Evidence-based Practice Center Systematic Review Protocol

Project Title: ***Maternal Morbidity and Mortality***

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(Amendments Details–see Section VII)

I. Background

Maternal morbidity describes any short- or long-term health problem resulting from pregnancy and childbirth,[1] and maternal mortality refers to the death of an individual from complications related to pregnancy or childbirth that occur during pregnancy or within 6 weeks after the pregnancy ends.[2] Maternal morbidity can impede a pregnant or birthing person's wellbeing and functional ability while leading to increased medical costs and longer hospitalization stays.[3] Certain individual-level factors—such as advanced maternal age,[4,5] preexisting chronic medical conditions,[6,7] and cesarean delivery[4,8]—increase risk of maternal morbidity. However, other risk factors, especially at the system level, are less well understood or acknowledged. For example, despite spending more on maternity care than any other country, the United States has seen maternal deaths rise since 2000, and risk of death from complications related to pregnancy and childbirth are greater in the U.S. than in any other high-income country.[9] Further, risk of maternal mortality is unevenly distributed, with Black and Indigenous women experiencing maternal mortality rates three to four times higher than their white counterparts.[10] Ultimately, racial disparities and their determinants in maternal mortality and morbidity are poorly studied and largely unexamined in the literature.

Single-study efforts to explain pronounced disparities in maternal outcomes have faced data source limitations, in part because clinical research has mainly focused on neonatal outcomes such as low birth weight and preterm birth.[11] Meanwhile, some researchers have concluded that disparities are multifactorial and no single intervention is likely to reduce them.[10] Finally, and importantly, although most maternal deaths are considered preventable,[12] research's limited focus on individual person and medical-clinical risk factors rather than system- and structural-level risk factors has obscured the lived experience of marginalized or vulnerable people, including Black, Indigenous, People of Color (BIPOC) individuals.[13] Important to recognize is that race itself is not a risk factor; rather, *racism* puts mothers at risk. Race is a social construct[14] used to categorize people within a hierarchical system of unearned advantage (privilege) and power that unequally provides access to material, cultural, and psychological resources based on presumed value judgements based on racial status. In turn, unequitable access to resources along with high exposure to cumulative stress resulting from discrimination and marginalization creates a "web of missed opportunities" (e.g., access to care, missed or delayed diagnoses, and unrecognized warning signs related to pregnancy-related death and morbidity).[12] Such missed opportunities threaten maternal health and deepen health disparities. Additionally, the rates of incarceration, illness, and death are greater among BIPOC than white mothers and their family members, and the lost or systematic removal of family members in BIPOC communities severs

access to practical knowledge of pregnancy, birthing, breastfeeding, and postpartum health.[15] Continuing the example of racism, not only do individuals who have lost their own mothers often experience profound grief during and after pregnancy, but, also, the resulting void of information is further compounded by lack of social and medical capital that is disproportionately experienced by BIPOC people.

Problematically, maternal health literature tends to assume that all pregnant or birthing people, regardless of socioeconomic status, geographic location racial or ethnic background, age, or other group identities, share the same experiences around motherhood. In turn, the concerns and priorities of vulnerable or underserved pregnant and birthing persons remain invisible, as do opportunities to address root causes of maternal morbidity and mortality and their intersection. We need to better understand how postpartum health for birthing persons is affected by multiple forms of discrimination and power and the way these forces intersect with race, sex, gender, class, and disability.[16] Intersectionality offers a valuable framework for illuminating how a person, group of people, or social problem is affected by two or more intersecting social forces that affect social position and shape experience.[17] While each person will confront unique patterns of intersection, research can benefit from identifying overarching themes and patterns that in turn suggest opportunities to intervene in this form of social determinants of health. Social determinants of health shape and promote certain risk factors for postpartum health of birthing persons such as chronic conditions, variation in access to health care including midwife-attended births[18], linguistically and culturally appropriate care,[19-21] and geographic/local access to and use of maternity units.[22] For example, a woman's likelihood of being screened for medical risk factors such as high blood pressure, preeclampsia, diabetes, and substance misuse is affected by social factors such as race and ethnicity,[23, 24] stable housing,[25] lack of food,[26, 27] and incarceration. [28, 29] Even properly identified medical risk factors of postpartum health may not be adequately addressed due to systemic biases (racial, ethnic, and other prejudices) during referral processes[28, 29] or followup appointments (e.g., failed shared decision-making reduces treatment adherence).[30]

In order to better understand the factors underlying maternal mortality and morbidity in the United States, the Office of Disease Prevention (ODP) requested this systematic review as part of a planned Pathways to Prevention workshop, cosponsored by NIH's Office of Research on Women's Health, the National Heart Lung and Blood Institute, the National Institute of Minority Health and Health Disparities, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. ODP anticipated complex patterns associated with social structural drivers of health, including maternal health at the intersections of race and other social group memberships. Therefore, we will focus primarily on research examining factors to which pregnant and birthing people have been exposed that may underlie poor postpartum health outcomes. Our scope does not include assessing the effectiveness of interventions aimed at improving maternal mortality and morbidity.

