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Multilevel Determinants of Racial/Ethnic Disparities in Maternal Morbidity and Mortality in the Context of the COVID-19 Pandemic: A Research Protocol

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Complete List of Authors:	Liu, Jihong; University of South Carolina, Department of Epidemiology & Biostatistics Hung, Peiyin ; University of South Carolina, Health Services Policy and Management Liang, Chen; University of South Carolina, Department of Health Services Policy & Management Zhang, Jiajia; University of South Carolina, Department of Epidemiology and Biostatistics, Arnold School of Public Health Qiao, Shan; University of South Carolina, Campbell, Berry; University of South Carolina, Department of Obstetrics and Gynecology; University of South Carolina, Department of Health Services Policy & Management Olatosi, Bankole; University of South Carolina Arnold School of Public Health, Health Services, Policy and Management Torres, Myriam; University of South Carolina System Hikmet, Neset; University of South Carolina, Department of Integrated Information Technology Li, Xiaoming; University of South Carolina Arnold School of Public Health
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Manuscripts

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3 **Multilevel Determinants of Racial/Ethnic Disparities in Maternal Morbidity and**
4 **Mortality in the Context of the COVID-19 Pandemic: A Research Protocol**
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7

8 **Authors:**
9

10 Jihong Liu, ScD, Department of Epidemiology & Biostatistics, Arnold School of Public Health,
11 University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
12
13

14
15 Peiyin Hung, PhD, Department of Health Services Policy & Management, Arnold School of
16 Public Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
17
18

19
20 Chen Liang, PhD, Department of Health Services Policy & Management, Arnold School of Public
21 Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
22
23

24
25 Jiajia Zhang, PhD, Department of Epidemiology & Biostatistics, Arnold School of Public Health,
26 University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
27
28

29
30 Shan Qiao, PhD, Department of Health Promotion, Education, & Behavior, Arnold School of
31 Public Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
32
33

34
35 Berry A. Campbell, MD, Department of Obstetrics and Gynecology, School of Medicine,
36 University of South Carolina. Two Medical Park, Columbia, SC 29203, USA.
37
38

39
40 Bankole Olatosi, PhD, Department of Health Services Policy & Management, Arnold School of
41 Public Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
42
43

44
45 Myriam Torres, PhD, Department of Epidemiology & Biostatistics, Arnold School of Public
46 Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
47
48

49
50 Neset Hikmet, PhD, Department of Integrated Information Technology, College of Engineering
51 and Computing, University of South Carolina. 550 Assembly Street, Columbia, SC 29208, USA.
52
53

1
2
3 Xiaoming Li, PhD, Department of Health Promotion, Education, & Behavior, Arnold School of
4
5 Public Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
6
7
8
9

10
11 **Corresponding author:**
12

13 Dr. Jihong Liu, Professor of Epidemiology, Department of Epidemiology & Biostatistics, Arnold
14
15 School of Public Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208,
16
17 USA. jliu@mailbox.sc.edu. Phone: 803 777 6854
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ABSTRACT

Introduction: The COVID-19 pandemic has affected communities of color the hardest. Non-Hispanic Black and Hispanic pregnant women appear to have disproportionate SARS-CoV-2 infection and death rates. Our overarching goal is to investigate racial/ethnic disparities in severe maternal morbidity and mortality (SMMM), the contributing roles and mediating pathways of social contexts (e.g., racial/ethnic residential segregation, racial discrimination in poverty, education, unemployment, and home ownership) and their health consequences postpartum.

Methods and analysis: We will use the socio-ecological framework and employ a concurrent triangulation, mixed methods study design to achieve three specific aims: 1) examine the impacts of the COVID-19 pandemic on racial/ethnic disparities in SMMM; 2) explore how social contexts have contributed to the widening of racial/ethnic disparities in SMMM during the pandemic and identify distinct mediating pathways through maternity care and mental health; and 3) determine the role of social contextual factors on racial/ethnic disparities in pregnancy-related morbidities using machine learning algorithms. We will leverage an existing South Carolina COVID-19 Cohort (S3C) by creating a pregnancy cohort that links COVID-19 testing data, electronic health records (EHR), birth and death certificate data, health care utilization data, and billing data for all births in South Carolina between 2018-2021. We will also conduct similar analyses using EHR data from the National COVID Cohort Collaborative (N3C). Nationwide social context databases and effects of time-varying COVID-19 severity and social distancing policies will be added. We will use a convergent parallel design which includes a quantitative analysis of data from South Carolina Pregnancy Risk Assessment and Monitoring System and qualitative interviews of 40 postpartum women and 20 maternal care providers to identify distinct mediating pathways.

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3 **Ethics and dissemination:** The study was approved by institutional review boards. Study
4 findings will be disseminated with key stakeholders including patients, presented at academic
5 conferences, and published in peer-reviewed journals.
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Strengths and limitations of this study

- This study is among the first efforts to investigate whether the COVID-19 pandemic, structural racism, and racial discrimination have contributed to the racial/ethnic disparities in SMMM in the context of the COVID-19 pandemic.
- This study employs a state-of-the-art design (i.e., a convergent parallel design) and machine learning models to rigorously examine the questions of interest.
- This study will use a large-scale population-based cohort study concurrently for both SC and the U.S., which will innovatively integrate COVID-19-related clinical, surveillance, EHR, and geospatial data at community, healthcare institutions, and system/policy levels.
- The county-level social contexts' effects may not be significant. If that happens, ZIP-code level social contexts will be calculated.
- The stagnant residential social contexts might not reflect their long-term exposures to neighborhood structural racism.

INTRODUCTION

Annually, nearly 60,000 women experience severe maternal morbidity (i.e., unexpected complications of labor and delivery) and mortality (SMMM).^{1,2} Between 1993-2014, SMMM rates in the U.S. tripled from 49.5 to 146.6 per 10,000 childbirths.³ For every 70 U.S. women who experienced a severe maternal morbidity, one died during or immediately after pregnancy.⁴ The severe maternal morbidity occurrences have also led to significant short- or long-term clinical impacts on women's health⁵ and added significant costs to women, their families, taxpayers and the healthcare system.⁶⁻⁸

Non-Hispanic Black (hereafter, Black) women experience a 3- to 4-fold risk of pregnancy-related deaths compared to non-Hispanic White women (hereafter, White).^{9,10} Black and Hispanic women were up to 110 percent more likely to experience SMMM,² despite their younger maternal age (often a protective factor for SMMM) as compared to non-Hispanic White women. Such racial/ethnic disparities in SMMM rates have persisted for over a decade – with increasing rates among all race/ethnic groups.¹¹ These SMMM rates are unevenly distributed socioeconomically and geographically – with the highest rate among low-income women who delivered at hospitals in the Deep South states.^{2,12-14}

The unprecedented COVID-19 pandemic hit communities of color the hardest.¹⁵⁻¹⁷ Pregnant Black and Hispanic women experienced disproportionate COVID-19 infection and death rates.¹⁸⁻²⁰ The impacts of COVID-19 on SMMM remain unclear. During the pandemic, as unemployment, income instability, and financial stress have affected many U.S. families, Black and Hispanic families have faced even higher hardship rates.²¹ These disproportionate consequences reflect longstanding inequities, often stemming from structural racism and discrimination (e.g., residential segregation, poverty, inadequate education, unemployment, and lack of home ownership).^{22,23} These inequities can lead to uneven access to quality healthcare, psychosocial stress, and unhealthy lifestyles among women of color, which further increases SMMM risk.^{24,25} Yet, the etiology of SMMM is complex, multifaceted, and time-varying. Prior

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3 research efforts on racial/ethnic disparities in SMMM have mostly focused on maternal and
4 healthcare factors,²⁶ leaving questions regarding the dynamics and interactions of multilevel
5 determinants, such as the broader social contexts of these risks, largely unanswered. Thus, there
6 is an urgent need to examine how social contexts of all types play out in SMMM rates, especially
7 during the COVID-19 pandemic.^{22,23}

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14 South Carolina (SC) ranked 11th in COVID-19 cases per capita as of December 23, 2021.²⁷
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16 Prior to the pandemic, SC ranked 42nd in the U.S. in overall health and 41st in maternal
17 mortality.²⁸ Births to Black women accounted for nearly 30% of all SC births.²⁹ Black women
18 living in SC experienced a 2- to 3-fold higher risk of SMMM than their White counterparts.³⁰
19
20 The majority of counties in SC are designated medically underserved areas.³¹ Considering SC's
21 poor health ranking, striking racial disparities in SMMM, racially diverse population, and
22 historical systemic Southern contexts, SC is an ideal environment in which to examine health
23 disparities in SMMM occurring during the COVID-19 pandemic.

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30 The overarching goal of this study is to investigate racial/ethnic disparities in SMMM, the
31 contributing roles and mediating pathways of social contexts (e.g., structural racism, racial
32 discrimination), and the long-standing health consequences of the pandemic by studying the
33 distributions of COVID-19 cases and multilevel determinants of maternal health in SC and the
34 U.S. Our study will: 1) examine the impacts of the COVID-19 pandemic on racial/ethnic
35 disparities in SMMM; 2) examine and explore how the key features of social contexts (including
36 structural racism and racial discrimination) have contributed to the widening racial/ethnic
37 disparities in SMMM during the pandemic and identify distinct mediating pathways through
38 maternity care and mental health; and 3) examine and identify the role of social contextual
39 factors and protective factors on racial/ethnic disparities in pregnancy-related long-standing
40 morbidities (e.g., hypertension, pulmonary embolism, diabetes, cardiovascular disease), using
41 machine-based learning algorithms.

METHODS AND ANALYSIS

Multilevel Conceptual Framework

The etiology of racial/ethnic disparities in SMMM is complex and multifaceted (**Figure 1**).²⁴ At the micro-level, in addition to maternal race/ethnicity, other socio-demographics (e.g., age, socioeconomic status [SES]), health behaviors (e.g., prenatal care adequacy, smoking, diet, physical activity, gestational weight gain), and preexisting maternal conditions (e.g., hypertension, pre-pregnancy body mass index (BMI), diabetes, HIV infection) potentially drive racial/ethnic disparities in SMMM.^{12,32} As compared to White women, Black and Hispanic women usually have higher poverty rates, lower educational levels, and higher rates of preexisting conditions or high-risk pregnancy.³² At the macro level, structural racism and discrimination - community and neighborhood factors (e.g., residential segregation, inadequate housing, lack of access to healthy food, no public transportation), healthcare institutional attributes (e.g., access to risk appropriate perinatal care), and system-level factors (e.g. policy) – may play a role in racial/ethnic disparities. These macro-level factors interact with micro-level factors to further exacerbate racial/ethnic disparities in SMMM.

Study Design

The above-mentioned multilevel conceptual framework guided our study design. We will employ a concurrent triangulation, mixed methods study design to rigorously examine racial/ethnic disparities in SMMM in SC and the U.S. This convergent parallel design will allow us to better understand the underlying mechanisms for social contexts and racial/ethnic disparities in SMMM via maternity care and mental health using the data from the statewide pregnancy survey and via qualitative interviews. Given the multilevel and multidomain nature of risk factors for pregnancy-related long-standing morbidities, we will use novel machine learning models to forecast the intertwining social context effects with multilevel factors on maternal health during the COVID-19 pandemic.

Data Sources

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3 We will leverage our statewide South Carolina COVID-19 Cohort (S3C) database, which
4 integrates COVID-19-related clinical, surveillance, electronic health records (EHR) and
5 geospatial and temporal data at community, healthcare institutional, and system levels to
6 comprehensively examine the roles of social contexts on racial/ethnic disparities in SMMM. To
7 ensure the generalizability of our findings, we will also examine them using EHR data from the
8 ongoing National COVID Cohort Collaborative (N3C).³³ Nationwide social context databases
9 (e.g. American Community Survey [ACS], American Hospital Association [AHA]) and time-
10 varying COVID-19 infection and social distancing policies data will be added to both S3C and
11 N3C. Postpartum women's survey responses and in-depth interview data will be analyzed to
12 understand complex pathways and multilevel determinants of maternal morbidities. **Table 1**
13 summarizes the objectives, key measures, and data sources for the study.
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18 *SC COVID-19 Cohort – Pregnancy (S3C-P) Database.* With support from the National
19 Institute of Allergy and Infectious Disease (NIAID) (R01A127203-4S1), our team has established
20 a statewide S3C database for COVID-19 research since 06/2020 by integrating various state-
21 level data sources including: 1) the COVID-19 testing data from the SC Department of Health
22 and Environmental Control (SC DHEC), 2) hospital encounter data for inpatient hospitalization,
23 outpatient surgery, home health, and emergency departments; 3) health utilization data from
24 large public and private health insurance plans (e.g., Medicaid, State Health Plan, BlueCross
25 BlueShield of SC); 4) EHR data from health systems (Prisma & MUSC), and 5) program data
26 from the SC Department of Mental Health (SC DMH). The database is updated every 6 months.
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31 In this study, with support from NIAID (R01A127203-5S2), our team will create a
32 population based S3C pregnant women cohort, which includes all women who gave birth
33 between 2018-2021 in SC (>200,000 births, 57.2% White, 31.1% Black, 4.6% Hispanic) and will
34 add vital record data (birth and death certificates) to complement existing linkages from the
35 parent S3C cohort. The identification of pregnancy status and COVID-19 infection will be cross-
36 verified using EHR, claims data, laboratory reports, and ongoing SC DHEC medical chart
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3 reviews among > 4,387 pregnant women with confirmed COVID-19 infections in SC as of
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5 December 2021. The SC Office of Revenue and Fiscal Affairs (SC RFA) will collate databases
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7 and provide our team with a de-identified linked database system.³⁴
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9 *National COVID Cohort Collaborative (N3C).* The N3C is a novel data consortium that
10 integrates EHR and medical claims data from 92 healthcare systems and institutes across 50
11 states. N3C enables data sharing, computable phenotypes, and collaborative data mining by
12 harmonizing EHR data of diverse standards using Observational Medical Outcomes Partnership
13 (OMOP) Clinical Data Model (CDM). N3C was created to study potential risk factors and
14 protective factors of COVID-19 and its long-term health consequences.³³ As of December 24,
15 2021, N3C has aggregated 9.4 million patients (3.3 million COVID-19 patients) with their EHR
16 dating back from January 2018, including 1.9 million women with COVID-19 (>61k pregnant
17 women), and 3.5 million women without COVID-19 (>209k pregnant women). The participants
18 in N3C represent diverse populations in the U.S. (e.g., geographic, socioeconomic,
19 racial/ethnic). Building on a secured cloud environment, N3C provides data harmonization,
20 privacy-preserving data linkage, and high-performance data analytics. Our team has already
21 gained access to the restricted N3C database including ZIP codes of patients and health systems
22 and dates of services.
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38 *Nationwide social context databases.* The 2015-2019 American Community Survey (ACS)
39 and the 2015-2019 American Hospital Association (AHA) Annual Survey will be used to
40 calculate county-level residential segregation measures, racial discrimination in SES, and ZIP-
41 level accessibility to hospital-based obstetric units.
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47 *Time-varying local COVID-19 infection and social-distancing policy data.* To better
48 understand local pandemic settings, we will also add the Centers for Disease Control and
49 Prevention (CDC) COVID-19 Case Surveillance restricted datasets for nationwide cases
50 confirmed since March 11, 2020, and CDC's state-level social distancing policies (e.g. emergency
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3 declaration, stay at home order, etc.) in early pandemic and telehealth services expansion data
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5 and each corresponding date of enactment.³⁵
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7 *SC Pregnancy Risk Assessment Monitoring System (PRAMS)*. SC PRAMS as a part of
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9 national PRAMS is an ongoing survey of SC mothers who have recently given birth.³⁶ These
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11 mothers are sampled from state birth certificates. After statistical weighting, PRAMS data are
12
13 representative of all mothers who gave birth in SC. SC PRAMS added 11 COVID-19-related
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15 questions for mothers who delivered in August 2020 and after in their survey. SC PRAMS
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17 routinely collects detailed psychosocial and behavioral risk factors for each participant, which
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19 are not available in S3C and N3C. Residential ZIP codes will be used to add in social contextual
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21 variables and other ZIP- or county-level characteristics. The unweighted sample size for SC
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23 2018-2021 PRAMS will be at least 2,000.
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26 Key Measures

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28 *Outcome measures*. The main outcomes of interest will be SMMM.³⁷ We will adapt from a
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30 previously validated algorithm by using the International Classification of Diseases, Tenth
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32 Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure codes to identify women
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34 with one or more of the 21 SMM indicators developed by the CDC and updated by the Alliance
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36 for Innovation on Maternal Health (AIM) program at the time of childbirth. Maternal mortality
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38 will be identified using statewide death certificate data from the childbirth date to up to one year
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40 postpartum. A composite variable of SMMM will be created to reflect SMM or maternal
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42 mortality incidence. We will also study maternal morbidity and mortality (MMM) composite,
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44 which includes mortality and morbidities related to hypertensive disorders of pregnancy,
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46 postpartum hemorrhage, and infections/sepsis that happen during pregnancy through 6 weeks
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48 postpartum.³⁸ Other outcomes to be studied include: 1) adverse maternal outcomes including
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50 intensive care unit (ICU) admission, invasive ventilation, receipt of extracorporeal membrane
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52 oxygenation (ECMO), etc.; 2) prolonged length of stay (LOS),^{39,40} and 3) hypertension,
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3 pulmonary embolism, type 2 diabetes, cardiovascular diseases (e.g. heart attack, myocardia
4 infraction, thrombus, stroke) diagnosed within one year after delivery (**Table 1**).

