UNIVERSITY OF CALIFORNIA SAN DIEGO
SAN DIEGO STATE UNIVERSITY

Substance use impacts maternal morbidity and maternal delivery outcomes in women who presented for delivery in a large healthcare system

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Interdisciplinary Research on Substance Use

by

Natasia S. Courchesne

Committee in Charge:

University of California San Diego
- Professor Carla Marienfeld, Chair
- Professor Christina Chambers
- Professor Laramie Smith

San Diego State University
- Professor María Luisa Zúñiga, Co-Chair
- Professor Mark Reed

2020

The Dissertation of Natasia S. Courchesne is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

_____

_____

_____

_____

Co-Chair

_____

Chair

University of California San Diego

San Diego State University

2020

TABLE OF CONTENTS

Signature Page iii
Table of Contents iv
List of Figures vi
List of Tables vii
Acknowledgements x
Vita and Publications xii
Abstract of the Dissertation xiii
CHAPTER 1: INTRODUCTION 1
OVERVIEW 1
BACKGROUND 3
Pregnant women with a substance related diagnosis 3
Preterm delivery 4
Cesarean delivery 5
Severe maternal morbidity 5
Gestation and parity 6
Sociodemographic indicators 7
Body mass index 8
Mental illness and pre-existing health conditions 9
CONCEPTUAL FRAMEWORK 10
AIMS AND HYPOTHESES 12
REFERENCES 15
CHAPTER 2: PREVALENCE AND CORRELATES OF A SUBSTANCE RELATED DIAGNOSIS AND PRETERM DELIVERY AND CESAREAN DELIVERY AMONG PREGNANT WOMEN..... 19
ABSTRACT 21
INTRODUCTION 21
METHODS 24
Study participants and procedures 24
Measures 26
Statistical Analysis 28
RESULTS 30
Sample characteristics 30
Prevalence and correlates of preterm delivery 31
Independent associations with preterm delivery 32
Prevalence and correlates of cesarean delivery 32
Independent associations with cesarean delivery 33
DISCUSSION 34
SRD and maternal morbidity 35
Andersen model covariates 37
Strengths and Limitations 38
CONCLUSION 39
ACKNOWLEDGEMENTS 40
TABLES 41
REFERENCES 49
CHAPTER 3: SEVERE MATERNAL MORBIDITY AMONG WOMEN WHO PRESENTED FOR DELIVERY WITH AND WITHOUT A SUBSTANCE RELATED DIAGNOSIS 53
ABSTRACT 53

INTRODUCTION …. 55
METHODS.... 57
Study Participants and Procedures 57
Measures 60
Statistical Analysis 62
RESULTS 64
Sample Characteristics 65
Prevalence and Correlates of SMM…….... 67
SMM Over Time in the Unmatched and Matched Cohort……..... 68
DISCUSSION 68
Strengths and Limitations 71
Conclusions ……..... 72
ACKNOWLEDGEMENTS 73
TABLES AND FIGURES.... 74
REFERENCES 81
CHAPTER 4: LATENT CLASSES OF SUBSATNCE RELATED DIAGNOSIS, MENTAL ILLNESS, PHYSICAL HEALTH CONDITIONS, AND SEVERE MATERNAL MORBIDITY AMONG PREGANT WOMEN ……..……..….. 84
ABSTRACT 84
INTRODUCTION 86
METHODS.... 89
Study Participants and Procedures 89
Measures 91
Statistical Analysis 93
RESULTS 94
Sample characteristics 94
SMM-specific latent classes……..... 95
DISCUSSION 97
Strengths and Limitations 100
Conclusions……..... 101
ACKNOWLEDGEMENTS 102
TABLES AND FIGURES....103
REFERENCES 106
CHAPTER 5: DISCUSSION 110
OVERVIEW 110
STRENGTHS AND LIMITATIONS 112
POTENTIAL IMPACT AND FUTURE DIRECTIONS 114
REFERENCES …..... 116
APPENDIX……..……..…… 117

LIST OF FIGURES

Figure 1.1: Pregnancy timeline defined by the antepartum, intrapartum, and postpartum periods….. 6

Figure 1.2: Aims 1-3 conceptual model adapted from the Andersen Model to investigate how predisposing, enabling, and need variables impact maternal morbidity (preterm delivery, cesarean delivery, severe maternal morbidity, blood transfusions) in pregnant women in a large healthcare system…… 11

Figure 1.3: Aim 1-2 directed acyclic graph (DAG) illustrating the relationship between substance related diagnosis and maternal morbidity (preterm delivery, cesarean delivery, and SMM) while controlling for the Andersen Model's covariates.…….. 12

Figure 2.1: Conceptual model adapted from the Andersen Model to investigate how predisposing, enabling, and need variables impact preterm delivery and cesarean delivery in pregnant women in a large healthcare system from April 1st, 2011- September 30th, 2019……. 24

Figure 3.1: Conceptual model adapted from the Andersen Model to investigate how predisposing, enabling, and need variables impact severe maternal morbidity in pregnant women in a large healthcare system from March 1st, 2016-August 30th, 2019…..…… 57

Figure 3.2: Prevalence rate of severe maternal morbidity (SMM; n = 558) by delivery month/year in 10,125 deliveries with (n= 692) and without (n=9,433) a substance related diagnosis (SRD) from a Southern California health system's electronic medical record (March 1st, 2016 - August 30th, 2019)…… 79

Figure 3.3: Prevalence rate of severe maternal morbidity (SMM; n = 558) by delivery month/year every three months in 10,125 deliveries with (n= 692) and without (n=9,433) a substance related diagnosis (SRD) from a Southern California health system's electronic medical record (March 1st, 2016 - August 30th, 2019) …. …… 80

Figure 3.4: Prevalence rate of severe maternal morbidity (SMM; n = 558) by delivery month/year every six months in 10,125 deliveries with (n= 692) and without (n=9,433) a substance related diagnosis (SRD) from a Southern California health system's electronic medical record (March 1st, 2016 - August 30th, 2019)…… …… 80

LIST OF TABLES

Table 1.1: Unmatched and matched characteristics of the Andersen Model covariates and preterm delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n=19,346)……. 41

Table 1.2: Unmatched and matched adjusted analysis of Andersen Model covariates associated with a preterm delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,346)…..…….. 42

Table 1.3: Unmatched and matched unadjusted analysis of substance related diagnoses associated with preterm delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,346)..…...… 43

Table 1.4: Unmatched and matched adjusted analysis of Andersen Model covariates associated with preterm delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,346)……..... 44

Table 1.5: Unmatched and matched unadjusted analysis of Andersen Model covariates associated with a cesarean delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,303)... 4

Table 1.6: Unmatched and matched unadjusted analysis of the Andersen Model covariates associated with a cesarean delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,303)…46

Table 1.7: Unmatched and matched unadjusted analysis of substance related diagnoses associated with cesarean delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,303).....…....47

Table 1.8: Unmatched and matched adjusted analysis of the Andersen Model covariates associated with a cesarean delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,303)…48

Table 2.1: Unmatched unadjusted analysis of factors associated with a severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125)……...……...….74

Table 2.2: Unmatched unadjusted analysis of substance related diagnoses associated with having severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).....75

Table 2.3: Severe maternal morbidity indicators identified in women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125)...……..…..…..…..…..…..…..…..…..…..……...…..…..…..…....75

Table 2.4: Unmatched unadjusted analysis of pregnancy outcomes in those with and without a blood transfusion among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125)…...……...…..…76

Table 2.5: Matched unadjusted analysis of factors associated with a severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 1,346)….....…….76

Table 2.6: Matched unadjusted analysis of substance related diagnoses associated with having severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 1,346).....…….77

Table 2.7: Unmatched and matched adjusted logistic regression analysis of factors associated with a severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019……..77

Table 2.8: Unmatched unadjusted analysis of delivery six-month timepoint and substance related diagnosis among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125)..….....……78

Table 2.9: Matched unadjusted analysis of delivery six-month timepoint and substance related diagnosis among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 1,346)…...78

Table 2.10: Changes over time in the unmatched cohort assessed with the Cochran-Armitage test by delivery month, three-months, and six-months in pregnant women with and without a substance related diagnosis in a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125)…..…….....…….....……..79

Table 3.1: Comparison of Baseline Models for the latent classes of mental and physical health among women with a documented delivery from a Southern California's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).….....……...….....…….……103

Table 3.2: The latent classes of mental and physical health among women with a documented delivery and their predictions of the Andersen Model's need variables (expressed as probabilities, %) from the two-class LCA model stratified by serious maternal morbidity (four classes). Data collected from a Southern California's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125) ……103

Table 3.3: The latent classes of substance related diagnosis, mental illness, and physical health among women with a documented delivery and their predictions of the Andersen Model's predisposing and enabling variables (expressed as probabilities, %) from the two-class LCA model stratified by serious maternal morbidity (four classes). Data collected from a Southern California's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).....104

Table 3.3: Unadjusted and adjusted relationship between high prevalence of co-occurring substance use related diagnosis, mental health, and physical health by the Andersen Model's predisposing and enabling variables among women with severe maternal morbidity and a documented delivery. Data collected from a Southern California's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).....105

ACKNOWLEDGEMENTS

I have many people acknowledge and thank for their guidance and support of my doctoral studies and dissertation. First, I'd like to thank Carla Marienfeld for her guidance and support through my doctoral training as my mentor. I learned a great deal working in her lab and I am grateful for the opportunity to grow as researcher under her counsel. I am thankful to her for always being available to brainstorm, answer questions, and solve issues, even during the busiest of times. I would like to thank María Luisa Zúñiga for developing the Joint Doctoral Program in Interdisciplinary Research on Substance Use (IRSU) and for her continuous support over the last four years. Through her guidance and my training in the IRSU program, I have developed skills that will propel my research related goals forward. I would like to thank Mark Reed and Susan Woodruff, who were my first mentors in the IRSU program before they moved on to new positions. My work in your labs fueled my interests in alcohol research and provided me with a strong foundation in substance use research. I would like to thank Christina Chambers for her guidance throughout this dissertation process and launching my interest in pregnancy and substance use in her Life Course seminar. I would like to thank Laramie Smith for encouraging me to use of theory to build strong framework for my research proposals and for advocating for vulnerable and stigmatized groups.

I gratefully acknowledge the contributions to this research by the Altman Clinical and Translational Research Institute's Virtual Research Desktop (VRD) analytics team and collaborators at University of California San Diego (supported by the National Institute of Health, Grant UL1TR001442 of CTSA Funding). This research is funded by Carla Marienfeld's research funds through the department of Psychiatry at the University of California San Diego School of Medicine.

I would like to thank Hala Madanat for my early graduate training and encouraging me to apply for the IRSU doctoral program. I would like to thank Anne Wallace for always supporting my

endeavors and being ready to assist and provide guidance in any way. I would like to thank Mark Wallace for his support and connecting me with the resources I needed to move forward in my studies and training. I would like to thank Richard Garfein for his guidance during my early graduate training. I'm also grateful to my fellow JDP IRSU cohort members Stephanie Meyers, Jennifer Jain, and Kevin Cummins who were always available to brainstorm and provide feedback.

Last, but definitely not least, thank you to my family and friends who supported me through this process. Thank you to my parents and close family members for always allowing me to dream big. Thank you to my partner Michael Krak for supporting me from day one and always being there to listen to me passionately discuss pregnancy, substance use, and mental health. Thank you to Michael's family for their unwavering support and kindness over the years. Thank you to my close friend and former colleague Johanna Schandera for the last-minute draft proofreads, constructive feedback, and guidance.

Chapter 2, "Prevalence and correlates of substance related diagnoses and preterm delivery and cesarean delivery among pregnant women." is currently being prepared for publication. Carla Marienfeld, María Luisa Zúñiga, Christina Chambers, Mark Reed, and Laramie Smith are co-authors.

Chapter 3, "Severe maternal morbidity among women who presented for delivery with and without a substance related diagnosis." is currently being prepared for publication. Carla Marienfeld, María Luisa Zúñiga, Christina Chambers, Mark Reed, and Laramie Smith are co-authors.

Chapter 4, "Latent classes of substance related diagnosis, mental illness, and physical health conditions and severe maternal morbidity among women who presented for delivery" is currently being prepared for publication. Carla Marienfeld, María Luisa Zúñiga, Christina Chambers, Mark Reed, and Laramie Smith are co-authors.

VITA AND PUBLICATIONS

VITA

2020 Doctor of Philosophy in Interdisciplinary Research on Substance Use
University of California San Diego/San Diego State University
(San Diego, CA)

2015 Master of Public Health (Health Promotion)
San Diego State University
(San Diego, CA)

2011 Bachelor of Arts (Anthropology)
University of Hawai'i at Mānoa
(Honolulu, Hawai'i)

PUBLICATIONS

Courchesne, N.S., Meyers, S., (2020) Chapter 16: Women and Pregnancy. In Marienfeld, C., (Eds.), *Absolute Addiction Psychiatry Review: An Essential Board Exam Study Guide.* Springer, 2020.

Courchesne, N.S., Muth, C., Barker, M., & Woodruff, S. I. 2019. Correlates of Breath Alcohol Concentration Among Driving Under the Influence Program Clients in Southern California. *Journal of Drug Issues*, 49(2), 279-295.

Saria, M., **Courchesne, N.S.**, Evangelista, L, Carter, J., MacManus, D., Gorman, M., Nyamathi, A., Phillips, L., Piccioni, D., Kesari, S., Maliski, S. 2017. Anxiety and Depression Associated with Burden in Caregivers of Patients with Brain Metastases. *Oncology Nursing Forum,* 44(3), 306.

Saria, M., **Courchesne, N.S.**, Evangelista, L., Carter, J., MacManus, D., Gorman, M., Nyamathi, A., Phillips, L., Piccioni, D., Kesari, S., Maliski, S. 2016. Cognitive Dysfunction in Patients with Brain Metastases: Influences on Caregiver Resilience and Coping. *Supportive Care in Cancer*, *25*(4), 1247-1256.

SUBMITTED AND UNDER REVIEW

Meyers, S. A., Earnshaw, V., D'Ambrosio, B., **Courchesne, N.S.**, Werb, D., & Smith, L. R. (2020). The intersection of gender and substance use-related stigma: A mixed methods systematic review and synthesis of the literature. *Social Science and Medicine.*

ABSTRACT OF THE DISSERTATION

Substance use impacts maternal morbidity and maternal delivery outcomes in women who presented for delivery in a large healthcare system

by

Natasia S. Courchesne

Doctor of Philosophy in Interdisciplinary Research on Substance Use

University of California San Diego, 2020

San Diego State University, 2020

Professor Carla Marienfeld (Chair)
Professor María Luisa Zúñiga (Co-Chair)

Background: Pregnant women with a substance related diagnosis (SRD) are a vulnerable population who may be experiencing disproportionate prevalence of maternal morbidity compared to pregnant women without an SRD. Although research on prenatal substance use is robust in terms of understanding fetal and newborn health, far less is known about morbidity among pregnant women with an SRD. The **primary goals** of this research were to evaluate the relationships between maternal

SRDs and preterm delivery, cesarean delivery, and severe maternal morbidity (SMM) in a large healthcare system.

Methods: This retrospective study retrieved electronic medical record data on women (ages ≥ 18 and ≤ 44 years) who delivered a single live or stillbirth at ≥ 20 weeks of gestation from April 1st, 2011-September 30th, 2019. The Andersen Model was applied to guide the analysis and structure patient characteristics. **Chapter 2** evaluates independent associations between an SRD and preterm delivery and cesarean delivery. **Chapter 3** evaluates associations and trends between an SRD and SMM (≥ 1 SMM and blood transfusions). **Chapter 4** uses latent class analysis to characterize the patterns of SRD, mental illness, and pre-existing health conditions among women with and without SMM.

Results: Chapter 2 shows that having an SRD was associated with preterm delivery (n=2,158, adjusted odds ratio (AOR) = 1.60 [95% CI, 1.20-2.14], p-value = 0.0192) and cesarean delivery (n=2,154, AOR = 1.50 [95% CI, 1.13-1.99], p-value = 0.0050). **Chapter 3** shows that having an SRD was associated with having SMM (AOR = 1.81 [95% CI, 1.14-2.88], p-value = 0.0124). **Chapter 4** reveals a two-class solution for those with and without SMM best fit the data producing clinically distinct classes. SRDs were common in the groups with high and moderate co-occurring mental and physical health outcomes in both the SMM and non-SMM classes.

Conclusion: Having an SRD is associated with preterm delivery, cesarean delivery, and SMM. Future research should focus on identifying strategies and therapeutic interventions in pregnant women with an SRD to prevent, screen, and treat maternal morbidity in this vulnerable population.

CHAPTER 1: INTRODUCTION

OVERVIEW

As a stigmatized and vulnerable population, pregnant women with a substance related diagnosis (SRD; i.e., use, misuse, abuse, or dependence of substances) may be experiencing disproportionate prevalence of preterm delivery (< 37 weeks' gestation), cesarean delivery, and severe maternal morbidity (SMM) compared to pregnant women without an SRD. SMM is defined as life-threatening labor and delivery conditions that result in significant short- or long-term consequences to a woman's health (e.g., hemorrhaging/blood transfusions, eclampsia). Studies have shown that women with a high proportion of SMM also have high prevalence of preterm and cesarean delivery. A study in California found that high proportion of women with a preterm delivery (75%) and cesarean delivery (63%) also had placental hemorrhage.[1] This indicates that preterm and cesarean delivery may be associated with common SMMs like blood transfusions due to hemorrhaging.[1]

Earlier and ongoing studies have provided a robust understanding of fetal and delivery outcomes associated with substance use in the perinatal period (i.e., pregnancy and postpartum).[2,3] However, less is known about the prevalence of preterm delivery, cesarean delivery, and SMMs in women with an SRD who presented for delivery. This gap in knowledge is likely due to the focus on neonatal outcomes (e.g., opioid related neonatal abstinence syndrome [NAS]) rather than maternal outcomes. Preterm delivery, cesarean delivery, and SMM have all been addressed in the literature.[1,4,5] However, the majority of the studies used data from the 1990's and early 2000's or investigating women outside of the United States.[6,7] More recently, some studies have included substance use as a covariate in their assessments of predictors related to maternal morbidity in small to moderate sample sizes.[8] These studies have found that SRDs, mental illness (e.g., depression, anxiety etc.), pre-existing health conditions (e.g., cardiovascular disease, non-gestational diabetes, cancer), limited and disrupted prenatal care, and environmental stressors (e.g., unstable home) are common and have been found to

lead to maternal and perinatal morbidity.[9,10] New research on maternal morbidity among women who presented for delivery with an SRD in the United States is required to develop preventive strategies and therapeutic interventions for this vulnerable population.

To address these gaps in knowledge, the **primary goals** of this proposed research are to evaluate the relationships between maternal SRDs and preterm delivery, cesarean delivery, and SMM in a large Southern California healthcare system. The specific aims of this dissertation are: **1)** Evaluate whether there are independent associations between an SRD and preterm delivery or cesarean delivery among women who presented for delivery from 2012-2019; **2)** Evaluate whether there are associations and trends of SRDs and SMM among women who presented for delivery from 2016-2019; and **3)** Characterize the patterns of SRD, mental illness, and physical health conditions by SMM and examine pattern correlates among women who presented for delivery from 2016-2019. This research will contribute to a better understanding of how SRDs are associated with preterm delivery, cesarean delivery, and SMM in this vulnerable population.

To meet these aims, this retrospective study retrieved electronic medical record (EMR) data on women (ages ≥ 18 and ≤ 44 years) who delivered a single live or stillbirth at ≥ 20 weeks of gestation (standard cut off rate indicating a neonate's capability of surviving outside of the body) from April 1st, 2011-September 30th, 2019 for Aim 1 (8.5 years of available data) and March 1st, 2016-August 30th, 2019 for Aims 2-3 (3.5 years of available data that includes procedure codes for blood transfusions, the most common SMM). All data was collected from a Southern California University Health System EMR. Because we requested deidentified EMR data without direct patient consent, ages ≥ 18 have been selected to protect adolescents under the age of 18 who are considered an extremely vulnerable population that may be at risk for identification due to small sample size. Those ≤ 44 years of age were selected because pregnancy over age 44 is not common and would lead to an increased morbidity risk as well as a small sample size. Propensity score matching was used to

decrease the potential imbalance and account for possible confounding across the predictor variables and the outcome variables in Aims 1-2.