We will examine short and long-term health problems stemming from pregnancy or birth and identified within a postpartum period divided into the following phases: immediate postpartum (first 24 hours after delivery), early postpartum (up to 6 weeks after birth), first 3 months postpartum, and up to 1 year postpartum. Our review will include medical or clinical causes of maternal mortality and severe morbidity, and also contributory factors such as modifiable features in health systems, quality of clinical care (health-facility factors); missed or delayed diagnosis and lack of continuity of care (provider factors); inadequate access to care or care coordination); health literacy including knowledge of warning signs (patient factors).

Additionally, we will examine pregnancy-associated causes of deaths occurring in the first year after pregnancy that are not directly related to pregnancy (e.g., homicide, interpersonal/partner violence).

Our findings will help improve understanding of the causes of poor postpartum health outcomes and the extent to which these vary according to complex patterns of biomedical, behavioral, healthcare, and psychosocial exposures, with an emphasis on how these patterns intersect with structural and social determinants of health. Our findings will help improve understanding of maternal morbidity and mortality by characterizing risks across a range of social, economic, environmental, health service, individual, and biomedical determinants. Our results will inform research on approaches to address risk factors and improve health outcomes over the postpartum period.

II. The Research Questions:

- **KQ1:** From a pregnant person's potential entry into prenatal care, what combinations of risk indicators have the greatest prediction of poor postpartum health outcomes?
    a. To what extent did these patterns of predictors of poor postpartum health outcomes vary by the person's race/ethnicity?
- **KQ2:** Immediately before or immediately after delivery and before release from birthing-related hospitalization/clinical care, what combinations of risk indicators to the birthing person have the greatest prediction of poor postpartum health outcomes?
    a. To what extent did these patterns of predictors of poor postpartum health outcomes vary by the race/ethnicity of the birthing person?

Table 1 provides details on the population, exposures, comparators, outcomes, timing, and setting (PECOTS) for the research questions.

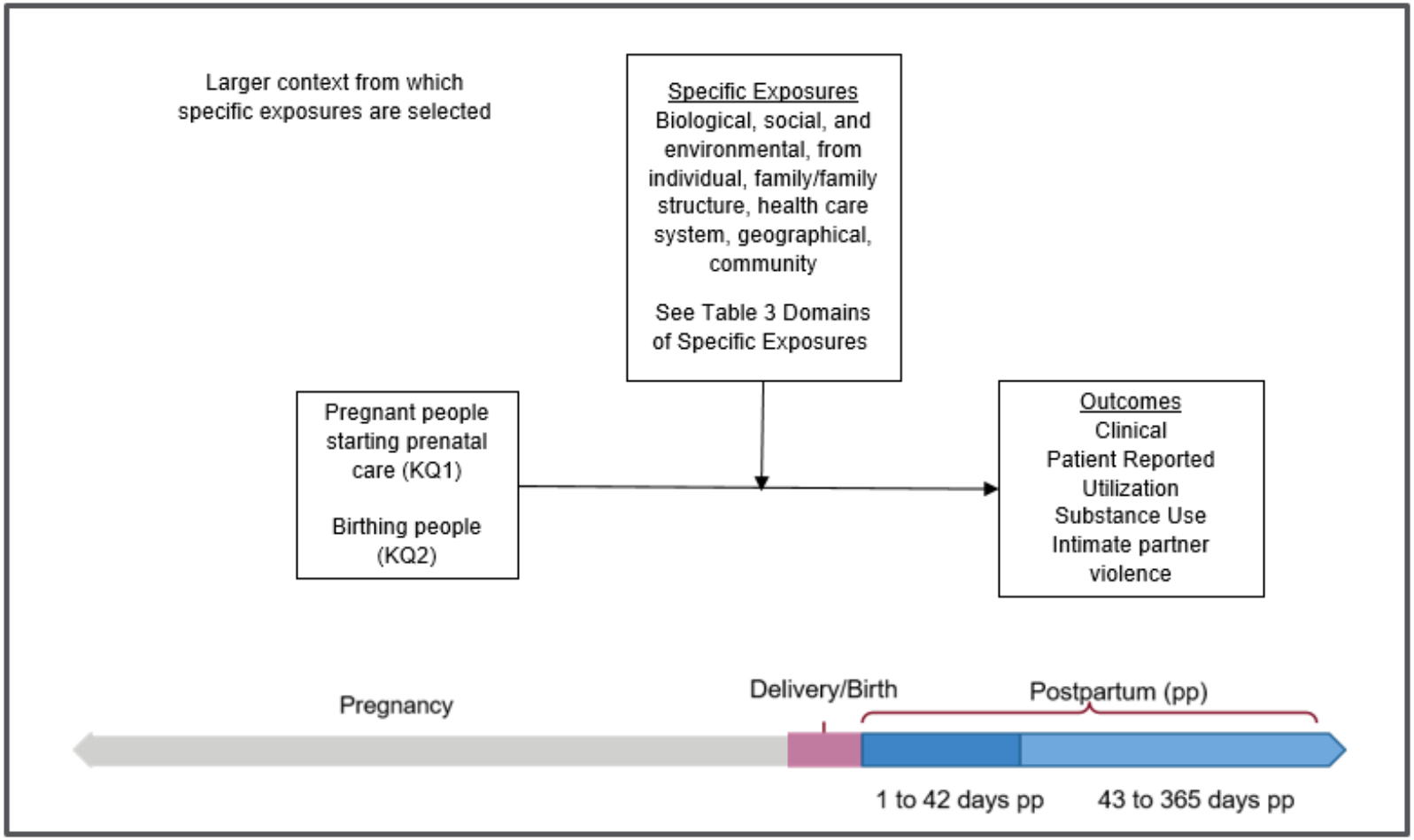
Table 1. Population, exposures, comparators, outcomes, timing, and setting

