1,123 (100%)	Continuous smokeless tobacco use (I) and continuous cigarette smoking (I)	Placental abruption, placental abruption expanded definition	Parity, pre-pregnancy BMI, maternal age	Good	-Thirty-nine percent of case deliveries were also preterm (compared with 7% of controls, [p<0.001]), and 9.8% were also complicated by pregnancy

					western Alaska, hospital administrative database					associated hypertension (compared with 7% of controls. [p=0.38]). -There were no significant associations between placental abruption and continuous smokeless tobacco use (aOR 1.11, [0.53-2.33] and continuous cigarette smoking (aOR 1.19, [0.43-3.29). -An expanded definition of abruption did not change this finding. There were no significant associations between continuous smokeless tobacco use (OR 1.07, [0.63-1.83]) or continuous cigarette smoking (aOR 1.04, [0.48-2.23]).

4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (C)	Disseminated intravascular coagulation (DIC), hysterectomy	Age, insurance payer, income, hospital region	Good	DIC -The incidence of DIC was greater but not significant among indigenous woman compared with white women (1.6% vs 0.9%, respectively) (aRR 1.1, [0.8-1.5]). -Within indigenous women, there was no difference between rural women and urban women (0.2% vs 0.2%, respectively) (aRR 0.8, [0.3-1.3]). Hysterectomy -The incidence of a hysterectomy was greater among indigenous woman compared with white women (0.1% vs 0.1%, respectively) (aRR 1.8, [1.0-2.6]). -Within indigenous women, there was a marginal increased risk but not significant of hysterectomy among rural women (aRR 1.3, [0.3-2.3]).

Appendix 4. Results of NIH quality assessments for included studies

For observational cohort and cross-sectional studies:

ID#	Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Yes %	Rating
119	Admon L, et al.	2018	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	NA	Yes	NR	NA	Yes	82%	Good
952	Booker W, et al.	2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	93%	Good
1178	Cameron, N. et al.	2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NA	No	83%	Good
1331	Chalouhi, S. et al.	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	No	92%	Good
1371	Chang, J et al	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	100%	Good
1861	deRavello, L. et al.	2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NA	No	83%	Good
3421	Interrante, J. et al.	2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	85%	Good
4010	Kozhimannil, K et al.	2020	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NR	NA	Yes	90%	Good
7372	Tiwari, R. et al	2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	92%	Good
8141	Zamora-Kapoor A., et al	2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	86%	Good

A study will be rated as “Good” if it receives a “Yes" response for ≥80% of the applicable NIH critical appraisal questions, “Fair” for 50%-79%, and “Poor” for ≤50%.

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).
Q1. Was the research question or objective in this paper clearly stated?
Q2. Was the study population clearly specified and defined?
Q3. Was the participation rate of eligible persons at least 50%?

Q4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
Q5. Was a sample size justification, power description, or variance and effect estimates provided?
Q6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
Q7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q10. Was the exposure(s) assessed more than once over time?
Q11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q12. Were the outcome assessors blinded to the exposure status of participants?
Q13. Was loss to follow-up after baseline 20% or less?
Q14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

For case-control studies:

ID#	Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Yes %	Rating
835	Best, L. et al	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	92%	Good
836	Best, L. et al.	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	92%	Good
837	Best, L et al.	2013	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	83%	Good
2230	England L, et al	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%	Good
2944	Hadley, M et al	2021	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	75%	Fair

A study will be rated as “Good” if it receives a “Yes" response for ≥80% of the applicable NIH critical appraisal questions, “Fair” for 50%-79%, and “Poor” for ≤50%.

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment of Case-Control Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools):
Q1. Was the research question or objective in this paper clearly stated and appropriate?
Q2. Was the study population clearly specified and defined?
Q3. Did the authors include a sample size justification?
Q4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
Q5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?
Q6. Were the cases clearly defined and differentiated from controls?
Q7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
Q8. Was there use of concurrent controls?
Q9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
Q10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
Q11. Were the assessors of exposure/risk blinded to the case or control status of participants?
Q12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Q, question; CD, cannot be determined; NA, not applicable; NR, not reported

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Individual and community level risk factors for maternal morbidity and mortality among Native American women in the United States: A systematic review

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TITLE

Individual and community level risk factors for maternal morbidity and mortality among Native American women in the United States: A systematic review

AUTHORS AND AFFILIATION

Martín F. Celaya[1,2], Alaa I. Zahlan[2], Chelsea Rock[3], Akshay Nathan[4], Aishwarya Acharya[2], Purnima Madhivanan[2], John Ehiri[2], Chengcheng Hu[2], Sydney Pettygrove[2], Velia Leybas Nuño[2]

1. Arizona Department of Health Services, Phoenix, Arizona, United States

2. Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona, United States

3. College of Health Solutions, Arizona State University, Phoenix, Arizona, United States

4. Boston University, Boston, Massachusetts, United States

AUTHORS' E-MAIL ADDRESSES

Martín F. Celaya, martin.celaya@azdhs.gov; Alaa I Zahlan, azahlan@arizona.edu; Chelsea Rock, chelsea.rock@azdhs.gov; Akshay Nathan, shayaknathan@gmail.com; Aishwarya Acharya, aishwaryaacharya@arizona.edu; Purnima Madhivanan, pmadhivanan@arizona.edu; John Ehiri, jehiri@arizona.edu; Chengcheng Hu, hucc@arizona.edu; Sydney Pettygrove, sydneyp@arizona.edu; Velia Leybas Nuño, vleybas@arizona.edu

SUBMITTING AND CORRESPONDING AUTHOR

Martín F. Celaya, martin.celaya@azdhs.gov

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Table 1. Outcomes of interest

Table 2. PubMed search strategy

Table 3. Summary of risk factors and outcomes by risk/association category

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Figure 1. PRISMA flow diagram

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Appendix 1. Search strategy by database

Appendix 2. Risk factors and outcomes by volume of studies

Appendix 3. Table of included studies

Appendix 4. Results of NIH Quality Assessments for included studies

KEYWORDS: American Indian or Alaska Native, Maternal Morbidity and Mortality, Risk Factors

ABSTRACT

Introduction and objective

Maternal morbidity and mortality (MMM) is a public health concern in the US, with Native American women experiencing higher rates than non-Hispanic White women. Research on risk factors for MMM among Native American women is limited. This systematic review comprehensively synthesizes and critically appraises the literature on risk factors for MMM experienced by Native American women.

Methods and analysis

A systematic search was conducted on 10 October 2022 in PubMed, Embase, CINAHL, and Scopus for articles published since 2012. Selection criteria included observational studies set in the US, involving Native American women in the perinatal period, and examining the relationship between risk factors and MMM outcomes. Three reviewers screened and extracted data from the included studies, with risk of bias assessed using National Institutes of Health quality assessment tools. Data were analyzed descriptively.

Results

Fifteen studies were included. All studies utilized administrative databases, with settings including nationwide (7 studies), statewide (4 studies), and Indian reservations (4 studies). The majority of studies focused on hypertensive disorders of pregnancy (8 studies) and severe maternal morbidity (SMM) (4 studies). Twenty-six risk factors were identified. Key risk factors included Native American race (6 studies), rural maternal residency (4 studies), overweight/obese body mass index (2 studies), maternal age (2 studies), nulliparity (2 studies), and preexisting medical conditions (1 study).

Conclusion

This review identified risk factors associated with MMM among Native American women, including rural residency, overweight or obesity, and advanced maternal age. However, the findings also reveal a scarcity of research specific to this population, limiting the ability to fully understand these risk factors and develop effective interventions. These results emphasize the need for further research and culturally relevant studies to inform public health and address disparities for Native American women, particularly those in rural areas.

PROSPERO registration number CRD42022363405.

ARTICLE SUMMARY

Strengths and limitations of this study

- The review searched a variety of scientific databases to identify a wide range of studies on maternal morbidity and mortality in Native American women in the United States.
- The review incorporated studies conducted on Indian reservations and within specific tribal health systems, providing insights tailored to the unique contexts and experiences of Native American women.
- The review synthesizes and critically appraises the limited existing literature on risk factors for maternal morbidity and mortality specifically among Native American women in the United States.
- Many included studies had small sample sizes or low percentages of Native American women, limiting the generalizability of the findings to this specific population.
- Included studies relied on administrative databases (i.e., hospital discharge database, vital recods registries, or electronic health records), which introduce potential reporting biases and misclassification issues, especially concerning the racial categorization of Native American participants.