BACKGROUND

Pregnant Women with a Substance Related Diagnosis (SRD)

According to the Substance Abuse and Mental Health Services Administration (SAMHSA), national alcohol and cigarette smoking rates during pregnancy increased from 10.6% and 8.3% to 14.7% to 11.5% from 2016 to 2017 respectively.[11] Other substance use (not alcohol or tobacco) in the past month among pregnant women 15 to 44 also increased from 2016 to 2017 (6.3% to 8.5%).[11] This includes both cannabis use (4.9% to 7.1%) and the misuse of psychotherapeutics such as pain relievers, tranquilizers, stimulants, and sedatives (1.4% to 1.8%).[11] As cannabis legalization continues across the United States, cannabis use is expected to increase. In 2017, cocaine (0.4%) and methamphetamine (0.1%) use among pregnant women were low, but opioid misuse (heroin or pain relievers) increased among this population from 2016 (1.2% to 1.4%). As a result of the current opioid epidemic, the number of women with opioid use diagnosis at labor and delivery has quadrupled from 1999-2014.[3]

Due to the changes in cannabis use laws in California, safety perceptions may impact use in pregnant women. In 2017, one study found that of the 306 women surveyed, 35% reported cannabis use at the time of their pregnancy diagnosis and 34% of those continued use.[12] Of all of the respondents, 10% reported that if cannabis was legal they would use it while pregnant. Those who did not believe that cannabis could be harmful during pregnancy were less likely to quit using cannabis while pregnant compared to those who did quit.[12] This suggests that there may be changes in cannabis safety perceptions among pregnant women. Maternal substance use is observed in all socioeconomic classes, ages, and races/ethnicities. However, an increased risk of use is observed in women who are younger, unmarried, and have lower educational achievement.[13]

Pregnant women with an SRD may have multiple intersecting barriers that need to be addressed. Unfortunately, most women presenting for primary care visits or prenatal care will not ask questions about their substance use or self-identify as being at-risk for SRDs.[14] Pregnant women who use substances have reported additional barriers to seeking prenatal care, including delays in discovering their pregnancy, physicians unwilling to initiate treatment for SRD in the third trimester, fear of involvement with child protective services, and/or incarceration.[15]

Research on the prevalence and impact of SRDs during the perinatal period on maternal morbidity is limited. One study reviewing maternal SRD and treatment from one year before conception and through delivery in Massachusetts from 2003-2007, found that women with a SRD accounted for 5.5% (n= 20,707) of the sample (total n= 375,851).[16] Women with a SRD used the emergency department (57%) and were hospitalized (67%) more often compared to women who did not have a SRD.[16] In addition, women with a SRD were also found to be poorer, less educated, have higher morbidity rates, less use of prenatal care, and increased rates of adverse obstetric and delivery outcomes compared to women without a SRD in the sample.

Preterm Delivery

In the United States, preterm delivery is defined as a delivery that occurs between 20-37 weeks of gestation. Most preterm deliveries are spontaneous (70-80%).[17] Preterm delivery may also be iatrogenic due to maternal or fetal complications that jeopardize maternal or fetal health (e.g., preeclampsia, placenta previa, fetal growth restriction).[17] Preterm delivery occurs in about 5%-18% of deliveries worldwide.[17] From 2014 to 2016, the preterm delivery rate increased from 9.57% to 9.85% per 100 deliveries respectively.[18] Risk factors include <17 or >35 years of age, lower educational achievement, single marital status, lower socioeconomic status, short interpregnancy interval (e.g., <6 months), poor access to medical care, physical abuse, body mass index ((BMI; <19 kg/m^2 or pre-pregnancy weight <50 kg [<120 lbs.]), poor nutritional status, and poor working conditions (e.g., long working hours [>80 hours/week], and hard physical labor (e.g., shift work,

standing >8 hours).[17] Those with prior obstetrics and gynecology history that includes prior preterm delivery, prior cervical surgery, and uterine anomalies are also at an increased risk for preterm delivery.[17] In older studies, substance use has also been linked to preterm delivery including smoking tobacco, heavy alcohol consumption, cocaine use, and heroin use.[17]

Cesarean Delivery:

In 2018, the Centers for Disease Control and Prevention (CDC) reported that cesarean deliveries accounted for 31.9% of all deliveries in the United States.[19] Cesarean delivery may be elective or required, however, elective cesareans are becoming less common. Some clinical indications for cesarean delivery include breech presentation, active herpes, and high human immunodeficiency virus (HIV) viral titers.[20] In the United States, it was estimated that 2.5% of all deliveries in 2013 are maternal requested cesarean deliveries.[21]

Currently, data on the impact of SRDs on delivery method (cesarean vs. vaginal) is limited. In a study investigating cannabis use during pregnancy (5,639 reported users and 92,873 nonusers) and maternal morbidity, risk difference of cannabis exposure was inversely associated (protective) with cesarean vs. spontaneous vaginal delivery but was not found to be significantly associated.[7]

Severe Maternal Morbidity (SMM)

SMM includes diagnoses and procedures during the perinatal period (≥ 20 weeks of gestation to 4 weeks after delivery) that results in significant short- or long-term adverse outcomes to maternal health.[22] The CDC and other clinical and public partners developed a list of 21 SMM diagnoses or procedures during delivery hospitalizations and their associated 10th revision of the International Classification of Diseases (ICD-10) codes (**Table A** in the appendix).[22] According to the CDC, SMM has been increasing in the United States and affected more than 50,000 women in 2014.[22] The CDC reported a 200% increase of SMM from 1993-2014 (49.5 to 144.0 per 10,000 delivery hospitalizations).[22] This large increase was mostly driven by blood transfusions (likely due to hemorrhaging) which increased 399% (rate from 24.5 to 122.3 per 10,000 delivery hospitalizations).

When blood transfusions are excluded, the most common SMM are hysterectomies or ventilation (55% increase) or temporary tracheostomy (93% increase) resulting in nearly a 20% overall increase (rate from 28.6 to 35.0) in SMMs.[22] These increases in SMM may be due to the changes in the population of women giving birth. For example, increases in maternal age,[23] chronic conditions (e.g., hypertension),[24,25] obesity,[26,27] and cesarean delivery[23,28] have been identified in the literature.

Research has shown that chronic hypertension and pregestational diabetes are also common during pregnancy and can lead to the development of preeclampsia or eclampsia.[24] Increasing rates of SMM lead to increased adverse outcomes for women, increased medical costs, and longer hospital stays.[3]

Gestation and Parity

The pregnancy timeline is categorized by the antepartum period (conception to ≤ 42 weeks), intrapartum period (labor and delivery), and the postpartum period (delivery to ≤ 4 weeks; Figure 1.1). The perinatal period is defined by ≥ 20 weeks of gestation to 4 weeks after delivery.

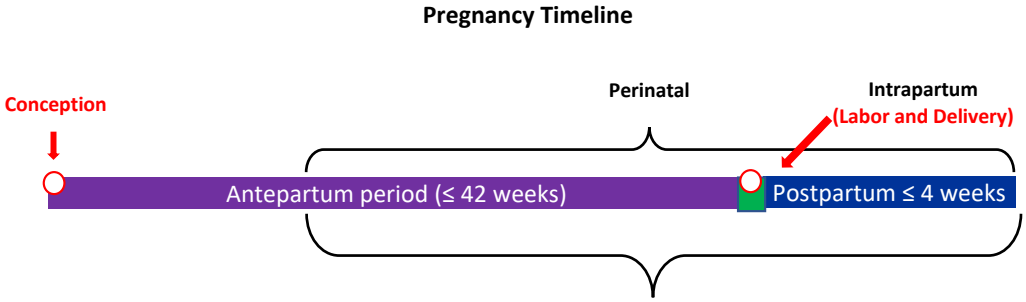

Figure 1.1: Pregnancy timeline defined by the antepartum, intrapartum, and postpartum periods.

According to the new American College of Obstetricians and Gynecologists (ACOG)'s official guidelines, delivery before 37 weeks of gestation is considered a preterm pregnancy.[29] Deliveries between 37-40 weeks is a full-term pregnancy and deliveries after 41 weeks is a late term pregnancy. One study found that pregnant women who died at delivery were more likely to have

delivered before 37 or after 40 weeks of gestation, showing that there is a relationship between short and late-term gestation and adverse health outcomes.[24]

Parity (number of pregnancies of ≥ 20 weeks) can be grouped into three categories: 1) nulliparity (no previous pregnancies), 2) low multiparity (1-3 previous pregnancies), and 3) grand multipara (4-8 previous pregnancies).[30] One study found that mothers of nulliparity and grand parity were at a high risk for obstetric complications, compared to mothers of low parity.[30] Significant odds ratios (OR) of the risk of maternal complications by parity include: antepartum hemorrhage (first birth), gestational diabetes mellitus (2 previous births), pregnancy-induced hypertension (4-8 previous births), pre-labor rupture of membranes >24 hours (2-8 births), threatened premature labor (first birth; 7-8 previous births), postpartum hemorrhage (4-8 previous births), and third-degree tear (6-8 previous births).[30]

Sociodemographic indicators:

Over the last decade, racial/ethnic minorities and immigrant populations have increased dramatically in the United States.[31,32] Of all live births in California from 2014-2016, Hispanic (47.2%), Asian/Pacific Islander (15.7%), Black (5.6%), and American Indian/Alaska Native (0.4%) women account for 68.9%.[33] In the most recent study on pregnancy and substance use in California (2005; n=1,551,017), substance misuse increased among non-Hispanic Whites (38.0% increase) and Hispanics (37.8% increase) and decreased among non-Hispanic Blacks (7.9% decrease) and Asian/Pacific Islanders (1.0% decrease).[10] In the same study, non-White race was found to be significantly associated with increased morbidity rate.

A national study investigating 55,781,965 pregnancy-related hospitalizations from 1999-2009 identified 138,224 cases of opioid use during pregnancy.[34] Pregnant women who had Medicare/Medicaid or “other” insurance and fell into the lowest household income quartile were found to have higher crude rates of opioid use during pregnancy compared to pregnant women with private insurance and those in the higher household income quartile. In another study assessing

prenatal and postpartum health service utilization among pregnant women, Hispanic women were found to be younger, had lower educational achievement, lower annual income, and were more likely to be uninsured compared to non-Hispanic White women.[35] Further, Hispanic women had higher odds of delayed or inadequate prenatal care compared to non-Hispanic White women.

Research has shown that marital status may impact maternal morbidity in pregnant women with an SRD. A 2011 systematic review and metanalysis on maternal marital status and birth outcomes in 21 studies found that the odds of preterm birth, low birth weight, and small for gestational age were higher among single mothers compared to married mothers.[36] The review suggests that the amount of support that a mother receives may elevate or suppress their psychosocial stress levels and lead to poor maternal morbidity. Studies have also found that marital status may be associated with mental health and substance use. For example, one study found that men and women who were previously married compared to stably married had an increased risk for first onset of mood, anxiety, and substance use disorders (SUD) and women had a higher risk for SUDs compared to men.[37] This suggests that being previously married (now divorced) may be a risk factor for women with an SRD. Another study looking at pregnant women and alcohol use, found that the prevalence of alcohol use and binge drinking during pregnancy was 2.4 and 4.6 times higher respectively among nonmarried women compared to married women.[38]

Body Mass Index (BMI)

Studies have shown that low and high BMI impacts maternal morbidity. One study found that those with increased BMI had an increased incidence of pre-eclampsia, macrosomia, gestational hypertension, and induction of labor and cesarean delivery.[5] In addition, women who were underweight demonstrated better outcomes than women with a normal BMI.[5] In these studies, SMM was not assessed. Further research on how these characteristics impact SMM is warranted.

Mental Illness and Pre-Existing Health Conditions

In the same California study mentioned previously, the prevalence of comorbidities (e.g., mental health conditions, substance use, maternal hypertension, diabetes, asthma, thyroid disorders, and obesity) among pregnant women (n=1,551,017) increased from 1999 to 2005 for hospital admissions associated with childbirth, demonstrating that morbidity rates may have been increasing over time.[10] The prevalence of substance misuse also increased from 1.1% in 1999 to 19.1% in 2005.

The National Institute of Mental Health (NIMH) defines mental illness in two categories, any mental illness (AMI) or serious mental illness (SMI).[39] AMI is described as any mental, behavioral, or emotional disorder. Those with AMI include impairments ranging from mild, moderate, and severe. SMI is described as a mental, behavioral, or emotional disorder that results in serious functional impairment (e.g., schizophrenia, bipolar disorder). SMIs significantly impedes on one or more major life activities. A full list of diagnoses and ICD-10 codes can be found in **Table A** in the appendix. In 2017, the prevalence of AMI and SMI was found to be higher among women (22.3% and 5.7% respectively) than men (15.1% and 3.3% respectively).[39] In the same report, the prevalence of AMI and SMI was highest among adults reporting two or more races/ethnicities (28.6% and 8.1% respectively), followed by Whites (20.4% and 5.2% respectively). The prevalence of AMI and SMI was lowest among Asian adults (14.5% and 2.4% respectively).

The 2017 SAMHSA report mentioned previously found about 8.5 million adults (3.4%) had co-occurring mental illness and at least one SUD and 3.1 million adults (1.3%) had co-occurring SMI and SUD in the past year.[40] In addition to co-occurring AMI and SRD, co-occurring SRDs may also be occuring.[9] Most of the current research is focused on prenatal poly-substance use (the use of multiple substances) instead of co-occurring SRDs among pregnant women. A 2016 review on substance use during pregnancy found that alcohol is the most frequently used substance, followed by tobacco, cannabis, and other substances such as opioids.[9]

Non-SMI include all of the mental illness categories not captured in the SMI category (e.g., depression, anxiety). A study investigating patterns and determinates of service use among persons with SMI compared to those with non-SMI, found that those with SMI had a higher reliance on outpatient services compared to those with non-SMI.[41] In another study, significant differences in substance use among the SMI and non-SMI groups were observed.[42] Specifically, in the SMI group, the order of substance preference was alcohol, cocaine, cannabis, and heroin. In the non-SMI group, the order of substance preference was cocaine, alcohol, heroin, and cannabis. These findings suggest that the severity of mental illness may determine the choice of substance.

Psychiatric comorbidities (e.g., depression, anxiety), prenatal polysubstance use, limited and disrupted prenatal care, and environmental stressors (e.g., unstable home and disordered home) are common and have been found to lead to adverse maternal outcomes.[9] Scant data on SMM and psychiatric comorbidities exists. However, one study found that children exposed to poly-substances in utero had more adverse outcomes compared to those exposed to only alcohol and those with no substance exposure (maternal morbidities were not reported).[43] Co-occurring SRDs and mental illness may have an impact on maternal morbidity and SMM.

CONCEPTUAL FRAMEWORK

The Andersen Model was used in **Aim 1-3** as an analytic and theoretical guide to structure patient characteristics and investigate the relationship between SRD and preterm delivery, cesarean delivery, and SMM (Figure 1.2). This model has been used to identify the **predisposing** (e.g., race/ethnicity), **enabling** (e.g., health insurance), and **need** (e.g., mental illness) covariates associated with health related outcomes such as health service utilization (e.g., hospitalizations), and morbidity.[44] The Andersen Model has been used to investigate factors associated with hospitalizations among homeless women,[45] prenatal care visits,[46] racial/ethnic differences in prenatal

care utilization,[47] and racial/ethnic impact on service utilization for individuals with co-occurring mental health and SRDs.[48]

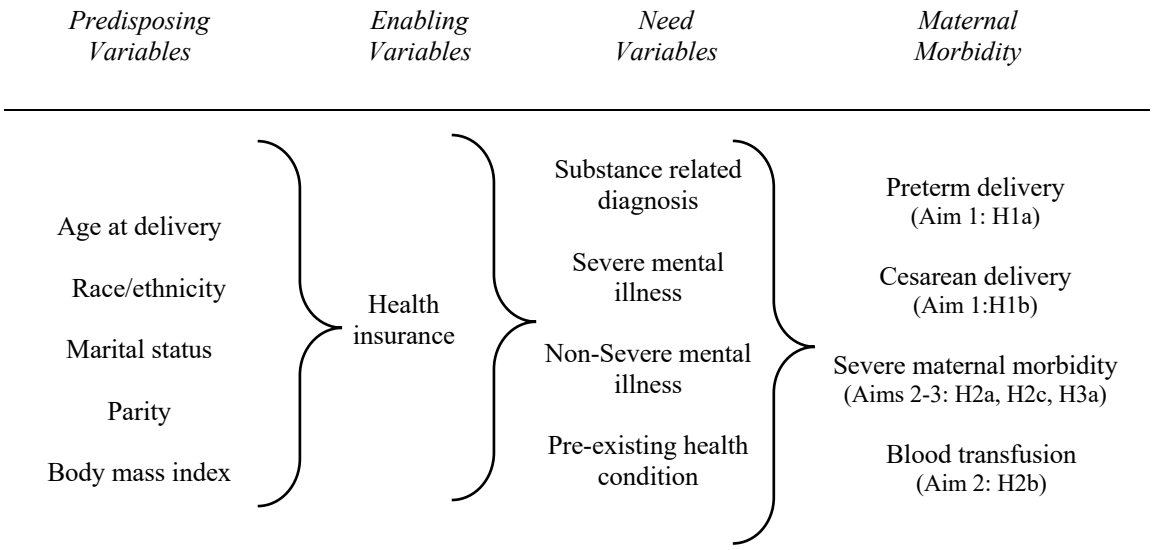

Figure 1.2: Aims 1-3 conceptual model adapted from the Andersen Model to investigate how predisposing, enabling, and need variables impact maternal morbidity (preterm delivery, cesarean delivery, severe maternal morbidity, blood transfusions) in pregnant women in a large healthcare system.

In **Chapter 2 (Aim 1)**, the relationship between Andersen Model's perinatal predisposing, enabling, and need covariates with preterm and cesarean delivery were evaluated. Having an SRD (yes/no) was included in the need category and was the focus of this aim. The remaining covariates were used as control variables to assess the independent relationships between an SRD and preterm delivery and cesarean delivery (Figure 1.3).

In **Chapter 3 (Aim 2),** the relationship between Andersen Model's perinatal predisposing, enabling, and need covariates with SMM were evaluated. Having an SRD (yes/no) was included in the need category and was the focus of this aim. The remaining covariates were used as control variables to assess the relationship of SRD and SMM (Figure 1.3). The prevalence of SRD and SMM over time was also assessed.

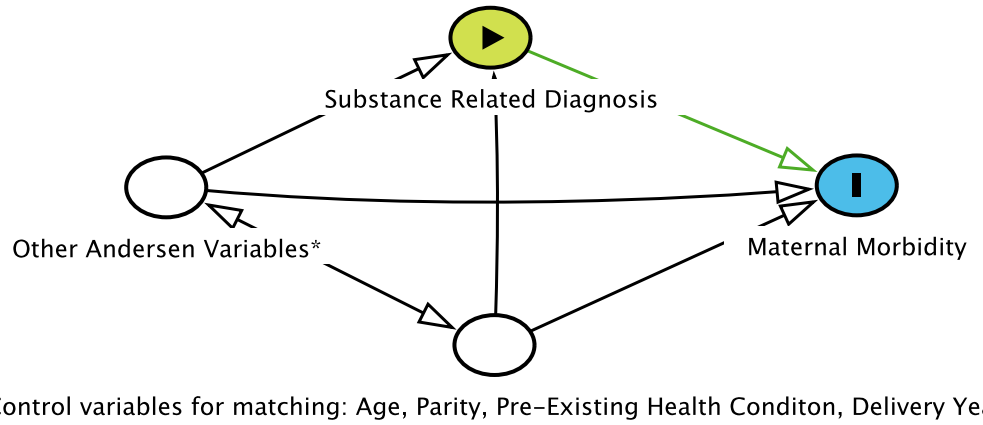

Figure 1.3: Aim 1-2 directed acyclic graph (DAG) illustrating the relationship between substance related diagnosis and maternal morbidity (preterm delivery, cesarean delivery, and SMM) while controlling for the Andersen Model's covariates. Control variables for matching include: age, parity, pre-existing health condition, delivery year; *Other Andersen variables include race/ethnicity, marital status, body mass index, health insurance, serious mental illness, and non-serious mental illness. The green arrow represents the direct relationship between the SRD (predictor) and maternal morbidity (outcome) while controlling for the other Andersen Model covariates.

Chapter 4 (Aim 3) used a latent class analysis (LCA) approach to create meaningful latent classes, or subgroups, of SRDs, serious mental illness (SMI), non-SMI, and pre-existing health conditions to understand if discrete classes of SRD, mental illness, and pre-existing co-morbidities would emerge in women with and without a SMM during the perinatal period. The identified latent classes among women with a documented delivery were then reported. The relationship between SMM class assignment and the Andersen Model predisposing and enabling covariates was assessed.