PECOTS	KQ1	KQ2
Population	Pregnant persons potential entry into prenatal care	Birthing persons just prior to, during, or immediately following delivery (before release from birthing setting)
Exposure/ Comparator	Include biological, social, and environmental factors from the individual, family/family structure, health care system, geographical and community levels, with a special interest in predictors related to access to quality care, patient-provider dynamics, and social and structural determinants of health, including racism.	Include biological, social, and environmental factors from the individual, family/family structure, health care system, geographical and community levels, with a special interest in predictors related to access to quality care, patient-provider dynamics, and social and structural determinants of health, including racism.
Outcomes	Postpartum health status outcome such as pregnancy-related or pregnancy-associated death, severe postpartum conditions (such as postpartum cardiomyopathy (PPCM), postpartum preeclampsia/eclampsia, and postpartum venous thrombosis), onset of new conditions (such as hypertension	Postpartum health status outcome such as pregnancy-related or pregnancy-associated death, severe postpartum conditions (such as postpartum cardiomyopathy (PPCM), postpartum preeclampsia/eclampsia, and postpartum venous thrombosis), onset of new conditions (such as hypertension and diabetes), emergency room visits, need for

	and diabetes), emergency room visits, need for rehospitalization, medical appointments, reports in medical records, patient reported outcomes, miss-use of substance/substance use disorder, and interpersonal/partner violence.	rehospitalization, medical appointments, reports in medical records, unnecessary medical procedures, patient reported outcomes, miss-use of substance/substance use disorder, and interpersonal/partner violence.
Timing	Outcomes of interest will be from the time of release from the birthing setting across the 1-year postpartum period	Outcomes of interest will be from the time just prior to, during, or immediately following delivery (before release from birthing setting) across the 1-year postpartum period
Setting	Non-U.S. excluded	Non-U.S. excluded

III. Analytic Framework

Figure 1 shows a visual representation of the analytic framework for the KQ's, illustrating the relationship of interventions and outcomes.



Abbreviations: KQ=key question

Table 2. Domains and examples of possible exposures

Coverage/Cost	Health care (access, investment, quality)	Racism as social and structural determinant of health	Other structural and social determinants of health	Biomedical determinants
• Insured vs uninsured • Payment Source/Insurance Type – may lead to differential pregnancy care, postpartum care, and/or maternal outcomes. • Underinsured – people who have insurance but have high deductibles or coverage isn't complete • Mental health coverage • Access to substance use disorder care • Medicaid coverage – up to 6 weeks postpartum vs. up to 1 year postpartum. • Adequate postpartum birth control coverage. • Coverage of doula care. • Lack of access to different models due to coverage/cost – e.g. group prenatal care, midwifery care, birth centers, home birth	• Distribution of primary care (rural, urban, etc.) • Access to quality primary care during preconception, pregnancy, and postpartum period • Access to quality specialty care during preconception, pregnancy, and postpartum period • Access to early and quality obstetric care • Access to doula care • Distribution of patient volume/ population • Lack of integrated behavioral health/co-located mental health services with primary care • Length of postpartum stay • Postpartum nursing staffing ratios (patients per nurse) • Screening for risk factors for high risk pregnancy • Healthcare & social service coordination – preconception, prenatal, perinatal, postpartum, interconceptional • ED utilization for postpartum care • Inadequate health communication • Patient-provider interactions and communication • Delayed care • Near misses • Clinical variation in care/quality of care	• "Weathering" – cumulative impacts of social, economic, and environmental exposures • Interpersonal racism, including implicit bias with immediate healthcare providers • Structural racism in health care and in the community (e.g., incarceration/ policing/police violence) • Medical mistrust • Lack of access to culturally congruent care, e.g., providers not taking cultural preferences or differences into account in treatment plans • Differential decision autonomy during labor and delivery • Racial disparities in unnecessary medical procedures – e.g., cesarean birth • Inadequate diversity in workforce (providers, staff, administrators) • Race being used in clinical guidelines and calculators • Proportion of BIPOC patients in the served community and outcomes • Influence of racism on quality of care	• Differential treatment due to insurance status • Housing status and stability • Transportation access • Social networks and social support • Effect of laws around mandatory reporting for substance use. • Return to work policies vary by occupation • Paid maternity leave – paid time off after delivery and/or during pregnancy • Postpartum childcare, including care for other children in household • Environmental exposures • Employment • Income • Time availability/ burden for daily activities • Breast-feeding supports • Inadequate support of community-based or engaged programs that foster resiliency and social support.	• Hemorrhage • Infection • Prevalence of chronic disease • Pre-pregnancy and pregnancy cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, tobacco use, obesity, physical inactivity) • Cardiac condition – e.g., cardiomyopathy, thrombotic pulmonary or other embolism • Severe bleeding • Hypertensive disorders of pregnancy • Amniotic fluid embolism • Anesthesia complications • Unnecessary medical procedures • Delivery complications • Disorders of mental health

Abbreviations: BIPOC=black, indigenous, people of color; ED=emergency department;

IV. Methods

Criteria for inclusion/exclusion of studies in the review:

Studies will be included in the review based on the PECOTS (Population, Exposures/Comparators, Outcomes, Timing, and Settings) framework in Table 1 above and inclusion criteria outlined in Table 3.