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7 *COVID-19 status and severity.* Eligible COVID-19 cases are those with a positive test for
8 SARS-CoV-2 since March 11, 2020, during pregnancy. Data on symptom status (symptomatic,
9 asymptomatic, unknown) is available, while severity will be defined using the World Health
10 Organization's (WHO) Clinical Progression Scale.⁴¹

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16 *Social context measures.* The five dimensions of county-level *residential segregation*,
17 including evenness, exposure, concentration, centralization, and clustering,^{42,43} will be
18 determined for each race/ethnic group (e.g., Black, Hispanic) using the ACS Census tract
19 data.^{44,45} Each index will be calculated across census tracts within residential counties. Higher
20 values indicate higher levels of segregation. We will create the group indicator for segregated
21 versus less segregated counties using the cutoffs for each dimension index.⁴⁵ Additional hyper-
22 segregation index – segregations scores at ≥ 0.6 on at least four aforementioned dimensions –
23 will be created to reflect the highest levels of segregation.⁴⁵ Within-county *racial/ethnic*
24 *discrimination in SES* will be calculated using the ACS county data,⁴⁴ including Black-White and
25 Hispanic-White ratios of poverty, unemployment, and home ownership rates.⁴⁶⁻⁵⁰ These
26 measures will be linked to databases via maternal residence counties.

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38 *Healthcare institution.* Using the AHA annual survey data on hospital location,⁵¹ we will
39 identify *loss of hospital-based obstetric units* using our published validated algorithm.⁵²⁻⁵⁴ An
40 indicator for whether a hospital or a hospital's obstetric service was closed for each year will be
41 created. In turn, women's access to hospital-based obstetric care within 30-mile distance for
42 years 2018-2020 using the ArcGIS fastest route network will be determined: 1) had access to; 2)
43 no access to; and 3) experienced the loss of all hospital-based obstetric units.

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51 *County-level COVID-19 infections and social distancing policies.* The CDC's COVID-19 Case
52 Surveillance will be used to compute monthly cumulative rates of in-county residents that had
53 been confirmed COVID-19 positive, hospitalized, admitted to an intensive care unit, and with
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3 mechanical ventilation (MV)/intubation as a result of COVID-19 disease. Number of months
4 elapsed since a county had each of the following policy orders will be calculated from a delivery
5 date: emergency declaration, closures of bars, restaurants, and/or other non-essential business,
6 stay at home order, and telehealth services expansion.
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10 11 Statistical Analyses

12 *Impacts of the COVID-19 pandemic on racial/ethnic disparities in SMMM.*

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15 We will examine the overall impacts of the COVID-19 pandemic on SMMM using the data
16 from the S3C-P and N3C (**Table 1**). We hypothesize that: 1) compared to pre-pandemic periods,
17 SMMM has increased during the pandemic and racial/ethnic disparities have widened during
18 the pandemic; and 2) compared to pregnant women without COVID-19 infection, women with
19 COVID-19 infection experienced higher proportions of SMMM, and racial/ethnic disparities in
20 SMMM have amplified among COVID-19 infected women.
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28 First, we will examine the distributions for all measures and clean the database (e.g. outliers,
29 data entry errors etc.) using appropriate statistical techniques. Second, we will conduct
30 preliminary analyses and examine descriptive statistics for outcome measures. Unadjusted and
31 adjusted associations of SMMM with key variables and covariates will be assessed using
32 appropriate statistical procedures (e.g., tests of proportions, chi-square tests, analysis of
33 variance).
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40 Women who gave birth between January 1, 2018 through March 10, 2020, will be
41 categorized as before pandemic, while women who gave birth between March 11, 2020 through
42 December 31, 2021, will be considered as during the pandemic. The pre-pandemic vs pandemic
43 impact on SMMM will be modeled via logistic regression. First, the crude model with the
44 pandemic indicator only will address SMMM change before and after the pandemic. Second, to
45 investigate whether racial/ethnic disparities in SMMM have widened during the pandemic, the
46 crude model will be further adjusted with race/ethnicity, interactions between race/ethnicity
47 and pandemic indicator, and months elapsed since March 11, 2020, on delivery dates. Then
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3 additional variables will be added, including individual-level characteristics (e.g., age, SES proxy
4 [i.e., Medicaid/uninsured status], parity, marital status, underlying health conditions). Variable
5 selection and goodness of model fit will be evaluated using the AIC, BIC, and likelihood ratio
6 test.
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11 We will also conduct analyses in women who delivered during the COVID-19 pandemic by
12 comparing pregnant women with and without COVID-19 infection. We will first create the
13 COVID infection indicator and then will perform the similar analysis as those for the pre-
14 pandemic vs pandemic impact. We will further adjust for county-level COVID-19 infections per
15 capita and social distancing policies at the appropriate time points using logistic regressions
16 with random effects accounting for correlations among counties.
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24 *Social contexts, racial/ethnic disparities in SMMM, and distinct mediating pathways.*
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26 We will study these issues using different databases and methods. First, we will examine the
27 association between social contexts and changes in racial/ethnic disparities in SMMM before
28 and during the pandemic. We hypothesize that racial/ethnic disparities SMMM are potentially
29 disproportionately widened in communities with higher racial/ethnic economic disparities
30 (measured by Black-White ratios of economic disadvantages, Hispanic-White ratios of economic
31 disadvantages) and in higher vs. less segregated Black or Hispanic counties (measured by
32 residential segregation). We will conduct a parallel analysis between social contexts and SMMM
33 using the data from S3C-P and N3C (**Table 1**). Similarly, we will examine the contributing roles
34 of social contexts to racial/ethnic disparities in SMMM in the overall sample (pre-pandemic vs
35 pandemic) and between COVID-19 positive vs COVID-19 negative women. The multilevel
36 variables that will be investigated include individual-level characteristics, community-level
37 characteristics (ZIP code accessibility of hospital obstetric units), and county-level characteristic
38 (social contexts: residential segregation and racial discrimination on SES; COVID-19 infection
39 per capita and social distancing policies). For exploratory analysis, the odds ratio (OR) of
40 SMMM among Black and White and the social context level at the county level pre-pandemic vs
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3 pandemic will be visualized via the spatial temporal map using GIS. The summary statistics in
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5 SMMM with respect to race/ethnicity will be calculated according to individual- and county-
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7 level characteristic.
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10 **Table 1. Summary of key measures and data sources by objectives**

Objectives	Key Outcomes	Key Independent Variables	Data Sources
COVID-19 pandemic and maternal health disparity	<ul style="list-style-type: none"> • SMMM (Primary) • MMM • Adverse maternal outcomes • Prolonged LOS 	<ul style="list-style-type: none"> • Race/ethnicity • Delivery time since March 2020 	S3C ¹ N3C ²
Social contexts, and maternal health disparity and distinct mediating pathways through maternity care and mental health during COVID-19	<ul style="list-style-type: none"> • SMMM (Primary) • MMM • Adverse maternal outcomes • Prolonged LOS 	<ul style="list-style-type: none"> • Race/ethnicity • Social contextual factors • COVID-19 status and severity • Delivery time since March 2020 	S3C ¹ N3C ²
	<ul style="list-style-type: none"> • MMM 	<ul style="list-style-type: none"> • Race/ethnicity • Social contextual factors • COVID-19 pandemic stressors • Mental health status • Perinatal care 	PRAMS
Social and clinical factors for disparities in long-standing morbidities	<ul style="list-style-type: none"> • Hypertensive disorder • Pulmonary embolism • Type II diabetes • Cardiovascular diseases 	<ul style="list-style-type: none"> • Maternal-level factors • Social contextual factors • System-level factors 	N3C ²

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38 ¹. SC COVID-19 Pregnancy Cohort (S3C-P) includes >200,000 women with childbirths in 01/2018-12/2021
39 and >4,387 pregnant women with confirmed COVID-19 infections as of December 2021.

40 ². National COVID Cohort Collaborative (N3C) contains >61K pregnant women with COVID and
41 >209K pregnant women without COVID-19.
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43 We will model SMMM via multilevel hierarchical logistic regression. Women who reside at
44 the same community- or county-level will be accounted for via random effects, which will be
45 further modeled in the regression model with a multivariate normal distribution to account for
46 the correlations among community or county. We plan to use an incremental modeling strategy:
47 1) crude model (race/ethnicity and social context factors); 2) adjusting for individual level
48 factors; and 3) additional adjustment of additional community- and county-levels
49 characteristics. For N3C data, we will further adjust for state or Census region. To further
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3 examine whether social contexts moderate racial/ethnic disparities in SMMM and whether
4 these disparities vary between pre-pandemic and pandemic, we will include two-way and three-
5 way interaction terms in the model (e.g., pandemic period*social context*race). To examine the
6 added impact of COVID-19 infections on SMMM, we will repeat the model by restricting it to all
7 women who gave birth during pandemic period (delivered after March 11, 2020) and including
8 maternal COVID-19 severity status in the model. Models will be compared using the AIC and
9 BIC criteria. In the modelling procedure, the outliers, missingness, multicollinearity, and
10 nonlinear will be addressed accordingly, and sensitivity analysis will be conducted comparing
11 models with or without the treatment of outliers or missing data. The magnitude and direction
12 racial/ethnic disparities will be assessed through OR and its 95% confidence interval.

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Second, we will evaluate the underlying pathways between social contexts and racial/ethnic
disparities in MMM via pandemic stressors, maternity care (prenatal and postpartum) and
mental health condition. We hypothesize that social contexts might hinder maternity care and
worsen mental health conditions among Black and Hispanic women during the pandemic and
exacerbate racial/ethnic disparities in MMM.

We will use a convergent parallel design to examine the impact of social contexts on
maternal health and complex pathways between multilevel determinants. We will analyze data
from the quantitative and qualitative methods independently and interpret findings jointly.

The quantitative analysis will be conducted using SC PRAMS data, which have unique data
elements that are not available in S3C-P and N3C. The 2018-2021 SC PRAMS data will provide a
more refined understanding of COVID-19 stressors, psychosocial stress, and healthcare
utilization through the questionnaire, including pandemic stressors (financial, job loss,
childcare, etc.), individual mitigation practices, changes in prenatal and postpartum care,
psychosocial stress, barriers to health services, intimate partner violence (IPV), prenatal and
postpartum care utilization, smoking, alcohol use, gestational weight gain, and mental health.
SC PRAMS asks respondents to assess how often they experienced depressive symptoms after

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3 delivery. Descriptive statistics will be used to examine pandemic-related changes in MMM and
4 psychosocial and behavioral changes between pre-pandemic (delivered before March 11, 2020)
5 and pandemic periods (March 11, 2020 and after). The weighted hierarchical regression model
6 will be applied to examine the association between social context and MMM. As previously
7 mentioned, community and county levels will also be modeled in the regression. Different from
8 the prior analyses above: 1) individual characteristics will mainly come from PRAMS or birth
9 certificates; 2) the weight based on complex survey design will be modeled; and 3) individual
10 reports of healthcare utilization and mental health condition included.

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12 We will conduct in-depth qualitative interviews among 40 postpartum women of color (~20
13 African American; ~20 Hispanic) stratified by COVID-19 infection status and 20 maternal care
14 providers (MCPs) who serve pregnant and postpartum women in Black and Latino
15 communities. The inclusion criteria of postpartum women include: 1) ≥ 18 years old; 2) either
16 African American or Hispanic; 3) have given birth within one year; and 4) living in SC. We will
17 purposely recruit postpartum women and MCPs through local OBGYN clinics and community
18 health organizations that serve a larger proportion of low-income Black and Hispanic women.
19 We will train female interviewers of the same race as the interviewees to obtain trust from the
20 postpartum women participants, and interviews in Spanish will be conducted as needed. Guided
21 by the conceptual framework, the main topics of the postpartum women interviews will include:
22 1) their perceptions toward their healthcare providers and institutions for perinatal care; 2)
23 experience with prenatal and postpartum care; 3) stressors in the COVID-19 pandemic; 4)
24 challenges in healthcare seeking (e.g., appointments, clinic visits), especially from structural
25 factors (racism and discrimination); and 5) their needs/recommendations for future healthcare.
26 The main topics of the MCPs include: 1) stressors and challenges of their clients; 2) clients'
27 mental health conditions; 3) impacts of COVID-19 on their care provision; and 4) their views on
28 health disparities caused by structural factors. The interviews will last 50 minutes and will be
29 recorded with each participant's consent. Audio recordings will be transcribed and coded using

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3 NVivo 11.0. We will employ thematic analyses.⁵⁵ The findings will complement the quantitative
4 data in providing a comprehensive picture on how COVID-19 affects psychosocial well-being of
5 the postpartum women of color; offer in-depth interpretation and explanation of quantitative
6 results; and explore the mediating pathways in which structural factors amplify existing
7 disparities in maternal health in the context of the pandemic.
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13 *Machine learning-based predictive models.*

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15 We will develop and evaluate machine learning-based predictive models to identify risk
16 factors of SMMM and forecast progression of hypertensive disorder, pulmonary conditions, type
17 2 diabetes mellitus, and cardiovascular diseases among postpartum women. The predictive
18 models will synthesize individuals' demographics, EHR, social contextual factors, and
19 community and healthcare system level data to make predictions of individuals' clinical
20 outcomes at key time points. Because data sources suggestive of these factors are variable and
21 high-dimensional, and these factors are inherently interconnected over time,⁵⁶ machine learning
22 is a superior approach to predicting clinical outcomes and proactively detecting the associated
23 risk factors for early intervention and treatment. Constructed models will demonstrate critical
24 factors predictive of clinical outcomes and how these factors interact over time.
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36 Supervised machine learning will be adopted for the predictive models. Using N3C, the
37 machine will learn from input variables and predict SMMM and long-standing morbidities (e.g.,
38 hypertension, pulmonary embolism, diabetes, cardiovascular diseases) over time. Input
39 variables will include maternal characteristics, e.g., socio-demographics, socio-behavioral data,
40 social context variables, diagnoses, procedures, laboratory tests, and medications. The
41 prediction of SMMM and long-standing morbidities will take place at critical time points: < 3, 6,
42 12 weeks, 6 and 12 months postpartum.⁵⁷ We will develop Deep Learning algorithms because of
43 their ability to integrate complex clinical data and social contexts from multiple sources with
44 superior predictive performance, including: 1) convolutional neural network (CNN) for its
45 ability to capture dynamic patterns among multilevel input variables; 2) recurrent neural
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3 network (RNN) with long short-term memory (LSTM) architecture for its ability of capturing
4 temporal patterns of clinical events (e.g., pre-infection conditions, childbirths); and 3) Deep
5 Boltzmann Machine (DBM) for its interpretable scoring mechanism for risk prediction.⁵⁸
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9 We will use a 10-fold cross validation. Specifically, S3C and N3C data will each be randomly
10 partitioned into ten splits. In each of the ten iterations, nine splits of data will be randomly
11 selected for model training and the 10th split used for testing. We will use F measure, precision,
12 recall, and the area under the Receiver Operating Characteristic curve (AUC), if unbalanced
13 data, to measure the predictive performance of models. We will use support vector machine
14 (SVM) as the baseline algorithm to compare against the performance of CNN, RNN (LSTM), and
15 DBM. The best-performed model will be identified based on F measure.
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19 We will rank input variables and/or clusters of input variables by calculating the importance
20 scores ⁵⁶ (e.g., mutual information, SVM-based recursive linear elimination). Two content co-
21 investigators will independently review the ranked results and identify clinical/social risk
22 factors. Disagreement between two reviewers will be resolved by panel discussion. Development
23 of sophisticated machine learning models for predicting long-standing morbidities will be used
24 to identify important risk factors prenatally, which can be used for early intervention, treatment,
25 and community-wide interventions.
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29 *Power and Sample Size Calculation.* We estimate that there are 200,000 women who gave
30 birth in S3C and 270,000 pregnant women in N3C for our study period. The primary outcome of
31 interest is SMM and the main exposures of interest are race (White vs Black) and pre-peri
32 COVID period. We assume that there are 64,000 (32%) Black and 114,000 (57%) White in S3C⁵⁹
33 and 38,070(14.1%) Black and 160,380 (59.4%) White in N3C.⁶⁰ We also assume that with the
34 same time length of pre and peri COVID-19, the prevalence of pregnancy will be similar (50%).
35 For all aims, we consider the logistic regression with mixed effects. Based on 1.5%-2.5%
36 incidence of SMM with 20%-50% increase due to the COVID -19 impact or race disparities, we
37 conduct the power analysis based on the logistic regression using SAS and conclude that
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3 200,000 sample size will be adequate to reach the power around 90%. **Figure 2** illustrates the
4 relationship of power and odds ratio with setting of $n=200,000$, significance at 0.05, variable of
5 interest with a ratio of 10:90. This will be the basic model considered, and it indicates strong
6 power for the prediction model.
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10 Patient and Public Involvement