INTRODUCTION

Maternal morbidity and mortality (MMM) are alarming public health problems in the United States (US). The Centers for Disease Control and Prevention (CDC) defines maternal mortality as the death of a woman during pregnancy, at delivery, or soon after delivery. [1] Severe maternal morbidity (SMM) refers to complications during labor and delivery with short- and long-term health consequences (e.g., sepsis, blood transfusion, preeclampsia, or hysterectomy). [2,3] The US has one of the highest maternal mortality ratios of any high-income country, reporting 26.4 maternal deaths per 100,000 live births.[4] In contrast, Finland has the lowest maternal mortality ratio of 3.8 deaths per 100,000 live births, a value nearly seven times lower that the U.S. [4] The SMM rate surged 75% from 1998-1999 to 129 per 10,000 delivery hospitalizations in 2008-2009.[2] Rising rates of blood transfusions, acute renal failure, shock, and other adverse outcomes primarily drove this increase.[2] The rising MMM rates involve complex interactions of factors at patients and families, providers or facilities, overall systems, and within the community at various points in a woman's reproductive life cylce. [5]

Significant racial and ethnic health inequities persist in maternal health. [6–9] Native American women are three to four times more likely to die than non-Hispanic White women from pregnancy-related complications and are three to five times more likely to experience SMM than non-Hispanic White women. [6,10,11] Historical trauma, racism, colonization, genocide, forced migration, reproductive coercion, and cultural erasure contribute to these adverse outcomes. [12–14] Native American women experience unique prolonged systemic barriers that create inequitable social conditions compared to other groups. [14–16] Some systemic barriers include limited access to providers and birthing facilities. [14,17,18] In addition, a history of forced

sterilization and forced infant and child separations has led to a strong distrust of the healthcare systems and providers, including the Indian Health Service. [19–21]

Rationale

A scoping review on Native American women and the leading causes of maternal mortality in the US identified risk factors like historical trauma, inequities in healthcare availability, access and utilization, preexisting health conditions, and rurality. [22] A separate review of social determinants on pregnancy-related mortality and morbidity identified that race was a significant factor. [3] However, the review did not provide a list of risk factors specific to Native American women, nor did it identify a study that evaluated maternal deaths among Native American women. [3] There is a need to explore further and assess the quality of research specific to MMM risk factors experienced by Native American women. Identifying this information can help identify areas for prevention focused on Native American communities.

Objective

To assess and critically appraise individual and community-level risk factors for pregnancy-related morbidity and mortality experienced by Native American women in the US.

METHODS

This systematic review follows a protocol previously published, which provides a comprehensive framework for examining pregnancy-related mortality and morbidity among Native American women. [23] Adhering to this pre-established protocol ensures methodological rigor and transparency, facilitating reproducibility and reliability in the findings presented.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination of this research.

Eligibility criteria

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Mata-Analyses (PRISMA) guidelines. [24] Inclusion criteria for studies were: 1) observational study design; 2) study set in the United States; 3) population was Native American women in the perinatal (i.e., the time surrounding childbirth) or puerperium period (i.e., the time after childbirth up to 6 weeks); 4) outcomes focused on measures of pregnancy-related mortality and morbidity; 5) examined the relationship between a risk factor/exposure and stated outcomes; and 6) had a publication date between 1 January 2012 and 10 October 2022. This timeframe aligns with a new standard for identifiying severe maternal morbidity published on 12 November 2012. [2] Studies focusing on a different population were included if they offered a stratified analysis by race and contained a racial category for Native Americans. Studies were excluded if: 1) studies focused only on birth, neonatal, or infant outcomes; 2) studies that did not examine the relationship between a risk factor/exposure and stated outcomes; 3) studies with settings outside of the United States; 4) studies that did not include findings for Native American women; 5) studies that focus on the preconception or postpartum phases; and 6) studies were published outside of the specified time.

Information sources and search strategy

The search was carried out on 10 October 2022. The review searched scientific databases (PubMed, Embase, CINAHL, and Scopus).. With technical assistance from a health sciences librarian, the team used search tools and strategies, including shortening keywords where

appropriate, using thesaurus terms, and using database-specific controlled vocabulary (e.g., Medical Subject Headings, MeSH). The search strategy combined terms and search strings with the appropriate Boolean operators. The complete search strategy is available in Appendix 1. Covidence was used to manage every stage of the systematic review, including screenings, data extractions, and risk of bias assessments. [25]

Selection process

Two independent reviewers screened titles and abstracts based on the eligibility criteria. If any disagreement occurred, a third reviewer arbitrated. After the titles and abstracts were screened, two independent reviewers screened full-text articles. The reasons for exclusion were noted at the full-text article stage.

Data collection process

Two independent reviewers extracted study details such as location, study design, eligibility criteria, methods, year of the article, year(s) of study, data source, objectives, sample size and population, independent (risk factors) and dependent (outcomes) variables, key findings, measures of effect/association with p-values and confidence intervals, and limitations. For any missing information, the lead author contacted the corresponding authors thrice via email or phone to request information. Any discrepancies within data extraction were reviewed and discussed in a team setting.

Data items

Primary outcomes of interest were maternal morbidity and mortality, including severe maternal morbidity (SMM) based on the CDC's list of 21 diagnoses and procedures (Table 1). [26]

Table 1 Outcomes of interest	
Mortality and near-misses	
Severe maternal morbidity diagnostic or procedural outcomes	Acute myocardial infarction Acute renal failure Adult respiratory Distress Syndrome Amniotic fluid embolism Aneurysm Cardiac arrest Disseminated intravascular coagulation Eclampsia Heart failure Puerperal cerebrovascular disorders Pulmonary edema Sepsis Severe anesthesia complications Shock Sickle cell anemia with crisis Thrombotic embolism Blood transfusion Conversion of cardiac rhythm Hysterectomy Temporary tracheostomy Ventilation
Additional morbidity outcomes	Postpartum hemorrhage Ectopic pregnancy Placental abruption Uterine atony

This list was used to identify additional articles that did not utilize a composite outcome of severe maternal morbidity or mortality. Given the scope of this review, the terms "pregnancy complications," "obstetric complications," "labor complications," and "near-miss" were added to the list of outcomes to increase the sensitivity of the review. Pregnancy, labor, and obstetric complications encompass conditions occurring during or after pregnancy, ranging from minor discomforts to severe diseases requiring medical intervention, including both pregnancy-related conditions and preexisting diseases in pregnant women.[27] A near-miss refers to a life-threatening event that does not result in death.[28] The search strategy was pilot-tested in

PubMed, finalized, and adapted to other databases (Table 2). The complete search strategy is available in Appendix 1. The results from each database-specific search strategy were downloaded from the respective databases and uploaded to the EndNote software. [29] After removing the duplicates, the citations were imported into Covidence.

Table 2 PubMed search strategy

#1 birth[tiab] OR labor[tiab] OR delivery[tiab] OR mothers[tiab] OR maternal[tiab] OR "peripartum period"[mesh] OR peripartum[tiab] OR "labor, obstetric"[mesh] OR "obstetric*"[mesh] OR "obstetric*"[tiab] OR "pregnancy"[mesh] OR "pregnan*"[tiab] OR "perinatal"[tiab] OR "prenatal"[tiab] OR "parturition"[mesh] OR "parturition"[tiab]
#2 "tribal" OR "tribe" OR "first nations" OR "indigenous peoples"[mesh] OR indigenous OR "health services, indigenous"[mesh] OR "american indians or alaska natives"[mesh] OR "american indian*" OR "indians, north american"[mesh] OR "native American" OR "alaska native"
#3 "severe maternal morbidity" OR "near miss" OR "adverse maternal outcomes" OR "maternal mortality" OR "Near Miss, Healthcare"[Mesh] OR "Pregnancy/Adverse Effects"[Mesh] OR "Pregnancy/Injuries"[Mesh] OR "Pregnancy/Mortality"[Mesh] OR "Pregnancy/complications"[Mesh] OR "Obstetric Labor Complications"[Mesh] OR "Delivery, Obstetric/adverse effects"[Mesh] OR "Delivery, Obstetric/complications"[Mesh] OR "Delivery, Obstetric/mortality"[Mesh] OR "Maternal Mortality"[Mesh] OR "mortality"[mesh] OR "morbidity"[mesh] OR "pregnancy complications" OR mortality OR morbidity OR "labor complications" OR "delivery complications"

#4 Search (#1 AND #2 AND #3)

Study risk of bias assessment and certainty assessment

Risk of bias was assessed using the NIH's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case-Control Studies to examine critical concepts for each study's validity. [30] Two independent reviewers assessed articles using the tool's criteria and rated them as "good," "fair," or "poor" quality. This rating was based on the percentage of "Yes" responses out of the total applicable questions in each tool. A study will be rated as "good" if it receives a "Yes" response for ≥80% of the applicable NIH critical appraisal questions, "fair" for 50%-79%, and "poor" for ≤49%. A "good" rating meant there was the least risk of bias, and the results were considered valid. [30] A "fair" rating indicated susceptibility to some bias but was insufficient to invalidate its results and would vary in their strengths and weaknesses. [30] A "poor" rating indicated a significant risk of bias and invalidated its results. [30] When the ratings differed, a third reviewer arbitrated an article's rating.

Effect measures

Measures of effect such as risk and odds ratios with 95% confidence intervals were extracted. Descriptive statistics like prevalence and incidence were also included.

Potential overlap in cohorts

Given the research scarcity on the population of interest and topic mentioned in this article, we attempted to manage for potential overlap in populations across different cohorts in the included studies. Several strategies were used to manage any potential overlap and ensure the integrity and accuracy of the findings: 1) data sources for cohorts were meticulously documented,

including specific populations covered by each study; 2) cohorts were often segmented by geographic regions and demographic characteristics relevant to Native American women and; 3) assessed study periods to identify and address any potential overlap in cohorts.

Synthesis methods

Appendix 2 provides a summary of study findings, including risk factors, outcomes, and study characteristics. A descriptive synthesis was used due to the diversity in study designs, risk factors, and outcomes, which precluded quantitative analysis. Risk factors were organized by socioecological levels (individual, family, community, society, or systems) and grouped by outcome. [31] For each risk factor, the table reports the number of studies analyzing it, and whether the effect was statistically significant.