Table 3. Study inclusion criteria for key questions

Category	Criteria for Inclusion
Study Enrollment	KQ1: Pregnant persons/ persons aware that they are pregnant. KQ2: Birthing persons just prior to, during, or immediately following delivery (before release from birthing setting).
Study Objective	KQ1: Evaluate the impact of exposures ***prior to, during, and after pregnancy*** on outcomes for the pregnant person. KQ2: Evaluate the impact of exposures ***immediately prior to, during, and after birthing*** on outcomes for the birthing person.
Study Design	Observational/retrospective analysis, prospective cohort designs, secondary analysis of RCTs if exposures of interest are sufficient to evaluate the impact of exposures for the population. Design must be comparative and must include some method to control for selection bias (e.g., propensity scores, instrumental variables, multivariate regression). Study design must connect social factors/context to biomedical or health behaviors.
Study Exposures	Studies are not excluded based on specific exposures (see Table 2 for example exposures).
Outcomes	Individual studies must include at least one medical or healthcare-related outcome. Studies are not excluded based on maternal health outcomes. Studies that report only neonatal or infant outcomes are excluded.
Timing	Includes study of any exposure(s) for pregnant persons on outcomes during pregnancy (KQ1), or immediately before/after delivery (KQ2), with outcomes measured up to 1 year postpartum.
Settings	KQ1: Any U.S. setting. KQ2: All/any U.S. birthing settings. Non-U.S. studies are excluded.
Publication type	Published in peer-reviewed journals with full text available (if sufficient information to assess eligibility and risk of bias are provided). Letters and abstracts are excluded due to the inability of such short publications to provide the information needed to fully describe exposures or allow risk of bias assessment.
Language of Publication	English only

Abbreviations: KQ=key question

Searching for Evidence:

We will search for literature in the following databases: MEDLINE (via Ovid), CINAHL (via EBSCOHost), and Social Sciences Citation Index (via Web of Science). The searches will include controlled vocabulary terms (e.g., MeSH or CINAHL headings), along with free-text words related to maternal mortality and morbidity, pregnancy, prenatal care, postpartum care, health disparities, and measures of risk indices. Search strategies will have no restrictions on publication date but will be limited to English language studies. Searches will be independently peer reviewed by a librarian using the PRESS checklist. All searches will be updated upon submission of the draft report for public review. We include the proposed search strategy for Medline (via Ovid) in Appendix A.

We will search reference lists of relevant existing systematic reviews for additional eligible studies, and screen (with identical eligibility criteria) any articles suggested to us from any source. We will use information from grey literature to assess publication and reporting bias and inform future research needs.

Duplicate citations will be removed prior to screening. Search results will be downloaded to EndNote X9 and screened in PICO Portal (www.picoportal.org, New York, NY). Two independent investigators will review titles and abstracts using predefined criteria based on PECOTS framework and Table 3 study inclusion criteria. Two independent investigators will perform full-text screening to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator. We will document the inclusion and exclusion status of citations at full text screening, noting reasons for exclusion. Throughout the screening process, team members will meet regularly to discuss training materials and issues that arise to ensure consistency of inclusion criteria application. Multiple publications relating to the same study will be grouped together.

Additionally, we will search grey literature to identify relevant completed studies that did not report outcomes and analyses in the published literature to help assess publication and reporting bias, and to identify and track ongoing studies that may contribute information to address the key questions in the future.

We will update searches while the draft report is under public review.

Data Abstraction and Data Management

Studies meeting inclusion criteria will be distributed among investigators for data extraction. Data fields will include: author, year of publication, PubMed Identification Number (if available), sample size, author representation, population including ascertainment criteria, exposure(s), confounders/co-exposures, outcome(s), outcome timing, study design, and setting. If studies report more than one outcome timing, we will extract the last possible time point. Relevant data will be extracted into "PECOTS" abstraction forms created in Microsoft Excel or Microsoft Word (if sorting or analysis is not required). Data will be extracted to evidence tables by one reviewer and verified for accuracy by a second reviewer.

Assessment of Methodological Risk of Bias of Individual Studies

Based on AHRQ guidance,[31] two independent reviewers will assess risk of bias of included studies. We will use the ROBINS-E tool, which is designed specifically to address risk factor research.[32, 33] ROBINS-E is under development by the University of Bristol and McMaster to modify the ROBINS-I to be appropriate for studies not intended to address efficacy/effectiveness questions. For example, confounders, co-exposures, and measurement validity is given heightened attention compared with ROBINS-I. Because of the preliminary status of the tool, risk of bias assessments will be presented to the entire team to review and reconcile differences in or confirm overall risk of bias for included studies. A flow chart is provided in Appendix B describing decision points at which risk of bias is concluded due to established critical assessment. Overall risk of bias assessments for studies will be classified as low, moderate, serious, or critical based on the rationale and judgement as to the overall predicted direction of bias for each outcome.