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13 No patient involvement in the design, conduct and reporting of our research. We will
14 actively reach out patients and public in the dissemination of our findings.
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18 **DISCUSSION**

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20 The COVID-19 pandemic has led to unprecedented societal disruptions to individuals,
21 communities, healthcare institutions, and society. Empirical data on the scope of possible
22 widening racial/ethnic disparities in SMMM during the COVID-19 pandemic and how historical
23 structural racism and discrimination of all types have impacted women of color
24 disproportionately are sparse. This study will be among the first efforts to investigate whether the
25 COVID-19 pandemic, structural racism, and racial discrimination— exposures with broad scale
26 and reach – have contributed to the racial/ethnic disparities in SMMM in the context of the
27 COVID-19 pandemic. Second, this proposed study employs a state-of-the-art design (i.e., a
28 convergent parallel design) to comprehensively examine the impacts of structural racism and
29 discrimination on maternal health and the complex pathways between multilevel determinants.
30 This design has the advantage of allowing us to weigh both quantitative and qualitative methods
31 equally and interpret the results together.⁶¹ Third, the proposed study will innovatively use
32 machine learning models to predict SMMM and chronic morbidities up to one year after
33 delivery in the context of the COVID-19 pandemic. Fourth, we propose a large-scale population-
34 based cohort study concurrently for both SC and the U.S., which will innovatively integrate
35 COVID-19-related clinical, surveillance, EHR, and geospatial data at community, healthcare
36 institutions, and system/policy levels. These newly integrated data sources will allow us to
37 examine multilevel determinants of maternal health during the pandemic and advance the
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3 investigation on racial/ethnic disparities in long-standing complications post-pandemic. In
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5 brief, this research represents a significant and innovative contribution to the research on the
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7 unacceptable racial/ethnic disparities in SMMM during pregnancy and postpartum in the
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9 context of COVID-19. By focusing on social contextual factors (e.g., structural racism), we seek
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11 to identify ways in which the largest number of women may be impacted by targeted programs
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13 and policies aiming to alter the context in which these morbidities and mortality occur.
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16 This study also has some limitations. First, it is possible that the county-level social contexts'
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18 effects in our data may not be significant. If that happens, we will calculate ZIP-code level social
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20 contexts. By assessing racial segregations, spatial distribution of economic disadvantage
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22 communities within a residence county and within-community racial discrimination, this study
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24 will provide evidence on the associations between distinct social contexts and maternal health
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26 disparities. Second, considering some women may move during pregnancy, the stagnant
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28 residential social contexts might not reflect their long-term exposures to neighborhood
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30 structural racism. Furthermore, in the case of inferior F measures (<0.7) of learning predictive
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32 models, we will apply feature selection algorithms and association rules in model training to
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34 maximize performance.
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37 In conclusion, the rising SMMM rate and persistent racial/ethnic disparities should trigger
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39 public health concerns, not only due to the immediate burden faced by vulnerable women, but
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41 also due to potentially lasting effects on women's health over a life course or along family lines
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43 across generations.⁶² This study will investigate racial/ethnic disparities in SMMM, the
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45 contributing roles and mediating pathways of social contexts (e.g., structural racism, racial
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47 discrimination), and the long-standing health consequences of the pandemic by studying the
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49 distributions of COVID-19 cases and multilevel determinants of maternal health in a racially,
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51 socioeconomically, and geographically diverse population of U.S. pregnant women. A rigorous
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53 examination of social contexts and racial/ethnic disparities in SMMM during the pandemic will
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55 contribute to the identification of factors with a broad scale and reach for programmatic and
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3 policy interventions to alter the context in which morbidity and mortality occur. Our findings
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5 will inform continuing efforts to reverse the rising trends of SMMM in the U.S.
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List of abbreviations

ACS: American Community Survey

AHA: American Hospital Association

AIM: Alliance for Innovation on Maternal Health program

AUC: Receiver Operating Characteristic Curve

Black: Non-Hispanic Black

BMI: Body Mass Index

CDC: Centers for Disease Control and Prevention

CDM: Clinical Data Model

CNN: Convolutional Neural Network

DBM: Deep Boltzmann Machine

ECMO: Extracorporeal Membrane Oxygenation

EHR: Electronic Health Records

ICU: Intensive Care Unit

ICD-10-CM: the International Classification of Diseases, Tenth Revision, Clinical Modification

IPV: Intimate Partner Violence

IRB: Institutional Review Board

LOS: Prolonged Length of Stay

LSTM: Long Short-Term Memory

MCPs: Maternal Care Providers

MMM: Maternal Morbidity and Mortality

MV: Mechanical Ventilation

N3C: National COVID Cohort Collaborative

NCATS: the National Center for Advancing Translational Sciences

NIAID: National Institute of Allergy and Infectious Disease

NIH: National Institutes of Health

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3 OMOP: Observational Medical Outcomes Partnership
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5 OR: Odds Ratio
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7 PRAMS: Pregnancy Risk Assessment and Monitoring System
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9 RNN: Recurrent Neural Network
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11 S3C: South Carolina COVID-19 Cohort
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13 S3C-P: South Carolina COVID-19 Cohort-Pregnancy
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15 SC: South Carolina
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17 SC DHEC: SC Department of Health and Environmental Control
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19 SC DMH: South Carolina Department of Mental Health
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21 SC RFA: SC Office of Revenue and Fiscal Affairs
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23 SES: Socioeconomic Status
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25 SMMM: Severe Maternal Morbidity and Mortality
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27 SVM: Support Vector Machine
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29 UofSC: University of South Carolina
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31 White: Non-Hispanic White
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33 WHO: World Health Organization
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Declarations

Ethics approval and consent to participate.

The study was approved by the institutional review boards at **University of South Carolina** (Pro00115169) and **SC Department of Health and Environmental Control** (DHEC IRB.21-030).

The NIH's N3C data access committee approved the data use request for this project (RP-2B9622).

Consent for publication

Not applicable.

Availability of data and materials

The South Carolina data (S3C) that support the findings for this study are available from the SC Office of Revenue and Fiscal Affairs (RFA) upon reasonable request. Per our contract with SC RFA, only approved users have access to the data and data cannot be made publicly available by authors. N3C data can be accessed through the NCATS N3C Data Enclave for approved users (<https://covid.cd2h.org>).

Author's contributions

JL conceptualized and designed the study and wrote the first draft. PH, CL, JZ, SQ and XL participated in writing sections of the original proposal. All authors critically reviewed and edited the manuscript and had final responsibility for the decision to submit for publication.

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Competing interests

The authors declare that they have no competing interests.

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6 [contribution/data-transfer-agreement-signatories](https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories)) and scientists who have contributed to the
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13 *Word Count*

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Figure 1. Compounding Effects of the COVID-19 Pandemic and Structural Racism and Discrimination

Figure 2. Estimated Power According to Prevalence of Outcomes and Odds Ratios

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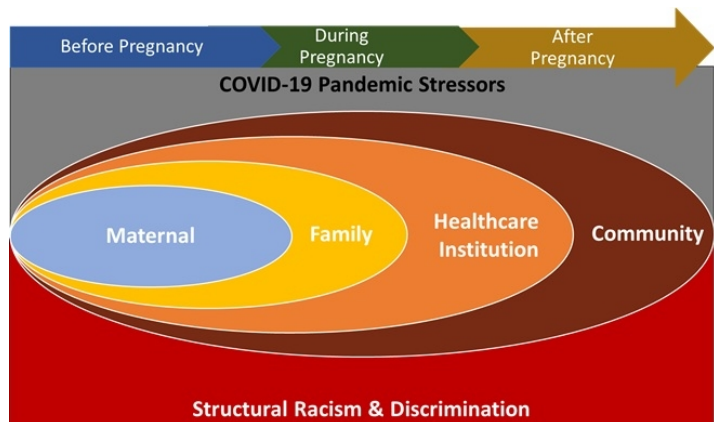


Figure 1

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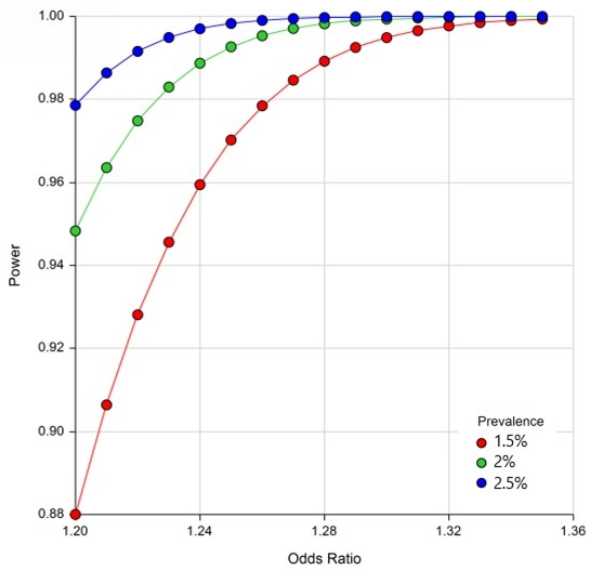


Figure 2
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BMJ Open

Multilevel determinants of racial/ethnic disparities in severe maternal morbidity and mortality in the context of the COVID-19 pandemic in the United States: protocol for a concurrent triangulation, mixed methods study

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Keywords:	COVID-19, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, EPIDEMIOLOGY, Maternal medicine < OBSTETRICS, PERINATOLOGY, PUBLIC HEALTH

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4 **and mortality in the context of the COVID-19 pandemic in the United States:**
5 **protocol for a concurrent triangulation, mixed methods study**
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10 **Jihong Liu,¹ Peiyin Hung,^{2,3} Chen Liang,^{2,3} Jiajia Zhang,^{1,3} Shan Qiao,³ Berry A.**
11 **Campbell,⁵ Bankole Olatosi,^{2,3} Myriam Torres,¹ Neset Hikmet,^{3,6} Xiaoming Li.^{3,4}**
12
13

14
15 ¹ Department of Epidemiology & Biostatistics, Arnold School of Public Health, University of
16 South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
17

18
19
20 ² Department of Health Services Policy & Management, Arnold School of Public Health,
21 University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
22

23
24 ³ Big Data Health Science Center, University of South Carolina, 915 Greene Street, Columbia, SC
25 29208, USA.
26

27
28
29 ⁴ Department of Health Promotion, Education, & Behavior, Arnold School of Public Health,
30 University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
31

32
33
34 ⁵ Berry A. Campbell, MD, Department of Obstetrics and Gynecology, School of Medicine,
35 University of South Carolina. Two Medical Park, Columbia, SC 29203, USA.
36

37
38
39 ⁶ Department of Integrated Information Technology, College of Engineering and Computing,
40 University of South Carolina. 550 Assembly Street, Columbia, SC 29208, USA.
41

42
43
44
45
46 **Corresponding author:**

47
48
49 Dr. Jihong Liu, Professor of Epidemiology, Department of Epidemiology & Biostatistics, Arnold
50 School of Public Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208,
51 USA. jliu@mailbox.sc.edu. Phone: 803 777 6854
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ABSTRACT

Introduction: The COVID-19 pandemic has affected communities of color the hardest. Non-Hispanic Black and Hispanic pregnant women appear to have disproportionate SARS-CoV-2 infection and death rates.

Methods and analysis: We will use the socio-ecological framework and employ a concurrent triangulation, mixed methods study design to achieve three specific aims: 1) examine the impacts of the COVID-19 pandemic on racial/ethnic disparities in severe maternal morbidity and mortality (SMMM); 2) explore how social contexts (e.g., racial/ethnic residential segregation) have contributed to the widening of racial/ethnic disparities in SMMM during the pandemic and identify distinct mediating pathways through maternity care and mental health; and 3) determine the role of social contextual factors on racial/ethnic disparities in pregnancy-related morbidities using machine learning algorithms. We will leverage an existing South Carolina COVID-19 Cohort (S3C) by creating a pregnancy cohort that links COVID-19 testing data, electronic health records (EHR), vital records data, healthcare utilization data, and billing data for all births in South Carolina (SC) between 2018-2021 (>200,000 births). We will also conduct similar analyses using EHR data from the National COVID Cohort Collaborative (N3C) including >209,000 women who had a childbirth between 2018-2021 in the United States. We will use a convergent parallel design which includes a quantitative analysis of data from the 2018-2021 SC Pregnancy Risk Assessment and Monitoring System (unweighted n > 2,000) and in-depth interviews of 40 postpartum women and 10 maternal care providers to identify distinct mediating pathways.

Ethics and dissemination: The study was approved by institutional review boards at the University of SC (Pro00115169) and the SC Department of Health and Environmental Control (DHEC IRB.21-030). Informed consent will be provided by the participants in the in-depth

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3 interviews. Study findings will be disseminated with key stakeholders including patients,
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5 presented at academic conferences, and published in peer-reviewed journals.
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8 **Strengths and limitations of this study**

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- 10 • This study investigates whether the COVID-19 pandemic, structural racism, and racial
11 discrimination have contributed to the racial/ethnic disparities in severe maternal
12 morbidity and mortality in the United States.
13
- 14 • This study employs a state-of-the-art design (i.e., a convergent parallel design) and
15 machine learning models to rigorously examine the questions of interest.
16
- 17 • This study will use a large-scale population-based cohort study concurrently for both
18 South Carolina and the United States, which will innovatively integrate COVID-19-
19 related clinical, surveillance, EHR, and geospatial data at community, healthcare
20 institutions, and system/policy levels.
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- 22 • The effects of both county- and ZIP-code-level social contexts will be calculated at the
23 maternal residence location.
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- 25 • The stagnant residential social contexts might not reflect their long-term exposures to
26 neighborhood structural racism.
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INTRODUCTION

Annually, nearly 60,000 women experience severe maternal morbidity (i.e., unexpected complications of labor and delivery) and mortality (SMMM).^{1,2} Between 1993-2014, SMMM rates in the U.S. tripled from 49.5 to 146.6 per 10,000 childbirths.³ For every 70 U.S. women who experienced a severe maternal morbidity, one died during or immediately after pregnancy.⁴ The severe maternal morbidity occurrences have also led to significant short- or long-term clinical impacts on women's health⁵ and added significant costs to women, their families, taxpayers and the healthcare system.⁶⁻⁸

Non-Hispanic Black (hereafter, Black) women experience a 3- to 4-fold risk of pregnancy-related deaths compared to non-Hispanic White women (hereafter, White).^{9,10} Black and Hispanic women were up to 110 percent more likely to experience SMMM,² despite their younger maternal age (often a protective factor for SMMM) as compared to non-Hispanic White women. Such racial/ethnic disparities in SMMM rates have persisted for over a decade – with increasing rates among all race/ethnic groups.¹¹ These SMMM rates are unevenly distributed socioeconomically and geographically – with the highest rate among low-income women who delivered at hospitals in the Deep South states.^{2,12-14}

The unprecedented COVID-19 pandemic hit communities of color the hardest.¹⁵⁻¹⁷ Pregnant Black and Hispanic women experienced disproportionate COVID-19 infection and death rates.¹⁸⁻²⁰ The impacts of COVID-19 on SMMM remain unclear. During the pandemic, as unemployment, income instability, and financial stress have affected many U.S. families, Black and Hispanic families have faced even higher hardship rates.²¹ These disproportionate consequences reflect longstanding inequities, often stemming from structural racism and discrimination (e.g., residential segregation, poverty, inadequate education, unemployment, and lack of home ownership).^{22,23} These inequities can lead to uneven access to quality healthcare, psychosocial stress, and unhealthy lifestyles among women of color, which further increases SMMM risk.^{24,25} Yet, the etiology of SMMM is complex, multifaceted, and time-varying. Prior

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3 research efforts on racial/ethnic disparities in SMMM have mostly focused on maternal and
4 healthcare factors,²⁶ leaving questions regarding the dynamics and interactions of multilevel
5 determinants, such as the broader social contexts of these risks, largely unanswered. Thus, there
6 is an urgent need to examine how social contexts of all types play out in SMMM rates, especially
7 during the COVID-19 pandemic.^{22,23}

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13 South Carolina (SC) ranked 11th in COVID-19 cases per capita as of December 23, 2021.²⁷
14 Prior to the pandemic, SC ranked 42nd in the U.S. in overall health and 41st in maternal
15 mortality.²⁸ Births to Black women accounted for nearly 30% of all SC births.²⁹ Black women
16 living in SC experienced a 2- to 3-fold higher risk of SMMM than their White counterparts.³⁰
17 The majority of counties in SC are designated medically underserved areas.³¹ Considering SC's
18 poor health ranking, striking racial disparities in SMMM, racially diverse population, and
19 historical systemic Southern contexts, SC is an ideal environment in which to examine health
20 disparities in SMMM occurring during the COVID-19 pandemic.