[INSERT FIGURE 1]

RESULTS

Study Selection and study characteristics

A total of 8,220 articles were identified, of which 357 duplicates were removed, resulting in 7,863 articles for screening (Figure 1). During the screening process, there were 6,967 agreements for inclusion and 896 conflicts resolved by an arbitrator, for an overall percent agreement of 88.6%. The selection process yielded 145 articles, of which 15 were included in the review. [10,11,32–41] The most common reasons for study exclusion were: the wrong patient population (41 studies), the wrong setting (22 studies), and the wrong type of publication (21 studies). Most (80.0%) studies used secondary data sources (i.e. hospital discharge records, vital records, as such) to examine associations between risk factors and outcomes. There was an equal

number of studies across three study designs (5 studies each). The sample size across all studies ranged from 196 to 51,685,525 with a mean sample size of 4,479,962, a median of 72,697, a standard deviation of 12,732,821.6, and an interquartile range of 2,123,375.0. Seven studies focused primarily on Native American women (i.e., the study sample comprised mainly of Native American women).[34–36,38–40,42] The remaining eight studies included Native American women as a subgroup in their sample.[10,11,32,33,37,41,43,44] Of these eight studies, the percentage of Native American women that were part of the overall sample ranged from 0.4% to 10.1%, and six of these studies had a proportion of Native American women in their sample that was ≤ 1.4%. The total number of Native American participants across all studies ranged from 196 to 492,771 with a mean of 57,266.5, a median of 7,107, a standard deviation of 129,234.2, and an interquartile range of 26,817.0. Study settings included nationwide (7/15 studies) [10,11,37,38,41,43,44] , statewide (4/15 studies) [32,33,39,40], and on Indian reservations (4/15 studies) [34–36,42].

Risk of bias in studies

Fourteen studies were rated as "good" and one was rated as "fair" according to the NIH's Study Quality Assessment Tools. See Appendix 4 for individual assessments of quality. All cohort and cross-sectional studies were rated "good." [11,32,33,37,38,41–45] Most studies did not assess the exposure more than once over time (7/10 studies). [32,33,37,41–43,45] A smaller proportion were unable to demonstrate that the exposure of interest was measured before the outcome being measured (5/10 studies) [11,38,41,44,45] or did not adjust models to include potential confounders to assess their impact on the relationship between exposure(s) and outcome(s) (3/10 studies).[38,42,44] The reviewers were unable to find evidence in some studies if the outcome assessors were blinded to the exposure status of participants (3/10 studies) [11,38,44] or whether

there was a loss to follow-up amongst the cohort studies (3/5 studies). [32,37,42] Amongst the case-control studies, four were rated as "good" [34–36,39] while one was rated as "fair." [40] The reviewers ascertained that some studies failed to provide a sample size justification (3/5 studies) [34–36] or did not randomly select cases and/or controls from the eligible study population (2/5 studies). [35,40]

Results of individual studies and syntheses

Nine outcomes were identified in the studies: hypertensive disorders of pregnancy (preeclampsia, severe preeclampsia, gestational hypertension, and hypertensive disorders of pregnancy), blood transfusions, postpartum hemorrhage, disseminated intravascular coagulation (DIC), hysterectomy, ectopic pregnancy, uterine atony, placental abruption, and SMM with mortality as a composite outcome. Twenty-six risk factors were identified, 24 of these were individual risk factors while two were community risk factors. No studies examined interpersonal/relationship or societal levels risk factors.

Appendix 2 lists the frequency by which each risk factor and outcome was studied in the literature. A majority of studies examined "hypertensive disorders of pregnancy" (8/15 studies) [32–37,39,44] and "severe maternal morbidity and/or mortality" (4/15 studies) [10,11,41,43] as outcomes. A majority of studies examined body mass index (BMI) (6/15 studies) [32–36,40], maternal age (6/15 studies) [34–38,42] , maternal race (5/15 studies) [10,33,41–43], and parity (5/15 studies) [34–36,40,42] as risk factors for various outcomes. Table 3 is a summary table that reports the number of studies grouped by outcome, the risk factors examined for associations, and the direction of those associations. Appendix 3 summarizes additional details on study design, sample size, and data sources, exposures and outcome variables, covariates, key findings, including the measures of effect and study quality ratings.

Table 3. Summary of risk factors and outcomes by risk/association category*

Outcome	↑Increased risk or positive association	—No association	↓Decreased risk or negative association
Hypertensive disorders of pregnancy (8 studies)			
Pregnancy-induced hypertension	***Rural maternal residency***[1178] Maternal age 35 years or older and smoked during pregnancy[1371]	Continuous smokeless tobacco use[2230] Continuous cigarette smoking[2230]	***Maternal age<35 years and smoked during pregnancy***[1371]
Pre-eclampsia	Native American maternal race[8141] ***Overweight/obese BMI***[7372, 835, 836, 837] ***Age at delivery***[835,836] ***Nulliparity***[835, 836, 837] Gestational diabetes[837] Genetic factors (Single Neuclotide Polymorphisms, SNPs) CRP_A, rs3093077, (T allele additive)[836] MBL2, rs1800451, (T allele dominant)[836] IL1A, rs3273550, (T allele dominant)[836] CTLA4, rs21775, (A allele dominant)[836] CRP, rs3093068, (G allele additive)[837] CRP, rs3093068, (G allele dominant)[837] CRP, rs876538, (C allele additive)[837] CRP, rs876538, (C allele recessive)[837] NOS3, rs1799983 (G allele recessive)[835] DDAH1, rs10158674 (C allele recessive)[835] DDAH1, rs233115 (A allele recessive)[835]	Continuous smokeless tobacco use[2230] Continuous cigarette smoking[2230] Age at delivery[837] BMI[8141] Genetic factors (SNPs) GNB3, rs5442 (A allele dominant)[835]	Genetic factors (SNPs) CRP_B, rs1205, (A allele dom)[836] CRP_C, rs1130864, (T allele dom)[836] CRP, rs876538, (C allele dominant)[837] NOS3, rs3918227 (A allele dominant)[835]

Severe pre-eclampsia	***Nulliparity[836, 837]*** ***Obese BMI[836,837]*** Age at delivery[836] Gestational diabetes[837] Genetic factors (SNPs) MBL2, rs1800451, (T allele dominant)[836] IL1A, rs3273550, (T allele dominant)[836] CTLA4, rs21775, (A allele dominant)[836] CRP, rs3093068, (G allele additive)[837] ***CRP, rs3093068, (G allele dominant)[837]*** CRP, rs876538, (C allele additive)[837] CRP, rs876538, (C allele recessive)[837]	Age at delivery[837]	Genetic factors (SNPs) CRP_A, rs3093077, (T allele additive)[836] ***CRP_B, rs1205, (A allele dom)[836]*** CRP_C, rs1130864, (T allele dom)[836] CRP, rs876538, (C allele dominant)[837]
Severe Maternal Morbidity and/or Mortality (4 studies)			
Severe maternal morbidity (SMM) with transfusions	***Native American maternal race[119]*** ***Any physical health condition[119]*** Any behavioral health condition[119] Multiple chronic conditions (2 or more)[119]	Native American maternal race[952]	
Severe maternal morbidity without transfusions		Native American maternal race[119] Rural maternal residency[4010]	
Severe maternal morbidity and mortality (SMMM)	***Rural maternal residency[3421]*** ***Native American race[4010]*** ***Medicaid funded births[3421]***	Urban maternal residency[3421]	
Blood Transfusions (2 studies)			
Blood transfusions	***Rural maternal residency[3421, 4010]*** ***Medicaid-funded births[3421]*** ***Native American maternal race[4010]***		
Postpartum Hemorrhage (2 studies)			
Postpartum hemorrhagePostpartum hemorrhage	***Native American Maternal race[1331]*** ***Gravidity<5[1131]*** ***Birthweight>4500g[1131]*** ***Retained placenta[1131]*** ***Magnesium sulfate use[1131, 2944]*** ***Antepartum bleeding[2944]*** ***Previous postpartum hemorrhage[2944]*** ***Third stage of labor≥20m[2944]*** ***Maternal rural residence[2944]*** ***Fetal macrosomia[2944]*** ***Oxytocin use>12h[2944]*** Routine aspirin use[2944] Prior uterine incision and vaginal delivery[2944]	Prior uterine incision[2944] BMI≥40[2944] Vitamin D supplementation[2944]	

	Pre-eclampsia without severe features without use of magnesium sulfate[2944] Parity≥5[2944] Length of second stage of labor≥ 1h[2944] Inpatient induction length≥ to 36h[2944]		
Other Outcomes (4 studies)			
Uterine atony	***Native American maternal race[1331]*** ***Birthweight>4500g[1331]***	Gravidity<5[1331] Induction augmentation[1331] Chorioamnionitis[1331]	
Ectopic pregnancy	***Maternal age≥19 years[1861]*** ***Indian Health Service region[1861]***		
Placental abruption	Continuous use of smokeless tobacco[2230] Continuous cigarette smoking[2230]		
Disseminated intravascular coagulation	Native American race[4010]	Rural maternal residency[4010]	
Hysterectomy	***Native American race[4010]*** Rural maternal residency[4010]		

*BMI, body mass index; h, hours; m, minutes; significant associations are italicized and bolded, significant association in the same direction as categorized

Specific to hypertensive disorders of pregnancy, having a rural residency (1/1 studies), an overweight or obese BMI (4/5 studies), age above 35 years also referred to as "advanced maternal age" (1/4 studies), and nulliparity (3/3 studies) were significantly associated with increased risk. [32,34–36,44] Genetic predispositions to hypertensive disorders of pregnancy were not significantly associated with increased risk (3/3 studies). [34–36] Studies that focused on SMMM identified being of Native American race (2/3 studies), having a physical health condition (1/1 study), a rural residency (1/2 studies), and births primarly paid by Medicaid (i.e., public government insurance) (1/1 study) as significantly associated with increased risk. The risk of blood transfusions was significantly associated with Native American race (1/1 study), rural residency (2/2 studies), and Medicaid-funded births (1/1 study). [10,11,41] Postpartum hemorrhage risk was significantly associated with being of Native American race when compared to other racial/ethnic groups, a gravidity ≤5, a birthweight of 4500g, having a retained

placenta, magnesium sulfate use (2/2 studies), antepartum bleeding, previous postpartum hemorrhage, being in third stage labor greater than 20 minutes, maternal rural residency, fetal macrosomia, and oxytocin use for longer than 12 hours. [40,42] Other outcomes are further described in Appendix 3.