Data Synthesis

We will summarize results in evidence tables and synthesize evidence for each unique population/exposure/outcome combination. We will organize results by Key Question, outcome, and broad type of exposure domain. Under each exposure domain, we will use subheadings for the domain of exposure (see Table 2) and report the exposure comparisons, co-exposures/confounders, and outcomes. We will group studies based on the exposures examined

in the included literature; while we provide in Table 2 a lengthy list of potential exposures, we do not anticipate many of them to be present in the literature.

For studies with low to serious risk of bias, we will summarize the results in evidence tables, and synthesize evidence for each exposure with meta-analysis when feasible and appropriate. We will describe patterns of risk factors and outcomes graphically (multi-level network diagram or arc diagram) or in-text. We will assess similarity within/across population, exposure, outcome measure(s) and, if appropriate, for pooling. When appropriate, we will synthesize data using random effects models and will calculate odds ratios (OR) with the corresponding 95 percent confidence intervals (CI) for binary outcomes, and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent confidence intervals for continuous outcomes. We will assess statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic. At minimum, a qualitative narrative synthesis using matrix table approaches will be used.

Grading the Strength of Evidence for Major Comparisons and Outcomes

Two investigators will independently assess strength of evidence for each exposure/outcome finding for included studies. Strength of evidence assessments will be presented to the entire team for consensus.

We will rate the evidence for outcomes when 1) at least two studies with sufficiently similar designs and populations examined the same risk factor in a comparable manner (i.e., numerical data available in comparable measurement units for reliably/validly similar constructs), or 2) a single study of at least moderate risk of bias and sufficiently large study population. Given the potentially widely varying exposure/outcome findings, we will query the Technical Expert Panel regarding prioritizing which findings to submit to full strength of evidence assessment.

We will evaluate overall strength of evidence for outcomes for KQs 1-2 within each comparison, based on five required domains: 1) study strengths and limitations (risk of bias); 2) directness (single, direct link between exposure and outcome); 3) consistency (similarity of effect direction and size); 4) precision (degree of certainty around an estimate); and 5) reporting bias.[34] Based on study design and risk of bias, we will rate study limitations as low, medium, or high. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study) based on whether exposure effects are similar in direction and magnitude, and statistical significance of all studies for each outcome assessed. Directness will be rated as either direct or indirect based on the need for indirect comparisons when inference requires observations across studies (i.e., reaching the conclusion requires more than one step). Precision will be rated as precise or imprecise based on the degree of certainty surrounding each effect estimate or qualitative finding. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For outcomes found to have at least moderate or high strength of evidence, we will evaluate reporting bias by the potential for publication bias, selective outcome reporting bias, and selective analysis reporting bias by comparing reported results with those mentioned in the methods section and an assessment of the grey literature to assess potentially unpublished studies. Other factors we may consider in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association.

Based on these factors, the overall strength of evidence for each outcome will be rated as:

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.

- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available, or the body of evidence precludes judgment.

Assessing Applicability

We will note the criteria used to identify people followed in a study to help understand who may be similarly be subject to the risk factor.

V. References

1. https://www.nichd.nih.gov/health/topics/maternal-morbidity-mortality#:~:text=Maternal%20morbidity%20describes%20any%20short,weeks%20after%20the%20pregnancy%20ends. Last accessed 9/27/2021
2. American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine, Kilpatrick SK, Ecker JL. Severe maternal morbidity: screening and review. Am J Obstet Gynecol. 2016;215(3):B17–B22.
3. Callaghan WM , Creanga AA , Kuklina EV. Severe maternal morbidity among delivery and post partum hospitalizations in the United States. Obstet Gynecol. 2012;120(5):1029-1036. doi:10.1097/AOG. 0b013e31826d60c5
4. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Matthews TJ. Births: final data for 2015. Nat Vital Stat Rep. 2017;66(1).
5. Hinkle SN, Sharma AJ, Kim SY. Prepregnancy obesity trends among low-income women, United States, 1999–2008. Matern Child Health J. 2012;16(7):1339-1348.
6. Campbell KH, Savitz D, Werner EF, Pettker CM, Goffman D, Chazotte C, Lipkind HS. Maternal morbidity and risk of death at delivery hospitalization. Obstet Gynecol. 2013;122(3):627–633.
7. Small MJ, James AH, Kershaw T, Thames B, Gunatilake R, Brown H. Near-miss maternal mortality: cardiac dysfunction as the principal cause of obstetric intensive care unit admissions. Obstet Gynecol. 2012;119(2 Pt 1):250–255.
8. Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. Obstet Gynecol. 2011;118(1):29–38.
9. Chinn JJ, Eisenberg E, Artis Dickerson S, King RB, Chakhtoura N, Lim IAL, Grantz KL, Lamar C, Bianchi DW. Maternal mortality in the United States: research gaps, opportunities, and priorities. Am J Obstet Gynecol. 2020 Oct;223(4):486-492.e6. doi: 10.1016/j.ajog.2020.07.021. Epub 2020 Jul 17. PMID: 32682858; PMCID: PMC7564012.
10. Creanga, A. A., Berg, C. J., Ko, J. Y., Farr, S. L., Tong, V. T., Bruce, F. C., & Callaghan, W. M. (2014). Maternal mortality and morbidity in the United States: where are we now?. Journal of women's health (2002), 23(1), 3–9. https://doi.org/10.1089/jwh.2013.4617
11. Jain JA, Temming LA, D'Alton ME, Gyamfi-Bannerman C, Tuuli M, Louis JM, Srinivas SK, Caughey AB, Grobman WA, Hehir M, Howell E, Saade GR, Tita ATN, Riley LE. SMFM Special Report: Putting the "M" back in MFM: Reducing racial and ethnic disparities in maternal morbidity and mortality: A call to action. Am J Obstet Gynecol. 2018 Feb;218(2):B9-B17. doi: 10.1016/j.ajog.2017.11.591. Epub 2017 Nov 26. PMID: 29183819.
12. Centers for Disease Control and Prevention. Pregnancy-Related Deaths. https://www.cdc.gov/vitalsigns/maternal-deaths/index.html Published 2019. Accessed June 1, 2021.
13. McLemore, M. R. (2019, May 1). To Prevent Women from Dying in Childbirth, First Stop Blaming Them. Scientific American. https://www.scientificamerican.com/article/to-prevent-women-from-dying-in-childbirth-first-stop-blaming-them/.
14. Boyd, R. W., Lindo, E. G., Weeks, L. D., & McLemore, M. R. (2020). “On Racism: A New Standard For Publishing On Racial Health Inequities.” Health Affairs Blog, 10.
15. Gunn J, Huebner CG, McCoy K. Perceptions of Adult Women on Losing Their Mothers at an Early Age: Implications for Nursing Care During Childbirth. MCN Am J Matern Child Nurs. 2018 May/Jun;43(3):126-132. doi: 10.1097/NMC.0000000000000429. PMID: 29489528.