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30 The overarching goal of this study is to investigate racial/ethnic disparities in SMMM, the
31 contributing roles and mediating pathways of social contexts (e.g., structural racism, racial
32 discrimination), and the long-standing health consequences of the pandemic by studying the
33 distributions of COVID-19 cases and multilevel determinants of maternal health in SC and the
34 U.S. Our study will: 1) examine the impacts of the COVID-19 pandemic on racial/ethnic
35 disparities in SMMM; 2) examine and explore how the key features of social contexts (including
36 structural racism and racial discrimination) have contributed to the widening racial/ethnic
37 disparities in SMMM during the pandemic and identify distinct mediating pathways through
38 maternity care and mental health; and 3) examine and identify the role of social contextual
39 factors and protective factors on racial/ethnic disparities in pregnancy-related long-standing
40 morbidities (e.g., hypertension, pulmonary embolism, diabetes, cardiovascular disease), using
41 machine learning algorithms.

METHODS AND ANALYSIS

Multilevel Conceptual Framework

The etiology of racial/ethnic disparities in SMMM is complex and multifaceted (**Figure 1**).²⁴ At the micro-level, in addition to maternal race/ethnicity, other socio-demographics (e.g., age, socioeconomic status [SES]), health behaviors (e.g., prenatal care adequacy, smoking, diet, physical activity, gestational weight gain), and preexisting maternal conditions (e.g., hypertension, pre-pregnancy body mass index (BMI), diabetes, HIV infection, obstetric comorbidity scores) potentially drive racial/ethnic disparities in SMMM.^{12,32,33} As compared to White women, Black and Hispanic women usually have higher poverty rates, lower educational levels, and higher rates of preexisting conditions or high-risk pregnancy.³² At the macro level, structural racism and discrimination - community and neighborhood factors (e.g., residential segregation, inadequate housing, lack of access to healthy food, no public transportation), healthcare institutional attributes (e.g., access to risk appropriate perinatal care), and system-level factors (e.g. COVID-19 pandemic, state public health emergency policies) may play a role in racial/ethnic disparities. These macro-level factors interact with micro-level factors to further exacerbate racial/ethnic disparities in SMMM.

Study Design

The above-mentioned multilevel conceptual framework guided our study design (Figure 2). We will employ a concurrent triangulation, mixed methods study design to rigorously examine racial/ethnic disparities in SMMM in SC and the U.S. This convergent parallel design will allow us to better understand the underlying mechanisms for social contexts and racial/ethnic disparities in SMMM via maternity care and mental health using the data from the statewide pregnancy survey and via qualitative interviews with pregnancy and postpartum women and maternity care providers. Given the multilevel and multidomain nature of risk factors for pregnancy-related long-standing morbidities, we will use novel machine learning models to forecast the intertwining social context effects with multilevel factors on maternal health during

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3 the COVID-19 pandemic. We will conduct data analyses using the quantitative and qualitative
4 methods concurrently. Then we will compare and contrast findings from these two methods for
5 similarities and incongruences and will interpret findings jointly.
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9 Data Sources

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11 We will leverage our statewide South Carolina COVID-19 Cohort (S3C) database, which
12 integrates COVID-19-related clinical, surveillance, electronic health records (EHR) and
13 geospatial and temporal data at community, healthcare institutional, and system levels to
14 comprehensively examine the roles of social contexts on racial/ethnic disparities in SMMM. To
15 ensure the generalizability of our findings, we will also examine them using EHR data from the
16 ongoing National COVID Cohort Collaborative (N3C).³⁴ Nationwide social context databases
17 (e.g. American Community Survey [ACS], American Hospital Association [AHA]) and time-
18 varying COVID-19 infection and social distancing policies data will be added to both S3C and
19 N3C. Postpartum women's survey responses and in-depth interview data will be analyzed to
20 understand complex pathways and multilevel determinants of maternal morbidities (Figure 2).
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32 *SC COVID-19 Cohort – Pregnancy (S3C-P) Database.* With support from the National
33 Institute of Allergy and Infectious Disease (NIAID) (R01A127203-4S1), our team has established
34 a statewide S3C database for COVID-19 research since 06/2020 by integrating various state-
35 level data sources including: 1) the COVID-19 testing data from the SC Department of Health
36 and Environmental Control (SC DHEC), 2) hospital encounter data for inpatient hospitalization,
37 outpatient surgery, home health, and emergency departments; 3) health utilization data from
38 large public and private health insurance plans (e.g., Medicaid, State Health Plan, BlueCross
39 BlueShield of SC); 4) EHR data from health systems (Prisma & MUSC), and 5) program data
40 from the SC Department of Mental Health (SC DMH). The database is updated every 6 months.
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51 In this study, as part of the National Institutes of Health (NIH)'s “Implementing a Maternal
52 health and PRenancy Outcomes Vision for Everyone” (IMPROVE) initiative supported by the
53 Office of Director, NIH (3R01A127203-5S2), our team will create a population based S3C
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3 pregnant women cohort (S3C-P), which includes all women who gave birth between 2018-2021
4 in SC (>200,000 births, 57.2% White, 31.1% Black, 4.6% Hispanic) and will add vital record data
5 (birth and death certificates) to complement existing linkages from the parent S3C cohort. The
6 identification of pregnancy status and COVID-19 infection will be cross-verified using EHR,
7 claims data, laboratory reports, and ongoing SC DHEC medical chart reviews among > 4,387
8 pregnant women with confirmed COVID-19 infections in SC as of December 2021. The SC
9 Office of Revenue and Fiscal Affairs (SC RFA) will collate databases and provide our team with a
10 de-identified linked database system.³⁵

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20 *National COVID Cohort Collaborative (N3C)*. The N3C is a novel data consortium that
21 integrates EHR and medical claims data from 92 healthcare systems and institutes across 50
22 states. N3C enables data sharing, computable phenotypes, and collaborative data mining by
23 harmonizing EHR data of diverse standards using Observational Medical Outcomes Partnership
24 (OMOP) Clinical Data Model (CDM). N3C was created to study potential risk factors and
25 protective factors of COVID-19 and its long-term health consequences.³⁴ As of December 24,
26 2021, N3C has aggregated 9.4 million patients (3.3 million COVID-19 patients) with their EHR
27 dating back from January 2018, including 1.9 million women with COVID-19 (>61k pregnant
28 women), and 3.5 million women without COVID-19 (>209k pregnant women). The participants
29 in N3C represent diverse populations in the U.S. (e.g., geographic, socioeconomic,
30 racial/ethnic). Building on a secured cloud environment, N3C provides data harmonization,
31 privacy-preserving data linkage, and high-performance data analytics. Our team has already
32 gained access to the restricted N3C database including ZIP codes of patients and health systems
33 and dates of services.

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49 *Nationwide social context databases*. The 2015-2019 American Community Survey (ACS)
50 and the 2018-2020 American Hospital Association (AHA) Annual Survey will be used to
51 calculate county-level residential segregation measures, racial discrimination in SES, and ZIP-
52 level accessibility to hospital-based obstetric units.

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3 *Time-varying local COVID-19 infection and social-distancing policy data.* To better
4 understand local pandemic settings, we will also add the Centers for Disease Control and
5 Prevention (CDC) COVID-19 Case Surveillance restricted datasets for nationwide cases
6 confirmed since March 11, 2020, and CDC's state-level social distancing policies (e.g. emergency
7 declaration, stay at home order, etc.) in early pandemic and telehealth services expansion data
8 and each corresponding date of enactment.³⁶

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16 *SC Pregnancy Risk Assessment Monitoring System (PRAMS).* SC PRAMS as a part of
17 national PRAMS is an ongoing survey of SC mothers who have recently given birth.³⁷ These
18 mothers are sampled from state birth certificates. After statistical weighting, PRAMS data are
19 representative of all mothers who gave birth in SC. SC PRAMS added 11 COVID-19-related
20 questions for mothers who delivered in August 2020 and after in their survey. SC PRAMS
21 routinely collects detailed psychosocial and behavioral risk factors for each participant, which
22 are not available in S3C and N3C. Residential ZIP codes will be used to add in social contextual
23 variables and other ZIP- or county-level characteristics. The unweighted sample size for SC
24 2018-2021 PRAMS will be at least 2,000.

25 26 27 28 29 30 31 32 33 34 Key Measures

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37 *Outcome measures.* The main outcomes of interest will be SMMM.³⁸ We will adapt from a
38 previously validated algorithm by using the International Classification of Diseases, Tenth
39 Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure codes to identify women
40 with one or more of the 21 severe maternal morbidity (SMM) indicators developed by the CDC
41 and updated by the Alliance for Innovation on Maternal Health (AIM) program at the time of
42 childbirth. Maternal mortality will be identified using statewide death certificate data from the
43 childbirth date to up to one year postpartum. A composite variable of SMMM will be created to
44 reflect SMM or maternal mortality incidence. We will also study maternal morbidity and
45 mortality (MMM) composite, which includes mortality and morbidities related to hypertensive
46 disorders of pregnancy, postpartum hemorrhage, and infections/sepsis that happen during
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3 pregnancy through 6 weeks postpartum.³⁹ Other outcomes to be studied include: 1) adverse
4 maternal outcomes including intensive care unit (ICU) admission, invasive ventilation, receipt
5 of extracorporeal membrane oxygenation (ECMO), etc.; 2) prolonged length of stay (LOS),^{40,41}
6 and 3) hypertension, pulmonary embolism, type 2 diabetes, cardiovascular diseases (e.g. heart
7 attack, myocardia infraction, thrombus, stroke) diagnosed within one year after delivery.
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13 *COVID-19 status and severity.* Eligible COVID-19 cases are those with a positive test for
14 SARS-CoV-2 since March 11, 2020, during pregnancy. Data on symptom status (symptomatic,
15 asymptomatic, unknown) is available, while severity will be defined using the World Health
16 Organization's (WHO) Clinical Progression Scale.⁴²
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21 *Social context measures.* The five dimensions of county-level *residential segregation*,
22 including evenness, exposure, concentration, centralization, and clustering,^{43,44} will be
23 determined for each race/ethnic group (e.g., Black, Hispanic) using the ACS Census tract
24 data.^{45,46} Each index will be calculated across census tracts within residential counties. Higher
25 values indicate higher levels of segregation. We will create the group indicator for segregated
26 versus less segregated counties using the cutoffs for each dimension index.⁴⁶ Additional hyper-
27 segregation index – segregations scores at ≥ 0.6 on at least four aforementioned dimensions –
28 will be created to reflect the highest levels of segregation.⁴⁶ Within-county *racial/ethnic*
29 *discrimination in SES* will be calculated using the ACS county data,⁴⁵ including Black-White and
30 Hispanic-White ratios of poverty, unemployment, and home ownership rates.⁴⁷⁻⁵¹ These
31 measures will be linked to databases via maternal residence counties.
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45 *Healthcare institution.* Using the AHA annual survey data on hospital location,⁵² we will
46 identify *loss of hospital-based obstetric units* using our published validated algorithm.⁵³⁻⁵⁵ An
47 indicator for whether a hospital or a hospital's obstetric service was closed for each year will be
48 created. In turn, women's access to hospital-based obstetric care within 30-mile distance for
49 years 2018-2020 using the ArcGIS fastest route network will be determined: 1) had access to; 2)
50 no access to; and 3) experienced the loss of all hospital-based obstetric units.
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3 *County-level COVID-19 infections and social distancing policies.* The CDC's COVID-19 Case
4 Surveillance will be used to compute monthly cumulative rates of in-county residents that had
5 been confirmed COVID-19 positive, hospitalized, admitted to an intensive care unit, and with
6 mechanical ventilation (MV)/intubation as a result of COVID-19 disease. Number of months
7 elapsed since a county had each of the following policy orders will be calculated from a delivery
8 date: emergency declaration, closures of bars, restaurants, and/or other non-essential business,
9 stay at home order, and telehealth services expansion.
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12 Statistical Analyses