This systematic review identified several factors related to maternal health among Native American women, including some that did not align with findings from other populations. For example, continuous smokeless tobacco use and cigaerrete smoking were found to have no significant association with pregnancy-induced hypertension in one study. [39] A separate study identified that women under 35 had a decreased risk of hypertensive disorders of pregnancy compared to those older than 35. [42] One study found no association between hypertensive disorders of pregnancy (e.g., preeclampsia) and having an overweight/obese BMI. [33] Genetic factors also demonstrated varying outcomes. One study identified that the CRP_B, rs1205 Single Nucleotide Polymophisms (SNPs) (A allele dominant) was associated with a decreased risk for pre-eclampsia while another study found the CRP rs3093068 SNP (G allele dominant) linked to an increased risk. [34,35] Other SNPs examined in these studies showed no sinigiifcant association with preeclampsia or other an increased risk while other SNPs showed no association or relationship. [34,35] In contrast to other studies, Native American race and rural residency were not assicated with severe maternal morbidity and/or mortality in three distinct studies. [10,41,43]. Another study found no significant association between uterine atony and factors such as high gravidity, induction augmentation, or chorioamnionitis. Interestingly, rural residency also did not appear to increase the risk of disseminated intravascular coagulation[10,40,42].

Reporting biases and certainty of evidence

All studies relied on administrative data sources to assess outcomes and exposures simultaneously, and all noted this as a considerable limitation in their study design. Four studies noted concerns with small sample sizes, missing exposure and outcome data, and critical demographic information that may have led to misclassification bias. Two studies considered reporting bias in their study designs, while almost all studies (14/15 studies) referred to the misidentification of Native American women based on predetermined guidelines for race designation.

DISCUSSION

This systematic review synthesized the literature by conducting a broad search of outcomes associated with maternal morbidity and mortality and identifying their associated risk factors for Native American women in the US. Despite the importance of understanding these outcomes for this population, we found a limited number of studies addressing these critical issues. All fifteen studies identified risk factors at the individual level, suggesting that an overweight or obese BMI, advanced maternal age (35 years or older) in certain situations, parity, and rural maternal residency are associated with Native American maternal morbidity or mortality. Few studies contradicted these findings and demonstrated no association with Native American race, rural maternal residency, or advanced maternal age. One study found no association with hypertensive disorders of pregnancy, including pregnancy-induced hypertension, preeclampsia, and severe preeclampsia with continuous smokeless tobacco use or continuous cigarette smoking. [39]

While advanced maternal age is often associated with higher risks for adverse maternal health otucomes in other populations, this review found both consistent and nuanced findings among Native American women. Specifically, advanced maternal age was associated with a higher risk of hypertensive disorders, including pregnancy-induced hypertension, especially among those

who smoked during pregnancy. However, two studies found no significant association between age at delivery and preeclampsia in this population. These results suggest that while advanced age can be a risk factor for some outcomes, such as hypertension, it may not uniformly affect all maternal health conditions. This could also indicate the presence of potential protective factors or differences in health profiles among Native American women that merit further investigation. Conversely, the higher risk of morbidities among public governmental health insurance (i.e., Medicare or Medicaid) recipients is concerning and suggests a need for targeted interventions within this subgroup. Studies showed that rural Native American Medicaid-funded births had the highest adjusted rate of severe maternal morbidity and mortality, indicating potential disparities in healthcare quality and access.[41,46]

Studies assessing the relationship between genetic factors and preeclampsia or severe preeclampsia were completed in an Indian Reservation within a specific tribal health system.[34–36] These studies uncovered that there were only two associations between genetic expression and preeclampsia for Native American women among those studies. These studies concurred that many of the risk factors, such as maternal age, nulliparity, and obesity, that are associated with preeclampsia and severe preeclampsia in other populations were also operative in Native American communities.[34–36]

At the community level, our review identified four studies that included risk factors such as maternal residency and the Indian Health Service Region. This limitation further indicates the need to expand research to identify and understand the role of community and society-level risk factors. Social determinants of health, such as access to behavioral and primary care services, housing, crime and violence, and health policies, have been demonstrated to contribute directly to maternal mortality and morbidity in more extensive population studies.[47] Studies

highlighted the higher incidence of SMM and mortality among rural Native American women compared to their urban counterparts, emphasizing the critical impact of geographic and systemic disparities. [40,42,45]

This review did not find information on prenatal care utilization and its association with maternal morbidity or mortality despite strong evidence supporting adequate prenatal care utilization in culturally competent healthcare institutions.[15,48,49] Early and adequate prenatal care is thought to promote healthy pregnancies through screening and managing a woman's risk factors and health conditions and promote healthy behaviors during pregnancy.[6]

This review did not consider the effects of historical trauma, discrimination, and racism, which are significant health determinants for Native Americans.[17] These experiences contribute to health deterioration over time, as explained by the weathering hypothesis, which suggests that cumulative stress from racism and socioeconomic disadvantages leads to worse health outcomes.[13]

Appraisal

Most studies were rated as "good" (14/15 studies), while one was rated as "fair." Despite this, we were able to highlight the methodological shortcomings of some of the studies, such as the failure to assess the exposure more than once over time, the inability to demonstrate that exposure was measured before outcome measurement, or not adjusting models to include potential confounders. Additionally, some studies failed to provide sample size justification or did not randomly select cases or controls from the eligible study population, posing bias risks.

We identified additional shortcomings in the available evidence. Racial/ethnic misclassification on administrative databases led to challenges with underreporting and further affected the

selection of study participants. Given the small percentage of Native American births in the United States, which is only 0.7%, minor errors in misclassification can significantly impact data analysis.[50] Multiple studies in this review reported small sample sizes, making it difficult to determine if a particular outcome was a true finding, possibly allowing for type II errors. Among studies that included samples that were not fully Native American, most reported a Native American sample size of ≤ 1.4%. The limited research in these communities hinders the identification of additional risk factors for morbidity and mortality specific to Native American women.[51] The measurement of maternal morbidity and mortality varied across the studies. This review used a broader definition of these outcomes, including conditions not listed by the CDC as severe maternal morbidity. This approach aimed to provide a complete understanding of the risk factors and health outcomes specific to Native American women. Lastly, relying heavily on administrative data presents unique challenges in identifying risk factors not traditionally included in these datasets, as their primary purpose may not align with the study's hypothesis.[52]

Strengths and limitations

Our systematic review faced some limitations despite our use of an expansive search strategy informed by other published reviews.[3,53] We were unable to translate all MesH terms into indexed language for other databases. There is also a risk of publication bias and selective reporting of significant findings in the studies. Using NIH's quality assessment tools, which are not independently published nor standardized may introduce bias due to the qualitative nature of the review. Despite this, other systematic reviews have built the evidence supporting the utility and practicality of utilizing this tool. [3] Furthermore, the review revealed significant variation in the risk factors and outcomes across different studies. This highlights the complexity and

heterogeneity of maternal health issues among Native American women. This variation presents a challenge in drawing definitive conclusions.

Despite these limitations, this systematic review is one of the few that identifies risk factors for severe maternal morbidity and mortality among Native American women in the US. The review addresses a critical gap in the literature by focusing on this historically marginalized and underserved population, providing valuable insights for targeted public health interventions and policies. Including various study designs allows for a more comprehensive understanding of the associated risk factors and outcomes. We comprehensively reviewed the current literature using multiple search strategies incorporating the CDC's list of procedural and diagnoses for SMM. This systematic review utilized recommended language to identify research in Native American communities following the National Library of Medicine guidance. [54] Rigorous quality assessment tools were employed to evaluate the methodological quality of the included studies, ensuring that the findings are based on reliable and valid evidence. Additionally, organizing the identified risk factors into socioecological levels provides a structured approach to understanding the complex interplay of factors influencing maternal health in Native American communities.

Implications for practice, policy, and future research

Our review demonstrates the lack of attention reflected in the scarcity of evidence available to understand this public health crisis among a population that is often ignored. The limited type of risk factors studied, the study designs, settings, and outcomes limit the ability of healthcare and public health organizations to properly design and implement tailored approaches to reduce disparities in this community further. Public health initiatives must prioritize culturally competent care and address the unique challenges faced by Native American women to mitigate the risks of maternal morbidity and mortality. By acknowledging and addressing these gaps in

the literature, public health can better inform policy, enhance clinical practices, and ultimately improve health outcomes for Native American mothers and their families.

OTHER INFORMATION

Registration and protocol: The registration and protocol information for this review can be accessed at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=363405, identifier: CRD42022363405. No amendments were submitted during implementation of the protocol.

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Competing interests: None declared by all authors.