AIMS AND HYPOTHESES

This retrospective cohort study used a series of quantitative methods to meet the three proposed aims and test the hypotheses. These quantitative methods were selected to assess preterm delivery, cesarean delivery, and SMM among women with a documented delivery in a large health system. Based on the conceptual framework described above and a review of the relevant literature

on maternal substance use and maternal morbidity, this dissertation has the following aims and corresponding hypotheses:

Aim 1: Evaluate whether there are associations between an SRD and preterm or cesarean delivery among women who presented for delivery from 2012-2019. Aim 1 included two **primary outcome** variables: 1) preterm delivery (gestational age at delivery at 20-36 weeks; yes/no) and 2) cesarean delivery (yes/no). Covariates include the Andersen Model's predisposing, enabling, and need variables.

- **Hypothesis 1a (H1a):** Pregnant women with an SRD will be more likely to have preterm delivery compared to pregnant women without an SRD.
- **Hypothesis 1b (H1b):** Pregnant women with an SRD will be more likely to have a cesarean delivery compared to pregnant women without an SRD.

Aim 2: Evaluate whether there is an association between an SRD and SMM among women who presented for delivery and assess trends of SRD and SMM from 2016-2019. Aim 2 includes two **primary outcomes** variable: 1) SMM (yes/no), 2) SMM prevalence rate from 2016-2019, and one **secondary outcome** variable: 1) blood transfusion (yes/no) during the perinatal period (time from ≥ 20 weeks of gestation to 4 weeks after delivery). Covariates include the Andersen Model's predisposing, enabling, and need variables.

- **Hypothesis 2a (H2a):** Pregnant women with an SRD will be more likely to have SMM compared to pregnant women without an SRD.
- **Hypothesis 2b (H2b):** Pregnant women with an SRD will be more likely to have a blood transfusion compared to pregnant women without an SRD.
- **Hypothesis 2c (H2c):** The prevalence of SMM over time will increase at a higher rate in pregnant women with an SRD compared to pregnant women without an SRD.

First, the number and type of the CDC's 21 SMM indicators during the perinatal period were identified in women who presented for delivery with and without an SRD and grouped into any SMM (yes/no). The unadjusted and adjusted associations between an SRD and SMM with all the

Andersen Model covariates were then evaluated and reported (**H2a)**. Next, the bivariate relationship between SRD and blood transfusions were evaluated and reported (**H2b**). Finally, the prevalence rate of SMM from 2016-2019 among all women (**group 1**), women with an SRD (**group 2**), and women without an SRD (**group 3**) during the perinatal period were assessed and reported (**H2c**). In addition, a visual graphical depiction of the month-to-month prevalence, three-month prevalence, and six-month prevalence of SMM was represented by a line graph comparing groups 2-3.

Aim 3: Characterize the patterns of SRD, mental illness, and physical health conditions by SMM and examine pattern correlates among women who presented for delivery from 2016-2019. Aim 3 includes one **primary outcome** variable: SMM during the perinatal period (time from ≥ 20 weeks of gestation to 4 weeks after delivery). LCA was used to create meaningful latent classes based off the Andersen Model's *need* covariates (SRD, SMI, non-SMI, pre-existing health condition). The latent classes were stratified SMM (yes/no) to identify how these *need* covariates are grouped in those with and without SMM. These observed covariates are assumed to be independent from each other when they have been conditioned on the latent variable.[49] Bivariate and multivariable regression was then used to assess the relationship between the Andersen Models' predisposing and enabling covariates and SMM class membership.

- **Hypothesis 3a (H3a):** Having an SRD will strongly influence SMM class membership.

Aim 3 utilized LCA to create meaningful latent classes of SRD, SMI, non-SMI, and pre-existing health conditions in pregnant women with and without SMM. With a latent model identified, regression using class assignment in those with SMM was performed for the Andersen's Model's predisposing and enabling covariates (**H3a**). This approach differs from Aim 1-2's approach in that this is a person-centered analysis using the relationships between individuals to identify distinct groups based on the individuals in the dataset.[50]

REFERENCES

1. Kilpatrick SJ, Abreo A, Gould J, Greene N, Main EK. Confirmed severe maternal morbidity is associated with high rate of preterm delivery. *Am J Obstet Gynecol*. 2016;215(2):233.e1-233.e7. doi:10.1016/J.AJOG.2016.02.026

2. Priester MA, Browne T, Iachini A, Clone S, DeHart D, Seay KD. Treatment Access Barriers and Disparities Among Individuals with Co-Occurring Mental Health and Substance Use Disorders: An Integrative Literature Review. *J Subst Abuse Treat*. 2016;61:47-59. doi:10.1016/j.jsat.2015.09.006

3. Callaghan, W. M., Creanga, A. A., & Kuklina E V. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. *Obstet Gynecol*. 2012;120(5):1029-1036.

4. Blanc J, Resseguier N, Goffinet F, et al. Association between gestational age and severe maternal morbidity and mortality of preterm cesarean delivery: a population-based cohort study. *Am J Obstet Gynecol*. 2019;220(4):399.e1-399.e9. doi:10.1016/J.AJOG.2019.01.005

5. Bhattacharya S, Campbell DM, Liston WA, Bhattacharya S. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. *BMC Public Health*. 2007;7(1):168. doi:10.1186/1471-2458-7-168

6. Kelly RH, Russo J, Holt VL, et al. Psychiatric and substance use disorders as risk factors for low birth weight and preterm delivery. *Obstet Gynecol*. 2002;100(2):297-304. doi:10.1016/S0029-7844(02)02014-8

7. Corsi DJ, Walsh L, Weiss D, et al. Association Between Self-reported Prenatal Cannabis Use and Maternal, Perinatal, and Neonatal Outcomes. *JAMA*. 2019;322(2):145. doi:10.1001/jama.2019.8734

8. Forray A, Foster D. Substance Use in the Perinatal Period. *Curr Psychiatry Rep*. 2015;17(11):91. doi:10.1007/s11920-015-0626-5

9. Forray A. Substance use during pregnancy. *F1000Research*. 2016;5. doi:10.12688/f1000research.7645.1

10. Fridman M, Korst LM, Chow J, Lawton E, Mitchell C, Gregory KD. Trends in maternal morbidity before and during pregnancy in California. *Am J Public Health*. 2014;104 Suppl 1(Suppl 1):S49-57. doi:10.2105/AJPH.2013.301583

11. Center for Behavioral Health Statistics and Quality. *2017 National Survey on Drug Use and Health: Detailed Tables.* Rockville, MD; 2018.

12. Mark K, Gryczynski J, Axenfeld E, Schwartz RP, Terplan M. Pregnant Women's Current and Intended Cannabis Use in Relation to Their Views Toward Legalization and Knowledge of Potential Harm. *J Addict Med*. 2017;11(3):211-216. doi:10.1097/ADM.0000000000000299

13. Chapman SLC, Wu L-T. Substance Use among Adolescent Mothers: A Review. *Child Youth*

Serv Rev. 2013;35(5):806-815. doi:10.1016/j.childyouth.2013.02.004

14. Shogren MD, Harsell C, Heitkamp T. Screening Women for At-Risk Alcohol Use: An Introduction to Screening, Brief Intervention, and Referral to Treatment (SBIRT) in Women's Health. *J Midwifery Womens Health*. 2017;62(6):746-754. doi:10.1111/jmwh.12659

15. Roberts SCM, Pies C. Complex Calculations: How Drug Use During Pregnancy Becomes a Barrier to Prenatal Care. *Matern Child Health J*. 2011;15(3):333-341. doi:10.1007/s10995-010-0594-7

16. Kotelchuck M, Cheng ER, Belanoff C, et al. The Prevalence and Impact of Substance Use Disorder and Treatment on Maternal Obstetric Experiences and Birth Outcomes Among Singleton Deliveries in Massachusetts. *Matern Child Health J*. 2017;21(4):893-902. doi:10.1007/s10995-016-2190-y

17. Robinson,Julian N., Norwitz, Errol R., Lockwood, Charles J., Barss VA. *Preterm Birth: Risk Factors, Interventions for Risk Reduction, and Maternal Prognosis*.; 2020. https://www.uptodate.com/contents/preterm-birth-risk-factors-interventions-for-risk-reduction-and-maternal-prognosis/print. Accessed April 29, 2020.

18. Martin JA, Osterman MJK. Describing the Increase in Preterm Births in the United States, 2014–2016. https://www.cdc.gov/nchs/products/databriefs/db312.htm?utm_source=STAT+Newsletters&utm_campaign=b026a2d06e-MR_COPY_09&utm_medium=email&utm_term=0_8cab1d79... Published 2018. Accessed April 29, 2020.

19. Center of Disease Control and Prevention. *FastStats - Births - Method of Delivery*.; 2018. https://www.cdc.gov/nchs/fastats/delivery.htm. Accessed April 29, 2020.

20. Gregory K, Jackson S, Korst L, Fridman M. Cesarean versus Vaginal Delivery: Whose Risks? Whose Benefits? *Am J Perinatol*. 2012;29(01):07-18. doi:10.1055/s-0031-1285829

21. American College of Obstetricians and Gynecologists. *Cesarean Delivery on Maternal Request*.; 2013. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2019/01/cesarean-delivery-on-maternal-request. Accessed April 29, 2020.

22. Division of Reproductive Health National Center for Chronic Disease Prevention and Health Propomotion Center for Disease Control and Prevention. *Severe Maternal Morbidity in the United States*.; 2017. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/severematernalmorbidity.html#anchor_References. Accessed May 9, 2019.

23. Center for Disease Control and Prevention, Hamilton BE, Osterman MJK, Driscoll AK, Rossen LM. Births : provisional data for 2017. 2018. https://stacks.cdc.gov/view/cdc/55172. Accessed May 9, 2019.

24. Campbell KH, Savitz D, Werner EF, et al. Maternal Morbidity and Risk of Death at Delivery Hospitalization. *Obstet Gynecol*. 2013;122(3):627-633. doi:10.1097/AOG.0b013e3182a06f4e

25. Small MJ, James AH, Kershaw T, Thames B, Gunatilake R, Brown H. Near-Miss Maternal Mortality. *Obstet Gynecol*. 2012;119(2, Part 1):250-255. doi:10.1097/AOG.0b013e31824265c7

26. Hinkle SN, Sharma AJ, Kim SY, et al. Prepregnancy Obesity Trends Among Low-Income Women, United States, 1999–2008. *Matern Child Health J*. 2012;16(7):1339-1348. doi:10.1007/s10995-011-0898-2

27. Fisher SC, Kim SY, Sharma AJ, Rochat R, Morrow B. Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003–2009. *Prev Med (Baltim)*. 2013;56(6):372-378. doi:10.1016/j.ypmed.2013.02.015

28. Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications Contributing to the Increasing Cesarean Delivery Rate. *Obstet Gynecol*. 2011;118(1):29-38. doi:10.1097/AOG.0b013e31821e5f65

29. American College of Obstetricians and Gynecologists. *Deliveries Before 39 Weeks*. https://www.acog.org/About-ACOG/ACOG-Departments/Deliveries-Before-39-Weeks?IsMobileSet=false. Accessed June 20, 2019.

30. Bai J, Wong FWS, Bauman A, Mohsin M. Parity and pregnancy outcomes. *Am J Obstet Gynecol*. 2002;186(2):274-278. doi:10.1067/MOB.2002.119639

31. US Census Bureau. *Demographic Trends in the 20th Century*. Washington, D.C.; 2002.

32. US Census Bureau. Profile of the foreign-born population in the United States, 2000. In: Government Printing Office, ed. *US Department of Commerce*. Washington, DC: Government Printing Office: US Census Bureau; 2001:Current Population Report P23–206.

33. March of Dimes. Perinatal Stats 2013-2015.

34. Whiteman VE, Salemi JL, Mogos MF, Cain MA, Aliyu MH, Salihu HM. Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. *J Pregnancy*. 2014;2014:906723. doi:10.1155/2014/906723

35. Bromley E, Nunes A, Phipps MG. Disparities in Pregnancy Healthcare Utilization Between Hispanic and Non-Hispanic White Women in Rhode Island. *Matern Child Health J*. 2012;16(8):1576-1582. doi:10.1007/s10995-011-0850-5

36. Shah PS, Zao J, Ali S. Maternal Marital Status and Birth Outcomes: A Systematic Review and Meta-Analyses. *Matern Child Health J*. 2011;15(7):1097-1109. doi:10.1007/s10995-010-0654-z

37. Scott KM, Wells JE, Angermeyer M, et al. Gender and the relationship between marital status and first onset of mood, anxiety and substance use disorders. *Psychol Med*. 2010;40(9):1495-1505. doi:10.1017/S0033291709991942

38. Tan CH, Denny CH, Cheal NE, Sniezek JE, Kanny D. Alcohol use and binge drinking among women of childbearing age - United States, 2011-2013. *MMWR Morb Mortal Wkly Rep*.

2015;64(37):1042-1046. doi:10.15585/mmwr.mm6437a3

39. National Institute of Mental Health. *Mental Illness*.; 2019.

40. Center for Behavioral Health Statistics and Quality. *Results from the 2016 National Survey on Drug Use and Health: Detailed Tables*. Rockville, MD; 2017. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf.

41. Narrow WE, Regier DA, Norquist G, Rae DS, Kennedy C, Arons B. Mental health service use by Americans with severe mental illnesses. *Soc Psychiatry Psychiatr Epidemiol*. 2000;35(4):147-155. doi:10.1007/s001270050197

42. Gandhi DH, Bogrov MU, Osher FC, Myers CP. A Comparison of the Patterns of Drug Use among Patients with and without Severe Mental Illness. *Am J Addict*. 2003;12(5):424-431. doi:10.1080/10550490390240792

43. Irner TB, Teasdale TW, Nielsen T, Vedal S, Olofsson M. Substance Use During Pregnancy and Postnatal Outcomes. *J Addict Dis*. 2012;31(1):19-28. doi:10.1080/10550887.2011.642765

44. Andrykowski MA, Cordova MJ. Factors associated with PTSD symptoms following treatment for breast cancer: Test of the Andersen model. *J Trauma Stress*. 1998;11(2):189-203. doi:10.1023/A:1024490718043

45. Stein JA, Andersen R, Gelberg L. Applying the Gelberg-Andersen Behavioral Model for Vulnerable Populations to Health Services Utilization in Homeless Women. *J Heal Psychol www.sagepublications.com*. 2007;12(5):791-804. doi:10.1177/1359105307080612

46. Ivanov LL. Use of a Western Theoretical Model to Investigate the Relationships Among Characteristics of Pregnant Women, Utilization, and Satisfaction with Prenatal Care Services in St. Petersburg, Russia. *Public Health Nurs*. 2000;17(2):111-120. doi:10.1046/j.1525-1446.2000.00111.x

47. LaVeist TA, Keith VM, Gutierrez ML. Black/white differences in prenatal care utilization: an assessment of predisposing and enabling factors. *Health Serv Res*. 1995;30(1):43-58. http://www.ncbi.nlm.nih.gov/pubmed/7721584. Accessed April 29, 2019.

48. Hatzenbuehler ML, Keyes KM, Narrow WE, Grant BF, Hasin DS. Racial/ethnic disparities in service utilization for individuals with co-occurring mental health and substance use disorders in the general population: results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry*. 2008;69(7):1112-1121. http://www.ncbi.nlm.nih.gov/pubmed/18517286. Accessed April 29, 2019.

49. Hagenaars, J. A., & McCutcheon AL. *Applied Latent Class Analysis*. Cambridge University Press; 2002.

50. Jung, T., & Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Soc Personal Psychol Compass*. 2008;2(1):302-317.

CHAPTER 2: PREVALENCE AND CORRELATES OF A SUBSTANCE RELATED DIAGNOSIS AND PRETERM AND CESAREAN DELIVERY AMONG PREGNANT WOMEN

ABSTRACT:

Background: Women with a substance related diagnoses (SRD) during pregnancy are a vulnerable population who may be experiencing disproportionate rates of preterm delivery and cesarean delivery compared to pregnant women without an SRD. The **primary goals** of this paper were to evaluate the associations between a SRD and preterm delivery and cesarean delivery among women who presented for delivery in a large healthcare system.

Methods: This retrospective study retrieved electronic medical record (EMR) data on women (ages ≥ 18 and ≤ 44 years) who delivered a single live or stillbirth at ≥ 20 weeks of gestation from April 1st, 2011-September 30th, 2019. Women without an SRD were matched at a 1:1 ratio. The Andersen Model was applied to guide the analysis and structure patient characteristics using predisposing, enabling, and need covariates. Adjusting for select covariates (e.g., age), we calculated odds ratios and 95% confidence intervals for preterm and cesarean delivery.

Results: In the unmatched cohort of 19,346 women, most were non-Hispanic/Latina White (43.6%) or other race/ethnicity (42.6%) with a mean age of 31 (standard deviation (SD) =5.4, range 18-44 years of age). An SRD was identified in 1,113 (5.8%) of women. In the preterm delivery matched adjusted cohort (n=2,152), having an SRD (adjusted odds ratio (AOR) = 1.60 [95% CI, 1.20-2.14], p-value = 0.0192) and pre-existing condition (e.g., hypertension; AOR = 1.78 [95% CI, 1.37-2.32], p-value = <0.0001) were significantly associated with preterm delivery. In the cesarean delivery matched adjusted cohort (n=2,148), age at delivery (AOR = 1.05 [95% CI, 1.03-1.07], p-value = <0.0001), BMI at delivery (AOR = 1.05 [95% CI, 1.04-1.07], p-value = <0.0001), having an SRD (AOR = 1.51 [95% CI, 1.23-1.85], p-value = <0.0001) and pre-existing condition (AOR = 1.67 [95% CI, 1.39-2.01], p-value = <0.0001) were significantly associated with cesarean delivery.

C**onclusion:** Pregnant women with an SRD are experiencing disproportionally higher odds of preterm or cesarean delivery compared to pregnant women without an SRD in Southern California. Further research on the role of SRDs on maternal outcomes is needed to develop new interventions that are tailored to meet the needs of this vulnerable population.

INTRODUCTION:

In the United States, less is known about the impact of substance related diagnoses (SRDs; e.g., alcohol, opioids, cannabis, stimulants) on preterm delivery (before 37 weeks) and cesarean delivery among pregnant women. This gap in knowledge may be due to a focus on neonatal outcomes related to substance use (e.g., opioid related neonatal abstinence syndrome [NAS]) rather than maternal outcomes. Studies have shown that increases in preterm and cesarean delivery may be due to the changes in the population of women giving birth. Increases in maternal age,[1] chronic conditions (e.g., hypertension),[2,3] and obesity[4,5] have all been identified in the literature as predictors of preterm or cesarean delivery. The majority of the studies that have investigated the relationship between substance use and preterm or cesarean delivery used data from the 1990's and early 2000's or investigated women outside of the United States.[6,7] More recently, some studies have included substance use as a covariate in their assessments of predictors related to preterm or cesarean delivery in small to moderate sample sizes.[8]

Maternal substance use is observed in all socioeconomic classes, ages, and races. However, an increased risk of use is observed in women who are younger, unmarried, and of lower educational achievement.[9] Studies that have examined the relationship between substance use (e.g., smoking tobacco, heavy alcohol consumption, cocaine use, and heroin use) and preterm delivery found mixed results.[10,11] In a recent study (2019) in Canada of 5,639 reported cannabis users and 92,873 nonusers, cannabis use was significantly associated with preterm delivery.[7] In addition, preterm delivery was significantly associated with cannabis use in women who also reported tobacco use. In the same study, cannabis use was inversely associated with cesarean vs. spontaneous vaginal derlivery.[7] The direct relationship between other substances such as stimulants and preterm or cesarean delivery were not assessed.