13 *Impacts of the COVID-19 pandemic on racial/ethnic disparities in SMMM.*

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15 We will examine the overall impacts of the COVID-19 pandemic on SMMM using the data
16 from the S3C-P and N3C. We hypothesize that: 1) compared to pre-pandemic periods, SMMM
17 has increased during the pandemic and racial/ethnic disparities have widened during the
18 pandemic; and 2) compared to pregnant women without COVID-19 infection, women with
19 COVID-19 infection experienced higher proportions of SMMM, and racial/ethnic disparities in
20 SMMM have amplified among COVID-19 infected women.
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24 First, we will examine the distributions for all measures and clean the database (e.g. outliers,
25 data entry errors etc.) using appropriate statistical techniques. Second, we will conduct
26 preliminary analyses and examine descriptive statistics for outcome measures. Unadjusted and
27 adjusted associations of SMMM with key variables and covariates will be assessed using
28 appropriate statistical procedures (e.g., tests of proportions, chi-square tests, analysis of
29 variance).
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33 Women who gave birth between January 1, 2018 through March 10, 2020, will be
34 categorized as before pandemic, while women who gave birth between March 11, 2020 through
35 December 31, 2021, will be considered as during the pandemic. The pre-pandemic vs pandemic
36 impact on SMMM will be modeled via logistic regression. First, the crude model with the
37 pandemic indicator only will address SMMM change before and after the pandemic. Second, to
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3 investigate whether racial/ethnic disparities in SMMM have widened during the pandemic, the
4 crude model will be further adjusted with race/ethnicity, interactions between race/ethnicity
5 and pandemic indicator, and months elapsed since March 11, 2020, on delivery dates. Then
6 additional variables will be added, including individual-level characteristics (e.g., age, SES proxy
7 [i.e., Medicaid/uninsured status], parity, marital status, underlying health conditions). Variable
8 selection and goodness of model fit will be evaluated using the AIC, BIC, and likelihood ratio
9 test.
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17 We will also conduct analyses in women who delivered during the COVID-19 pandemic by
18 comparing pregnant women with and without COVID-19 infection. We will first create the
19 COVID infection indicator and then will perform the similar analysis as those for the pre-
20 pandemic vs pandemic impact. We will further adjust for county-level COVID-19 infections per
21 capita and social distancing policies at the appropriate time points using logistic regressions
22 with random effects accounting for correlations among counties.
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30 *Social contexts, racial/ethnic disparities in SMMM, and distinct mediating pathways.*
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32 We will study these issues using different databases and methods. First, we will examine the
33 association between social contexts and changes in racial/ethnic disparities in SMMM before
34 and during the pandemic. We hypothesize that racial/ethnic disparities SMMM are potentially
35 disproportionately widened in communities with higher racial/ethnic economic disparities
36 (measured by Black-White ratios of economic disadvantages, Hispanic-White ratios of economic
37 disadvantages) and in higher vs. less segregated Black or Hispanic counties (measured by
38 residential segregation). We will conduct a parallel analysis between social contexts and SMMM
39 using the data from S3C-P and N3C (**Figure 2**). Similarly, we will examine the contributing
40 roles of social contexts to racial/ethnic disparities in SMMM in the overall sample (pre-
41 pandemic vs pandemic) and between COVID-19 positive vs COVID-19 negative women. The
42 multilevel variables that will be investigated include individual-level characteristics,
43 community-level characteristics (ZIP code accessibility of hospital obstetric units), and county-
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3 level characteristic (social contexts: residential segregation and racial discrimination on SES;
4 COVID-19 infection per capita and social distancing policies). For exploratory analysis, the odds
5 ratio (OR) of SMMM among Black and White and the social context level at the county level pre-
6 pandemic vs pandemic will be visualized via the spatial temporal map using GIS. The summary
7 statistics in SMMM with respect to race/ethnicity will be calculated according to individual- and
8 county-level characteristic.
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11 We will model SMMM via multilevel hierarchical logistic regression. Women who reside at
12 the same community- or county-level will be accounted for via random effects, which will be
13 further modeled in the regression model with a multivariate normal distribution to account for
14 the correlations among community or county. We plan to use an incremental modeling strategy:
15 1) crude model (race/ethnicity and social context factors); 2) adjusting for individual level
16 factors; and 3) additional adjustment of additional community- and county-levels
17 characteristics. For N3C data, we will further adjust for state or Census region. To further
18 examine whether social contexts moderate racial/ethnic disparities in SMMM and whether
19 these disparities vary between pre-pandemic and pandemic, we will include two-way and three-
20 way interaction terms in the model (e.g., pandemic period*social context*race). To examine the
21 added impact of COVID-19 infections on SMMM, we will repeat the model by restricting it to all
22 women who gave birth during pandemic period (delivered after March 11, 2020) and including
23 maternal COVID-19 severity status in the model. Models will be compared using the AIC and
24 BIC criteria. In the modelling procedure, the outliers, missingness, multicollinearity, and
25 nonlinear will be addressed accordingly, and sensitivity analysis will be conducted comparing
26 models with or without the treatment of outliers or missing data. The magnitude and direction
27 racial/ethnic disparities will be assessed through OR and its 95% confidence interval.
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30 Second, we will use a convergent parallel design to evaluate the underlying pathways
31 between social contexts and racial/ethnic disparities in MMM via pandemic stressors, maternity
32 care (prenatal and postpartum) and mental health condition. We hypothesize that social
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3 contexts might hinder maternity care and worsen mental health conditions among Black and
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5 Hispanic women during the pandemic and exacerbate racial/ethnic disparities in MMM.
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7 The quantitative analysis will be conducted using SC PRAMS data, which have unique data
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9 elements that are not available in S3C-P and N3C. The 2018-2021 SC PRAMS data will provide a
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11 more refined understanding of COVID-19 stressors, psychosocial stress, and healthcare
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13 utilization through the questionnaire, including pandemic stressors (financial, job loss,
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15 childcare, etc.), individual mitigation practices, changes in prenatal and postpartum care,
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17 psychosocial stress, barriers to health services, intimate partner violence (IPV), prenatal and
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19 postpartum care utilization, smoking, alcohol use, gestational weight gain, and mental health.
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21 SC PRAMS asks respondents to assess how often they experienced depressive symptoms after
22
23 delivery. Descriptive statistics will be used to examine pandemic-related changes in MMM and
24
25 psychosocial and behavioral changes between pre-pandemic (delivered before March 11, 2020)
26
27 and pandemic periods (March 11, 2020 and after). The weighted hierarchical regression model
28
29 will be applied to examine the association between social context and MMM. As previously
30
31 mentioned, community and county levels will also be modeled in the regression. Different from
32
33 the prior analyses above: 1) individual characteristics will mainly come from PRAMS or birth
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35 certificates; 2) the weight based on complex survey design will be modeled; and 3) individual
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37 reports of healthcare utilization and mental health condition included.
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40 We will conduct in-depth interviews among 40 postpartum women of color (~20 African
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42 American; ~20 Hispanic) stratified by COVID-19 infection status and 10 maternal care
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44 providers (MCPs) who serve pregnant and postpartum women in Black and Latino
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46 communities. The inclusion criteria of postpartum women include: 1) ≥ 18 years old; 2) either
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48 African American or Hispanic; 3) have given birth in 2021; and 4) living in SC. We will
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50 purposely recruit postpartum women and MCPs through local OBGYN clinics and community
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52 health organizations that serve a larger proportion of low-income Black and Hispanic women.
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54 We will train female interviewers of the same race as the interviewees to obtain trust from the
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3 postpartum women participants, and interviews in Spanish will be conducted as needed. Guided
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5 by the conceptual framework, the main topics of the postpartum women interviews will include:
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7 1) their perceptions toward their healthcare providers and institutions for perinatal care; 2)
8
9 experience with prenatal and postpartum care; 3) stressors in the COVID-19 pandemic; 4)
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11 challenges in healthcare seeking (e.g., appointments, clinic visits), especially from structural
12
13 factors (racism and discrimination); and 5) their needs/recommendations for future healthcare.
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15 The main topics of the MCPs include: 1) stressors and challenges of their clients; 2) clients'
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17 mental health conditions; 3) impacts of COVID-19 on their care provision; and 4) their views on
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19 health disparities caused by structural factors. The interviews will last 50 minutes and will be
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21 recorded with each participant's consent. Audio recordings will be transcribed and coded using
22
23 NVivo 11.0. We will employ thematic analyses.⁵⁶ The findings will complement the quantitative
24
25 data in providing a comprehensive picture on how COVID-19 affects psychosocial well-being of
26
27 the postpartum women of color; offer in-depth interpretation and explanation of quantitative
28
29 results; and explore the mediating pathways in which structural factors amplify existing
30
31 disparities in maternal health in the context of the pandemic.

32 33 34 *Machine learning-based predictive models.*

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36 We will develop and evaluate machine learning-based predictive models to identify risk
37
38 factors of SMMM and forecast progression of hypertensive disorder, pulmonary conditions, type
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40 2 diabetes mellitus, and cardiovascular diseases among postpartum women. The predictive
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42 models will synthesize individuals' demographics, EHR, social contextual factors, and
43
44 community and healthcare system level data to make predictions of individuals' clinical
45
46 outcomes at key time points. Because data sources suggestive of these factors are variable and
47
48 high-dimensional, and these factors are inherently interconnected over time,⁵⁷ machine learning
49
50 is a superior approach to predicting clinical outcomes and proactively detecting the associated
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52 risk factors for early intervention and treatment. Constructed models will demonstrate critical
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54 factors predictive of clinical outcomes and how these factors interact over time.
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3 Supervised machine learning algorithm will be adopted for the predictive models. Using
4 N3C, the algorithm will learn from input variables and predict SMMM and long-standing
5 morbidities (e.g., hypertension, pulmonary embolism, diabetes, cardiovascular diseases) over
6 time. Input variables will include maternal characteristics, e.g., socio-demographics, socio-
7 behavioral data, social context variables, diagnoses, procedures, laboratory tests, and
8 medications. The prediction of SMMM and long-standing morbidities will take place at critical
9 time points: <3, 6, 12 weeks, 6 and 12 months postpartum.⁵⁸ We will develop Deep Learning
10 algorithms because of their ability to integrate complex clinical data and social contexts from
11 multiple sources with superior predictive performance, including: 1) convolutional neural
12 network (CNN) for its ability to capture dynamic patterns among multilevel input variables; 2)
13 recurrent neural network (RNN) with long short-term memory (LSTM) architecture for its
14 ability of capturing temporal patterns of clinical events (e.g., onset of pre-infection conditions,
15 viral infections and clinical events marked with gestational weeks, and the date of childbirths);
16 and 3) Deep Boltzmann Machine (DBM) for its interpretable scoring mechanism for risk
17 prediction.⁵⁹

18
19 We will use a 10-fold cross validation. Specifically, S3C and N3C data will each be randomly
20 partitioned into ten splits. In each of the ten iterations, seven splits of data will be randomly
21 selected for model training, two splits of data will be used for internal validation (finetuning
22 hyperparameters), and the 10th split used for testing. We will use F measure, precision, recall,
23 and the area under the Receiver Operating Characteristic curve (AUC), if unbalanced data, to
24 measure the predictive performance of models. We will use support vector machine (SVM) as
25 the baseline algorithm to compare against the performance of CNN, RNN (LSTM), and DBM.
26 The best-performed model will be identified based on F measure.

27
28 We will rank input variables and/or clusters of input variables by calculating the importance
29 scores ⁵⁷ (e.g., mutual information, SVM-based recursive linear elimination). Two content co-
30 investigators will independently review the ranked results and identify clinical/social risk

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3 factors. Disagreement between two reviewers will be resolved by panel discussion. Development
4 of sophisticated machine learning models for predicting long-standing morbidities will be used
5 to identify important risk factors prenatally, which can be used for early intervention, treatment,
6 and community-wide interventions.
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11 *Power and Sample Size Calculation.* We estimate that there were 200,000 women who gave
12 birth in S3C and 270,000 pregnant women in N3C for our study period. The primary outcome of
13 interest is SMM and the main exposures of interest are race (White vs Black) and pre-peri
14 COVID period. We assume that there are 64,000 (32%) Black and 114,000 (57%) White in S3C⁶⁰
15 and 38,070(14.1%) Black and 160,380 (59.4%) White in N3C.⁶¹ We also assume that with the
16 same time length of pre and peri COVID-19, the prevalence of pregnancy will be similar (50%).
17 For all aims, we consider the logistic regression with mixed effects. Based on 1.5%-2.5%
18 incidence of SMM with 20%-50% increase due to the COVID -19 impact or race disparities, we
19 conduct the power analysis based on the logistic regression using SAS and conclude that
20 200,000 sample size will be adequate to reach the power around 90%. **Figure 3** illustrates the
21 relationship of power and odds ratio with setting of n=200,000, significance at 0.05, variable of
22 interest with a ratio of 10:90. This will be the basic model considered, and it indicates strong
23 power for the prediction model.
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30 Current status and anticipated timeline

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32 As of April 2022, we have received the linked core databases for the S3C cohort for the
33 period of January 2018- June 2021 and full datasets will be available by the Fall of 2022. Our
34 team is also actively constructing N3C analytic data of women with childbirths during January
35 2018-December 2021 for statistical analysis and machine learning. Furthermore, our team is
36 conducting in-depth interviews with our targeted populations according to our protocols
37 described here. We anticipate completing our main analyses in May 2023.
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40 Patient and Public Involvement

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3 No patient involvement in the design, conduct and reporting of our research. We will
4 actively reach out patients and public in the dissemination of our findings.
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7 Ethics and dissemination

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9 The study was approved by institutional review boards at the University of South
10 Carolina (Pro00115169) and the South Carolina Department of Health and Environmental
11 Control (DHEC IRB.21-030). Informed consent will be completed for the participants to be
12 enrolled in the in-depth interviews. Furthermore, the NIH's N3C data access committee
13 approved the data use request for this project (RP-2B9622). Study findings will be disseminated
14 with key stakeholders including patients, presented at academic conferences, and published in
15 peer-reviewed journals.
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26 **DISCUSSION**

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28 The COVID-19 pandemic has led to unprecedented societal disruptions to individuals,
29 communities, healthcare institutions, and society. Empirical data on the scope of possible
30 widening racial/ethnic disparities in SMMM during the COVID-19 pandemic and how historical
31 structural racism and discrimination of all types have impacted women of color
32 disproportionately are sparse. This study will be among the first efforts to investigate whether the
33 COVID-19 pandemic, structural racism, and racial discrimination— exposures with broad scale
34 and reach – have contributed to the racial/ethnic disparities in SMMM in the context of the
35 COVID-19 pandemic. Second, this proposed study employs a state-of-the-art design (i.e., a
36 convergent parallel design) to comprehensively examine the impacts of structural racism and
37 discrimination on maternal health and the complex pathways between multilevel determinants.
38 This design has the advantage of allowing us to weigh both quantitative and qualitative methods
39 equally and interpret the results together.⁶² Third, the proposed study will innovatively use
40 machine learning models to predict SMMM and chronic morbidities up to one year after
41 delivery in the context of the COVID-19 pandemic. Fourth, we propose a large-scale population-
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3 based cohort study concurrently for both SC and the U.S., which will innovatively integrate
4 COVID-19-related clinical, surveillance, EHR, and geospatial data at community, healthcare
5 institutions, and system/policy levels. These newly integrated data sources will allow us to
6 examine multilevel determinants of maternal health during the pandemic and advance the
7 investigation on racial/ethnic disparities in long-standing complications post-pandemic. In
8 brief, this research represents a significant and innovative contribution to the research on the
9 unacceptable racial/ethnic disparities in SMMM during pregnancy and postpartum in the
10 context of COVID-19. By focusing on social contextual factors (e.g., structural racism), we seek
11 to identify ways in which the largest number of women may be impacted by targeted programs
12 and policies aiming to alter the context in which these morbidities and mortality occur.

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24 This study also has some limitations. First, it is possible that the county-level social contexts'
25 effects in our data may not be significant. If that happens, we will calculate ZIP-code level social
26 contexts. By assessing racial segregations, spatial distribution of economic disadvantage
27 communities within a residence county and within-community racial discrimination, this study
28 will provide evidence on the associations between distinct social contexts and maternal health
29 disparities. Second, considering some women may move during pregnancy, the stagnant
30 residential social contexts might not reflect their long-term exposures to neighborhood
31 structural racism. Furthermore, in the case of inferior F measures (<0.7) of learning predictive
32 models, we will apply feature selection algorithms and association rules in model training to
33 maximize performance.

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45 In conclusion, the rising SMMM rate and persistent racial/ethnic disparities should trigger
46 public health concerns, not only due to the immediate burden faced by vulnerable women, but
47 also due to potentially lasting effects on women's health over a life course or along family lines
48 across generations.⁶³ This study will investigate racial/ethnic disparities in SMMM, the
49 contributing roles and mediating pathways of social contexts (e.g., structural racism, racial
50 discrimination), and the long-standing health consequences of the pandemic by studying the
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3 distributions of COVID-19 cases and multilevel determinants of maternal health in a racially,
4 socioeconomically, and geographically diverse population of U.S. pregnant women. A rigorous
5 examination of social contexts and racial/ethnic disparities in SMMM during the pandemic will
6 contribute to the identification of factors with a broad scale and reach for programmatic and
7 policy interventions to alter the context in which morbidity and mortality occur. Our findings
8 will inform continuing efforts to reverse the rising trends of SMMM in the U.S.
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For peer review only

List of abbreviations

ACS: American Community Survey

AHA: American Hospital Association

AIM: Alliance for Innovation on Maternal Health program

AUC: Receiver Operating Characteristic Curve

Black: Non-Hispanic Black

BMI: Body Mass Index

CDC: Centers for Disease Control and Prevention

CDM: Clinical Data Model

CNN: Convolutional Neural Network

DBM: Deep Boltzmann Machine

ECMO: Extracorporeal Membrane Oxygenation

EHR: Electronic Health Records

ICU: Intensive Care Unit

ICD-10-CM: the International Classification of Diseases, Tenth Revision, Clinical Modification

IMPROVE: Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone

IPV: Intimate Partner Violence

IRB: Institutional Review Board

LOS: Prolonged Length of Stay

LSTM: Long Short-Term Memory

MCPs: Maternal Care Providers

MMM: Maternal Morbidity and Mortality

MUSC: Medical University of South Carolina

MV: Mechanical Ventilation

N3C: National COVID Cohort Collaborative

NCATS: the National Center for Advancing Translational Sciences

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3 NIAID: National Institute of Allergy and Infectious Disease
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5 NIH: National Institutes of Health
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7 OMOP: Observational Medical Outcomes Partnership
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9 OR: Odds Ratio
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11 PRAMS: Pregnancy Risk Assessment and Monitoring System
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13 RNN: Recurrent Neural Network
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15 S3C: South Carolina COVID-19 Cohort
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17 S3C-P: South Carolina COVID-19 Cohort-Pregnancy
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19 SC: South Carolina
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21 SC DHEC: SC Department of Health and Environmental Control
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23 SC DMH: South Carolina Department of Mental Health
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25 SC RFA: SC Office of Revenue and Fiscal Affairs
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28 SES: Socioeconomic Status
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30 SMM: Severe Maternal Morbidity
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32 SMMM: Severe Maternal Morbidity and Mortality
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34 SVM: Support Vector Machine
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36 UofSC: University of South Carolina
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38 White: Non-Hispanic White
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40 WHO: World Health Organization
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Declarations

Consent for publication

Not applicable.

Availability of data and materials

The South Carolina data (S3C) that were analyzed to produce the findings of this study are available from the SC Office of Revenue and Fiscal Affairs (RFA) upon reasonable request. Per our contract with SC RFA, only approved users have access to the data and data cannot be made publicly available by authors. N3C data can be accessed through the NCATS N3C Data Enclave for approved users (<https://covid.cd2h.org>).

Author's contributions

JL conceptualized and designed the study and wrote the first draft. PH, CL, JZ, SQ and XL participated in writing sections of the original proposal. All authors critically reviewed and edited the manuscript and had final responsibility for the decision to submit for publication.

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Competing interests

The authors declare that they have no completing interests.