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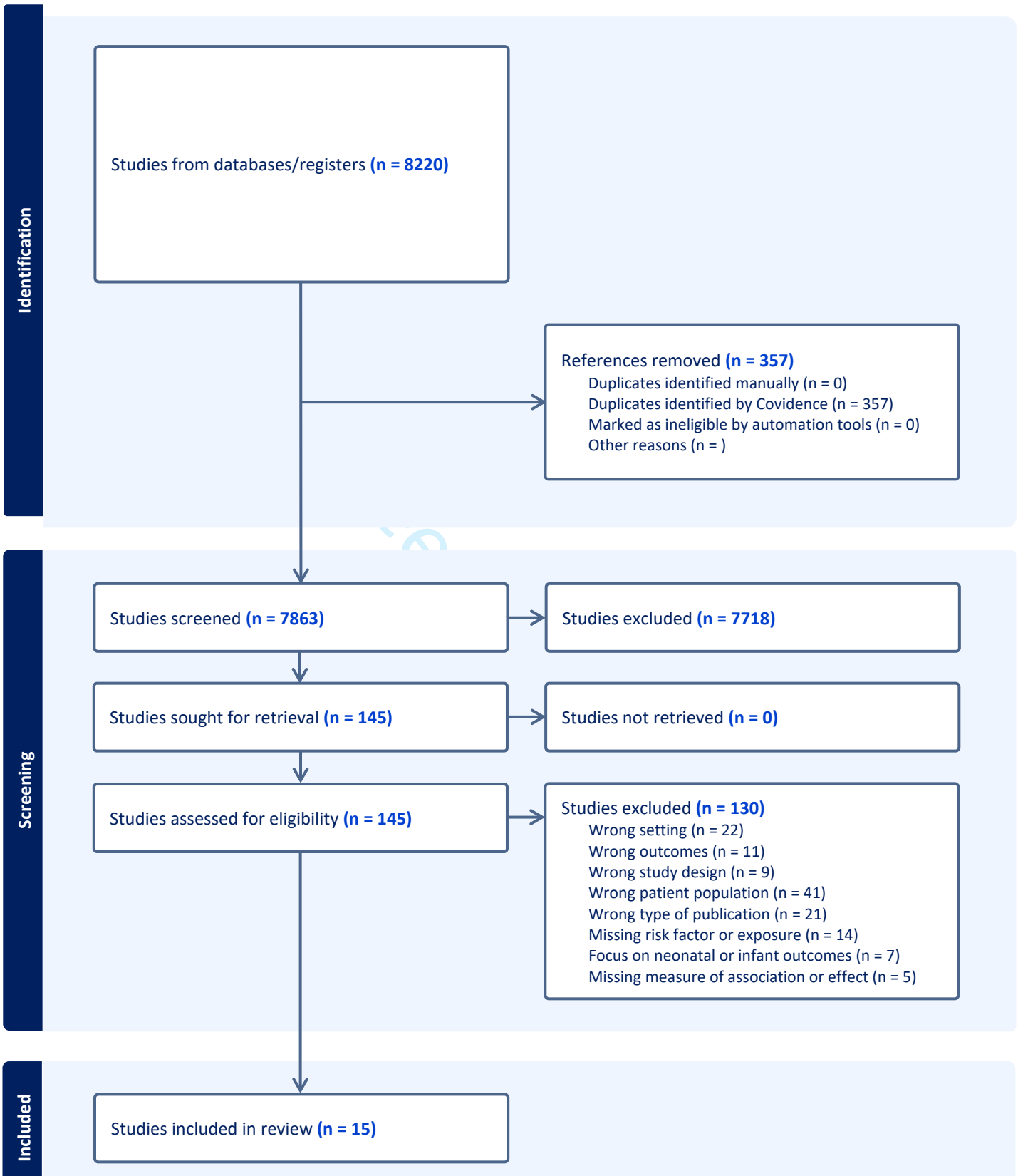
Figure Legend:

Figure 1 - PRISMA flow diagram

Individual and community level risk factors for maternal morbidity and mortality among Native American women in the United States



Appendix 1. Search strategy by database

PubMed Search Strategy

#1 birth[tiab] OR labor[tiab] OR delivery[tiab] OR mothers[tiab] OR maternal[tiab] OR "peripartum period"[mesh] OR peripartum[tiab] OR "labor, obstetric"[mesh] OR "obstetric*"[mesh] OR "obstetric*"[tiab] OR "pregnancy"[mesh] OR "pregnan*"[tiab] OR "perinatal"[tiab] OR "prenatal"[tiab] OR "parturition"[mesh] OR "parturition"[tiab]

#2 "tribal" OR "tribe" OR "first nations" OR "indigenous peoples"[mesh] OR indigenous OR "health services, indigenous"[mesh] OR "american indians or alaska natives"[mesh] OR "american indian*" OR "indians, north american"[mesh] OR "native American" OR "alaska native"

#3 "severe maternal morbidity" OR "near miss" OR "adverse maternal outcomes" OR "maternal mortality" OR "Near Miss, Healthcare"[Mesh] OR "Pregnancy/Adverse Effects"[Mesh] OR "Pregnancy/Injuries"[Mesh] OR "Pregnancy/Mortality"[Mesh] OR "Pregnancy/complications"[Mesh] OR "Obstetric Labor Complications"[Mesh] OR "Delivery, Obstetric/adverse effects"[Mesh] OR "Delivery, Obstetric/complications"[Mesh] OR "Delivery, Obstetric/mortality"[Mesh] OR "Maternal Mortality"[Mesh] OR "mortality"[mesh] OR "morbidity"[mesh] OR "pregnancy complications" OR mortality OR morbidity OR "labor complications" OR "delivery complications"

#4 Search (#1 AND #2 AND #3)

EMBASE Search Strategy

('delivery:ab,ti' OR 'birth:ab,ti' OR 'labor:ab,ti' OR 'mothers':ab,ti OR 'maternal':ab,ti OR 'peripartum':ab,ti OR 'obstetric':ab,ti OR 'pregnancy':ab,ti OR 'perinatal':ab,ti OR 'prenatal':ab,ti OR 'parturition':ab,ti OR 'perinatal period'/exp OR 'labor'/exp OR 'pregnancy'/exp OR 'birth'/exp)

AND

(tribe OR 'indian health service' OR indigenous OR tribal OR 'first nations' OR 'american indian' OR 'native american' OR 'alaska native' OR 'indigenous people'/exp OR 'indigenous health care'/exp OR 'american indian'/exp)

AND

('severe maternal morbidity' OR 'adverse maternal outcomes' OR 'maternal mortality' OR 'pregnancy complications' OR 'mortality' OR 'morbidity' OR 'labor complications' OR 'delivery complications' OR 'near miss (health care)'/exp OR 'near miss' OR 'pregnancy complication'/exp OR 'maternal mortality'/exp OR 'labor complication'/exp OR 'maternal outcome'/exp OR 'delivery complications'/exp OR 'maternal morbidity'/exp OR 'morbidity'/exp OR 'mortality'/exp)

CINAHL Search Strategy

((TI delivery OR AB delivery) OR (TI birth OR AB birth) OR (TI labor OR AB labor) OR (TI mothers OR AB mothers) OR (TI maternal OR AB maternal) OR (TI peripartum OR AB peripartum) OR (TI obstetrics OR AB obstetrics) OR (TI pregnancy OR AB pregnancy) OR (TI perinatal OR AB perinatal) OR (TI prenatal OR AB prenatal) OR (TI parturition OR AB parturition) OR (TI delivery OR AB delivery) OR MM "Perinatal Period" OR MM "Obstetric Patients" OR MM "Delivery, Obstetric+" OR MM "Pregnancy+" OR MM "Labor+" OR MM "Obstetrics+" OR MM "Childbirth+")

AND

(tribe OR "indian health service" OR Indigenous OR "native american" OR "american indian" OR Tribal OR "first nations people" OR "alaska native" OR MM "Indigenous Peoples+" OR MM "Health Services, Indigenous" OR MM "Native Americans+")

AND

("severe maternal morbidity" OR "near miss" OR "pregnancy complications" OR "obstetric complications" OR mortality OR morbidity OR "maternal mortality" OR "maternal morbidity" OR "delivery complications" OR MM "near-death experiences" OR MM "maternal mortality" OR MM "obstetric emergencies" OR MM "Pregnancy Complications+" OR MM "labor complications" OR MM "maternal mortality" OR MM "morbidity+" OR MM "mortality+")

SCOPUS Search Strategy

("severe maternal morbidity" OR "near miss" OR "pregnancy complications" OR mortality OR morbidity OR "labor complications" OR "delivery complications" OR "maternal mortality" OR "maternal morbidity" OR "obstetric complications")

AND

(indigenous OR "native american" OR "american indian" OR tribal OR "alaska native" OR "first nations" OR tribe OR "indian health service")

AND

(TITLE-ABS (mother) OR TITLE-ABS (maternal) OR TITLE-ABS (peripartum) OR TITLE-ABS (obstetric) OR TITLE-ABS (pregnancy) OR TITLE-ABS (perinatal) OR TITLE-ABS (prenatal) OR TITLE-ABS (parturition) OR TITLE-ABS (labor) OR TITLE-ABS (birth) OR TITLE-ABS (delivery))