From 1999 to 2014, maternal opioid use disorder rates at delivery more than quadrupled showing that maternal opioid use continues to increase in the United States.[12] National data shows

that natural and syntenic opioids (i.e., heroin, legally available pain relievers such as oxycodone and fentanyl) are increasingly used by women compared to men.[13] In an older study from 1998 to 2011, maternal opioid use was found to be associated with maternal death, cardiac arrest, intrauterine growth restriction, placental abruption, length of stay more than seven days, preterm delivery, oligohydramnios, blood transfusion, stillbirth, premature rupture of membranes, and cesarean delivery.[14]

Stimulant use (i.e., cocaine, methamphetamines, ecstasy, prescription stimulants) has been increasing in the United States, and is now the second most common SRD after cannabis use in pregnant women.[15] Stimulants increase central nervous system (CNS) activity and are widely used for medical purposes (e.g., mood disorders, impulse control, attend deficit disorder, sleep disorders, obesity[16–19]) or recreational purposes. In a recent study that conducted a global review to synthesize data on the prevalence, harms, and interventions for stimulant use (mostly cocaine and amphetamines) in adults, stimulant use was associated with elevated mortality, poor mental health (e.g., psychosis, depression, violence, and suicidality), increased incidence of human immunodeficiency virus (HIV) and hepatitis C infection, as well risk of cardiovascular events.[20]

Health behavior models are helpful for guiding and investigating of health outcomes. The Andersen health behavior model has been used to investigate health service utilization through predisposing (sociodemographic characteristics), enabling (economic characteristics), and need (health outcomes) factors.[21] The predisposing factors reflect characteristics that may impact an individual's ability to attain healthcare services. The enabling factors represent the resources that may facilitate access to health services. Finally, the need factors reflect potential needs such as chronic health conditions or self-perceived health. By assessing the predisposing, enabling, and need covariates, this model can identify which of these levels have the greatest impact on maternal health.[21] This model has been used to investigate utilization of prenatal care services,[22] racial/ethnic

differences in prenatal care utilization,[23] and racial/ethnic differences in health service utilization for individuals with co-occurring mental health and SRDs.[24]

In light of the increasing rates of maternal stimulant use, opioid use, and the recent legalization of cannabis in California (2018), updated prevalence and correlates of preterm delivery and cesarean delivery in pregnant women with an SRD is warrented.[25,26]

To address the current gap in the literature on the current associations between SRDs and preterm and cesarean delivery, we conducted a retrospective cohort study of pregnant women to evaluate whether there are independent associations between an SRD and preterm delivery and cesarean delivery in a large healthcare system. Looking at these associations will provide information on the relationship between an SRD and preterm or cesarean delivery in this vulnerable population. We hypothesized that pregnant women with an SRD would have higher prevalence of preterm delivery (Hypothesis 1a (**H1a)**) and cesarean delivery (Hypothesis 1b (**H1b**)) compared to pregnant women without an SRD. Electronic medical record (EMR) data on women (ages ≥ 18 and ≤ 44 years) who delivered a single live or stillbirth at ≥ 20 weeks of gestation (standard cut off rate indicating capability of surviving outside of the body) was retrieved from a large healthcare system in Southern California.

The **Andersen Model** was applied to guide the analyses and structure the analysis using **predisposing** (age, race/ethnicity, marital status, body mass index (BMI) at delivery, parity (>1 previous pregnancy ending in livebirth or stillbirth), **enabling** (health insurance type), and **need** (SRD, severe mental illness (SMI), non-SMI, pre-existing health conditions) covariates (**Figure 2.1)**.

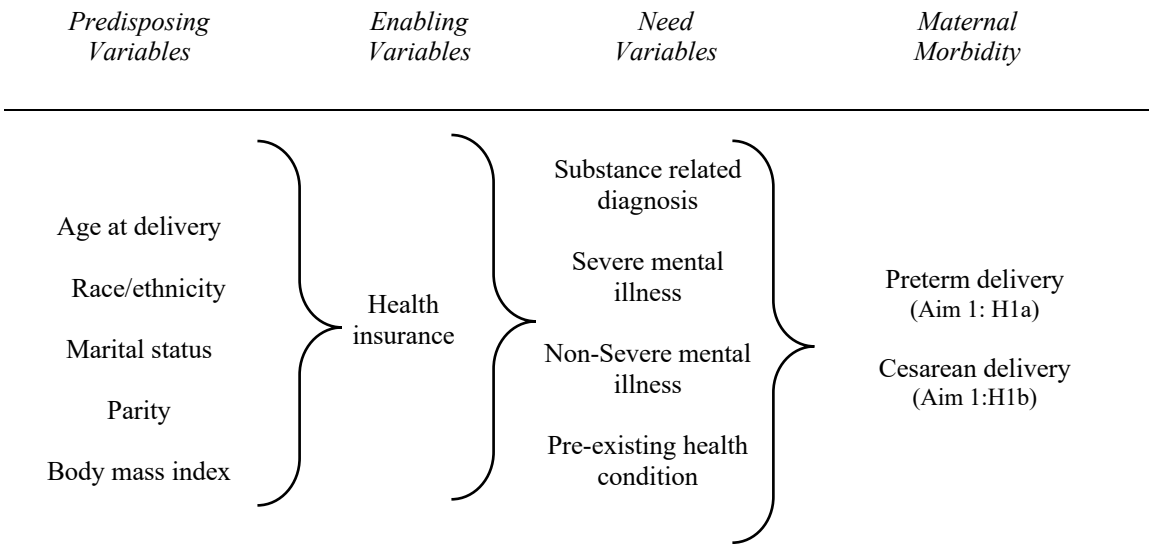

Figure 2.1: Conceptual model adapted from the Andersen Model to investigate how predisposing, enabling, and need variables impact preterm delivery and cesarean delivery in pregnant women in a large healthcare system from April 1st, 2011-September 30th, 2019.

METHODS

Study Participants and Procedures

Deidentified electronic medical record (EMR) data on any woman (age 18 – 44) who delivered a single live or stillbirth at ≥ 20 weeks of gestation was collected from a large health system in Southern California from the day the EMR became available at the study site (April 1st, 2011) through the date the data was requested from the EMR team (September 30th, 2019; 8 years and 6 months). Because deidentified EMR data was requested without direct patient consent, ages ≥ 18 have been selected to protect adolescents under the age of 18 who are considered an especially vulnerable population that may be identifiable due to small sample sizes.

Because pregnancy may be identified at various stages of the woman's pregnancy (1st, 2nd, 3rd, trimester or at delivery), only women with an International Classification of Diseases, 10th edition (ICD-10) code for delivery (Z37.xx) for a single live or stillborn after ≥ 20 weeks of gestation were

used in the dataset for analysis. Deliveries of multiple gestation (e.g., twins) were omitted due to potential differences in maternal morbidity related to gestation. Medical record data was collected from the antepartum (conception to ≤42 weeks) and intrapartum (labor and delivery). When an individual record had more than one delivery carried to a gestational age of ≥ 20 weeks over the 8.5 years of data, each patient identification (PID) number and its unique delivery date represented one subject. The number of previous pregnancies for each delivery by PID was identified by delivery codes that appear before the most recent delivery in the dataset.

All medical diagnoses and procedures were identified using ICD-10 Clinical Modification (CM) codes. A full list of the codes used to meet the aim of this study can be found in **Table A** in the appendix. ICD-10 codes are assigned to prenatal encounters and at labor and delivery.[27] ICD-10 uses "Z" codes to identify reasons for encounters (Z3A.xx for specific week of gestation, Z34.xx for supervision/routine prenatal visit of normal pregnancy by trimester). Each trimester is counted from the first day of the patient's last menstrual period: first trimester (0-13 weeks), second trimester (14-28 weeks), and third trimester (28-42 weeks).[28] Therefore, a Z3A.40 code would indicate 40 weeks' gestation and Z34.03 would indicate an encounter for supervision of normal first pregnancy, third trimester.[28] A code for Z37.xx represents the outcome of delivery (e.g., single live birth, single still birth, twins' live birth etc.) and should be included on every maternal record when a delivery has occurred.

ICD-10 codes for SRDs and other mental illness diagnoses correspond with the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), which provides a more detailed description of each diagnosis. An SRD and other mental illness diagnoses may be included in a patient chart during any outpatient visit (e.g., prenatal visit with their obstetrician, psychiatric visit), inpatient visit (e.g., hospitalization), emergency department visit (e.g., delivery), or during one of the many other types of healthcare related visits.

The University Human Research Protection Program (HRPP) and the Institutional Review Board (IRB) approved the study protocol. All of the data was collected from the health center's biomedical informatics team through their standardized data request process. Data was provided by staff in a secured Health Insurance Portability and Accountability Act (HIPAA) approved Virtual Research Desktop (VRD; supported by the National Institute of Health, Grant UL1TR001442 of CTSA Funding). The VRD interface is protected by multi-factor authentication and is managed and monitored by the biomedical informatics team. Servers are behind firewalls configured to allow access only to credentialed personnel within the network. No removable media services were used with this data. All of the data was electronic and was not accessible to the internet.

Measures

Outcome measures: The **primary outcomes** are **preterm delivery** (20-36-week gestation; yes/no) and **cesarean delivery** (yes/no). Because the type of delivery in the EMR includes vaginal, cesarean, and spontaneous or therapeutic abortion, the sample used to assess cesarean delivery only included those with a cesarean or vaginal delivery. As such, those with a spontaneous or therapeutic abortion (n=43) were omitted from the analysis for cesarean delivery but not for preterm delivery.

Predictor variable: The **primary predictor** variable is pre-existing and/or new **SRD** (yes/no) during the antepartum and intrapartum period. The SRD variable was grouped into the Andersen Model's *need* category but was the main predictor variable of interest. The **secondary predictors** include alcohol related diagnosis (F10.xx; yes/no), opioid related diagnosis (F11.xx; yes/no), cannabis related diagnosis (F12.xx; yes/no), stimulants related diagnosis (F14.xx [cocaine], F15.xx [other stimulants]; yes/no), nicotine related diagnosis (F17.xx; yes/no), and non-specific SRDs (F19.xx) or other (F13.xx [sedatives], F16.xx [hallucinogens], F18.xx [inhalants]). SRDs that were only identified after the intrapartum period were not included in the analysis due to the potential cofounding associated with substance use after delivery.

Andersen Model variables

Predisposing variables: **age** (18-44) and **race/ethnicity** (Hispanic/Latina, non-Hispanic/Latina Black, non-Hispanic/Latina White, and other race/ethnicity [American Indian/Alaskan Native, Asian/Pacific Islander, and other race or mixed)]) at delivery were included in the predisposing category. On intake, patients are asked to include their race (e.g., Black, White) and ethnicity (e.g., African American, Caucasian) as separate categories. In the race and ethnicity categories, the EMR has the option of "other race or mixed" and "unknown" respectively. If neither of the race or ethnicity selections were listed as Hispanic/Latina, non-Hispanic/Latina Black or non-Hispanic/Latina White then the patient was grouped into the "other" category. Other predisposing variables include **marital status** (single, divorced/separated/widowed, or married), and **body mass index** (BMI; calculated as weight in kilograms divided by height in meters squared) at delivery [Figure 2.1]). **Parity** (no previous pregnancies or ≥ 1 previous pregnancy carried to a gestational age of ≥ 20 weeks and ending in livebirth or stillbirth) was identified to assess the impact of previous pregnancies on maternal morbidity.

Enabling variable: Health insurance type at delivery was the enabling variable of interest (**Figure 1**). **Health insurance** was defined as private (e.g., commercial, managed care), public (e.g., Medicaid) and no insurance. Those who were grouped in the private insurance category could also have public insurance. However, those grouped in the public insurance category did not have private insurance.

Need variables: Pre-existing illness before delivery represented the need variables and were identified using ICD-10 codes. A summary variable for **SMI** included bipolar (F31-F31.9), manic episode (F30-F30.9) major depressive disorder severe (F32.2-F32.3, F33.2-F33.2), schizophrenia (F20-F20.9), schizotypal disorder (F21-F21.9), persistent delusional disorder (F22), and schizoaffective disorder (F25-F25.9; a full list can be found in the Table A in the appendix).

A summary variable for **non-SMI** included persistent mood disorder (F39), major depressive disorder mild or moderate (F32.0-F32.1, F32.4-F32.9, F33.0-F33.1, F33.4-F33.9), delusional disorders (F22), brief psychotic disorders (F23), other psychotic disorder not due to a substance or known physiologic condition (F28), unspecified psychosis (F29), reaction to severe stress, and adjustment disorders (includes post-traumatic stress syndrome [PTSD]; F43-F43.9), obsessive compulsive disorder (F42-F42.9), phobic anxiety disorder (F40-F40.9), other anxiety disorder (F41-F41.9), eating disorder (F50-F50.9), specific personality disorder (F60-F60.9), or impulse disorder (F63-F63.9; a full list can be found in the Table A in the appendix).

A summary variable for **pre-existing health condition** included cardiovascular disease, diabetes (non-gestational), anemia, kidney failure, hypertension, lupus, epilepsy, pulmonary disease, cancer, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hepatitis c virus (HCV), and tuberculosis (TB; ICD-10 codes supplied on request).

Statistical Analysis

Descriptive statistics were used to identify the number and type of SRD during the antepartum period (≥ 20 weeks of gestation to delivery). A summary variable for SRD (yes/no) was created for any record with an ICD-10 code for SRD. The type of SRD was then sub-grouped into independent categories for alcohol related diagnosis (yes/no), opioid related diagnosis (yes/no), cannabis related diagnosis (yes/no), stimulant related diagnosis (yes/no), nicotine related diagnosis (yes/no), and non-specific or other substances related diagnosis (yes/no).

Unadjusted and adjusted analyses of the Andersen Model covariates and the outcome measures (preterm delivery and cesarean delivery) were conducted in the unmatched and matched cohorts using analysis of variance (ANOVA) for continuous data and Chi-square (X^2) tests of significance for categorical data. To determine the effect/magnitude of the associations, unadjusted

odds ratios (ORs) were calculated and reported. Two-sided tests with p-values significant at ≥ 0.05 and OR 95% CIs that cross 1 indicating that there was no significant difference were used to determine whether a covariate would be included in the final adjusted regression model in both the unmatched and matched cohorts.

In addition to the overall unmatched cohort of women with and without an SRD, women with an SRD in the sample were randomly matched to those without an SRD on key baseline characteristics using a propensity score method.[29] Specifically, imbalance in measured maternal sociodemographic and obstetrical characteristics between those with and without an SRD was attenuated using propensity score matching, yielding a matched 1:1 sample.[30] Women who presented for delivery with and without an SRD were matched by age at delivery, BMI at delivery, parity (>1 previous pregnancy ending in livebirth or stillbirth), pre-existing health condition, and delivery year (2012-2019). All of these variables have been identified as predictors of maternal morbidity such as preterm delivery and cesarean delivery in the literature.[25,31,32] Standardize mean differences were used to examine the balance of covariate distribution between the two groups.

The unadjusted and adjusted regression analyses in the unmatched and matched cohorts were analyzed and reported separately for preterm delivery and cesarean delivery to reduce confounding from the two interrelated outcome variables (e.g., women can have preterm delivery and cesarean delivery at the same time). As mentioned previously, the sample set used to assess cesarean delivery only included those with a cesarean or vaginal delivery. Cases that resulted in abortive outcomes (n=43) were omitted from the cesarean delivery dataset and analysis. This resulted in small differences in sample size for SRD for each outcome variable (preterm delivery and SRD = 1,113; cesarean delivery and SRD = 1,111).

Unadjusted and adjusted analyses of the Andersen Model covariates and the outcome measures (preterm delivery and cesarean delivery) were then conducted in the matched cohorts using

ANOVA for continuous data and X^2 tests of significance for categorical data. To determine the effect/magnitude of the associations, ORs were calculated and reported. Two-sided tests with p-values significant at ≥ 0.05 and OR 95% CIs that cross 1 indicating that there was no significant difference were used to determine whether a covariate would be included in the final adjusted regression model in both the unmatched and matched cohorts.

Multivariable logistic regression in the unmatched and matched cohorts was then conducted to determine the Andersen Model covariates that were associated with having an SRD compared to those without an SRD (**H1a-H1b**). Standardized betas (β), standard errors (SE(β)), adjusted odds ratios (AOR) and the respected CI and p-values are reported. All analyses were conducted with SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Sample Characteristics

There was a total of 19,350 deliveries with an ICD-10 code for a single delivery at ≥ 20 weeks' gestation. Four individuals were diagnosed with an SRD after delivery and were removed from the full dataset. In the final unmatched cohort of 19,346 deliveries, most were Non-Hispanic/Latina White (43.6%) or other race/ethnicity (42.6%) with a mean age of 31 (standard deviation (SD) =5.4, range 18-44 years of age; **Table 1.1**). Most were married (70.3%), had no previous pregnancies (86.7%), and had private health insurance (65.4%). An SRD was documented for 5.8% (n= 1,113) of the sample. Of those, any SRD for alcohol (0.58%), opioids (1.2%), cannabis (1.9%), stimulants (1.6%), nicotine (1.9%), or non-specific and other (1.9%) were observed (**Table 1.3**). SMI and non-SMIs were documented for 1.9% and 18.6% respectively. Pre-existing health conditions were documented for 31.9%. Preterm delivery was documented in 2,159 (11.2%) women.

Due to the large sample size (n = 19,346), almost all of the comparisons in the unadjusted analysis revealed differences that were found to be significantly associated with preterm delivery (yes/no). Imbalance in measured maternal sociodemographic and obstetrical characteristics between those with and without a preterm delivery was attenuated using matching, yielding a matched 1:1 sample of 2,158.

In the preterm delivery matched cohort of 2,158 deliveries, most were Non-Hispanic/Latina White (38.9%) or of other race/ethnicity (41.3%) with a mean age of 29.9 ([SD] =5.6, range 18-44 years of age; **Table 1.1**). Most were married (48.7%) or single (47.3%), had no previous pregnancies (92.0%), had private health insurance (67.8%), and a mean BMI at delivery of 32.6 ([SD] =7.6, range 14.4-101.2). SRD was documented for 50.0% (n=1,079) of the sample due to matching. Of those, any SRD for alcohol (5.1%), opioids (9.9%), cannabis (16.2%), stimulants (13.9%), nicotine (16.4%), or non-specific and other (1.9%) were identified (**Table 1.3**). SMI and non-SMIs were documented for 7.6% and 32.9% respectively. Pre-existing health conditions were documented for 49.9% (n= 1,078) due to matching.

Prevalence and Correlates of Preterm Delivery

In the unmatched unadjusted analysis, preterm delivery was associated with being non-Hispanic/Latina Black (OR = 2.40 [95% CI, 2.01-2.88], p-value = <0.0001), other race/ethnicity (OR = 1.90 [95% CI, 1.71-2.11], p-value = 0.0020), single (OR = 1.61 [95% CI, 1.46-1.77], p-value = 0.0014), a higher BMI at delivery (OR = 1.01, [95% CI, 1.01-1.02] p-value = <0.0001), no previous pregnancies (OR = 1.47 [95% CI, 1.27-1.71], p-value = <0.0001), public health insurance (OR = 1.36 [95% CI, 1.22-1.51], p-value = <0.0001), SRD (OR = 1.64 [95% CI, 1.39-1.94], p-value = <0.0001), SMI (OR = 1.52 [95% CI, 1.15-2.01], p-value = 0.0036), and pre-existing health conditions (OR = 1.81 [95% CI, 1.65-1.98], p-value = <0.0001; **Table 1.2**). When grouped by SRD type, preterm delivery was found to be associated with an alcohol related diagnosis (OR = 2.00 [95% CI, 1.22-3.12], p-value = <0.0001), opioid related diagnosis (OR = 2.09 [95% CI, 1.51-2.90], p-value = <0.0001),

cannabis related diagnosis (OR = 1.49 [95% CI, 1.15-1.99], p-value = 0.0069), stimulant related diagnosis (OR = 2.58 [95% CI, 1.98-3.35], p-value = <0.0001), nicotine related diagnosis (OR = 1.59 [95% CI, 1.20-2.10], p-value = 0.0012), and non-specific and other substance related diagnosis (OR = 1.59 [95% CI, 1.20-2.11], p-value = 0.0014; **Table 1.3**).

In the matched unadjusted analysis (n=2,158), preterm delivery was associated with being non-Hispanic/Latina Black (OR = 1.94 [95% CI, 1.28-2.93], p-value = 0.0478), SRD (OR = 1.66 [95% CI, 1.28-2.14], p-value = 0.0001), and pre-existing health conditions (OR = 1.78 [95% CI, 1.38-2.30], p-value = <0.0001; **Table 1.2**). When grouped by SRD type, preterm delivery was found to be associated with alcohol related diagnosis (OR = 1.64 [95% CI, 1.00-2.69], p-value = 0.0400) opioid related diagnosis (OR = 1.86 [95% CI, 1.30-2.67], p-value = 0.0007), and stimulant related diagnosis (OR = 2.22 [95% CI, 1.65-3.07], p-value = <0.0001; **Table 1.3**).