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1
2
3 contribution/data-transfer-agreement-signatories) and scientists who have contributed to the
4 on-going development of N3C database [<https://doi.org/10.1093/jamia/ocaa196>].
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3 **Figure 1. Multilevel conceptual framework to examine racial/ethnic disparities in**
4 **severe maternal morbidity and mortality in the context of COVID-19 Pandemic**
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6 **Figure 2. Using concurrent triangulation mixed methods design to investigate**
7 **racial/ethnic disparities in severe maternal morbidity and mortality during the**
8 **COVID-19 pandemic**
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10 **Figure 3. Estimated power according to prevalence of outcomes and odds ratios**
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Figure 1. Multilevel conceptual framework to examine racial/ethnic disparities in severe maternal morbidity and mortality in the context of COVID-19 pandemic

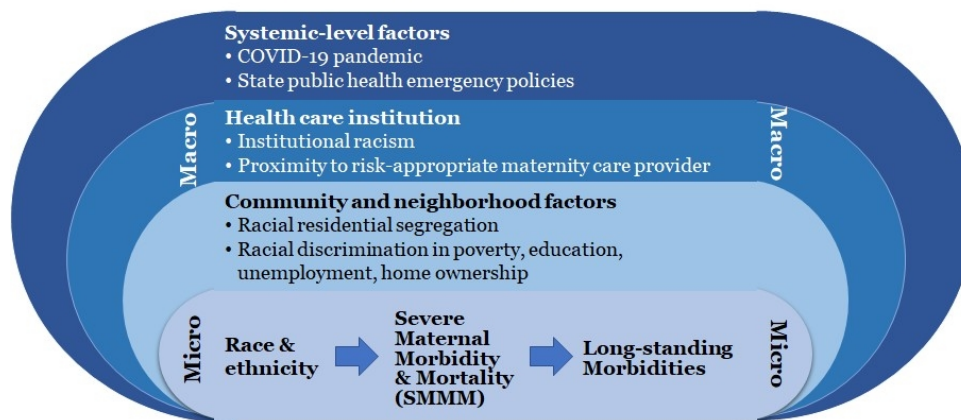


Figure 1

248x202mm (96 x 96 DPI)

Figure 2. Using concurrent triangulation mixed methods design to investigate racial/ethnic disparities in severe maternal morbidity and mortality during the COVID-19 pandemic

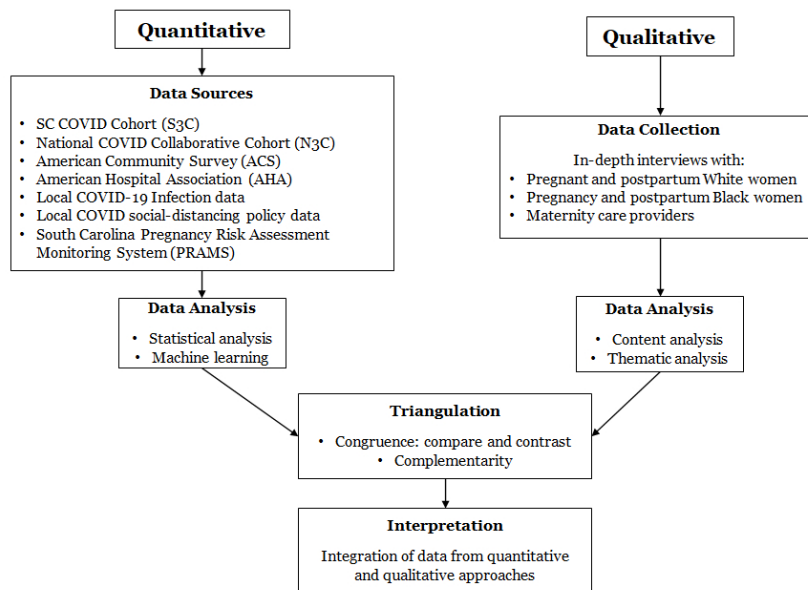


Figure 2

699x510mm (38 x 38 DPI)

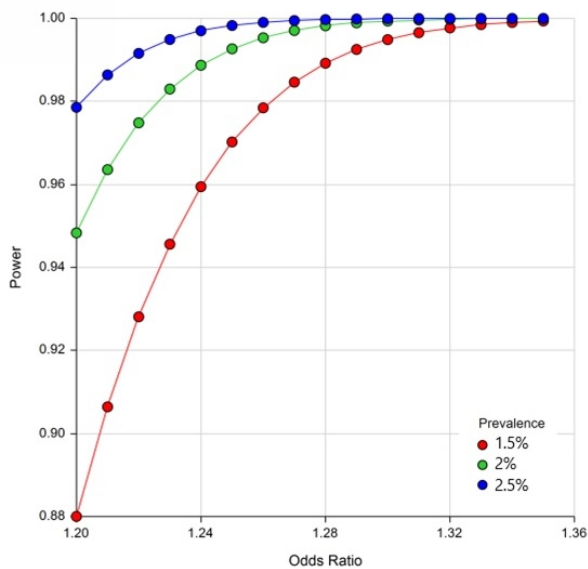


Figure 3

195x128mm (120 x 120 DPI)

BMJ Open

Multilevel determinants of racial/ethnic disparities in severe maternal morbidity and mortality in the context of the COVID-19 pandemic in the United States: protocol for a concurrent triangulation, mixed methods study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062294.R2
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Date Submitted by the Author:	12-May-2022
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Health informatics, Qualitative research, Obstetrics and gynaecology
Keywords:	COVID-19, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, EPIDEMIOLOGY, Maternal medicine < OBSTETRICS, PERINATOLOGY, PUBLIC HEALTH

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3 **Multilevel determinants of racial/ethnic disparities in severe maternal morbidity**
4 **and mortality in the context of the COVID-19 pandemic in the United States:**
5 **protocol for a concurrent triangulation, mixed methods study**
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10 *Jihong Liu,¹ Peiyin Hung,^{2,3} Chen Liang,^{2,3} Jiajia Zhang,^{1,3} Shan Qiao,³ Berry A. Campbell,⁵*
11 *Bankole Olatosi,^{2,3} Myriam Torres,¹ Neset Hikmet,^{3,6} Xiaoming Li.^{3,4}*
12
13
14
15
16

17 ¹ Department of Epidemiology & Biostatistics, Arnold School of Public Health, University of
18 South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
19

20 ² Department of Health Services Policy & Management, Arnold School of Public Health,
21 University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
22
23

24 ³ Big Data Health Science Center, University of South Carolina, 915 Greene Street, Columbia, SC
25 29208, USA.
26
27

28 ⁴ Department of Health Promotion, Education, & Behavior, Arnold School of Public Health,
29 University of South Carolina. 915 Greene Street, Columbia, SC 29208, USA.
30
31

32 ⁵ Berry A. Campbell, MD, Department of Obstetrics and Gynecology, School of Medicine,
33 University of South Carolina. Two Medical Park, Columbia, SC 29203, USA.
34
35

36 ⁶ Department of Integrated Information Technology, College of Engineering and Computing,
37 University of South Carolina. 550 Assembly Street, Columbia, SC 29208, USA.
38
39
40
41

42
43
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45
46
47
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49 **Correspondence to:**
50
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52
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1
2
3 Dr. Jihong Liu, Professor of Epidemiology, Department of Epidemiology & Biostatistics, Arnold
4 School of Public Health, University of South Carolina. 915 Greene Street, Columbia, SC 29208,
5
6
7 USA. jliu@mailbox.sc.edu. Phone: 803 777 6854
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ABSTRACT

Introduction: The COVID-19 pandemic has affected communities of color the hardest. Non-Hispanic Black and Hispanic pregnant women appear to have disproportionate SARS-CoV-2 infection and death rates.

Methods and analysis: We will use the socio-ecological framework and employ a concurrent triangulation, mixed methods study design to achieve three specific aims: 1) examine the impacts of the COVID-19 pandemic on racial/ethnic disparities in severe maternal morbidity and mortality (SMMM); 2) explore how social contexts (e.g., racial/ethnic residential segregation) have contributed to the widening of racial/ethnic disparities in SMMM during the pandemic and identify distinct mediating pathways through maternity care and mental health; and 3) determine the role of social contextual factors on racial/ethnic disparities in pregnancy-related morbidities using machine learning algorithms. We will leverage an existing South Carolina COVID-19 Cohort (S3C) by creating a pregnancy cohort that links COVID-19 testing data, electronic health records (EHR), vital records data, healthcare utilization data, and billing data for all births in South Carolina (SC) between 2018-2021 (>200,000 births). We will also conduct similar analyses using EHR data from the National COVID Cohort Collaborative (N3C) including >209,000 women who had a childbirth between 2018-2021 in the United States. We will use a convergent parallel design which includes a quantitative analysis of data from the 2018-2021 SC Pregnancy Risk Assessment and Monitoring System (unweighted n > 2,000) and in-depth interviews of 40 postpartum women and 10 maternal care providers to identify distinct mediating pathways.

Ethics and dissemination: The study was approved by institutional review boards at the University of SC (Pro00115169) and the SC Department of Health and Environmental Control (DHEC IRB.21-030). Informed consent will be provided by the participants in the in-depth

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3 interviews. Study findings will be disseminated with key stakeholders including patients,
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5 presented at academic conferences, and published in peer-reviewed journals.
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8 **Strengths and limitations of this study**

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- 10 • This study investigates whether the COVID-19 pandemic, structural racism, and racial
11 discrimination have contributed to the racial/ethnic disparities in severe maternal
12 morbidity and mortality in the United States.
 - 13 • This study employs a state-of-the-art design (i.e., a convergent parallel design) and
14 machine learning models to rigorously examine the questions of interest.
 - 15 • This study will use a large-scale population-based cohort study concurrently for both
16 South Carolina and the United States, which will innovatively integrate COVID-19-
17 related clinical, surveillance, EHR, and geospatial data at community, healthcare
18 institutions, and system/policy levels.
 - 19 • The effects of both county- and ZIP-code-level social contexts will be calculated at the
20 maternal residence location.
 - 21 • The stagnant residential social contexts might not reflect their long-term exposures to
22 neighborhood structural racism.
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INTRODUCTION

Annually, nearly 60,000 women experience severe maternal morbidity (i.e., unexpected complications of labor and delivery) and mortality (SMMM).^{1,2} Between 1993-2014, SMMM rates in the U.S. tripled from 49.5 to 146.6 per 10,000 childbirths.³ For every 70 U.S. women who experienced a severe maternal morbidity, one died during or immediately after pregnancy.⁴ The severe maternal morbidity occurrences have also led to significant short- or long-term clinical impacts on women's health⁵ and added significant costs to women, their families, taxpayers and the healthcare system.⁶⁻⁸

Non-Hispanic Black (hereafter, Black) women experience a 3- to 4-fold risk of pregnancy-related deaths compared to non-Hispanic White women (hereafter, White).^{9,10} Black and Hispanic women were up to 110 percent more likely to experience SMMM,² despite their younger maternal age (often a protective factor for SMMM) as compared to non-Hispanic White women. Such racial/ethnic disparities in SMMM rates have persisted for over a decade – with increasing rates among all race/ethnic groups.¹¹ These SMMM rates are unevenly distributed socioeconomically and geographically – with the highest rate among low-income women who delivered at hospitals in the Deep South states.^{2,12-14}

The unprecedented COVID-19 pandemic hit communities of color the hardest.¹⁵⁻¹⁷ Pregnant Black and Hispanic women experienced disproportionate COVID-19 infection and death rates.¹⁸⁻²⁰ The impacts of COVID-19 on SMMM remain unclear. During the pandemic, as unemployment, income instability, and financial stress have affected many U.S. families, Black and Hispanic families have faced even higher hardship rates.²¹ These disproportionate consequences reflect longstanding inequities, often stemming from structural racism and discrimination (e.g., residential segregation, poverty, inadequate education, unemployment, and lack of home ownership).^{22,23} These inequities can lead to uneven access to quality healthcare, psychosocial stress, and unhealthy lifestyles among women of color, which further increases SMMM risk.^{24,25} Yet, the etiology of SMMM is complex, multifaceted, and time-varying. Prior

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3 research efforts on racial/ethnic disparities in SMMM have mostly focused on maternal and
4 healthcare factors,²⁶ leaving questions regarding the dynamics and interactions of multilevel
5 determinants, such as the broader social contexts of these risks, largely unanswered. Thus, there
6 is an urgent need to examine how social contexts of all types play out in SMMM rates, especially
7 during the COVID-19 pandemic.^{22,23}

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13 South Carolina (SC) ranked 11th in COVID-19 cases per capita as of December 23, 2021.²⁷
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15 Prior to the pandemic, SC ranked 42nd in the U.S. in overall health and 41st in maternal
16 mortality.²⁸ Births to Black women accounted for nearly 30% of all SC births.²⁹ Black women
17 living in SC experienced a 2- to 3-fold higher risk of SMMM than their White counterparts.³⁰
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19 The majority of counties in SC are designated medically underserved areas.³¹ Considering SC's
20 poor health ranking, striking racial disparities in SMMM, racially diverse population, and
21 historical systemic Southern contexts, SC is an ideal environment in which to examine health
22 disparities in SMMM occurring during the COVID-19 pandemic.

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30 The overarching goal of this study is to investigate racial/ethnic disparities in SMMM, the
31 contributing roles and mediating pathways of social contexts (e.g., structural racism, racial
32 discrimination), and the long-standing health consequences of the pandemic by studying the
33 distributions of COVID-19 cases and multilevel determinants of maternal health in SC and the
34 U.S. Our study will: 1) examine the impacts of the COVID-19 pandemic on racial/ethnic
35 disparities in SMMM; 2) examine and explore how the key features of social contexts (including
36 structural racism and racial discrimination) have contributed to the widening racial/ethnic
37 disparities in SMMM during the pandemic and identify distinct mediating pathways through
38 maternity care and mental health; and 3) examine and identify the role of social contextual
39 factors and protective factors on racial/ethnic disparities in pregnancy-related long-standing
40 morbidities (e.g., hypertension, pulmonary embolism, diabetes, cardiovascular disease), using
41 machine learning algorithms.

METHODS AND ANALYSIS

Multilevel conceptual framework

The etiology of racial/ethnic disparities in SMMM is complex and multifaceted (**Figure 1**).²⁴ At the micro-level, in addition to maternal race/ethnicity, other socio-demographics (e.g., age, socioeconomic status [SES]), health behaviors (e.g., prenatal care adequacy, smoking, diet, physical activity, gestational weight gain), and preexisting maternal conditions (e.g., hypertension, pre-pregnancy body mass index (BMI), diabetes, HIV infection, obstetric comorbidity scores) potentially drive racial/ethnic disparities in SMMM.^{12,32,33} As compared to White women, Black and Hispanic women usually have higher poverty rates, lower educational levels, and higher rates of preexisting conditions or high-risk pregnancy.³² At the macro level, structural racism and discrimination - community and neighborhood factors (e.g., residential segregation, inadequate housing, lack of access to healthy food, no public transportation), healthcare institutional attributes (e.g., access to risk appropriate perinatal care), and system-level factors (e.g. COVID-19 pandemic, state public health emergency policies) may play a role in racial/ethnic disparities. These macro-level factors interact with micro-level factors to further exacerbate racial/ethnic disparities in SMMM.