Appendix 2. Risk Factors and Outcomes by Volume of Studies

	Outcome*									
Risk Factor	**SMMM**	**HDP†**	**BT**	**PPH**	**DIC**	**Hyst**	**EP**	**UA**	**PA**	**No. of Studies Examining Each Risk Factor$^{\alpha}$**
Body mass index		5		1			1	1		7
Age		4		1			1	1		6
Maternal race	3	1	2	1	1	1		1		5
Parity		3		1				1		5
Maternal residence	2	1	2		1	1				3
Gene expressions		3								3
Tobacco use		2							1	2
Birth primary payer type	1		1							1
Magnesium Sulfate use				2				1		2
Inpatient induction				2				1		2
Augmentation				1				1		1
Birthweight				1				1		1
Physical health/ chronic health status	1									1
Gestational diabetes		1								1
Behavioral health status (depression or substance use disorder)	1									1
Indian Health Service region							1			1
Gravidity					1			1		1
Routine aspirin use				1						1
Prior uterine incision or vaginal birth after cesarean				1						1
Macrosomia				1						1
Antepartum Bleeding				1						1
Previous PPH				1						1
Length of labor				1						1
Oxytocin use				1						1
Chorioamnionitis				1				1		1
Retained placenta				1				1		1
No. of Studies Examining Each Outcome$^{\alpha}$	4	8	2	2	2	1	1	1	1	15

*Severe maternal morbidity and mortality (SMMM), hypertensive disorders of pregnancy (HDP), blood transfusion (BT), postpartum hemorrhage (PPH), disseminated intravascular coagulation (DIC), hysterectomy (Hyst), ectopic pregnancy (EP), uterine atony (UA), and placental abruption (PA), blank cells represent no studies found. † The HDP category includes pre-eclampsia, severe pre-eclampsia, gestational hypertension, and hypertensive disorders of pregnancy. α Row and column figures do not represent totals since a study can include multiple risk factors or outcomes.

Appendix 3. Table of included studies

Study #	Authors	Year	Study Design	Location	Sample Size, Data Source	Native American subsample size (% of total sample)	Risk Factor (Social ecological level)	Outcome(s)	Covariates	Quality Rating	Key Findings ([95% Confidence Intervals] unless otherwise stated
Hypertensive Disorders of Pregnancy (8)											
1178	Cameron, N et al.	2022	Cross Sectional	Nationwide	51,685,525 all live births in the US to individuals aged 15-44 years, birth vital records	492,771 (9.3%)	Maternal residence (C)	Pregnancy induced hypertension	None	Good	-The incidence of hypertensive disorders of pregnancy differed by racial and ethnic identity within both rural and urban areas. The highest age-adjusted incidence of hypertensive disorders of pregnancy was observed among individuals who identify as American Indian/ Alaskan Native. -Significant increase in the incidence of hypertension disorders of pregnancy among Native American women in rural areas compared to those in urban areas in 2007 and 2014 (2017 RR=1.21, [1.11-1.33] and 2014 RR=1.17, [1.08-1.13]) -No significant increase in the incidence of hypertension disorders of pregnancy among

										Native American women living in rural areas compared to those in urban areas was observed in 2019 (2019 RR=1.03, [0.96-1.11])
2230	England, L et al.	2013	Case Control	Anchorage, AK	1,123 singleton deliveries from 1997-2005 to AN women residing in western Alaska, hospital administrative database / 503 cases and 502 controls	1,123 (100%)	Continuous smokeless tobacco use (I) and continuous cigarette smoking (I)	Pregnancy associated hypertension, pre-eclampsia, and gestational hypertension	Parity, pre-pregnancy BMI, maternal age	Good	-No significant associations were observed between smokeless tobacco use and pregnancy-associated hypertension (aOR 0.92, [0.56–1.51]). -No significant associations were observed between smokeless tobacco use and pre-eclampsia (aOR 0.90, [0.52–1.56]). -No significant associations were observed between smokeless tobacco use and gestational hypertension (aOR 0.93, [0.42–2.03). -No significant associations were observed between continuous cigarette smoking and pregnancy-associated hypertension (aOR 0.65, [0.31–1.37]). -No significant associations were observed between

										continuous cigarette smoking and pre-eclampsia (aOR 0.69, [0.30–1.58]). -No significant associations were observed between continuous cigarette smoking and gestational hypertension (aOR 0.52, [0.14–1.90).
8141	Zamora-Kapoor, A et al.	2016	Cohort	Washington State	71,080 singleton live births from 2003-2013 to Whit and AI/AN women, linked birth-hospital discharge records	7,189 (10.1%)	Maternal race (I), BMI (I)	Pre-eclampsia	Birth year, maternal age, educational attainment, marital status, Medicaid insurance, WIC participation, prenatal smoking, BMI	Good	-AI/ANs had an increased risk of pre-eclampsia compared to Whites after controlling for all covariates except BMI (OR 1.17 [1.06–1.29]). After further adjustment for BMI, the racial disparity in pre-eclampsia risk was greatly attenuated (aOR 1.05, [0.95–1.16]). -AI/ANs who were underweight (OR 1.39, [0.64-3.02]), normal weight (OR 1.02, [0.83-1.22]), overweight (OR 1.23, [0.93, 1.36]), or obese (OR 1.00, [0.86, 1.17]) generally had relative risks of pre-eclampsia comparable, or slightly (but not statistically significantly) greater than those of their White counterparts.

1371	Chang, J et al.	2014	Cohort	Nationwide	3,113,164 singleton births between 20-44 weeks gestation without major fetal anomalies in 2010, US natality file	34,348 (1.10%)	Cigarette use during pregnancy (I), maternal age (I)	Pregnancy induced hypertension (inclusive of pre-eclampsia and eclampsia)	Prenatal care adequacy, weight gain, parity, diabetes, marital status, chronic hypertension, preeclampsia, eclampsia, tobacco use	Good	-The odds of pregnancy induced hypertension was greater in non-Hispanic American Indian women 35 years or older who smoked during pregnancy (aOR 1.29, [0.88-1.89]). -A reduced odds of PIH was evident in non-Hispanic American Indian women younger than 35 years old who smoked during pregnancy based (aOR 0.76, [0.66-0.87]).
7372	Tiwari, R et al.	2021	Cohort	Washington State	105,466 singleton live births from 22 facilities from 2018-2018, hospital administrative database	978 (0.92%)	Pre-pregnancy BMI (I)	Pre-eclampsia	Maternal age, parity, delivery hospital, government health insurance, substance abuse, nicotine use, and alcohol use	Good	-The strength of the association of overweight/obesity with preeclampsia was much greater among NH AI/AN women (aRR 5.24; [1.92–14.30]) and NH Native Hawaiian/Other Pacific Islander women than among other race/ethnicities (aRR 5.88, [1.30-36.51]).
835	Best, L et al.	2012	Case Control	Belcourt, ND	299 women tribal members of the Turtle Mountain Band of Chippewa who sought care in an IHS	299 (100%)	Age at delivery (I), nulliparity (I), BMI (I), Single nucleotide polymorphisms [NOS3, rs1799983	Pre-eclampsia	Nulliparity, BMI, age at delivery	Good	-Age at delivery (aOR 1.0823, [p=0.0185]) , nulliparity (aOR 6.8628, [p<0.001]), and obesity (aOR 1.0951, [p<0.001]) show robust independent effects associated with preeclampsia.

					hospital or clinic from 2004-2009, electronic medical records / 101 cases and 198 matched controls		(G allele recess), NOS3, rs3918227 (A allele dom), GNB3, rs5442 (A allele dom), DDAH1, rs10158674 (C allele recess), DDAH1, rs233115 (A allele recess)] (I)			-There was no significant association between any of single nucleotide polymorphisms studied and pre-eclampsia. -NOS3, rs1799983 (G allele recess) (aOR 1.4087, [p=0.2354]) -NOS3, rs3918227 (A allele dom) (aOR 0.7356, [p=0.4611]) -GNB3, rs5442 (A allele dom) (aOR 0.9147, [p=0.8655]) -DDAH1, rs10158674 (C allele recess) (aOR 1.0165, [p=0.9898]) -DDAH1, rs233115 (A allele recess) (aOR 2.2227. [p=0.1578])
836	Best, L et al.	2012	Case Control	Belcourt, ND	196 women tribal members of the Turtle Mountain Band of Chippewa who sought care in an IHS hospital or clinic from 2004-2009, electronic medical records / 66 cases and	196 (100%)	Age at delivery (I), nulliparity (I), BMI (I), single nucleotide polymorphisms [CRP_A rs3093077 (T allele additive), CRP_B rs1205 (A allele dom), CRP_C rs1130864	Pre-eclampsia, severe pre-eclampsia	Nulliparity, weight at first prenatal visit, BMI, birthweight of infant, gestational diabetes, age at delivery	Good	-Age at delivery did not show a significant association with pre-eclampsia (aOR 1.036, [p=0.398]) and severe preeclampsia (aOR 1.027, [p=0.586]). -Nulliparity (aOR 4.274, [p=0.003] and aOR 4.520, [p=0.009])) and obesity (aOR 1.093, [p=0.002] and aOR 1.094, [p=0.007]) show robust independent associations with