Independent Associations with Preterm Delivery

In the final unmatched adjusted regression, being of older age at delivery (adjusted odds ratio [AOR] = 6.74, p-value = 0.0094), non-Hispanic/Latina Black (AOR = 1.95 [95% CI, 1.61-2.36], p-value = 0.0002), other race/ethnicity (AOR = 1.75 [95% CI, 1.57-1.95], p-value = 0.0005), having no previous pregnancies (AOR = 1.37 [95% CI, 1.17-1.59], p-value = <0.0001), having no public health insurance (AOR = 1.18 [95% CI, 1.05-1.33], p-value = 0.0034), having an SRD (AOR = 1.25 [95% CI, 1.04-1.51], p-value = 0.0192), and pre-existing health condition (AOR = 1.69 [95% CI, 1.53-1.86], p-value = <0.0001) were significantly associated with having an preterm delivery (**Table 1.3**).

In the final matched adjusted regression, having an SRD (AOR = 1.60 [95% CI, 1.20-2.14], p-value = 0.0192), and pre-existing health condition (AOR = 1.78 [95% CI, 1.27-2.32], p-value = <0.0001) were significantly associated with having an preterm delivery (**Table 1.4**).

Prevalence and Correlates of Cesarean Delivery

Cesarean delivery was documented in 5,847 (30.3%) women. Due to the large sample size (n = 19,303), almost all of the comparisons in the unadjusted analysis revealed differences that were

found to be significantly associated with Cesarean delivery (yes/no). Imbalance in measured maternal sociodemographic and obstetrical characteristics between those with and without a Cesarean delivery was attenuated using matching, yielding a matched 1:1 sample of 2,154.

In the unmatched unadjusted analysis, cesarean delivery was associated with older age at delivery (OR = 1.05 [95% CI, 1.04-1.05], p-value = <0.0001), being non-Hispanic/Latina Black (OR = 1.82 [95% CI, 1.60-2.08], p-value = <0.0001), divorced/separated/widowed (OR = 1.85 [95% CI, 1.52-2.26], p-value = <0.0001), a higher BMI at delivery (OR = 1.07 [95% CI, 1.06-1.07], p-value = <0.0001), no previous pregnancies (OR = 1.48 [95% CI, 1.33-1.62], p-value = <0.0001), public health insurance (OR = 1.19 [95% CI, 1.10-1.28], p-value = <0.0001), SRD (OR = 1.87 [95% CI, 1.62-2.11], p-value = <0.0001), SMI (OR = 1.74 [95% CI, 1.41-2.14], p-value = <0.0001), non-SMI (OR = 1.26 [95% CI, 1.17-1.37], p-value = <0.0001), and pre-existing health conditions (OR = 2.11 [95% CI, 1.98-2.25], p-value = <0.0001; **Table 1.6**). When grouped by SRD type, cesarean delivery was found to be associated with alcohol related diagnosis (OR = 1.55 [95% CI, 1.06-2.26], p-value = 0.0234), opioid related diagnosis (OR = 1.72 [95% CI, 1.32-2.25], p-value = <0.0001), cannabis related diagnosis (OR = 1.48 [95% CI, 1.19-1.83], p-value = 0.0004), stimulant related diagnosis (OR = 2.46 [95% CI, 1.97-3.08], p-value = <0.0001), nicotine related diagnosis (OR = 2.07 [95% CI, 1.68-2.55], p-value = <0.0001), and non-specific and other SRD (OR = 2.26 [95% CI, 1.84-2.79], p-value = <0.0001; **Table 1.7**).

In the matched unadjusted analysis (n=2,154), cesarean delivery was identified in 833 (38.7%) deliveries and was associated with older age at delivery (OR = 1.05 [95% CI, 1.05-1.07], p-value = <0.0001), divorced/separated/widowed marital status (OR = 2.37 [95% CI, 1.53-3.70], p-value = 0.0010), a higher BMI at delivery (OR = 1.05 [95% CI, 1.04-1.07], p-value = <0.0001), SRD (OR = 1.61 [95% CI, 1.35-1.92], p-value = <0.0001), SMI (OR = 1.61 [95% CI, 1.35-2.34], p-value = 0.0013), and pre-existing health conditions (OR = 1.84 [95% CI, 1.54-2.19], p-value = <0.0001; **Table 1.6**). When grouped by SRD type, cesarean delivery was found to be associated with stimulant

related diagnosis (OR = 1.93 [95% CI, 1.51-2.46], p-value = <0.0001), nicotine related diagnosis (OR = 1.56 [95% CI, 1.24-1.97], p-value = 0.0001), and non-specific and other SRD (OR = 1.75 [95% CI, 1.40-2.21], p-value = <0.0001; **Table 1.7**).

Independent Associations with Cesarean Delivery

In the final unmatched adjusted regression (n= 18,381), being of older age at delivery (AOR = 1.06, [95% CI, 1.06-1.07], p-value <0.0001), non-Hispanic/Latina Black (AOR = 1.38 [95% CI, 1.19-1.60], p-value = 0.0090), other race/ethnicity (AOR = 1.28 [95% CI, 1.19-1.37], p-value = 0.0308), being divorced/separated/widowed (AOR = 1.31 [95% CI, 1.06-1.63], p-value = 0.0543), having a higher BMI (AOR = 1.06 [95% CI, 1.06-1.07], p-value = <0.0001), having no previous pregnancies (AOR = 1.56 [95% CI, 1.41-1.73], p-value = <0.0001), having an SRD (AOR = 1.56 [95% CI, 1.35-1.79], p-value = <0.0001), and pre-existing health condition (AOR = 1.80 [95% CI, 1.68-1.93], p-value = <0.0001) were significantly associated with having an a cesarean delivery (**Table 1.7**).

In the final matched adjusted regression (n=2,148), age at delivery (AOR = 1.05 [95% CI, 1.03-1.07], p-value = <0.0001), BMI at delivery (AOR = 1.05 [95% CI, 1.04-1.07], p-value = <0.0001), having an SRD (AOR = 1.51 [95% CI, 1.23-1.85], p-value = <0.0001), and pre-existing health condition (AOR = 1.67 [95% CI, 1.39-2.01], p-value = <0.0001) were significantly associated with having a cesarean delivery (**Table 1.7**).

DISCUSSION

Using a large healthcare system-based pregnancy cohort, this retrospective study evaluated the relationships between an SRD and preterm and cesarean delivery among pregnant women who presented for delivery in a large healthcare system from 2012-2019. Having any SRD was found to be significantly associated with preterm and cesarean delivery in all of the unmatched and matched cohorts. Although there are limitations to determining underlying effects of maternal substance use

on maternal morbidity using observational epidemiology, this study aimed to address a set of known confounders using propensity score matching to improve estimates of SRD and preterm or cesarean delivery.

SRD and Maternal Morbidity

When stratified by substance type, alcohol, opioids, and stimulant related diagnoses remained significantly associated with preterm delivery in the matched unadjusted analysis (adjusted analysis not completed for substance types). Our findings differ from the large study done in Canada in 2019 mentioned previously, which investigated the impact of cannabis use on preterm and cesarean delivery. In the Canada study, cannabis use and cannabis with tobacco use was significantly associated with preterm delivery while alcohol and opioids were not found to be associated.[7] The direct relationship between stimulants (amphetamines and cocaine) were not evaluated. In our study, cannabis was not found to be associated with preterm or cesarean delivery in the bivariate analysis. Multivariable analyses by substances were not assessed.

Differences in our results may be explained by co-occurring SRDs. Maternal polysubstance use (more than 1 substance) is common and has been associated with increased risk of preterm delivery.[33] One study found that women on methadone with preterm delivery had co-occurring use of 0 (24%), 1 (26%), 2 (45%), or ≥ 3 (65%) SRDs.[33]

The link between alcohol consumption during antepartum period and preterm delivery is controversial. Numerous studies have examined this specific relationship and have found mixed results.[10] In a recent review of prenatal alcohol exposure and preterm delivery, the authors identified concerns over methodological weaknesses in previous work and its impact on null findings. This includes concerns with small sample size, inadequate assessment of alcohol exposure, failure to control for confounding factors appropriately, and unreliable gestational dating due to menstrual cycle dates vs. ultrasound dates.[10] In the current study, we adequately addressed all of these concerns excluding the risk to inadequate assessment of alcohol exposure. Overall, measuring substance

exposure in this current study is dependent on ICD-10 codes inputted in the EMR by healthcare providers. It is possible that SRDs are missed due to misclassification because substance use was not the primary reason of the visit. Providers may also not have been comfortable entering mental health and substance use diagnoses into the legal medical record, or the patients were reluctant to disclose their use due to stigma and/or fear of legal ramifications. Regardless, our data show a consistent relationship between alcohol, opioid, and stimulant use and preterm delivery.[34]

A study assessing the role of preterm delivery as a mediator of the relationship between prenatal exposure to methadone and buprenorphine and its impact on NAS found that preterm delivery was more common in methadone-exposed deliveries (25%) compared to the buprenorphine-exposed deliveries (14%).[35] This suggests that there may be maternal and neonatal physiological changes related to opioid withdrawal during pregnancy and the use of medication assisted treatments (MATs) such as methadone or buprenorphine. Research has also shown that preterm neonates have a lower incidence of NAS compared to neonates delivered full term.[36] Additional research on how methadone or buprenorphine use during pregnancy impacts maternal morbidity is needed to determine the safety and utility of these essential medications.

A systematic review and meta-analysis of 31 studies found that pregnant women who used cocaine were at an increased risk for preterm delivery, low birth weight (<2,500 g), small for gestational age infants, earlier gestational age at delivery, and reduced birth weight.[25] The relationship between stimulant use (e.g., amphetamines, cocaine) and preterm delivery may be explained by additional physiological stress put on the body during the perinatal period. A newly published study investigating the impact of amphetamine and opioid use on trends in incidence and maternal outcomes from 2005-2015 found that a higher incidence of preterm delivery, preeclampsia, severe maternal morbidity, and mortality was observed in the stimulant-related deliveries compared to the opioid-related deliveries.[37]

In the current study, SRD was found to be significantly associated with and cesarean delivery in both the unmatched and matched cohorts. The majority of the current literature on substance use and cesarean delivery is focused on persistent opioid use post-cesarean delivery.[38] In the large cohort from Canada mentioned previously, cannabis exposure was inversely associated with cesarean vs. spontaneous vaginal derlivery.[7] However, the risk difference was not found to be significantly associated. Because cesarean delivery can be elective (though uncommon in the U.S.), it is difficult to identify how SRD directly impacts this type of outcome. Future research should investigate the purpose of the delivery method (e.g., elective vs. required) in those with and without an SRD.

Andersen Model Covariates

In the matched adjusted analyses of the Andersen Model covariates and preterm delivery, only pre-existing health conditions remained significantly associated. This indicates that the *need* characteristics play a significant role on maternal health. Pre-existing health conditions such as non-gestational diabetes, cardiovascular disease, and hypertension and maternal morbidity have been well documented in the literature. In a recent study, an increased risk of preterm and early term delivery in women with pre-existing diabetes was observed in a cohort of women with at least two deliveries.[39] In the same study, women who reported substance use during the second pregnancy were 9.0 times more likely to deliver before 32 weeks of gestation.

In the matched adjusted analyses of the other Andersen Model covariates and cesarean delivery, older age at delivery, higher BMI at delivery, and pre-existing health conditions remained significantly associated. These predisposing and need covariates are likely interrelated and increase the risk of cesarean delivery when grouped together. The mean age in our study was 30-31 years of age. Increased age is a known risk factor for maternal morbidity and is well documented in the literature.[40] One study investigating obstetric complications by maternal age found that women who were older (age 45 years or older) had more chronic medical conditions (pre-existing diabetes present in 5.4% and chronic hypertension present in 9.5%) compared to women who were younger.[41]

Numerous studies have found associations between high BMI and maternal morbidity.[42] For example, one study found that those with increased BMI had an increased incidence of pre-eclampsia, macrosomia, gestational hypertension, and induction of labor and cesarean delivery.[42] In addition, women who were underweight demonstrated better outcomes than women with a normal BMI.[42] Another study found that women with the highest BMIs were more likely to have cesarean delivery compared to those with lower BMIs.[43] Prevention of cesarean delivery is needed for women with high BMIs. Obesity prevention efforts should begin at an early age and continue through the reproductive years.

Pregnant women of older age, high BMI, an SRD, and pre-existing health conditions should be monitored by healthcare providers for maternal morbidly. Further research is needed to explore how interventions addressing these predisposing and need covariates can be implemented in clinical care.

Study Strengths and Limitations

The research presented in this study addressed significant gaps in the literature on the relationship between an SRD and preterm delivery and cesarean delivery in pregnant women. Having access to a large health record dataset allows for in-depth review of the prevalence and correlates of SRDs and maternal morbidity. This study is strengthened by the large sample size of women who presented for delivery with (n= 1,111 [5.8%]) and without (n= 18,192 [94.2%]) an SRD over 8.5 years of EMR data.

This study was also strengthened by the use of propensity score matching to control for confounding in the unstructured EMR data. By matching on age at delivery, BMI at delivery, parity, pre-existing health condition, and delivery year, a greater portion of potential bias was eliminated when estimating the effects of SRD on maternal morbidity.[44]

Using ICD-10 codes from the EMR has strengths and limitations. Because providers are required to enter all of the medical data in the EMR directly, a large amount of data can be captured

over a long period of time. As such, using EMR data allows for a unique perspective on maternal morbidities among a large sample of women with and without an SRD, which is focused on accurate diagnoses and outcomes instead of self-report. However, some health-related diagnoses (e.g., SRD, SMI) may be missing or not adequately assigned in the EMR. It is possible that patients may have omitted their substance use or providers did not know how to appropriately diagnose an SRD at the time of the clinical visit. Providers may also be reluctant to enter diagnoses such as SRDs or a SMIs into the permanent medical record if it is not the focus of the encounter. Another limitation includes the fact that these codes are designed to identify diagnoses and procedures for billing purposes. This limitation is clearly observed in the way many SRDs are identified in the EMR as "non-specified substance related disorder." Further exploration of the factors contributing to a clinical provider's decision to classify a patient with an SRD in this ambiguous category instead of a designated substance type would be helpful to improve code classification in the EMR. It would also be advantageous to clearly identify the severity of the SRD in the EMR.

Because maternal morbidity varies over time and across regions, generalizability is limited by the restriction to Southern California and to one healthcare system.

CONCLUSION:

Findings from this study show that having an SRD or a pre-existing health condition are strong predictors for preterm or cesarean delivery among pregnant women in Southern California. In addition, age and BMI at delivery are also predictors of cesarean delivery in this population. When stratified by substance type in unadjusted matched models, alcohol, opioids, and stimulants were significantly associated with preterm delivery. When stratified by substance type in the unadjusted matched models, stimulants, nicotine, and non-specific substance and other substances were associated with caesarean delivery. Future studies should investigate how the type of SRD and polysubstance use impacts maternal morbidity. This study contributes to important knowledge on the

associations between SRDs and maternal morbidity. Healthcare providers should identify pregnant women with older age, higher BMI, an SRD, or a pre-existing health condition early to address how to prevent preterm or cesarean delivery. Further research on role of SRDs on maternal outcomes is needed to develop new interventions that identify these predisposing and need covariates early in pregnancy to reduce the risk of preterm or cesarean delivery. Interventions should be tailored to meet the needs of this vulnerable population and inform future improvements in maternal health and clinical care.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contributions to this research by the Altman Clinical and Translational Research Institute's Virtual Research Desktop (VRD) analytics team and collaborators at University of California San Diego (supported by the National Institute of Health, Grant UL1TR001442 of CTSA Funding). This research is funded by Dr. Carla Marienfeld research funds through the department of Psychiatry at the University of California San Diego School of Medicine.

Table 1.1: Unmatched and matched characteristics of the Andersen Model covariates and preterm delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,346).

Parameter	Preterm delivery Unmatched cohort (n= 19,346)			Preterm delivery matched cohort (n= 2,158)		
	Total n (%)/ Mean (SD)	Preterm Delivery n (%)/ Mean (SD)	No Preterm Delivery n (%)/ Mean (SD)	Total n (%)/ Mean (SD)	Preterm Delivery n (%)/ Mean (SD)	No Preterm Delivery n (%)/ Mean (SD)
All	19,346 (100.0)	2,159 (11.2)	17,187 (88.8)	2,158 (100.0)	281 (13.0)	1,877 (87.0)
Predisposing Variables						
Age at delivery (range 18-44)	31.0 (5.4)	30.9 (5.90)	31.0 (5.33)	29.9 (5.6)	29.9 (6.1)	29.9 (5.6)
Race/ethnicity						
Hispanic/Latino	1,543(8.2)	198 (9.5)	1,345 (8.05)	201 (9.6)	27 (9.8)	174 (9.6)
Non-Hispanic/Latino Black	1,058 (5.6)	176 (8.4)	882 (5.3)	214 (10.2)	38 (13.8)	176 (9.7)
Other	8,006 (42.6)	1,091 (52.1)	6,915 (41.4)	815 (38.9)	124 (44.9)	691 (86.8)
Non-Hispanic/Latino White	8,193 (43.6)	628 (30.0)	7,565 (42.3)	867 (41.3)	87 (31.5)	780 (42.8)
Marital status						
Single	5,321 (27.5)	782 (36.3)	4,539 (26.4)	1,017 (47.3)	158 (56.4)	859 (45.9)
Divorced, separated, widowed	418 (2.2)	59 (2.7)	359 (2.09)	88 (4.1)	13 (4.6)	75 (4.1)
Married	13,582 (70.3)	1,316 (61.0)	12,266 (71.5)	1,047 (48.7)	109 (38.9)	938 (50.1)
BMI at delivery	31.0 (6.5)	31.5 (7.4)	30.9 (6.4)	32.6 (7.6)	31.8 (7.6)	32.1 (7.6)
Parity						
No previous pregnancies	16,770 (86.7)	211 (9.8)	2,365 (13.8)	172 (8.0)	22 (7.8)	150 (8.0)
≥ 1 previous pregnancy	2,576 (13.3)	1,948 (90.2)	14,822 (86.2)	1,986 (92.0)	259 (92.2)	1,727 (92.0)
Enabling Variables						
Health insurance						
Public	3,927 (20.3)	539 (25.0)	3,388 (19.7)	483 (22.4)	71 (25.3)	412 (22.0)
No insurance	2,767 (14.3)	291 (13.5)	2,476 (14.4)	212 (9.8)	23 (8.2)	189 (10.0)
Private	12,652 (65.4)	1,329 (61.6)	11,323 (65.9)	1,463 (67.8)	187 (66.6)	1,276 (68.0)
Need Variables						
Substance related diagnosis						
Yes	1,113 (5.8)	185 (8.6)	928 (5.4)	1,079 (50.0)	171 (60.9)	908 (48.4)
No	18,233 (94.3)	1,974 (91.4)	16,259 (94.6)	1,079 (50.0)	110 (39.2)	969 (51.6)
Serious mental illness						
Yes	371 (1.9)	59 (2.7)	312 (1.8)	163 (7.6)	29 (10.3)	134 (7.1)
No	18,975 (98.1)	2,100 (97.3)	16,875 (98.2)	1,995 (92.5)	252 (89.7)	1,743 (92.9)
Non-SMI						
Yes	3,599 (18.6)	422 (19.6)	3,177 (18.5)	710 (32.9)	100 (35.6)	610 (35.5)
No	15,747 (81.4)	1,737 (80.5)	14,010 (81.5)	1,448 (67.1)	181 (64.1)	1,267 (67.5)
Pre-existing health condition						
Yes	6,173 (31.9)	952 (44.1)	5,221 (30.4)	1,078 (49.9)	175 (62.3)	903 (48.1)
No	13,173 (68.1)	1,207 (55.9)	11,966 (69.6)	1,080 (50.1)	106 (37.7)	974 (51.9)

Age at delivery by preterm delivery: n = 2,159, median = 31, range = 18-44. Age at delivery by non-preterm delivery: n = 17,187, median = 31, range = 18-44. BMI at delivery by preterm delivery: n = 2,065, median = 30.1, range = 16.4-71.5. BMI at delivery by non-preterm delivery: n= 16,905, median = 29.5, range = 14.4-101.2. Matched age at delivery by preterm delivery: n = 281, median = 30, range = 18-42. Matched age at delivery by non-preterm delivery: n = 1,877, median = 30, range = 18-44. Matched BMI at delivery by preterm delivery: n = 2, median = 30.1, range = 16.4-71.5. Matched BMI at delivery by non-preterm delivery: n= 2,158, median = 31.0, range = 14.4-101.2.). Variable totals may not sum to column totals due to missing data.