16. Massey DS. Segregation and stratification: a biosocial perspective. DuBois Rev. Soc. Sci. Rev. Race. 2004;1:7–25.
17. Flowers, H. NIH Community. Intersectionality Part One: Intersectionality defined. Last accessed November 4, 2021 https://www.edi.nih.gov/blog/communities/intersectionality-part-one-intersectionality-defined
18. Attanasio, L., & Kozhimannil, K. B. (2018). Relationship Between Hospital-Level Percentage of Midwife-Attended Births and Obstetric Procedure Utilization. Journal of Midwifery & Women's Health, 63(1), 14-22. https://doi.org/10.1111/jmwh.12702
19. Johnsen, H., Ghavami Kivi, N., Morrison, C. H., Juhl, M., Christensen, U., & Villadsen, S. F. (2020). Addressing ethnic disparity in antenatal care: a qualitative evaluation of midwives' experiences with the MAMAACT intervention. BMC Pregnancy & Childbirth, 20(1), 118. https://doi.org/https://dx.doi.org/10.1186/s12884-020-2807-4
20. Mozooni, M., Pennell, C. E., & Preen, D. B. (2020). Healthcare factors associated with the risk of antepartum and intrapartum stillbirth in migrants in Western Australia (2005-2013): A retrospective cohort study. Plos Medicine, 17(3), Article e1003061. https://doi.org/10.1371/journal.pmed.1003061
21. Thomas, P. E., Beckmann, M., & Gibbons, K. (2010). The effect of cultural and linguistic diversity on pregnancy outcome. Australian & New Zealand Journal of Obstetrics & Gynaecology, 50(5), 419-422. https://doi.org/10.1111/j.1479-828X.2010.01210.x
22. Williams, A. D., Messer, L. C., Kanner, J., Ha, S., Grantz, K. L., & Mendola, P. (2020). Ethnic Enclaves and Pregnancy and Behavior Outcomes Among Asian/Pacific Islanders in the USA. Journal of Racial & Ethnic Health Disparities, 7(2), 224-233. https://doi.org/https://dx.doi.org/10.1007/s40615-019-00650-4
23. Admon, L. K., Bart, G., Kozhimannil, K. B., Richardson, C. R., Dalton, V. K., & Winkelman, T. N. A. (2019). Amphetamine- and Opioid-Affected Births: Incidence, Outcomes, and Costs, United States, 2004-2015. American Journal of Public Health, 109(1), 148-154. https://doi.org/https://dx.doi.org/10.2105/AJPH.2018.304771
24. Kozhimannil, K. B., Graves, A. J., Levy, R., & Patrick, S. W. (2017). Nonmedical Use of Prescription Opioids among Pregnant U.S. Women. Womens Health Issues, 27(3), 308-315. https://doi.org/https://dx.doi.org/10.1016/j.whi.2017.03.001
25. DiTosto, J. D., Holder, K., Soyemi, E., Beestrum, M., & Yee, L. M. (2021). Housing Instability and Adverse Perinatal Outcomes: a Systematic Review. American Journal of Obstetrics & Gynecology MFM, 100477.
26. Laraia, B. A., Siega-Riz, A. M., & Gundersen, C. (2010). Household food insecurity is associated with self-reported pregravid weight status, gestational weight gain, and pregnancy complications. Journal of the American Dietetic Association, 110(5), 692-701
27. Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980-2007. Obstet Gynecol. 2011 Apr;117(4):837-843. doi: 10.1097/AOG.0b013e3182113c10. PMID: 21422853.
28. Winkelman, T. N. A., Ford, B. R., Shlafer, R. J., McWilliams, A., Admon, L. K., & Patrick, S. W. (2020). Medications for opioid use disorder among pregnant women referred by criminal justice agencies before and after Medicaid expansion: A retrospective study of admissions to treatment centers in the United States. Plos Medicine, 17(5), Article e1003119. https://doi.org/10.1371/journal.pmed.1003119 p