					130 matched controls		(T allele dom), MBL2 rs1800451 (T allele dom, IL1A rs3783550 (T allele dom), CTLA4 rs231775 (A allele dom)](I)			preeclampsia and severe pre-eclampsia. -There was no significant association between any of single nucleotide polymorphisms studied with pre-eclampsia and severe pre-eclampsia except CRP_B, rs1205, (A allele dom). -CRP_B, rs1205, (A allele dom) was the only single nucleotide polymorphism that showed a significant association with severe pre-eclampsia (aOR 0.259, [p=0.020]).
837	Best, L et al.	2013	Case Control	Belcourt, ND	410 women tribal members of the Turtle Mountain Band of Chippewa who sought care at an IHS hospital or clinic from 2004-2012, electronic medical records / 140 cases and 270 matched controls	410 (100%)	Age at delivery (I), nulliparity (I), BMI (I), gestational diabetes (I), single nucleotide polymorphisms [CRP rs3093068 (G allele add), CRP rs3093068 (G allele recess, CRP rs3093068 (G allele dom), CRP	Pre-eclampsia, severe pre-eclampsia	Nulliparity, weight at first prenatal visit, BMI, birthweight of infant, gestational diabetes	Good	-Age at delivery did not show a significant association with pre-eclampsia (aOR 1.053, [p=0.076]) and severe preeclampsia (aOR 1.052, [p=0.166]). -Gestational diabetes did not show a significant association with pre-eclampsia (aOR 1.684, [p=0.278]) and severe pre-eclampsia (aOR 2.241, [p=0.166]). -Independent effects of nulliparity (aOR 5.6, [p=0.001] and aOR 4.17, [p=0.001]) and

							rs876538 (C allele add), CRP , rs876538 (C allele recess), CRP rs876538 (C allele dom), rs3093068 (G dom) and rs876538 (C recess) add risk score] (I)				obesity (aOR 1.061, [p=0.002] and aOR 1.059, [p=0.001]) on pre-eclampsia and severe pre-eclampsia were observed. -There was no significant association between any of single nucleotide polymorphisms studied with pre-eclampsia and severe pre-eclampsia except CRP rs3093068 (G allele add) and CRP rs3093068 (G allele dom) with severe pre-eclampsia (aOR 2.587, [p=0.05] and aOR 2.587, [p=0.050]) -The rs3093068 (G dom) and rs876538 (C recess) additive risk score showed significant association with pre-eclampsia (aOR 1.779, [p=0.016]) and severe pre-eclampsia (aOR 2.035, [p=0.013]).
	Severe Maternal Morbidity and Mortality (4)										
119	Admon, L et al.	2018	Cross Sectional	Nationwide	2,523,528 all hospital deliveries that occurred between 2012-2015,	20,447 (0.810%)	No chronic conditions, any physical health condition (I), any	SMM	Age, income, payer, rural vs. urban residence, and	Good	-The incidence of severe maternal morbidity was significantly higher among deliveries to women in every racial and ethnic minatory

					National Inpatient Sample		behavioral health condition (I), multiple chronic conditions (I), maternal race (I)		hospital region.	category compared with deliveries among non-Hispanic white women. -American Indian/Alaska Native women are at increased risk of severe maternal morbidity compared to non-Hispanic white women (aRR 1.5, [1.3-1.7]) . This is not significant when blood transfusions are not included in severe maternal morbidity (aRR 0.90, [0.68-1.2]). -Among deliveries to women with comorbid physical and behavioral health conditions, significant differences in severe maternal morbidity were identified among racial and ethnic minority compared with non-Hispanic white women and the largest disparities were identified among women with multiple chronic conditions. -In comparing deliveries among American Indian/Alaskan Native women with non-Hispanic white women, the rate difference for severe maternal

											morbidity incidence increased from 66.6 [95% CI 39.9-93.3] to 101.3 [95% CI -41.0-243.5] per 10,000 delivery hospitalizations, respectively, in comparing deliveries in which no and multiple chronic conditions were identified. -American Indian/Alaskan Native women compared to non-Hispanic white women are at increased risk for severe maternal morbidity when any physical health condition is present (aRR 1.5, [1.3-1.7]), any behavioral health condition is present (aRR 1.2, [0.90-1.6]), and having multiple (2 or more) chronic conditions (aRR 1.4, [0.93-2.20]).
3421	Interrante, J et al.	2022	Cross Sectional	Nationwide	6,357,796 maternal records from childbirth hospitalizations from 2007-2015, National Inpatient Sample	43,929 (0.691%)	Primary payer type (I), maternal residence (C), maternal race (I)	SMM and Mortality (SMMM)	Maternal race and ethnicity, maternal residence, maternal age, childbirth year, bottom quartile of	Good	-Rural Indigenous Medicaid-funded births had the highest adjusted predicted rate of SMMM (224.9 per 10,000 births, [187.0-262.9]). -Among rural residents, births by Indigenous people had the greatest differences in rates

									income, hospital region, cesarean birth, substance use disorder, depression, HIV or AIDS, pulmonary hypertension, systemic lupus erythematosus, chronic kidney disease, chronic heart disease, diabetes, chronic hypertension, and chronic respiratory disease	between Medicaid-funded and privately insured births (aRD, 97.8, [50.4–145.3]). -When examining the intersection of rurality and race and ethnicity, births among Indigenous rural residents had significant additive interaction, with 40% (aAP 0.40, [0.11-0.69]) of SMMM cases in that population owing to the interaction. -When examining the intersection of urban status and race and ethnicity, births among Indigenous urban residents did not have an additive interaction (aAP 0.06, [-0.20-0.32]). -If the excess risk of SMMM associated with Medicaid could be mitigated (i.e., if the risk of SMMM among Medicaid-funded births could be decreased to the risk among the privately insured), this would not only prevent the 23 cases per 10,000 births that occur among white urban residents, but an additional 98 cases per 10,000 births

											among Indigenous rural residents.
952	Booker, W et al.	2018	Cohort	Nationwide	1,724,694 delivery hospitalizations from women aged 40-54 years between 1998-2014, National Inpatient Sample	7,107 (0.412%)	Maternal race (I)	SMM, SMM excluding blood transfusions	Year, bed size, insurance status, hospital location, income quartile, hospital region, hospital teaching status, and race	Good	-The incidence of SMM was greater among Native American women but not significant compared to Non-Hispanic white women (aRR 1.08, [0.93-1.25]). -Risk for severe morbidity excluding transfusion among Native Americans is not demonstrated because of small denominators.
4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (I)	SMMM, SMMM excluding blood transfusion	Age, insurance payer, income, hospital region	Good	-The incidence of SMMM was greater among indigenous women compared with white women (aRR 1.8, [1.6–2.0]). -Within each racial group, incidence of SMMM was higher among rural compared with urban residents (2.3% for rural indigenous women vs 1.8% for urban indigenous women) (a RR 1.3, [1.0–1.6]); (1.3% for rural white women vs 1.2% for urban white women) (aRR 1.1, [1.1–1.2]). -Within indigenous women, the incidence

										of SMM (excluding transfusions) among rural compared to urban residents was not significant (aRR 0.7, [0.4-1.0)].
	Blood Transfusions (2)									
3421	Interrante, J et al.	2022	Cross Sectional	Nationwide	6,357,796 maternal records from childbirth hospitalizations from 2007-2015, National Inpatient Sample	43,929 (0.691%)	Primary payer type (I), maternal residence (C), maternal race (I)	Blood transfusions	Maternal race and ethnicity, maternal residence, maternal age, childbirth year, bottom quartile of income, hospital region, cesarean birth, substance use disorder, depression, HIV or AIDS, pulmonary hypertension, systemic lupus erythematosus, chronic kidney disease, chronic	Good	-Rural residents had greater odds of blood transfusion for both Medicaid-funded (aOR 1.15, [1.06-1.25]) and privately insured (aOR 1.20, [1.11-1.31]) hospital births compared to urban residents. -Medicaid-funded (aOR 1.71, [1.39-2.11]) and privately insured hospital (aOR 1.42, [1.05-1.92]) indigenous births had the second highest odds of blood transfusions compared to other racial/ethnic groups. This yielded an additive interaction p-value of 0.006.

									heart disease, diabetes, chronic hypertension, and chronic respiratory disease		
4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (I)	Blood transfusions	Age, insurance payer, income, hospital region	Good	-The incidence of blood transfusions was greater among indigenous women compared with white women (aRR 1.8, [1.5–2.0]). -The incidence of blood transfusion among rural indigenous women compared to urban indigenous women was statistically greater (aRR 1.6, [1.2-2.0]).
Postpartum Hemorrhage (PPH) (2)											
1331	Chalouhi, S et al	2015	Cohort	Gallup, NM	1,062 women who delivered vaginally at the Rehoboth McKinley Hospital, medical records	751 (70.7%)	Maternal race (I), age (I), parity (I), gravidity (I), birthweight (I), retained placenta (I), magnesium sulfate use (I), induction augmentation (I),	Postpartum hemorrhage	None	Good	-A significantly higher proportion of Native Americans than non-native women developed PPH (11.6% vs 7.0%, [p= 0.02]). -In multivariable logistic regression analysis, the significant predictors of PPH were Native American ethnic origin (OR 1.8, [1.1-3.0]), decreased gravidity of fewer than

							chorioamnionitis (I)			5 (OR 1.2, [1.1-1.4]), increased birth weight greater than 4500 grams (OR 1.1, [1.0-1.0]), retained placenta (OR 51.0, [9.8-288.2]), and use of magnesium sulfate (OR 3.5, [1.4-9.0]).
2944	Hadley, M et al	2021	Case Control	Anchorage, AK	384 deliveries between 2018-2019 at the Alaska Native Medical Center, medical records / 128 cases and 256 controls	384 (100%)	BMI (I), antepartum bleeding (I), routine aspirin used prescribed (I), prior uterine incision (I), prior uterine incision and vaginal delivery (I), parity (I), macrosomia, pre-eclampsia without severe features with magnesium sulfate during labor (I), pre-eclampsia with severe features and use of	Postpartum hemorrhage	Not reported	Fair	-In the bivariate analysis, the following risk factors were significantly associated with a higher likelihood of postpartum hemorrhage: BMI of 40 or more (OR 2.6, [1.4-4.5]), antepartum bleeding (OR 6.3, [1.2-31.6]), previous postpartum hemorrhage (OR 5.0, [2.6-9.8]), suspected macrosomia with estimated fetal weight of 4000 g or more (OR 2.7, [1.4-5.3]), pre-eclampsia with severe features and use of magnesium sulfate during labor (OR 4.7, [2.4-9.2], length of third stage labor longer than 20 min (OR 2.2, [1.1-4.4]), and use of oxytocin for more than 12 h (OR 5.0, [2.3-10.6]). -Residence in a rural community (OR 2.2, [1.4-3.6]) and vitamin