Table 1.2: Unmatched and matched unadjusted analysis of the Andersen Model covariates associated with a preterm delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,346).

Parameter	Total n (%)/Mean (SD)	Preterm delivery Unmatched cohort (n= 19,346) Odds Ratio 95% (CI)	X^2/F	P	Preterm delivery matched cohort (n= 2,158) Odds Ratio 95% (CI)	X^2/F	P
All	19,346 (100.0)						
Predisposing Variables							
Age at delivery (range 18-44)	31.0 (5.4)	1.00 (0.99-1.00)	0.90	0.3437	1.00 (1.00-1.02)	0.01	0.9149
Race/ethnicity							
Hispanic/Latino	1,543(8.2)	1.77 (1.50-2.10)	0.64	0.4223	1.39 (0.88-2.21)	0.04	0.8262
Non-Hispanic/Latino Black	1,058 (5.6)	2.40 (2.01-2.88)	28.68	<0.0001	1.94 (1.28-2.93)	3.92	0.0478
Other	8,006 (42.6)	1.90 (1.71-2.11)	0.67	0.0020	1.61 (1.20-2.16)	1.10	0.2948
Non-Hispanic/Latino White	8,193 (43.6)	—			—		
Marital status							
Single	5,321 (27.5)	1.61 (1.46-1.77)	10.21	0.0014	1.58 (1.22-2.06)	2.06	0.1511
Divorced, separated, widowed	418 (2.2)	1.53 (1.16-2.03)	1.77	0.1832	1.49 (0.80-2.78)	0.31	0.5804
Married	13,582 (70.3)	—			—		
BMI at delivery (range 14.4-101.2)	31.0 (6.5)	1.01 (1.01-1.02)	15.08	0.0001	0.98 (0.97-1.00)	3.38	0.0550
Parity							
No previous pregnancies	16,770 (86.7)	1.47 (1.27-1.71)	26.13	<0.0001	1.02 (0.64-1.63)	0.01	0.9259
≥ 1 previous pregnancy	2,576 (13.3)	—			—		
Enabling Variables							
Health insurance							
Public	3,927 (20.3)	1.36 (1.22-1.51)	27.77	<0.0001	1.18 (0.88-1.58)	2.15	0.2528
No insurance	2,767 (14.3)	1.00 (0.88-1.15)	4.96	0.0260	0.83 (0.53-1.31)	1..31	0.2528
Private	12,652 (65.4)	—			—		
Need Variables							
Substance related diagnosis							
Yes	1,113 (5.8)	1.64 (1.39-1.94)	34.88	<0.0001	1.66 (1.28-2.14)	15.0	0.0001
No	18,192 (94.2)	—			—		
Serious mental illness							
Yes	371 (1.9)	1.52 (1.15-2.01)	8.46	0.0036	1.50 (0.98-2.28)	3.50	0.0614
No	18,975 (98.1)	—			—		
Non-SMI							
Yes	3,599 (18.6)	1.07 (0.97-1.20)	1.43	0.2324	0.97 (0.76-1.25)	0.054	0.8165
No	15,747 (81.4)	—			—		
Pre-existing health condition							
Yes	6,173 (31.9)	1.81 (1.65-1.98)	162.73	<0.0001	1.78 (1.38-2.30)	19.27	<0.0001
No	13,173 (68.1)						

β = standardized betas, SE(β) = standard errors, CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data and analysis of variance (ANOVA) for continuous data.

Table 1.3: Unmatched and matched unadjusted analysis of substance related diagnoses associated with preterm delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,346).

	Preterm delivery Unmatched cohort (n= 19,346)				Preterm delivery matched cohort (n= 2,158)			
Parameter	Yes n (%)	No n (%)	Odds Ratio 95% (CI)	X^2	Yes n (%)	No n (%)	Odds Ratio 95% (CI)	X^2
Any substance related diagnosis								
Yes	185 (8.6)	928 (5.4)	1.64 (1.39-1.94)	34.88***	171 (60.9)	908 (48.4)	1.66 (1.28-2.14)	15.0***
No	1,974 (91.4)	16,259 (94.6)	__		110 (39.2)	969 (51.6)	__	
Alcohol								
Yes	22 (1.0)	90 (0.5)	2.00 (1.22-3.12)	7.89***	21 (7.5)	88 (4.7)	1.64 (1.00-2.69)	3.88*
No	2,137 (99.0)	17,097 (99.5)	__		260 (92.5)	1,789 (95.3)	__	
Opioids								
Yes	46 (2.1)	177 (1.0)	2.09 (1.51-2.90)	19.54***	44 (15.7)	170 (9.1)	1.86 (1.30-2.67)	11.61***
No	2,113 (97.9)	17,010 (99.0)	__		237 (84.3)	1,707 (90.9)	__	
Cannabis								
Yes	56 (2.6)	302 (84.4)	1.49 (1.15-1.99)	7.30**	296 (15.8)	53 (18.9)	1.24 (0.99-1.72)	1.72
No	2,103 (97.4)	16,885 (88.9)	__		1,581 (84.2)	228 (81.1)	__	
Stimulants								
Yes	76 (3.5)	240 (1.4)	2.58 (1.98-3.35)	50.14***	67 (23.8)	232 (12.4)	2.22 (1.63-3.02)	25.94***
No	2,083 (96.5)	16,947 (98.6)	__		214 (76.2)	1,645 (87.6)		
Nicotine								
Yes	60 (2.8)	304 (1.8)	1.59 (1.20-2.10)	10.42***	56 (19.9)	298 (15.9)	1.32 (0.96-1.81)	2.91
No	2,099 (97.2)	16,883 (98.2)	__		225 (80.1)	1,579 (84.1)	__	
Non-specific substance and other								
Yes	59 (2.7)	299 (1.7)	1.59 (1.20-2.11)	10.24***	59 (17.8)	299 (15.8)	1.15 (0.85-1.57)	0.82
No	2,100 (97.3)	16,888 (98.3)	__		273 (82.2)	1,595 (84.2)	__	

Non-specific substance and other include sedatives only (ICD-10 F13.xx), hallucinogens/inhalants only (ICD-10 F16.xx/F18.xx), and other psychoactive substance related disorders (F19.xx). SD = standard deviation, CI = confidence interval. P-values based on Chi-square (X^2) tests of significance for categorical data. Variable totals may not sum to column totals due to missing data. P-value significance * = $P \leq 0.05$, ** = $P \leq 0.01$, *** = $P \leq 0.001$

Table 1.4: Unmatched and matched adjusted analysis of the Andersen Model covariates associated with a preterm delivery among women with a documented delivery from a Southern California health system's electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,346).

	Preterm delivery unmatched cohort (n=18,423)				Preterm delivery matched cohort (n = 2,152)			
Parameter	*B*	SE (β)	Adjusted Odds Ratio (95% CI)	X^2/F	*B*	SE (β)	Adjusted Odds Ratio (95% CI)	X^2/F
All								
Predisposing Variables								
Age at delivery (range 18-44)	0.01	0.00	1.01 (1.00-1.02)	6.74**				
Race/ethnicity								
Hispanic/Latina	0.03	0.06	1.57 (1.32-1.88)	0.26	-0.02	0.16	1.34 (0.84-2.14)	0.11
Non-Hispanic/Latina Black	0.25	0.69	1.95 (1.61-2.36)	12.71***	0.15	0.15	1.59 (1.04-2.43)	1.00
Other	0.14	0.04	1.75 (1.57-1.95)	11.95***	0.18	0.11	1.64 (1.21-2.21)	2.82
Non-Hispanic/Latina White	—				—			
Marital status								
Single	0.09	0.57	1.34 (1.01-1.49)	2.66	0.11	0.12	1.25 (0.93-1.67)	0.75
Divorced, separated, widowed	0.10	0.10	1.35 (1.01-1.49)	1.14	0.01	0.21	1.13 (0.59-2.15)	0.00
Married	—				—			
BMI at delivery	0.00	0.00	1.00 (1.00-1.00)	1.23				
Parity								
No previous pregnancies	0.16	0.04	1.37 (1.17-1.59)	15.91***				
≥ 1 previous pregnancy	—							
Enabling Variables								
Health insurance								
Public	0.12	0.04	1.18 (1.05-1.33)	8.56**				
No insurance	0.07	0.05	0.97 (0.84-1.12)	2.31				
Private	—							
Need Variables								
Substance related diagnosis								
Yes	0.11	0.05	1.25 (1.04-1.51)	5.48**	0.23	0.07	1.60 (1.20-2.14)	10.10**
No	—				—			
Serious mental illness								
Yes	0.11	0.08	1.25 (0.92-1.69)	2.06				
No	—							
Pre-existing health condition								
Yes	0.26	0.02	1.69 (1.53-1.86)	110.00***	0.29	0.07	1.78 (1.37-2.32)	18.29***
No	—				—			

β = standardized betas, SE(β) = standard errors, CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data and analysis of variance (ANOVA) for continuous data. P-value significance * = P ≤ 0.05, ** = P ≤ 0.01, *** = P ≤ 0.001

Table 1.5: Unmatched and matched unadjusted analysis of the Andersen Model covariates associated with a cesarean delivery among women with a documented delivery from a Southern California electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,303).

Parameter	Cesarean delivery unmatched cohort (n=19,303)			Cesarean delivery matched cohort (n = 2,154)		
	Total n (%)/ Mean (SD)	Cesarean delivery n (%)/ Mean (SD)	Vaginal delivery n (%)/ Mean (SD)	Total n (%)/ Mean (SD)	Cesarean delivery n (%)/ Mean (SD)	Vaginal delivery n (%)/ Mean (SD)
All	19,303 (100.0)	5,847 (30.3)	13,456 (69.7)	2,158 (100.0)	833 (38.7)	1,321 (61.3)
Predisposing Variables						
Age at delivery (range 18-44)	31.0 (5.4)	31.9 (5.5)	30.6 (5.3)	29.9 (5.6)	30.8 (5.6)	29.3 (5.5)
Race/ethnicity						
Hispanic/Latino	1,539 (8.2)	496 (8.8)	1,043 (8.0)	201 (9.6)	80 (9.9)	121 (9.4)
Non-Hispanic/Latina Black	1.054 (5.6)	410 (2.2)	644 (4.9)	211 (10.8)	95 (11.7)	116 (9.1)
Other	7,991 (42.6)	2,630 (46.5)	5,361 (40.9)	815 (38.9)	317 (39.1)	498 (38.9)
Non-Hispanic/Latina White	8.174 (43.6)	2,116 (37.4)	6,058 (46.8)	866 (41.4)	319 (29.3)	547 (42.7)
Marital status						
Single	5,306 (27.5)	1,809 (31.0)	3,497 (26.0)	1,015 (47.3)	418 (50.4)	597 (42.3)
Divorced, separated, widowed	418 (2.2)	177 (3.0)	241 (1.8)	88 (4.1)	49 (5.9)	39 (3.0)
Married	13,554 (70.3)	3,848 (66.0)	9,706 (72.2)	1,045 (48.7)	362 (43.7)	683 (51.8)
BMI at delivery	31.0 (6.5)	31.4 (7.7)	30.2 (5.8)	32.6 (7.6)	34.4 (8.3)	31.4 (6.8))
Parity						
No previous pregnancies	16,732 (86.7)	5,238 (89.7)	11,494 (85.4)	1,982 (92.0)	774 (92.9)	1,208 (91.4)
≥ 1 previous pregnancy	2,571 (13.3)	609 (10.4)	1,962 (14.6)	172 (8.0)	59 (7.1)	113 (8.6)
Enabling Variables						
Health insurance						
Public	3,914 (20.3)	1,302 (22.3)	2,612 (19.4)	481 (22.3)	199 (23.9)	282 (21.4)
No insurance	2,766 (14.3)	813 (13.9)	1,953 (14.5)	212 (9.8)	81 (9.7)	131 (9.9)
Private	12,623 (65.3)	3,732 (63.8)	8,891 (66.1)	1,461 (67.8)	553 (66.4)	908 (68.7)
Need Variables						
Substance related diagnosis						
Yes	1,111 (5.8)	487 (8.3)	624 (4.6)	1,077 (50.0)	477 (57.3)	600 (45.5)
No	1,8192 (94.2)	5,360 (91.7)	12,832 (95.4)	1,077 (50.0)	356 (42.7)	721 (54.6)
Serious mental illness						
Yes	370 (1.9)	158 (2.7)	212 (1.6)	162 (7.5)	82 (9.8)	80 (6.1)
No	18,933 (98.1)	5,689 (97.3)	13,244 (98.4)	1,992 (92.5)	751 (90.2)	1,241 (93.9)
Non-SMI						
Yes	3,590 (18.6)	1,236 (21.1)	2,354 (17.5)	708 (32.9)	287 (34.5)	421 (31.9)
No	15,713 (81.4)	4,611 (78.9)	11,102 (82.5)	1,446 (67.1)	546 (65.6)	900 (68.1)
Pre-existing health condition						
Yes	6,160 (31.9)	2,552 (43.7)	3,608 (26.8)	1,076 (49.9)	493 (59.2)	583 (44.1)
No	13,143 (68.1)	3,295 (56.3)	9,848 (73.2)	1,078 (50.1)	340 (40.8)	738 (55.9)

n (19,303) differs from total 19,346 because 43 had abortive delivery without cesarean or vaginal delivery. Age at delivery by cesarean delivery: n = 5,890, median = 32, range = 18-44. Age at delivery by vaginal delivery: n = 13,499, median = 31, range = 18-44. BMI at delivery by cesarean delivery: n = 5,796, median = 30.4, range = 15.0-83.5. BMI at delivery by vaginal delivery: n= 13,217, median = 29.0, range = 14.4-101.2. Matched age at delivery by cesarean delivery: n = 837, median = 31, range = 18-44. Matched age at delivery by vaginal delivery: n = 1,325, median = 29, range = 18-44. Matched BMI at delivery by cesarean delivery: n = 837, median = 32.8, range = 20.1-72.3. Matched BMI at delivery by vaginal delivery: n= 1,325, median = 30.2, range = 14.4-101.2. Variable totals may not sum to column totals due to missing data.

Table 1.6: Unmatched and matched unadjusted analysis of the Andersen Model covariates associated with a cesarean delivery among women with a documented delivery from a Southern California electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,303).

		Cesarean delivery unmatched cohort (n=19,303)			Cesarean delivery matched cohort (n = 2,154)		
Parameter	Total n (%)/Mean (SD)	Odds Ratio 95% (CI)	X^2/F	P	Odds Ratio 95% (CI)	X^2/F	P
All	19,303 (100.0)						
Predisposing Variables							
Age at delivery (range 18-44)	31.0 (5.4)	1.05 (1.04-1.05)	222.35	<0.0001	1.05 (1.04-1.07)	38.56	<0.0001
Race/ethnicity							
Hispanic/Latino	1,543(8.2)	1.36 (1.21-1.53)	0.01	0.9359	1.13 (0.83-1.55)	0.02	0.9133
Non-Hispanic/Latina Black	1,058 (5.6)	1.82 (1.60-2.08)	33.14	<0.0001	1.40 (1.04-1.90)	3.19	0.0739
Other	8,006 (42.6)	1.40 (1.31-1.50)	0.95	0.3288	1.09 (0.90-1.33)	0.45	0.5031
Non-Hispanic/Latina White	8,193 (43.6)	—			—		
Marital status							
Single	5,321 (27.5)	1.31 (1.22-1.40)	0.53	0.4670	1.32 (1.12-1.58)	1.41	0.2352
Divorced, separated, widowed	418 (2.2)	1.85 (1.52-2.26)	23.16	<0.0001	2.37 (1.53-3.70)	10.89	0.0010
Married	13,582 (70.3)	—			—		
BMI at delivery (range 14.4-101.2)	31.0 (6.5)	1.07 (1.06-1.07)	720.67	<0.0001	1.05 (1.04-1.07)	73.08	<0.0001
Parity							
No previous pregnancies	16,770 (86.7)	1.48 (1.33-1.62)	60.65	<0.0001	1.23 (0.88-1.70)	1.51	0.2205
≥ 1 previous pregnancy	2,576 (13.3)	—			—		
Enabling Variables							
Health insurance							
Public	3,927 (20.3)	1.19 (1.10-1.28)	18.43	<0.0001	1.16 (0.94-1.43)	1.37	0.2426
No insurance	2,767 (14.3)	0.99 (0.91-1.09)	4.18	<0.0001	1.02 (0.76-1.37)	0.15	0.6987
Private	12,652 (65.4)	—			—		
Need Variables							
Substance related diagnosis							
Yes	1,111 (5.8)	1.87 (1.65-2.11)	99.67	<0.0001	1.61 (1.35-1.92)	28.50	<0.0001
No	18,192 (94.2)	—			—		
Serious mental illness							
Yes	371 (1.9)	1.74 (1.41-2.14)	26.89	<0.0001	1.69 (1.23-2.34)	10.35	0.0013
No	18,975 (98.1)	—			—		
Non-SMI							
Yes	3,599 (18.6)	1.26 (1.17-1.37)	35.67	<0.0001	1.18 (0.99-1.41)	45.87	0.0725
No	15,747 (81.4)	—			—		
Pre-existing health condition							
Yes	6,173 (31.9)	2.11 (1.98-2.25)	521.87	<0.0001	1.84 (1.54-2.19)	45.87	<0.0001
No	13,173 (68.1)	—			—		

n (19,303) differs from total 19,346 because 43 had abortive delivery without cesarean or vaginal delivery. SD = standard deviation, CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data and analysis of variance (ANOVA) for continuous data. Variable totals may not sum to column totals due to missing data.

Table 1.7: Unmatched and matched unadjusted analysis of substance related diagnoses associated with cesarean delivery among women with a documented delivery from a Southern California electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,303).

	Cesarean delivery unmatched cohort (n=19,303)				Cesarean delivery matched cohort (n = 2,154)			
Parameter	Yes	No	Odds Ratio 95% (CI)	X^2	Yes	No	Odds Ratio 95% (CI)	X^2
Any substance related diagnosis								
Yes	487 (8.3)	624 (4.6)	1.87 (1.65-2.11)	99.67***	477 (57.3)	600 (45.4)	1.61 (1.35-1.92)	28.5***
No	5,360 (91.7)	12, 832 (95.4)	__		356 (42.7)	721 (54.6)	__	
Alcohol								
Yes	45 (0.8)	67 (0.5)	1.55 (1.06-2.26)	5.14*	44 (5.3)	65 (4.9)	1.08 (0.73-1.60)	0.14
No	5,802 (99.2)	13,389 (99.5)	__		789 (94.7)	1,256 (95.1)	__	
Opioids								
Yes	95 (1.6)	128 (1.0)	1.72 (1.32-2.25)	15.81***	93 (11.2)	121 (9.2)	1.13 (0.94-1.70)	2.29
No	5,752 (98.4)	13,328 (99.0)	__		740 (88.8)	1,200 (90.8)	__	
Cannabis								
Yes	139 (2.4)	218 (1.6)	1.48 (1.19-1.83)	12.72***	136 (16.3)	212 (16.1)	1.02 (0.81-1.29)	0.03
No	5,708 (97.6)	13,238 (98.4)	__		697 (83.7)	1,109 (84.0)	__	
Stimulants								
Yes	162 (2.8)	154 (1.1)	2.46 (1.97-3.08)	62.82***	157 (18.9)	142 (10.8)	1.93 (1.51-2.46)	27.40***
No	5,685 (97.2)	13,302 (98.9)	__		676 (81.2)	1,179 (89.3)	__	
Nicotine								
Yes	170 (2.9)	192 (1.4)	2.07 (1.68-2.55)	46.60***	168 (20.2)	184 (13.9)	1.56 (1.24-1.97)	14.41***
No	5,677 (97.1)	13,264 (98.6)	__		665 (79.8)	1,137 (86.1)	__	
*Non-specific substance and other**								
Yes	176 (3.0)	182 (1.4)	2.26 (1.84-2.79)	58.40***	173 (20.8)	172 (61.3)	1.75 (1.40-2.21)	22.45***
No	5,671 (97.0)	13,274 (98.7)			660 (79.2)	1,149 (87.0)		

*Other substances only include sedatives only (ICD-10 F13.xx), hallucinogens/inhalants only (ICD-10 F16.xx/F18.xx), and other psychoactive substance related disorders (F19.xx). SD = standard deviation, CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data and analysis of variance (ANOVA) for continuous data. P-value significance * = P ≤ 0.05, ** = P ≤ 0.01, *** = P ≤ 0.001Variable totals may not sum to column totals due to missing data.