Study design

The above-mentioned multilevel conceptual framework guided our study design (Figure 2). We will employ a concurrent triangulation, mixed methods study design to rigorously examine racial/ethnic disparities in SMMM in SC and the U.S. This convergent parallel design will allow us to better understand the underlying mechanisms for social contexts and racial/ethnic disparities in SMMM via maternity care and mental health using the data from the statewide pregnancy survey and via qualitative interviews with pregnancy and postpartum women and maternity care providers. Given the multilevel and multidomain nature of risk factors for pregnancy-related long-standing morbidities, we will use novel machine learning models to forecast the intertwining social context effects with multilevel factors on maternal health during

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3 the COVID-19 pandemic. We will conduct data analyses using the quantitative and qualitative
4 methods concurrently. Then we will compare and contrast findings from these two methods for
5 similarities and incongruences and will interpret findings jointly.
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8 9 Data sources

10 We will leverage our statewide South Carolina COVID-19 Cohort (S3C) database, which
11 integrates COVID-19-related clinical, surveillance, electronic health records (EHR) and
12 geospatial and temporal data at community, healthcare institutional, and system levels to
13 comprehensively examine the roles of social contexts on racial/ethnic disparities in SMMM. To
14 ensure the generalizability of our findings, we will also examine them using EHR data from the
15 ongoing National COVID Cohort Collaborative (N3C).³⁴ Nationwide social context databases
16 (e.g. American Community Survey [ACS], American Hospital Association [AHA]) and time-
17 varying COVID-19 infection and social distancing policies data will be added to both S3C and
18 N3C. Postpartum women's survey responses and in-depth interview data will be analyzed to
19 understand complex pathways and multilevel determinants of maternal morbidities (Figure 2).
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32 *SC COVID-19 Cohort – Pregnancy (S3C-P) Database.* With support from the National
33 Institute of Allergy and Infectious Disease (NIAID) (R01A127203-4S1), our team has established
34 a statewide S3C database for COVID-19 research since 06/2020 by integrating various state-
35 level data sources including: 1) the COVID-19 testing data from the SC Department of Health
36 and Environmental Control (SC DHEC), 2) hospital encounter data for inpatient hospitalization,
37 outpatient surgery, home health, and emergency departments; 3) health utilization data from
38 large public and private health insurance plans (e.g., Medicaid, State Health Plan, BlueCross
39 BlueShield of SC); 4) EHR data from health systems (Prisma & MUSC), and 5) program data
40 from the SC Department of Mental Health (SC DMH). The database is updated every 6 months.
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51 In this study, as part of the National Institutes of Health (NIH)'s “Implementing a Maternal
52 health and PRenancy Outcomes Vision for Everyone” (IMPROVE) initiative supported by the
53 Office of Director, NIH (3R01A127203-5S2), our team will create a population based S3C
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3 pregnant women cohort (S3C-P), which includes all women who gave birth between 2018-2021
4 in SC (>200,000 births, 57.2% White, 31.1% Black, 4.6% Hispanic) and will add vital record data
5 (birth and death certificates) to complement existing linkages from the parent S3C cohort. The
6 identification of pregnancy status and COVID-19 infection will be cross-verified using EHR,
7 claims data, laboratory reports, and ongoing SC DHEC medical chart reviews among > 4,387
8 pregnant women with confirmed COVID-19 infections in SC as of December 2021. The SC Office
9 of Revenue and Fiscal Affairs (SC RFA) will collate databases and provide our team with a de-
10 identified linked database system.³⁵

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20 *National COVID Cohort Collaborative (N3C)*. The N3C is a novel data consortium that
21 integrates EHR and medical claims data from 92 healthcare systems and institutes across 50
22 states. N3C enables data sharing, computable phenotypes, and collaborative data mining by
23 harmonizing EHR data of diverse standards using Observational Medical Outcomes Partnership
24 (OMOP) Clinical Data Model (CDM). N3C was created to study potential risk factors and
25 protective factors of COVID-19 and its long-term health consequences.³⁴ As of December 24,
26 2021, N3C has aggregated 9.4 million patients (3.3 million COVID-19 patients) with their EHR
27 dating back from January 2018, including 1.9 million women with COVID-19 (>61k pregnant
28 women), and 3.5 million women without COVID-19 (>209k pregnant women). The participants
29 in N3C represent diverse populations in the U.S. (e.g., geographic, socioeconomic,
30 racial/ethnic). Building on a secured cloud environment, N3C provides data harmonization,
31 privacy-preserving data linkage, and high-performance data analytics. Our team has already
32 gained access to the restricted N3C database including ZIP codes of patients and health systems
33 and dates of services.

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49 *Nationwide social context databases*. The 2015-2019 American Community Survey (ACS)
50 and the 2018-2020 American Hospital Association (AHA) Annual Survey will be used to
51 calculate county-level residential segregation measures, racial discrimination in SES, and ZIP-
52 level accessibility to hospital-based obstetric units.

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3 *Time-varying local COVID-19 infection and social-distancing policy data.* To better
4 understand local pandemic settings, we will also add the Centers for Disease Control and
5 Prevention (CDC) COVID-19 Case Surveillance restricted datasets for nationwide cases
6 confirmed since March 11, 2020, and CDC's state-level social distancing policies (e.g. emergency
7 declaration, stay at home order, etc.) in early pandemic and telehealth services expansion data
8 and each corresponding date of enactment.³⁶

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16 *SC Pregnancy Risk Assessment Monitoring System (PRAMS).* SC PRAMS as a part of
17 national PRAMS is an ongoing survey of SC mothers who have recently given birth.³⁷ These
18 mothers are sampled from state birth certificates. After statistical weighting, PRAMS data are
19 representative of all mothers who gave birth in SC. SC PRAMS added 11 COVID-19-related
20 questions for mothers who delivered in August 2020 and after in their survey. SC PRAMS
21 routinely collects detailed psychosocial and behavioral risk factors for each participant, which
22 are not available in S3C and N3C. Residential ZIP codes will be used to add in social contextual
23 variables and other ZIP- or county-level characteristics. The unweighted sample size for SC
24 2018-2021 PRAMS will be at least 2,000.

25 Key measures

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36 *Outcome measures.* The main outcomes of interest will be SMMM.³⁸ We will adapt from a
37 previously validated algorithm by using the International Classification of Diseases, Tenth
38 Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure codes to identify women
39 with one or more of the 21 severe maternal morbidity (SMM) indicators developed by the CDC
40 and updated by the Alliance for Innovation on Maternal Health (AIM) program at the time of
41 childbirth. Maternal mortality will be identified using statewide death certificate data from the
42 childbirth date to up to one year postpartum. A composite variable of SMMM will be created to
43 reflect SMM or maternal mortality incidence. We will also study maternal morbidity and
44 mortality (MMM) composite, which includes mortality and morbidities related to hypertensive
45 disorders of pregnancy, postpartum hemorrhage, and infections/sepsis that happen during
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3 pregnancy through 6 weeks postpartum.³⁹ Other outcomes to be studied include: 1) adverse
4 maternal outcomes including intensive care unit (ICU) admission, invasive ventilation, receipt
5 of extracorporeal membrane oxygenation (ECMO), etc.; 2) prolonged length of stay (LOS),^{40,41}
6 and 3) hypertension, pulmonary embolism, type 2 diabetes, cardiovascular diseases (e.g. heart
7 attack, myocardia infraction, thrombus, stroke) diagnosed within one year after delivery.
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13 *COVID-19 status and severity.* Eligible COVID-19 cases are those with a positive test for
14 SARS-CoV-2 since March 11, 2020, during pregnancy. Data on symptom status (symptomatic,
15 asymptomatic, unknown) is available, while severity will be defined using the World Health
16 Organization's (WHO) Clinical Progression Scale.⁴²
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21 *Social context measures.* The five dimensions of county-level *residential segregation*,
22 including evenness, exposure, concentration, centralization, and clustering,^{43,44} will be
23 determined for each race/ethnic group (e.g., Black, Hispanic) using the ACS Census tract
24 data.^{45,46} Each index will be calculated across census tracts within residential counties. Higher
25 values indicate higher levels of segregation. We will create the group indicator for segregated
26 versus less segregated counties using the cutoffs for each dimension index.⁴⁶ Additional hyper-
27 segregation index – segregations scores at ≥ 0.6 on at least four aforementioned dimensions –
28 will be created to reflect the highest levels of segregation.⁴⁶ Within-county *racial/ethnic*
29 *discrimination in SES* will be calculated using the ACS county data,⁴⁵ including Black-White and
30 Hispanic-White ratios of poverty, unemployment, and home ownership rates.⁴⁷⁻⁵¹ These
31 measures will be linked to databases via maternal residence counties.
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45 *Healthcare institution.* Using the AHA annual survey data on hospital location,⁵² we will
46 identify *loss of hospital-based obstetric units* using our published validated algorithm.⁵³⁻⁵⁵ An
47 indicator for whether a hospital or a hospital's obstetric service was closed for each year will be
48 created. In turn, women's access to hospital-based obstetric care within 30-mile distance for
49 years 2018-2020 using the ArcGIS fastest route network will be determined: 1) had access to; 2)
50 no access to; and 3) experienced the loss of all hospital-based obstetric units.
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3 *County-level COVID-19 infections and social distancing policies.* The CDC's COVID-19 Case
4 Surveillance will be used to compute monthly cumulative rates of in-county residents that had
5 been confirmed COVID-19 positive, hospitalized, admitted to an intensive care unit, and with
6 mechanical ventilation (MV)/intubation as a result of COVID-19 disease. Number of months
7 elapsed since a county had each of the following policy orders will be calculated from a delivery
8 date: emergency declaration, closures of bars, restaurants, and/or other non-essential business,
9 stay at home order, and telehealth services expansion.
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17 Statistical analyses

18 *Impacts of the COVID-19 pandemic on racial/ethnic disparities in SMMM*

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20 We will examine the overall impacts of the COVID-19 pandemic on SMMM using the data from
21 the S3C-P and N3C. We hypothesize that: 1) compared to pre-pandemic periods, SMMM has
22 increased during the pandemic and racial/ethnic disparities have widened during the pandemic;
23 and 2) compared to pregnant women without COVID-19 infection, women with COVID-19
24 infection experienced higher proportions of SMMM, and racial/ethnic disparities in SMMM
25 have amplified among COVID-19 infected women.
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34 First, we will examine the distributions for all measures and clean the database (e.g. outliers,
35 data entry errors etc.) using appropriate statistical techniques. Second, we will conduct
36 preliminary analyses and examine descriptive statistics for outcome measures. Unadjusted and
37 adjusted associations of SMMM with key variables and covariates will be assessed using
38 appropriate statistical procedures (e.g., tests of proportions, chi-square tests, analysis of
39 variance).
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47 Women who gave birth between January 1, 2018 through March 10, 2020, will be
48 categorized as before pandemic, while women who gave birth between March 11, 2020 through
49 December 31, 2021, will be considered as during the pandemic. The pre-pandemic vs pandemic
50 impact on SMMM will be modeled via logistic regression. First, the crude model with the
51 pandemic indicator only will address SMMM change before and after the pandemic. Second, to
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3 investigate whether racial/ethnic disparities in SMMM have widened during the pandemic, the
4 crude model will be further adjusted with race/ethnicity, interactions between race/ethnicity
5 and pandemic indicator, and months elapsed since March 11, 2020, on delivery dates. Then
6 additional variables will be added, including individual-level characteristics (e.g., age, SES proxy
7 [i.e., Medicaid/uninsured status], parity, marital status, underlying health conditions). Variable
8 selection and goodness of model fit will be evaluated using the AIC, BIC, and likelihood ratio
9 test.
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17 We will also conduct analyses in women who delivered during the COVID-19 pandemic by
18 comparing pregnant women with and without COVID-19 infection. We will first create the
19 COVID infection indicator and then will perform the similar analysis as those for the pre-
20 pandemic vs pandemic impact. We will further adjust for county-level COVID-19 infections per
21 capita and social distancing policies at the appropriate time points using logistic regressions
22 with random effects accounting for correlations among counties.
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30 *Social contexts, racial/ethnic disparities in SMMM, and distinct mediating pathways*

31 We will study these issues using different databases and methods. First, we will examine the
32 association between social contexts and changes in racial/ethnic disparities in SMMM before
33 and during the pandemic. We hypothesize that racial/ethnic disparities SMMM are potentially
34 disproportionately widened in communities with higher racial/ethnic economic disparities
35 (measured by Black-White ratios of economic disadvantages, Hispanic-White ratios of economic
36 disadvantages) and in higher vs. less segregated Black or Hispanic counties (measured by
37 residential segregation). We will conduct a parallel analysis between social contexts and SMMM
38 using the data from S3C-P and N3C (**Figure 2**). Similarly, we will examine the contributing
39 roles of social contexts to racial/ethnic disparities in SMMM in the overall sample (pre-
40 pandemic vs pandemic) and between COVID-19 positive vs COVID-19 negative women. The
41 multilevel variables that will be investigated include individual-level characteristics,
42 community-level characteristics (ZIP code accessibility of hospital obstetric units), and county-
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3 level characteristic (social contexts: residential segregation and racial discrimination on SES;
4 COVID-19 infection per capita and social distancing policies). For exploratory analysis, the odds
5 ratio (OR) of SMMM among Black and White and the social context level at the county level pre-
6 pandemic vs pandemic will be visualized via the spatial temporal map using GIS. The summary
7 statistics in SMMM with respect to race/ethnicity will be calculated according to individual- and
8 county-level characteristic.
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11 We will model SMMM via multilevel hierarchical logistic regression. Women who reside at
12 the same community- or county-level will be accounted for via random effects, which will be
13 further modeled in the regression model with a multivariate normal distribution to account for
14 the correlations among community or county. We plan to use an incremental modeling strategy:
15 1) crude model (race/ethnicity and social context factors); 2) adjusting for individual level
16 factors; and 3) additional adjustment of additional community- and county-levels
17 characteristics. For N3C data, we will further adjust for state or Census region. To further
18 examine whether social contexts moderate racial/ethnic disparities in SMMM and whether
19 these disparities vary between pre-pandemic and pandemic, we will include two-way and three-
20 way interaction terms in the model (e.g., pandemic period*social context*race). To examine the
21 added impact of COVID-19 infections on SMMM, we will repeat the model by restricting it to all
22 women who gave birth during pandemic period (delivered after March 11, 2020) and including
23 maternal COVID-19 severity status in the model. Models will be compared using the AIC and
24 BIC criteria. In the modelling procedure, the outliers, missingness, multicollinearity, and
25 nonlinear will be addressed accordingly, and sensitivity analysis will be conducted comparing
26 models with or without the treatment of outliers or missing data. The magnitude and direction
27 racial/ethnic disparities will be assessed through OR and its 95% confidence interval.
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31 Second, we will use a convergent parallel design to evaluate the underlying pathways
32 between social contexts and racial/ethnic disparities in MMM via pandemic stressors, maternity
33 care (prenatal and postpartum) and mental health condition. We hypothesize that social
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3 contexts might hinder maternity care and worsen mental health conditions among Black and
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5 Hispanic women during the pandemic and exacerbate racial/ethnic disparities in MMM.
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7 The quantitative analysis will be conducted using SC PRAMS data, which have unique data
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9 elements that are not available in S3C-P and N3C. The 2018-2021 SC PRAMS data will provide a
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11 more refined understanding of COVID-19 stressors, psychosocial stress, and healthcare
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13 utilization through the questionnaire, including pandemic stressors (financial, job loss,
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15 childcare, etc.), individual mitigation practices, changes in prenatal and postpartum care,
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17 psychosocial stress, barriers to health services, intimate partner violence (IPV), prenatal and
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19 postpartum care utilization, smoking, alcohol use, gestational weight gain, and mental health.
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21 SC PRAMS asks respondents to assess how often they experienced depressive symptoms after
22
23 delivery. Descriptive statistics will be used to examine pandemic-related changes in MMM and
24
25 psychosocial and behavioral changes between pre-pandemic (delivered before March 11, 2020)
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27 and pandemic periods (March 11, 2020 and after). The weighted hierarchical regression model
28
29 will be applied to examine the association between social context and MMM. As previously
30
31 mentioned, community and county levels will also be modeled in the regression. Different from
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33 the prior analyses above: 1) individual characteristics will mainly come from PRAMS or birth
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35 certificates; 2) the weight based on complex survey design will be modeled; and 3) individual
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37 reports of healthcare utilization and mental health condition included.
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40 We will conduct in-depth interviews among 40 postpartum women of color (~20 African
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42 American; ~20 Hispanic) stratified by COVID-19 infection status and 10 maternal care
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44 providers (MCPs) who serve pregnant and postpartum women in Black and Latino
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46 communities. The inclusion criteria of postpartum women include: 1) ≥ 18 years old; 2) either
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48 African American or Hispanic; 3) have given birth in 2021; and 4) living in SC. We will
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50 purposely recruit postpartum women and MCPs through local OBGYN clinics and community
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52 health organizations that serve a larger proportion of low-income Black and Hispanic women.
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54 We will train female interviewers of the same race as the interviewees to obtain trust from the
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3 postpartum women participants, and interviews in Spanish will be conducted as needed. Guided
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5 by the conceptual framework, the main topics of the postpartum women interviews will include:
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7 1) their perceptions toward their healthcare providers and institutions for perinatal care; 2)
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9 experience with prenatal and postpartum care; 3) stressors in the COVID-19 pandemic; 4)
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11 challenges in healthcare seeking (e.g., appointments, clinic visits), especially from structural
12
13 factors (racism and discrimination); and 5) their needs/recommendations for future healthcare.
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15 The main topics of the MCPs include: 1) stressors and challenges of their clients; 2) clients'
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17 mental health conditions; 3) impacts of COVID-19 on their care provision; and 4) their views on
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19 health disparities caused by structural factors. The interviews will last 50 minutes and will be
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21 recorded with each participant's consent. Audio recordings will be transcribed and coded using
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23 NVivo 11.0. We will employ thematic analyses.⁵⁶ The findings will complement the quantitative
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25 data in providing a comprehensive picture on how COVID-19 affects psychosocial well-being of
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27 the postpartum women of color; offer in-depth interpretation and explanation of quantitative
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29 results; and explore the mediating pathways in which structural factors amplify existing
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31 disparities in maternal health in the context of the pandemic.
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34 *Machine learning-based predictive models*

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36 We will develop and evaluate machine learning-based predictive models to identify risk factors
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38 of SMMM and forecast progression of hypertensive disorder, pulmonary conditions, type 2
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40 diabetes mellitus, and cardiovascular diseases among postpartum women. The predictive
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42 models will synthesize individuals' demographics, EHR, social contextual factors, and
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44 community and healthcare system level data to make predictions of individuals' clinical
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46 outcomes at key time points. Because data sources suggestive of these factors are variable and
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48 high-dimensional, and these factors are inherently interconnected over time,⁵⁷ machine learning
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50 is a superior approach to predicting clinical outcomes and proactively detecting the associated
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52 risk factors for early intervention and treatment. Constructed models will demonstrate critical
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54 factors predictive of clinical outcomes and how these factors interact over time.
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3 Supervised machine learning algorithm will be adopted for the predictive models. Using
4 N3C, the algorithm will learn from input variables and predict SMMM and long-standing
5 morbidities (e.g., hypertension, pulmonary embolism, diabetes, cardiovascular diseases) over
6 time. Input variables will include maternal characteristics, e.g., socio-demographics, socio-
7 behavioral data, social context variables, diagnoses, procedures, laboratory tests, and
8 medications. The prediction of SMMM and long-standing morbidities will take place at critical
9 time points: <3, 6, 12 weeks, 6 and 12 months postpartum.⁵⁸ We will develop Deep Learning
10 algorithms because of their ability to integrate complex clinical data and social contexts from
11 multiple sources with superior predictive performance, including: 1) convolutional neural
12 network (CNN) for its ability to capture dynamic patterns among multilevel input variables; 2)
13 recurrent neural network (RNN) with long short-term memory (LSTM) architecture for its
14 ability of capturing temporal patterns of clinical events (e.g., onset of pre-infection conditions,
15 viral infections and clinical events marked with gestational weeks, and the date of childbirths);
16 and 3) Deep Boltzmann Machine (DBM) for its interpretable scoring mechanism for risk
17 prediction.⁵⁹

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19 We will use a 10-fold cross validation. Specifically, S3C and N3C data will each be randomly
20 partitioned into ten splits. In each of the ten iterations, seven splits of data will be randomly
21 selected for model training, two splits of data will be used for internal validation (finetuning
22 hyperparameters), and the 10th split used for testing. We will use F measure, precision, recall,
23 and the area under the Receiver Operating Characteristic curve (AUC), if unbalanced data, to
24 measure the predictive performance of models. We will use support vector machine (SVM) as
25 the baseline algorithm to compare against the performance of CNN, RNN (LSTM), and DBM.
26 The best-performed model will be identified based on F measure.