29. Paynter MJ, Drake EK, Cassidy C, Snelgrove-Clarke E. Maternal health outcomes for incarcerated women: A scoping review. J Clin Nurs. 2019 Jun;28(11-12):2046-2060. doi: 10.1111/jocn.14837. Epub 2019 Mar 12. PMID: 30786097.
30. Yee, L. M., Janik, M. C., Dorman, R. M., Chong, P. S., Garcia, P. M., & Miller, E. S. (2018). Relationship between intimate partner violence and antiretroviral adherence and viral suppression in pregnancy. Sexual & Reproductive HealthCare, 17, 7-11. https://doi.org/10.1016/j.srhc.2018.05.001
31. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions AHRQ. 2012.
32. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
33. Bero, L., Chartres, N., Diong, J. *et al.* The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Syst Rev* 7, 242 (2018). https://doi.org/10.1186/s13643-018-0915-2
34. Berkman ND, Lohr KN, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the Agency for Healthcare Research and Quality: an update. 2013.

VI. Definition of Terms

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
2/22/2022	Table 3 Study Enrollment inclusion/ exclusion criteria	No change to original. New language added.	Pregnancy/birthing is defined as a sustained pregnancy through at least 20 weeks gestation. Because the focus is on broad populations, studies were excluded if they focused solely on risk factors in birthing persons with specific medical conditions requiring specialty care diagnosed prior to pregnancy; for example, multiple sclerosis.	The change refines the inclusion/exclusion criteria to provide more specificity. It focuses review resources on the population with the broadest applicability.
2/22/2022	Table 3 Study Objectives inclusion/ exclusion criteria	No change to original. New language added.	The study must aim to understand the impact of some interpersonal factor(s) indicative of social determinants of health. Studies that examine only intrapersonal factors are excluded. For example, social stigma related to substance use and its impact on depression would be interpersonal, while mere existence of substance use would be intrapersonal.	The change refines the inclusion/exclusion criteria to provide more specificity. Potential study objectives and study designs to explore and examine risk factors related to maternal health are myriad and overlapping, with considerable zones of questionable relevance, and resulted in an overwhelmingly large set of possibly included studies. This clarification further

				focuses the review on literature most relevant to the review purpose.
2/22/2022	Table 3 Study Exposures inclusion/ exclusion criteria	Studies are not excluded based on specific exposures (see Table 3 for example exposures).	Table 2 provides example exposures that would be eligible for inclusion. Table 2 should not be viewed as an exhaustive list. However, exposures related to assistive reproductive technologies (ART) are excluded as these exposures are less commonly available or used by marginalized populations.	ART was one exposure determined not of interest as it is less likely to be accessible to and used by marginalized communities. Also, the typo for Table 2 was corrected.
2/22/2022	Table 3 Outcomes inclusion/ exclusion criteria	Individual studies must include at least one medical or healthcare-related outcome. Studies are not excluded based on maternal health outcomes. Studies that report only neonatal or infant outcomes are excluded.	Individual studies must include at least one maternal medical or healthcare-related outcome. Studies that report only neonatal or infant outcomes are excluded. Intermediate outcomes, such as blood pressure, lab values, or psychometric scales that are not intended for diagnostics, are excluded unless they are used in an explicit fashion to explain pathways through which social determinants of health may work. Stress outcomes are included if they are operationalized as a global measure of stress. Examples may include using chronic inflammation or reactivation of Epstein-Barr virus as indications of stress-induced homeostatic weakness. Perceived stress scale scores are included if they are used as a direct measure of response to social determinant of health. Stress responses, such as cortisol level, are excluded.	The change refines the inclusion/exclusion criteria to provide more specificity. It provides clarity on the eligibility of intermediate outcomes and how stress will be operationalized, while focusing the review resources on the outcomes of most relevance.

VIII. Review of Key Questions

National Institutes of Health ODP provided the initial Key Questions to inform their P2P Workshop. The EPC refined and finalized the Key Questions with input from AHRQ and the NIH/ODP Working Group. This input was intended to ensure that the Key Questions are specific and relevant.

IX. NIH/ODP Working Group

National Institutes of Health ODP provided input on the Key Questions, PICOTS, and inclusion criteria for studies to inform a P2P Workshop. The NIH/ODP Working Group gave feedback on the Topic Refinement, participated in monthly calls, and will participate with AHRQ, the EPC, and a Content Area Expert Group in a Webinar to refine the project scope.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and

identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XIII. Role of the Funder

This project was funded under Contract No. 75Q80120D00008 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. Search Algorithm

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 18, 2021>

1 Birth Setting/ or Delivery, Obstetric/ or Labor, Obstetric/ or exp Labor Onset/ or Obstetrics/ or Parturition/ or Prenatal Care/ or Postpartum Period/ or Pregnancy/ or exp Pregnancy Complications/ or Pregnant Women/ or Pregnancy, High-Risk/ or (antenatal* or ante-natal* or antepartum or ante-partum or birth or birthing or intrapartum or intra-partum or obstetric* or parturition or parturient* or peripartum or peri-partum or postpartum or post-partum or pregnan* or prenatal* or pre-natal* or puerperium).ti,ab,kw. 1333770