Table 1.8: Unmatched and matched adjusted analysis of the Andersen Model covariates associated with a cesarean delivery among women with a documented delivery from a Southern California electronic medical record from April 1st, 2011-September 30th, 2019 (n= 19,303).

	Cesarean delivery unmatched cohort (n=18,381)				Cesarean matched cohort (n = 2,148)			
Parameter	B	SE (β)	Adjusted Odds Ratio (95% CI)	X^2	B	SE (β)	Adjusted Odds Ratio (95% CI)	X^2
All								
Predisposing Variables								
Age at delivery (range 18-44)	0.06	0.00	1.06 (1.06-1.07)	328.95***	0.05	0.01	1.05 (1.03-1.07)	33.34***
Race/ethnicity								
Hispanic/Latina	-0.03	0.05	1.16 (1.02-1.32)	0.41				
Non-Hispanic/Latina Black	0.14	0.05	1.38 (1.19-1.60)	6.82**				
Other	0.66	0.03	1.28 (1.19-1.37)	4.66*				
Non-Hispanic/Latina White	—							
Marital status								
Single	-0.01	0.04	1.13 (1.04-1.23)	0.04	-0.04	0.09	1.17 (1.00-1.44)	0.16
Divorced, separated, widowed	0.14	0.07	1.31 (1.06-1.63)	3.70*	0.23	0.15	1.54 (1.00-2.45)	2.29
Married	—							
BMI at delivery	0.06	0.00	1.06 (1.06-1.07)	493.15***	0.05	0.01	1.05 (1.04-1.07)	63.25***
Parity								
Nulliparity	0.21	0.03	1.56 (1.41-1.73)	71.53***				
≥ 1 previous pregnancy	—							
Enabling Variables								
Health insurance								
Public	0.05	0.03	1.13 (1.04-1.23)	3.08				
No insurance	0.02	0.03	1.10 (0.99-1.21)	0.33				
Private	—							
Need Variables								
Substance related diagnosis								
Yes	0.22	0.03	1.56 (1.35-1.79)	37.85***	0.21	0.05	1.51 (1.23-1.85)	15.60***
No	—				—			
Serious mental illness								
Yes	0.10	0.06	1.23 (0.97-1.55)	2.99	0.08	0.11	1.20 (0.85-1.69)	1.03
No	—				—			
Pre-existing health condition								
Yes	0.29	0.02	1.80 (1.68-1.93)	272.64***	0.29	0.07	1.67 (1.39-2.01)	30.21***
No	—				—			

β = standardized betas, SE(β) = standard errors, CI = confidence interval, P-value significance * = P ≤ 0.05, ** = P ≤ 0.01, *** = P ≤ 0.001

REFERENCES

1. Center for Disease Control and Prevention, Hamilton BE, Osterman MJK, Driscoll AK, Rossen LM. Births : provisional data for 2017. 2018. https://stacks.cdc.gov/view/cdc/55172. Accessed May 9, 2019.

2. Campbell KH, Savitz D, Werner EF, et al. Maternal Morbidity and Risk of Death at Delivery Hospitalization. *Obstet Gynecol*. 2013;122(3):627-633. doi:10.1097/AOG.0b013e3182a06f4e

3. Small MJ, James AH, Kershaw T, Thames B, Gunatilake R, Brown H. Near-Miss Maternal Mortality. *Obstet Gynecol*. 2012;119(2, Part 1):250-255. doi:10.1097/AOG.0b013e31824265c7

4. Hinkle SN, Sharma AJ, Kim SY, et al. Prepregnancy Obesity Trends Among Low-Income Women, United States, 1999–2008. *Matern Child Health J*. 2012;16(7):1339-1348. doi:10.1007/s10995-011-0898-2

5. Fisher SC, Kim SY, Sharma AJ, Rochat R, Morrow B. Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003–2009. *Prev Med (Baltim)*. 2013;56(6):372-378. doi:10.1016/j.ypmed.2013.02.015

6. Kelly RH, Russo J, Holt VL, et al. Psychiatric and substance use disorders as risk factors for low birth weight and preterm delivery. *Obstet Gynecol*. 2002;100(2):297-304. doi:10.1016/S0029-7844(02)02014-8

7. Corsi DJ, Walsh L, Weiss D, et al. Association Between Self-reported Prenatal Cannabis Use and Maternal, Perinatal, and Neonatal Outcomes. *JAMA*. 2019;322(2):145. doi:10.1001/jama.2019.8734

8. Forray A, Foster D. Substance Use in the Perinatal Period. *Curr Psychiatry Rep*. 2015;17(11):91. doi:10.1007/s11920-015-0626-5

9. Chapman SLC, Wu L-T. Substance Use among Adolescent Mothers: A Review. *Child Youth Serv Rev*. 2013;35(5):806-815. doi:10.1016/j.childyouth.2013.02.004

10. Bailey BA, Sokol RJ. Prenatal Alcohol Exposure and Miscarriage, Stillbirth, Preterm Delivery, and Sudden Infant Death Syndrome. *Alcohol Res Heal*. 2011;34(1):86. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3860553/. Accessed April 28, 2020.

11. Robinson,Julian N., Norwitz, Errol R., Lockwood, Charles J., Barss VA. *Preterm Birth: Risk Factors, Interventions for Risk Reduction, and Maternal Prognosis*.; 2020. https://www.uptodate.com/contents/preterm-birth-risk-factors-interventions-for-risk-reduction-and-maternal-prognosis/print. Accessed April 29, 2020.

12. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid Use Disorder

Documented at Delivery Hospitalization — United States, 1999–2014. *MMWR Morb Mortal Wkly Rep*. 2018;67(31):845-849. doi:10.15585/mmwr.mm6731a1

13. National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. *Sex and Gender Differences in Substance Use*.; 2018. https://www.drugabuse.gov/publications/drugfacts/substance-use-in-women.

14. Maeda A, Bateman BT, Clancy CR, Creanga AA, Leffert LR. Opioid Abuse and Dependence during Pregnancy: Temporal Trends and Obstetrical Outcomes. *Anesthesiology*. 2014;121(6):1158-1165. doi:10.1097/ALN.0000000000000472

15. SMID MC, METZ TD, GORDON AJ. Stimulant Use in Pregnancy: An Under-recognized Epidemic Among Pregnant Women. *Clin Obstet Gynecol*. 2019;62(1):168-184. doi:10.1097/GRF.0000000000000418

16. Fisher BL, Schauer P. Medical and surgical options in the treatment of severe obesity. *Am J Surg*. 2002;184(6):S9-S16. doi:10.1016/S0002-9610(02)01173-X

17. McCabe SE, Teter CJ, Boyd CJ. Medical Use, Illicit Use and Diversion of Prescription Stimulant Medication. *J Psychoactive Drugs*. 2006;38(1):43-56. doi:10.1080/02791072.2006.10399827

18. Gyllenhaal C, Merritt SL, Peterson SD, Block KI, Gochenour T. Efficacy and safety of herbal stimulants and sedatives in sleep disorders. *Sleep Med Rev*. 2000;4(3):229-251. doi:10.1053/SMRV.1999.0093

19. Arnsten AFT. Stimulants: Therapeutic Actions in ADHD. *Neuropsychopharmacology*. 2006;31(11):2376-2383. doi:10.1038/sj.npp.1301164

20. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5

21. Ivanov LL. Use of a Western Theoretical Model to Investigate the Relationships Among Characteristics of Pregnant Women, Utilization, and Satisfaction with Prenatal Care Services in St. Petersburg, Russia. *Public Health Nurs*. 2000;17(2):111-120. doi:10.1046/j.1525-1446.2000.00111.x

22. LaVeist TA, Keith VM, Gutierrez ML. Black/white differences in prenatal care utilization: an assessment of predisposing and enabling factors. *Health Serv Res*. 1995;30(1):43-58. http://www.ncbi.nlm.nih.gov/pubmed/7721584. Accessed April 29, 2019.

23. Hatzenbuehler ML, Keyes KM, Narrow WE, Grant BF, Hasin DS. Racial/ethnic disparities in service utilization for individuals with co-occurring mental health and substance use disorders in the general population: results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry*. 2008;69(7):1112-1121.

http://www.ncbi.nlm.nih.gov/pubmed/18517286. Accessed April 29, 2019.

24. Gouin K, Murphy K, Shah PS. Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses. *Am J Obstet Gynecol*. 2011;204(4):340.e1-340.e12. doi:10.1016/J.AJOG.2010.11.013

25. National Conference of State Legislatures. State Medical Marijuana Laws. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed June 21, 2019.

26. ICD10Data.com. 2019 ICD-10-CM Codes. https://www.icd10data.com/ICD10CM/Codes. Accessed May 14, 2019.

27. eMDs. ICD 10 Code for Pregnancy: OB-GYN. http://www.e-mds.com/revenue-cycle-management-age-icd-10-primer-ob-gyn. Accessed May 9, 2019.

28. Ho DE, Imai K, King G, Stuart EA. Matching as Nonparametric Preprocessing for Reducing Model Dependence in Parametric Causal Inference. *Polit Anal*. 2007;15(3):199-236. doi:10.1093/pan/mpl013

29. Iacus SM, King G, Porro G. Causal Inference without Balance Checking: Coarsened Exact Matching. *Polit Anal*. 2012;20(1):1-24. doi:10.1093/pan/mpr013

30. Creanga AA, Berg CJ, Ko JY, et al. Maternal Mortality and Morbidity in the United States: Where Are We Now? *J Women's Heal*. 2014;23(1):3-9. doi:10.1089/jwh.2013.4617

31. Blanc J, Resseguier N, Goffinet F, et al. Association between gestational age and severe maternal morbidity and mortality of preterm cesarean delivery: a population-based cohort study. *Am J Obstet Gynecol*. 2019;220(4):399.e1-399.e9. doi:10.1016/J.AJOG.2019.01.005

32. Almario C V., Seligman NS, Dysart KC, Berghella V, Baxter JK. Risk factors for preterm birth among opiate-addicted gravid women in a methadone treatment program. *Am J Obstet Gynecol*. 2009;201(3):326.e1-326.e6. doi:10.1016/J.AJOG.2009.05.052

33. Bohnert ASB, Zivin K, Welsh DE, Kilbourne AM. Ratings of Patient–Provider Communication Among Veterans: Serious Mental Illnesses, Substance Use Disorders, and the Moderating Role of Trust. *Health Commun*. 2011;26(3):267-274. doi:10.1080/10410236.2010.549813

34. Lemon LS, Naimi A, Caritis SN, Platt RW, Venkataramanan R, Bodnar LM. The Role of Preterm Birth in the Association Between Opioid Maintenance Therapy and Neonatal Abstinence Syndrome. *Paediatr Perinat Epidemiol*. 2018;32(2):213-222. doi:10.1111/ppe.12443

35. Dysart, K., Hsieh, H. C., Kaltenbach, K., & Greenspan JS. Sequela of preterm versus term infants born to mothers on a methadone maintenance program: differential course of neonatal abstinence syndrome. *J Perinat Med*. 2007;35(4):344-346. https://www.degruyter.com/view/journals/jpme/35/4/article-p344.xml. Accessed April 28, 2020.

36. Admon LK, Bart G, Kozhimannil KB, Richardson CR, Dalton VK, Winkelman TNA. Amphetamine- and Opioid-Affected Births: Incidence, Outcomes, and Costs, United States, 2004–2015. *Am J Public Health*. 2019;109(1):148-154. doi:10.2105/AJPH.2018.304771

37. Bateman BT, Franklin JM, Bykov K, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naïve women. *Am J Obstet Gynecol*. 2016;215(3):353.e1-353.e18. doi:10.1016/J.AJOG.2016.03.016

38. Yang J, Baer RJ, Berghella V, et al. Recurrence of Preterm Birth and Early Term Birth. *Obstet Gynecol*. 2016;128(2):364. doi:10.1097/AOG.0000000000001506

39. Lisonkova S, Potts J, Muraca GM, et al. Maternal age and severe maternal morbidity: A population-based retrospective cohort study. *PLoS Med*. 2017;14(5). doi:10.1371/JOURNAL.PMED.1002307

40. Timofeev J, Reddy UM, Huang C-C, Driggers RW, Landy HJ, Laughon SK. Obstetric Complications, Neonatal Morbidity, and Indications forCesarean Delivery by Maternal Age. *Obstet Gynecol*. 2013;122(6):1184. doi:10.1097/AOG.0000000000000017

41. Bhattacharya S, Campbell DM, Liston WA, Bhattacharya S. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. *BMC Public Health*. 2007;7(1):168. doi:10.1186/1471-2458-7-168

42. Dietz PM, Callaghan WM, Morrow B, Cogswell ME. Population-Based Assessment of the Risk of Primary Cesarean Delivery Due to Excess Prepregnancy Weight Among Nulliparous Women Delivering Term Infants. *Matern Child Health J*. 2005;9(3):237-244. doi:10.1007/s10995-005-0003-9

43. Austin PC. Some Methods of Propensity-Score Matching had Superior Performance to Others: Results of an Empirical Investigation and Monte Carlo simulations. *Biometrical J*. 2009;51(1):171-184. doi:10.1002/bimj.200810488

CHAPTER 3: SEVERE MATERNAL MORBIDITY AMONG WOMEN WHO PRESENTED FOR DELIVERY WITH AND WITHOUT A SUBSTANCE RELATED DIAGNOSIS

ABSTRACT:

Background: Pregnant women with a substance related diagnosis (SRD) are a vulnerable population who may be experiencing higher prevalence of severe maternal morbidity (SMM; e.g., hemorrhage) compared to pregnant women without an SRD. The **primary goals** of this paper are to evaluate the prevalence and trends of SMM in women who presented for delivery with and without an SRD in a large healthcare system.

Methods: This retrospective study retrieved electronic medical record data on women (ages ≥ 18 and ≤ 44 years) who delivered a single live or stillbirth at ≥ 20 weeks of gestation from March 1st, 2016-August 30th, 2019. Women without an SRD were matched at a 1:1 ratio. The Andersen Model was applied to guide the analysis and structure patient characteristics using predisposing, enabling, and need covariates. Adjusting for these covariates, we calculated odds ratios and 95% confidence intervals for SMM. The trend in SMM prevalence in those with and without an SRD was also assessed.

Results: In the unmatched cohort of 10,125 deliveries, participants were non-Hispanic/Latina White (42.7%) or other race/ethnicity (42.6%) with a mean age of 31 (standard deviation (SD) =5.4, range 18-44 years of age). In total, an SRD and SMM was identified in 692 (6.8%) and 558 (5.5%) women respectively. In the matched adjusted regression (n=1,341), having an SRD (adjusted odds ratio (AOR) = 1.81 [95% CI, 1.14-2.88], p-value = 0.0124) and pre-existing health condition (AOR = 3.21 [95% CI, 1.96-5.26], p-value = <0.0001) were associated with having SMM. In the matched cohort, SMM prevalence increased from 72 (12.9%) to 100 (17.9%) women with and without and SRD from March 2016 to August 2019. The observed increase in SMM prevalence was not found to be significantly associated with SRD.

Conclusions: Having an SRD and a pre-existing condition were significantly associated with SMM. However, there was not a significant difference in the observed increase in SMM prevalence over time in the SRD and non-SRD groups. Further research on how to screen for and prevent SMM in pregnant women with and without an SRD is warranted.

INTRODUCTION:

Pregnant women with a substance related diagnosis (SRD; i.e., use, misuse, abuse, or dependence of substances) are a vulnerable and stigmatized population who may be experiencing disproportionate rates and trends of severe maternal morbidity (SMM) compared to pregnant women without an SRD. SMM is a term that refers to life-threatening labor and delivery outcomes that result in significant short- or long-term consequences to a woman's health (e.g., blood transfusions, eclampsia).[1] The Center for Disease Control and Prevention (CDC) and other clinical and public partners developed a list of 21 SMM diagnoses or procedures during delivery hospitalizations and their associated 10th revision of the International Classification of Diseases (ICD-10) codes (Table B in the appendix).[1] The CDC reported a 200% increase of SMM in the United States from 1993-2014 (49.5 to 144.0 per 10,000 delivery hospitalizations).[1] In 2014, SMM affected more than 50,000 women nationally.[1] This large increase was mostly driven by blood transfusions (likely due to hemorrhaging) which increased 399% (rate from 24.5 to 122.3 per 10,000 delivery hospitalizations). When blood transfusions are excluded, the most common SMM are hysterectomies or ventilation (55% increase) or temporary tracheostomy (93% increase) resulting in nearly a 20% overall increase (rate from 28.6 to 35.0) in SMMs.[1]

These increases in SMM may be due to the changes in the population of women giving birth. For example, increases in maternal age,[2] chronic conditions (e.g., hypertension),[3,4] obesity,[5,6] and cesarean delivery[2,7] have been identified in the literature. Research has shown that chronic hypertension and pregestational diabetes are also common during pregnancy and can lead to the development of preeclampsia or eclampsia (a type of SMM).[3] Increasing rates of SMM lead to increased adverse outcomes for women, increased medical costs, and longer hospital stays.[8]

Earlier and ongoing studies have provided a rich understanding of fetal and birth outcomes associated with substance use in the perinatal period (i.e., pregnancy and postpartum).[8,9] However, less is known about the prevalence and trends of SMM in the context of women who presented for

delivery with an SRD. This gap in knowledge is likely due to the focus on neonatal outcomes (e.g., opioid related neonatal abstinence syndrome (NAS)) rather than maternal outcomes. The prevalence and trends of SMM among pregnant women with an SRD who presented for delivery in the United States are currently not available.

Limited and disrupted prenatal care, psychiatric comorbidities (e.g., anxiety), prenatal polysubstance use, and environmental stressors (e.g., unstable home) are also common and have been found to lead to adverse maternal outcomes.[10]

Health behavior models can be used to guide and structure analyses of adverse maternal health outcomes. The Andersen health behavior model has been used to investigate health service utilization through predisposing (sociodemographic characteristics), enabling (economic characteristics), and need (health outcomes) factors.[11] The predisposing factors reflect characteristics that may impact an individual's ability to attain healthcare services. The enabling factors represent the resources that may facilitate access to health services. Finally, the need factors reflect potential needs such as chronic health conditions or self-perceived health. By assessing the predisposing, enabling, and need covariates, this model can identify which of these levels have the greatest impact on SMM. This model has been used to investigate utilization of prenatal care services,[12] racial/ethnic differences in prenatal care utilization,[13] and racial/ethnic differences in health service utilization for individuals with co-occurring mental health and SRDs.[14]

Currently, there is a significant gap in the literature on the relationship between maternal substance use and SMMs. Evaluating associations between an SRD and SMM among women who presented for could inform future improvements in maternal health and clinical care for this vulnerable population. As such, the **primary goals** of this research were to evaluate whether there are associations between an SRD and SMM among women who presented for delivery and assess trends of SRD and SMM from 2016-2019. The **primary outcomes** include SMM (yes/no) and 2) SMM prevalence rate from 2016-2019. Because blood transfusions are the most common form of

SMM, the **secondary outcome** variable is blood transfusion (yes/no) during the perinatal period (time from ≥ 20 weeks of gestation to 4 weeks after delivery). Covariates include the Andersen Model's predisposing, enabling, and need variables (Figure 3.1). It was hypothesized that pregnant women with an SRD will be more likely to have SMM (Hypothesis 2a [**H2a**]) and will be experiencing increased prevalence of SMM over time compared to women without an SRD (Hypothesis 2c [**H2c**]). It was also hypothesized that pregnant women with an SRD will be more likely to have blood transfusions compared to pregnant women without an SRD (Hypothesis 2b [**H2b**]).