27
28 We will rank input variables and/or clusters of input variables by calculating the importance
29 scores ⁵⁷ (e.g., mutual information, SVM-based recursive linear elimination). Two content co-
30 investigators will independently review the ranked results and identify clinical/social risk

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3 factors. Disagreement between two reviewers will be resolved by panel discussion. Development
4 of sophisticated machine learning models for predicting long-standing morbidities will be used
5 to identify important risk factors prenatally, which can be used for early intervention, treatment,
6 and community-wide interventions.
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11 *Power and sample size calculation.* We estimate that there were 200,000 women who gave
12 birth in S3C and 270,000 pregnant women in N3C for our study period. The primary outcome of
13 interest is SMM and the main exposures of interest are race (White vs Black) and pre-peri
14 COVID period. We assume that there are 64,000 (32%) Black and 114,000 (57%) White in S3C⁶⁰
15 and 38,070(14.1%) Black and 160,380 (59.4%) White in N3C.⁶¹ We also assume that with the
16 same time length of pre and peri COVID-19, the prevalence of pregnancy will be similar (50%).
17 For all aims, we consider the logistic regression with mixed effects. Based on 1.5%-2.5%
18 incidence of SMM with 20%-50% increase due to the COVID -19 impact or race disparities, we
19 conduct the power analysis based on the logistic regression using SAS and conclude that
20 200,000 sample size will be adequate to reach the power around 90%. **Figure 3** illustrates the
21 relationship of power and odds ratio with setting of n=200,000, significance at 0.05, variable of
22 interest with a ratio of 10:90. This will be the basic model considered, and it indicates strong
23 power for the prediction model.
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30 Current status and anticipated timeline

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32 As of April 2022, we have received the linked core databases for the S3C cohort for the period of
33 January 2018- June 2021 and full datasets will be available by the Fall of 2022. Our team is also
34 actively constructing N3C analytic data of women with childbirths during January 2018-
35 December 2021 for statistical analysis and machine learning. Furthermore, our team is
36 conducting in-depth interviews with our targeted populations according to our protocols
37 described here. We anticipate completing our main analyses in May 2023.
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40 Patient and public involvement

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3 No patients were involvement in the design, conduct and reporting of our research. We will
4 actively reach out patients and public in the dissemination of our findings.
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8 9 **ETHICS AND DISSEMINATION**

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11 The study was approved by institutional review boards at the University of South Carolina
12 (Pro00115169) and the South Carolina Department of Health and Environmental Control
13 (DHEC IRB.21-030). Informed consent will be completed for the participants to be enrolled in
14 the in-depth interviews. Furthermore, the NIH's N3C data access committee approved the data
15 use request for this project (RP-2B9622). Study findings will be disseminated with key
16 stakeholders including patients, presented at academic conferences, and published in peer-
17 reviewed journals.
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28 **DISCUSSION**

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30 The COVID-19 pandemic has led to unprecedented societal disruptions to individuals,
31 communities, healthcare institutions, and society. Empirical data on the scope of possible
32 widening racial/ethnic disparities in SMMM during the COVID-19 pandemic and how historical
33 structural racism and discrimination of all types have impacted women of color
34 disproportionately are sparse. This study will be among the first efforts to investigate whether the
35 COVID-19 pandemic, structural racism, and racial discrimination— exposures with broad scale
36 and reach – have contributed to the racial/ethnic disparities in SMMM in the context of the
37 COVID-19 pandemic. Second, this proposed study employs a state-of-the-art design (i.e., a
38 convergent parallel design) to comprehensively examine the impacts of structural racism and
39 discrimination on maternal health and the complex pathways between multilevel determinants.
40 This design has the advantage of allowing us to weigh both quantitative and qualitative methods
41 equally and interpret the results together.⁶² Third, the proposed study will innovatively use
42 machine learning models to predict SMMM and chronic morbidities up to one year after
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3 delivery in the context of the COVID-19 pandemic. Fourth, we propose a large-scale population-
4 based cohort study concurrently for both SC and the U.S., which will innovatively integrate
5 COVID-19-related clinical, surveillance, EHR, and geospatial data at community, healthcare
6 institutions, and system/policy levels. These newly integrated data sources will allow us to
7 examine multilevel determinants of maternal health during the pandemic and advance the
8 investigation on racial/ethnic disparities in long-standing complications post-pandemic. In
9 brief, this research represents a significant and innovative contribution to the research on the
10 unacceptable racial/ethnic disparities in SMMM during pregnancy and postpartum in the
11 context of COVID-19. By focusing on social contextual factors (e.g., structural racism), we seek
12 to identify ways in which the largest number of women may be impacted by targeted programs
13 and policies aiming to alter the context in which these morbidities and mortality occur.
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16 This study also has some limitations. First, it is possible that the county-level social contexts'
17 effects in our data may not be significant. If that happens, we will calculate ZIP-code level social
18 contexts. By assessing racial segregations, spatial distribution of economic disadvantage
19 communities within a residence county and within-community racial discrimination, this study
20 will provide evidence on the associations between distinct social contexts and maternal health
21 disparities. Second, considering some women may move during pregnancy, the stagnant
22 residential social contexts might not reflect their long-term exposures to neighborhood
23 structural racism. Furthermore, in the case of inferior F measures (<0.7) of learning predictive
24 models, we will apply feature selection algorithms and association rules in model training to
25 maximize performance.
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28 In conclusion, the rising SMMM rate and persistent racial/ethnic disparities should trigger
29 public health concerns, not only due to the immediate burden faced by vulnerable women, but
30 also due to potentially lasting effects on women's health over a life course or along family lines
31 across generations.⁶³ This study will investigate racial/ethnic disparities in SMMM, the
32 contributing roles and mediating pathways of social contexts (e.g., structural racism, racial
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3 discrimination), and the long-standing health consequences of the pandemic by studying the
4 distributions of COVID-19 cases and multilevel determinants of maternal health in a racially,
5 socioeconomically, and geographically diverse population of U.S. pregnant women. A rigorous
6 examination of social contexts and racial/ethnic disparities in SMMM during the pandemic will
7 contribute to the identification of factors with a broad scale and reach for programmatic and
8 policy interventions to alter the context in which morbidity and mortality occur. Our findings
9 will inform continuing efforts to reverse the rising trends of SMMM in the U.S.
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List of abbreviations

ACS: American Community Survey

AHA: American Hospital Association

AIM: Alliance for Innovation on Maternal Health program

AUC: Receiver Operating Characteristic Curve

Black: Non-Hispanic Black

BMI: Body Mass Index

CDC: Centers for Disease Control and Prevention

CDM: Clinical Data Model

CNN: Convolutional Neural Network

DBM: Deep Boltzmann Machine

ECMO: Extracorporeal Membrane Oxygenation

EHR: Electronic Health Records

ICU: Intensive Care Unit

ICD-10-CM: the International Classification of Diseases, Tenth Revision, Clinical Modification

IMPROVE: Implementing a Maternal health and PRenancy Outcomes Vision for Everyone

IPV: Intimate Partner Violence

IRB: Institutional Review Board

LOS: Prolonged Length of Stay

LSTM: Long Short-Term Memory

MCPs: Maternal Care Providers

MMM: Maternal Morbidity and Mortality

MUSC: Medical University of South Carolina

MV: Mechanical Ventilation

N3C: National COVID Cohort Collaborative

NCATS: the National Center for Advancing Translational Sciences

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3 NIAID: National Institute of Allergy and Infectious Disease
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5 NIH: National Institutes of Health
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7 OMOP: Observational Medical Outcomes Partnership
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9 OR: Odds Ratio
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11 PRAMS: Pregnancy Risk Assessment and Monitoring System
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13 RNN: Recurrent Neural Network
14
15 S3C: South Carolina COVID-19 Cohort
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17 S3C-P: South Carolina COVID-19 Cohort-Pregnancy
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19 SC: South Carolina
20
21 SC DHEC: SC Department of Health and Environmental Control
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23 SC DMH: South Carolina Department of Mental Health
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25 SC RFA: SC Office of Revenue and Fiscal Affairs
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28 SES: Socioeconomic Status
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30 SMM: Severe Maternal Morbidity
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32 SMMM: Severe Maternal Morbidity and Mortality
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34 SVM: Support Vector Machine
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36 UofSC: University of South Carolina
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38 White: Non-Hispanic White
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40 WHO: World Health Organization
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Declarations

Consent for publication

Not applicable.

Data availability statement

The South Carolina data (S3C) that were analyzed to produce the findings of this study are available from the SC Office of Revenue and Fiscal Affairs (RFA) upon reasonable request. Per our contract with SC RFA, only approved users have access to the data and data cannot be made publicly available by authors. N3C data can be accessed through the NCATS N3C Data Enclave for approved users (<https://covid.cd2h.org>).

Contributors

JL conceptualized and designed the study and wrote the first draft and PH, CL, JZ, SQ and XL participated in writing sections of the original proposal. All authors critically reviewed and edited the manuscript. JL, PH, CL, and BO acquired the data and completed IRB approvals. JL, PH, CL, JZ, BAC, NH, BO, XL participated in quantitative data analysis and data interpretation. JL, SQ, and MT participated in qualitative data collection, data analysis and data interpretation. JL and XL secured the funding.

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Competing interests

The authors declare that they have no completing interests.

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2
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7 on-going development of N3C database [<https://doi.org/10.1093/jamia/ocaa196>].
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3 **Figure 1. Multilevel conceptual framework to examine racial/ethnic disparities in**
4 **severe maternal morbidity and mortality in the context of COVID-19 Pandemic**
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6 **Figure 2. Using concurrent triangulation mixed methods design to investigate**
7 **racial/ethnic disparities in severe maternal morbidity and mortality during the**
8 **COVID-19 pandemic**
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10 **Figure 3. Estimated power according to prevalence of outcomes and odds ratios**
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For peer review only

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Figure 1. Multilevel conceptual framework to examine racial/ethnic disparities in severe maternal morbidity and mortality in the context of COVID-19 pandemic

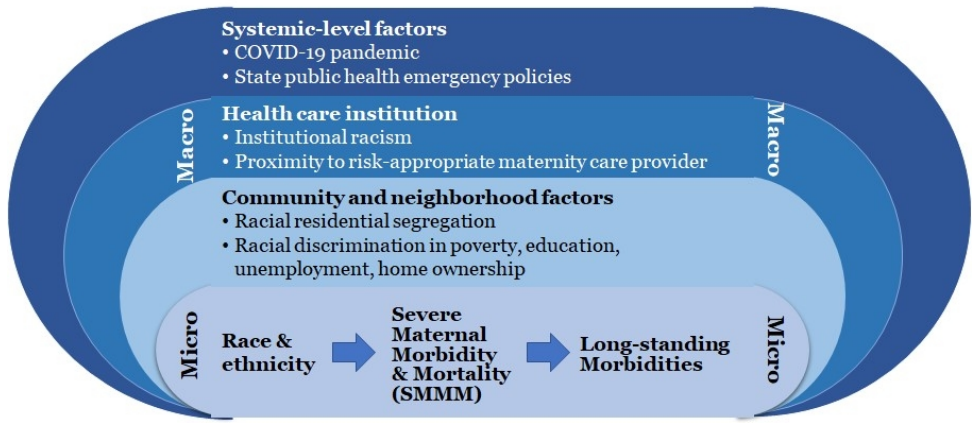


Figure 1

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Figure 2. Using concurrent triangulation mixed methods design to investigate racial/ethnic disparities in severe maternal morbidity and mortality during the COVID-19 pandemic

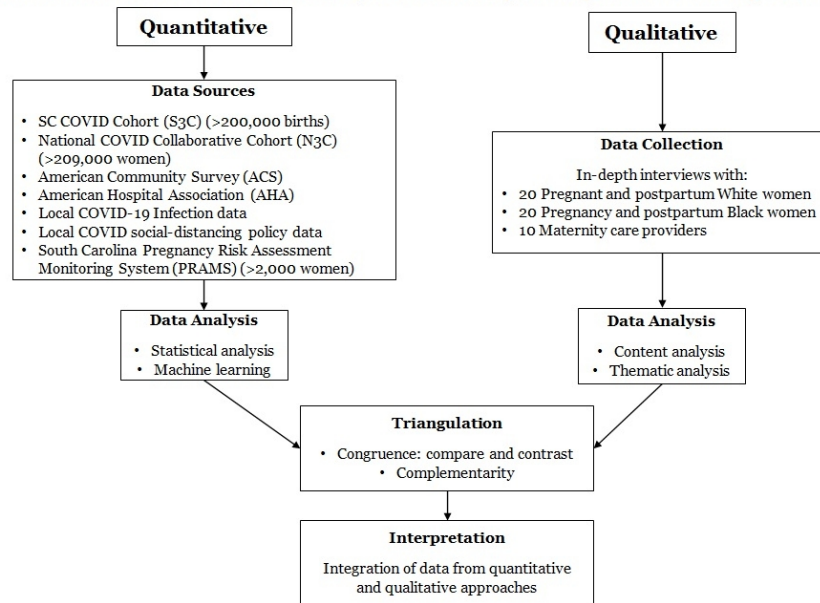


Figure 2

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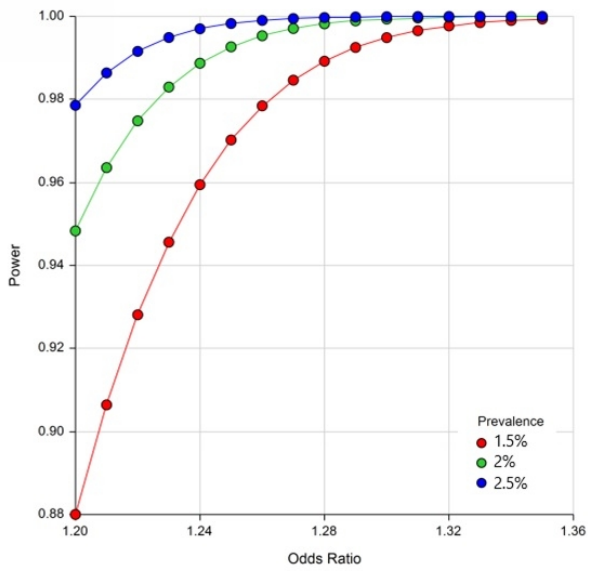


Figure 3
195x128mm (120 x 120 DPI)