							magnesium sulfate (I), previous postpartum hemorrhage (I), length of 2nd stage of labor (I), length of 3rd stage of labor (I), rural residence (C), and oxytocin (I), and inpatient induction length (I)			D supplementation (OR 1.7, [1.1-2.6]) were also significantly associated with postpartum hemorrhage. -Multivariate condition logistic regression analyses found that antepartum bleeding (OR 8.8, [1.6-48.5]) , pre-eclampsia with severe features and use of magnesium sulfate (OR 5.3, [2.4-11.9]), previous postpartum hemorrhage (OR 2.7, [1.2-6.1]), third stage of labor of 20min or more (OR 2.9, [1.2-6.9]), rural residence (OR 2.0, [1.2-3.5]), fetal macrosomia (OR 4.0, [2.1-7.5]), and oxytocin use for more than 12h (OR 3.0, [1.1-8.0]) all remained significantly associated with an increased risk of hemorrhage in Native American women. -Routine aspirin use (OR 1.7, [0.9-3.4]), prior uterine incision (OR 1.0, [0.52-2.1]), prior uterine incision and vaginal delivery (OR 1.6, [0.58-4.4]), a parity of 5 or more (OR 1.8, [0.87-3.9]), pre-eclampsia without severe features without

											use of magnesium sulfate (OR 2.1, [0.98-4.4]), length of second stage of labor grater or equal to 1 hour (OR 1.6, [0.88-3.0]), and an inpatient induction length of greater or equal to 36 hours (OR 2.3, [0.4-12.8]) were not significantly associated with a higher likelihood of postpartum hemorrhage.
Misc. Outcomes (5)											
1331	Chalouhi, S et al	2015	Cohort	Gallup, NM	1,062 women who delivered vaginally at the Rehoboth McKinley Hospital, medical records	751 (70.7%)	Maternal race (I), age (I), parity (I), gravidity (I), birthweight (I), retained placenta (I), magnesium sulfate use (I), induction augmentation (I), chorioamnionitis (I)	Uterine atony	None	Good	-Uterine atony was recorded in a significantly higher proportion of Native Americans than non-native patients (9.6% vs 4.8%; [p=0.01]). -In univariate analysis, factors predicting uterine atony were native race (p=0.01), decreasing gravidity (p=0.02), induction augmentation (p=0.1), increasing birthweight (p=0.07), and chorioamnionitis (p=0.08). -In multivariable logistic regression analysis, Native American ethnic origin

											(OR 2.0, [1.1–3.7]) and increasing birthweight (OR 1.0, [1.0 1.0]) were significant predictors of uterine atony.
1861	deRavello, L et al	2015	Cross Sectional	Nationwide	229,986 American Indian and Alaska Native (AI/AN) women aged 15–44 years seeking care at Indian Health Service (IHS), Tribal, and urban Indian health facilities during 2002–2009, Indian Health Service National Patient Information Reporting System	229,986 (100%)	Maternal age (I), IHS region (C)	Ectopic pregnancy	None	Fair	-The ectopic pregnancy (EP) rate among AI/AN women was lowest in the 15–19 years age group (5.5 EPs per 1,000 pregnancies) and highest among 35–39 year old (18.7 EPs per 1,000 pregnancies). -Compared to AI/AN women aged 15-18 years, women aged 35-39 years were 3.4 times more likely to have an EP (RR 3.4, [2.90-4.03]). Compared to AI/AN women aged 15-18 years, the risk of an EP increased with age from 1.56-3.42, except in women aged 40-44 years were the risk was less at 2.62 times (RR 2.62, [2.02-3.36]). -EP rates varied by geographic region, ranging between 6.9 and 24.4 per 1,000 pregnancies in the Northern Plains East and the East region, respectively. -Compared to AI/AN women who received

											care in the Northern Plains East region, women who received care in the East region were 3.55 times more likely to have an EP (RR 3.55, [2.75-4.57]), in the Alaska region the risk was 2.17 times (RR 2.17, [1.73-2.72]), in the Southern plains region the risk was 1.56 times (RR 1.57, [1.25-1.95]), in the West region the risk was 1.39 times (RR 1.39, [1.09-1.77]), in the Norther Plains West region the risk was 1.36 times (1.36, [1.08-1.71]), and in the Southwest region the risk was lowest at 1.33 times (RR 1.33, [1.07-1.65]). -We found relatively stable annual rates of EP among AI/AN women receiving care at IHS-affiliated facilities during 2002–2009, but considerable variation by age group and geographic region.
2230	England, L et al.	2013	Case Control	Anchorage, AK	1,123 singleton deliveries from 1997-2005 to AN women residing in	1,123 (100%)	Continuous smokeless tobacco use (I) and continuous cigarette smoking (I)	Placental abruption, placental abruption expanded definition	Parity, pre-pregnancy BMI, maternal age	Good	-Thirty-nine percent of case deliveries were also preterm (compared with 7% of controls, [p<0.001]), and 9.8% were also complicated by pregnancy

					western Alaska, hospital administrative database					associated hypertension (compared with 7% of controls. [p=0.38]). -There were no significant associations between placental abruption and continuous smokeless tobacco use (aOR 1.11, [0.53-2.33] and continuous cigarette smoking (aOR 1.19, [0.43-3.29). -An expanded definition of abruption did not change this finding. There were no significant associations between continuous smokeless tobacco use (OR 1.07, [0.63-1.83]) or continuous cigarette smoking (aOR 1.04, [0.48-2.23]).

4010	Kozhimannil, K et al.	2020	Cross Sectional	Nationwide	7,561,729 hospital live births from white and indigenous women between 2012-2015, National Inpatient Sample	101,943 (1.35%)	maternal residence (C), maternal race (C)	Disseminated intravascular coagulation (DIC), hysterectomy	Age, insurance payer, income, hospital region	Good	DIC -The incidence of DIC was greater but not significant among indigenous woman compared with white women (1.6% vs 0.9%, respectively) (aRR 1.1, [0.8-1.5]). -Within indigenous women, there was no difference between rural women and urban women (0.2% vs 0.2%, respectively) (aRR 0.8, [0.3-1.3]). Hysterectomy -The incidence of a hysterectomy was greater among indigenous woman compared with white women (0.1% vs 0.1%, respectively) (aRR 1.8, [1.0-2.6]). -Within indigenous women, there was a marginal increased risk but not significant of hysterectomy among rural women (aRR 1.3, [0.3-2.3]).

Appendix 4. Results of NIH quality assessments for included studies

For observational cohort and cross-sectional studies:

ID#	Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Yes %	Rating
119	Admon L, et al.	2018	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	NA	Yes	NR	NA	Yes	82%	Good
952	Booker W, et al.	2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	93%	Good
1178	Cameron, N. et al.	2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NA	No	83%	Good
1331	Chalouhi, S. et al.	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	No	92%	Good
1371	Chang, J et al	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	100%	Good
1861	deRavello, L. et al.	2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NA	No	83%	Good
3421	Interrante, J. et al.	2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	85%	Good
4010	Kozhimannil, K et al.	2020	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NR	NA	Yes	90%	Good
7372	Tiwari, R. et al	2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	92%	Good
8141	Zamora-Kapoor A., et al	2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	86%	Good

A study will be rated as “Good” if it receives a “Yes" response for ≥80% of the applicable NIH critical appraisal questions, “Fair” for 50%-79%, and “Poor” for ≤50%.

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).
Q1. Was the research question or objective in this paper clearly stated?
Q2. Was the study population clearly specified and defined?
Q3. Was the participation rate of eligible persons at least 50%?

Q4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
Q5. Was a sample size justification, power description, or variance and effect estimates provided?
Q6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
Q7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q10. Was the exposure(s) assessed more than once over time?
Q11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q12. Were the outcome assessors blinded to the exposure status of participants?
Q13. Was loss to follow-up after baseline 20% or less?
Q14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

For case-control studies:

ID#	Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Yes %	Rating
835	Best, L. et al	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	92%	Good
836	Best, L. et al.	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	92%	Good
837	Best, L et al.	2013	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	83%	Good
2230	England L, et al	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%	Good
2944	Hadley, M et al	2021	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	75%	Fair

A study will be rated as “Good” if it receives a “Yes" response for ≥80% of the applicable NIH critical appraisal questions, “Fair” for 50%-79%, and “Poor” for ≤50%.

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment of Case-Control Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools):
Q1. Was the research question or objective in this paper clearly stated and appropriate?
Q2. Was the study population clearly specified and defined?
Q3. Did the authors include a sample size justification?
Q4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
Q5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?
Q6. Were the cases clearly defined and differentiated from controls?
Q7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
Q8. Was there use of concurrent controls?
Q9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
Q10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
Q11. Were the assessors of exposure/risk blinded to the case or control status of participants?
Q12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Q, question; CD, cannot be determined; NA, not applicable; NR, not reported