2 Maternal Death/ or Maternal Health/ or Maternal Mortality/ or (maternal adj3 (adverse or comorbid* or complication* or death* or health or morbid* or mortalit* or outcome*)).ti,ab,kw. 62327

3 ((intrapartum or intra-partum or obstetric* or parturition or parturient* or* or peripartum or peri-partum or postpartum or post-partum or puerperal or puerperium) adj3 (adverse or comorbid* or complication* or death* or health or morbid* or mortalit* or outcome*)).ti,ab,kw. 18874

4 (wom?n* adj3 (adverse or comorbid* or complication* or death* or health or morbid* or mortalit* or outcome*)).ti,ab,kw. 72214

5 (birthing adj (people or person or persons) adj5 (death or mortalit* or morbidit* or complication* or health or outcome*)).ti,ab,kw. 8

6 or/2-5 138356

7 1 and 686736

8 quality assurance, health care/ or near miss, healthcare/ or health status indicators/ or apache/ or patient acuity/ or "severity of illness index"/ or early warning score/ or organ dysfunction scores/ or sickness impact profile/ or "outcome and process assessment, health care"/ or outcome assessment, health care/ or patient outcome assessment/ or treatment outcome/ or watchful waiting/ or process assessment, health care/ or risk/ or logistic models/ or Probability/ or Predictive Value of Tests/ or risk assessment/ or risk management/ or risk factors/ or uncertainty/ or forecasting/ or early diagnosis/ or "reproducibility of results"/ or Regression Analysis/ or Quality Improvement/ or Practice Patterns, Physicians'/ 3316235

9 ("health status indicators" or "apache" or "patient acuity" or "quality improvement" or "outcome assessment" or "patient assessment" or "process assessment" or "reproducibility of results" or "early warning" or "organ dysfunction scores" or "watchful waiting" or "regression analysis" or regression model* or "correlation analysis" or "predictive value" or hazard model* or logistic regression or "near miss").ti,ab,kw. 775160

10 (risk* adj3 (assess* or factor* or score* or model*)).ti,ab,kw. 821353

11 Health Status Disparities/ or Healthcare Disparities/ or Race Factors/ or Racism/ or exp Socioeconomic Factors/ or exp "Social Determinants of Health"/ 504634

12 ((health adj3 (discriminat* or disparit* or social determinant*)) or sociodemographic* or socio-demographic* or socioeconomic* or socio-ecomonic* or racism).ti,ab,kw. 220525

13 (ethnic* adj3 (differen* or discriminat* or disparit* or inequality or inequity or social determinant* or unequal)).ti,ab,kw. 30528

14 ((racial or racist or race) adj3 (differen* or discriminat* or disparit* or inequality or inequity or social determinant* or unequal)).ti,ab,kw. 27970

15 or/8-144482739

16 United States/ or ("United States" or USA).ti,ab,kw.1174644

17 African Americans/ or Alaskan Natives/ or American Natives/ or Asian Americans/ or exp Ethnic Groups/ or Hispanic Americans/ or Indians, North American/ or Medicaid/ or Mexican Americans/ or (American* or Alaskan natives or Chicana* or Hispanic* or Nonhispanic* or Non-hispanic* or Latina* or Alabama or Alaska or Arizona or Arkansas or California or Colorado or Connecticut or Delaware or Florida or Georgia or Hawaii or Idaho or Illinois or Indiana or Iowa or Kansas or Kentucky or Louisiana or Maine or Maryland or Massachusetts or Michigan or Minnesota or Mississippi or Missouri or Montana or Nebraska or Nevada or New Hampshire or New Jersey or New Mexico or New York or North Carolina or North Dakota or Ohio or Oklahoma or Oregon or Pennsylvania or Rhode Island or South Carolina or South Dakota or Tennessee or Texas or Utah or Vermont or Virginia or Washington or West Virginia or Wisconsin or Wyoming or Appalachia* or Albuquerque or Anchorage or Atlanta or Austin or Baltimore or Billings or Baton Rouge or Boise or Boston or Birmingham or Charlotte or Cheyenne or Chicago or Cincinnati or Cleveland or Columbus or Dallas or Denver or Des Moines or Detroit or District of Columbia or Fargo or Houston or Honolulu or Indianapolis or Jacksonville or Lafayette or Las Vegas or Little Rock or Lexington or Los Angeles or Louisville or Miami or Milwaukee or Minneapolis or Nashville or New England or New Orleans or Newark or Omaha or Philadelphia or Phoenix or Pittsburgh or Portland or Providence or Richmond or Rochester or San Antonio or Salt Lake City or San Francisco or San Diego or Sacramento or Seattle or Sioux Falls or St Paul or Tampa or Wichita or Medicaid).ti,ab,kw. 1043630

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19 6 and 7 and 15 and 186323

20 limit 19 to english language 6222

21 limit 20 to (clinical trial, veterinary or clinical trials, veterinary as topic or congress or consensus development conference or editorial or "expression of concern" or festschrift or government publication or guideline or interview or lecture or legal case or legislation or letter or

news or newspaper article or observational study, veterinary or practice guideline or randomized controlled trial, veterinary or "review") 831

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