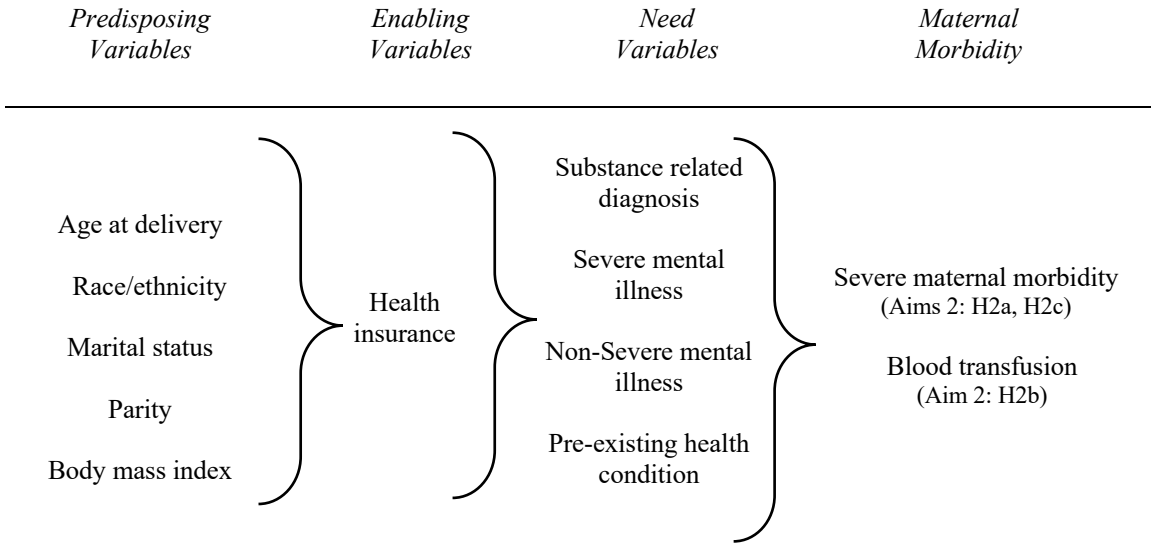

Figure 3.1: Conceptual model adapted from the Andersen Model to investigate how predisposing, enabling, and need variables impact severe maternal morbidity in pregnant women in a large healthcare system from March 1st, 2016-August 30th, 2019.

METHODS

Study Participants and Procedures

Deidentified electronic medical record (EMR) data on any woman (age 18 – 44) who delivered a single live or stillbirth at ≥ 20 weeks of gestation was collected from a large health system in Southern California from March 1st, 2016 (42 weeks after the procedure codes (different

from diagnosis codes) for blood transfusions (the largest SMM indicator) became available in the EMR at the study site) through the date the data was requested from the EMR team (August 30th, 2019; 3 years and 6 months). Because deidentified EMR data was requested without direct patient consent, ages ≥ 18 have been selected to protect adolescents who are considered an especially vulnerable population that may be at risk for identification due to small sample sizes.

Because pregnant women may engage with the health system at various stages of their pregnancy (1st, 2nd, 3rd, trimester or at delivery), only women with an International Classification of Diseases, 10th edition (ICD-10) code for delivery (Z37.xx) for a single live or stillborn after ≥ 20 weeks of gestation were used in the dataset for analysis. Deliveries of multiple gestation (e.g., twins) were omitted due to potential differences in maternal morbidity related to gestation. Medical record data was collected from the antepartum (conception to ≤42 weeks), intrapartum (labor and delivery), and postpartum (4 weeks from delivery) periods. Based on the CDC's recommendations, data was requested for the 4 weeks after delivery to capture maternal morbidity-related ICD-10 codes. When an individual record had more than one delivery carried to a gestational age of ≥ 20 weeks over the 3.5 years of data, each patient identification (PID) number and its unique delivery date represented one subject. The number of previous pregnancies for each delivery by PID was identified by delivery codes that appear before the most recent delivery in the dataset.

All medical diagnoses and procedures were identified using ICD-10 Clinical Modification (CM) and Procedure Coding System (PCS) codes. A full list of the codes used to meet the aim of this study can be found in **Table A-B** in the appendix. ICD-10 CM codes are assigned to prenatal encounters and at labor and delivery.[15] ICD-10 CM uses "Z" codes to identify reasons for encounters (Z3A.xx for specific week of gestation, Z34.xx for supervision/routine prenatal visit of normal pregnancy by trimester). Each trimester is counted from the first day of the patient's last menstrual period: first trimester (0-13 weeks), second trimester (14-28 weeks), and third trimester (28-42

weeks).[16] Therefore, a Z3A.40 code would indicate 40 weeks' gestation and Z34.03 would indicate an encounter for supervision of normal first pregnancy, third trimester.[16] A code for Z37.xx represents the outcome of delivery (e.g., single live birth, single still birth, twins' live birth etc.) and should be included on every maternal record when a delivery has occurred. Complications in pregnancy and childbirth are identified using "O" codes and include a routine visit for high-risk pregnancy (O09.xx), full-term normal delivery without complications (O80), and complications in labor and delivery (O67.xx-O77.xx). ICD-10 PCS codes are used to identify procedures such as blood transfusions (e.g., 30233H1). These codes were used to create the SMM variable outlined in Table B.

ICD-10 codes for SRDs and other mental illness diagnosis correspond with the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), which provides a more detailed description of each diagnosis. An SRD and other mental illness diagnoses may be included in a patient chart during any outpatient visit (e.g., prenatal visit with their obstetrician, psychiatric visit), inpatient visit (e.g., hospitalization), emergency department visit (e.g., delivery), or during one of the many other types of healthcare related visits.

The Human Research Protection Program (HRPP) and the Institutional Review Board (IRB) approved the study protocol. All of the data was collected from the health center's biomedical informatics team through their standardized data request process. Data was provided in a secured Health Insurance Portability and Accountability Act (HIPAA) approved Virtual Research Desktop (VRD; supported by the National Institute of Health, Grant UL1TR001442 of CTSA Funding). The VRD interface is protected by multi-factor authentication and is managed and monitored by the biomedical informatics team. Servers are behind firewalls configured to allow access only to credentialed personnel within the network. No removable media services were used with this data. All of the data was electronic and was not accessible to the internet.

Measures

Outcome measures: The **primary outcomes** are any of the CDC's 21 SMM indicators identified by ICD-10 CM and PCS codes during the perinatal period (conception to 4 weeks post-delivery; yes/no; Table B) and SMM prevalence rate from 2016-2019. Because blood transfusions are the most common form of SMM, the **secondary outcome** of interest is blood transfusion (yes/no). SMM may be included in a patient chart during any clinical outpatient visit (e.g., primary, obstetric, psychiatric), emergency department visit (e.g., delivery), or inpatient stay (e.g., hospitalization).

Predictor variables: The **primary predictor** variable is pre-existing and/or new **SRD** (yes/no) during the antepartum and intrapartum period. The SRD variable was grouped into the Andersen Model's *need* category but was the main predictor variable of interest. The **secondary predictors** include alcohol related diagnosis (F10.xx; yes/no), opioid related diagnosis (F11.xx; yes/no), cannabis related diagnosis (F12.xx; yes/no), stimulants related diagnosis (F14.xx [cocaine], F15.xx [other stimulants]; yes/no), nicotine related diagnosis (F17.xx; yes/no), and non-specific SRDs (F19.xx) or other (F13.xx [sedatives], F16.xx [hallucinogens], F18.xx [inhalants]). SRDs that were only identified after the intrapartum period were not included in the analysis due to the potential cofounding associated with substance use after delivery.

Andersen Model Variables

Predisposing variables: **age** (18-44) and **race/ethnicity** (Hispanic/Latina, non-Hispanic/Latina Black, non-Hispanic/Latina White, and other race/ethnicity [American Indian/Alaskan Native, Asian/Pacific Islander, and other race or mixed]) at delivery were included in the predisposing category. On intake, patients are asked to include their race (e.g., Black, White) and ethnicity (e.g., African American, Caucasian) as separate categories. In the race and ethnicity categories, the EMR has the option of "other race or mixed" and "unknown" respectively. If neither of the race or ethnicity selections were listed as Hispanic/Latina, non-Hispanic/Latina Black or non-Hispanic/Latina White then they were grouped into the "other" category. Other predisposing

variables include **marital status** (single, divorced/separated/widowed, or married), and **body mass index** (BMI; calculated as weight in kilograms divided by height in meters squared) at delivery [Figure 2.1]). **Parity** (no previous pregnancies or ≥ 1 previous pregnancy carried to a gestational age of ≥ 20 weeks and ending in livebirth or stillbirth) was identified to assess the impact of previous pregnancies on maternal morbidity.

*Enabling variable**:*** Health insurance type at delivery was the enabling variable of interest (Figure 3.1). **Health insurance** was defined as private (e.g., commercial, managed care), public (e.g., Medicaid) and no insurance. Those who were grouped in the private insurance category could also have public insurance. However, those with grouped in the public insurance category did not have private insurance.

Need variables: Pre-existing illness before delivery represented the need variables and were identified using ICD-10 codes. A summary variable for **SMI** included bipolar (F31-F31.9), manic episode (F30-F30.9) major depressive disorder severe (F32.2-F32.3, F33.2-F33.2), schizophrenia (F20-F20.9), schizotypal disorder (F21-F21.9), persistent delusional disorder (F22), schizoaffective disorder (F25-F25.9; a full list can be found in the Table A in the appendix).

A summary variable for **non-SMI** included persistent mood disorder (F39), major depressive disorder mild or moderate (F32.0-F32.1, F32.4-F32.9, F33.0-F33.1, F33.4-F33.9), delusional disorders (F22), brief psychotic disorders (F23), other psychotic disorder not due to a substance or known physiologic condition (F28), unspecified psychosis (F29), reaction to severe stress, and adjustment disorders (includes post-traumatic stress syndrome (PTSD; F43-F43.9), obsessive compulsive disorder (F42-F42.9), phobic anxiety disorder (F40-F40.9), other anxiety disorder (F41-F41.9), eating disorder (F50-F50.9), specific personality disorder (F60-F60.9), or impulse disorder (F63-F63.9; a full list can be found in the Table A in the appendix).

A summary variable for **pre-existing health condition** included cardiovascular disease, diabetes (non-gestational), anemia, kidney failure, hypertension, lupus, epilepsy, pulmonary disease, cancer, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hepatitis c virus (HCV), and tuberculosis (TB; ICD-10 codes supplied on request).

Statistical Analysis

Descriptive statistics were first used to identify the number and type of the CDC's 21 SMM indicators during the perinatal period (≥ 20 weeks of gestation to 4 weeks after delivery), in women who presented for delivery. Summary variables for SMM (yes/no) and blood transfusion (yes/no) were created for any record with an ICD-10 code for SMM. The number and type of SRD during the antepartum period (≥ 20 weeks of gestation to delivery) were then identified and a summary variable for SRD (yes/no) was created for any record with an ICD-10 code for SRD. The type of SRD was then sub-grouped into independent categories for alcohol related diagnosis (yes/no), opioid related diagnosis (yes/no), cannabis related diagnosis (yes/no), stimulant related diagnosis (yes/no), nicotine related diagnosis (yes/no), and non-specific or other substances related diagnosis (yes/no).

In addition to the overall unmatched cohort of women with and without an SRD, women with an SRD in the sample were randomly matched to those without an SRD on key baseline characteristics using a propensity score method.[17] Specifically, imbalance in measured maternal sociodemographic and obstetrical characteristics between those with and without an SRD was attenuated using propensity score matching, yielding a matched 1:1 sample of 1,346 (673 with an SRD and 673 without an SRD).[18] Women who presented for delivery with and without an SRD were matched by age at delivery, BMI at delivery, parity (>1 previous pregnancy ending in livebirth or stillbirth; yes/no), pre-existing health condition (yes/no), and delivery year (2016-2019). Standardize mean differences were used to examine the balance of covariate distribution between the two groups.

Unadjusted and adjusted analyses of the Andersen Model covariates and the outcome measures (SMM and blood transfusions) were then conducted in the unmatched and matched cohorts using ANOVA for continuous data and X^2 tests of significance for categorical data. To determine the effect/magnitude of the associations, ORs were calculated and reported. Two-sided tests with p-values significant at ≥ 0.05 and OR 95% CIs that cross 1 indicating that there was no significant difference were used to determine whether a covariate would be included in the final adjusted regression model in both the unmatched and matched cohorts.

Multivariable logistic regression in the unmatched and matched cohorts was conducted to determine the Andersen Model covariates that were associated with having an SMM compared to those without an SMM (**H2a**). Standardized betas (β), standard errors (SE(β)), adjusted odds ratios (AOR) and the respective confidence intervals and p-values were reported.

Prevalence Rate Over Time

The prevalence rate of SMM from 2016-2019 among all women (**group 1**), women with an SRD (**group 2**), and women without an SRD (**group 3**) during the perinatal period were assessed and reported. A visual graphical depiction of the month-to-month prevalence, three-month prevalence, and six-month prevalence of SMM was also represented by a line graph comparing groups 2-3.

First, the SMM prevalence rate over time (2016-2019) was determined for women with and without an SRD from March 1st, 2016-August 30th, 2019 (3.5 years). The prevalence rate of SMM over time was first inspected graphically by delivery month. Because the one-month assessment proved to be too small to show meaningful relevance, three-month assessments (14 time points; e.g., March 2016-May 2016), and six-month assessments (7 time points; e.g., March 2016 – August 2016, September 2016 – March 2017) were reviewed and reported. Due to the unexpected decrease in SMM among those with an SRD during time point 5 in the six-month assessment (March 2018 to August 2018; Figure 3.4), a change-point analysis (CPT) was performed to identify whether the

unexpected break in the SRD prevalence was statistically relevant in the six-month assessment. We applied the Markov Chain Monte Carlo (MCMC) to create and fit Bayesian change-point models for the SMM data. The standardized mean of the change point (cp) was then reviewed to identify if it corresponds to the gap between time point 4 and 6. The posterior distribution of the changepoints were then visually inspected. The posterior distribution was assessed, and a kernel density plot was then generated to show the relative variability of the posterior distribution on the data plot. The Cochran and Armitage test was also conducted in both unmodified and modified trends to assess whether there was a significant monotonic relationship between SMM and delivery time in those with and without an SRD for the one-month and three-month assessments. All analyses were conducted with SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Sample Characteristics in the Unmatched Cohort

There was a total of 10,129 deliveries with an ICD-10 code for a single delivery at ≥ 20 weeks' gestation from March 1, 2016 to August 30, 2019. Four individuals were diagnosed with an SRD after delivery and were removed from the full dataset. In the final cohort of 10,125 deliveries, most were non-Hispanic/Latina White (42.7%) or other race/ethnicity (41.7%) with a mean age of 31.3 (standard deviation (SD) =5.3, range 18-44 years of age; **Table 2.1**). Most were married (71.0%), had no previous pregnancies (81.4%), had a mean BMI at delivery of 31.1 (SD = 6.6, range = 17.2-83.5), and had private health insurance (74.6%). SMI and non-SMIs were documented for 2.3% and 22.2% respectively. Of those with a non-SMI, 12.8% (n=1,298) had mild or moderate depressive disorder and 14.2% (n=1,436) had an anxiety disorder (not shown in tables). Pre-existing health conditions were documented for 34.3%. An SRD was documented in 692 (6.8%) deliveries.

Of these, any SRD for alcohol (0.8%), opioids (1.5%), cannabis (2.5%), stimulants (2.0%), nicotine (2.7%), or non-specific and other (1.8%) were identified (**Table 2.2**).

Prevalence and Correlates of SMM in the Unmatched Cohort

The CDC's list of 21 SMM indicators are identified in **Table 2.3**. Of the 10,125 deliveries in the unmatched cohort, an SMM diagnosis was documented for 558 (5.5%) deliveries. The most common include blood transfusions (n=227 [2.2%]), sepsis (n=111 [1.1%]), acute renal failure (n=84 [0.8%]), disseminated intravascular coagulation (n=79 [0.8%]) pulmonary edema/acute heart failure (n=40 [0.4%]), puerperal cerebrovascular disorders (n=38 [0.4%]) air and thrombotic embolism (n=36 [0.4%]), shock (29 [0.3%]) acute myocardial infarction (24 [0.2%]), eclampsia (19 [0.2%]), and hysterectomy (17 [0.2%]).

In the unmatched bivariate analysis, SMM was associated with being non-Hispanic/Latina Black (OR = 1.86 [95% CI, 1.33-2.60], p-value = 0.0144), divorced/separated/widowed (OR = 2.74 [95% CI, 1.77-4.26], p-value = 0.0003), a higher BMI at delivery (OR = 1.03 [95% CI, 1.01-1.04], p-value = <0.0001), no previous pregnancies (OR = 1.48 [95% CI, 1.15-1.89], p-value = 0.0020), SRD (OR = 1.84 [95% CI, 1.40-2.42, p-value = <0.0001), non-SMI (OR = 1.76 [95% CI, 1.47-2.12], p-value = <0.0001), and pre-existing health conditions (OR = 3.06 [95% CI, 2.57-3.64], p-value = <0.0001; **Table 2.1**). When grouped by SRD type, SMM was found to be associated with any alcohol related diagnosis (OR = 3.88 [95% CI, 2.16-6.97], p-value = <0.0001), stimulant related diagnosis (OR = 2.46 [95% CI, 1.60-3.77], p-value = <0.0001), nicotine related diagnosis (OR = 2.22 [95% CI, 1.51-3.29], p-value = <0.0001), and non-specific and other substance related diagnosis (OR = 2.31 [95% CI, 1.46-3.68], p-value = <0.0001; **Table 2.2**). Blood transfusions were not found to be associated with any SRD (OR = 1.25 [95% CI, 0.78-2.02, p-value = 0.3543; **Table 2.4**).

Sample Characteristics in the Matched Cohort

In the matched cohort, there was a total of 1,346 deliveries with an ICD-10 code for a single delivery at ≥ 20 weeks' gestation from March 1, 2016 to August 30, 2019. Most were non-

Hispanic/Latina White (42.6%) or other race/ethnicity (36.5%) with a mean age of 29.9 (standard deviation (SD) =5.6, range 18-44 years of age; **Table 2.5**). Most were married (48.8%) or single (46.6%), had a mean BMI of 32.3 (SD = 7.2, range = 17.2-83.5), had no previous pregnancies (90.2%), and had private health insurance (71.9%). Serious and non-SMIs were documented for 8.5% and 48.1% respectively. Pre-existing health conditions were documented for 51.9% due to matching. An SRD was documented in 673 (50.0%) deliveries. Of these, any SRD for alcohol (5.6%), opioids (10.6%), cannabis (17.9%), stimulants (14.3%), nicotine (19.2%), or non-specific and other (13.0%) were reported (**Table 2.6**).

Prevalence and Correlates of SMM in the Matched Cohort

In the matched bivariate analysis (n=1,346), SMM was associated with SRD (OR = 1.93 [95% CI, 1.26-3.00, p-value = 0.0032), non-SMI (OR = 1.67 [95% CI, 1.09-2.54], p-value = 0.0175), and pre-existing health conditions (OR = 3.27 [95% CI, 2.00-5.34], p-value = <0.0001; **Table 2.5**). When grouped by SRD type, SMM was found to be associated with alcohol related diagnosis (OR = 3.08 [95% CI, 1.63-5.84], p-value = 0.0006), stimulant related diagnosis (OR = 1.93 [95% CI, 1.17-3.20], p-value = 0.0105), nicotine related diagnosis (OR = 1.78 [95% CI, 1.11-2.85], p-value = 0.0159), and non-specific and other substance related diagnosis (OR = 1.91 [95% CI, 1.14-3.22], p-value = 0.0148; **Table 2.6**). Blood transfusions were not found to be associated with any SRD (OR = 1.29 [95% CI, 0.64-2.63, p-value = 0.4753; data not shown in tables).

Multivariable Associations with SMM in the Unmatched and Matched Cohorts

In the unmatched adjusted regression, being divorced/separated/widowed (Adjusted Odds Ratio (AOR) = 2.10 [95% CI, 1.33-3.32], p-value = 0.0045), no previous pregnancies (AOR = 1.42 [95% CI, 1.10-1.83], p-value = 0.0067), non-SMI (AOR = 1.56 [95% CI, 1.28-1.90], p-value = <0.0001), and pre-existing health condition (AOR = 2.76 [95% CI, 2.30-3.31], p-value = <0.0001) were significantly associated with having SMM (**Table 2.7)**.

In the matched adjusted regression (n=1,346), having an SRD (AOR = 1.81 [95% CI, 1.14-2.88], p-value = 0.0124) and pre-existing health condition (AOR = 3.21 [95% CI, 1.96-5.26], p-value = <0.0001) were significantly associated with having SMM (**Table 2.7)**.

Prevalence and Correlates of SMM Over Time in the Unmatched Cohort

In the unmatched cohort, SMM prevalence increased over the six-month delivery intervals from March 2016 to August 2019 (1-7 six-month timepoints; **Table 2.8**). From March 2016 to August 2019, SMM prevalence increased from 72 (12.9%) to 100 (17.9%). Despite in the observed increase in SMM over time, six-month delivery timepoints were not found to be significantly associated with SMM. An unexpected decrease in SMM was identified during September 2017-March 2019 to 70 (12.5%; Figure 2.1).

Prevalence and Correlates of SMM Over Time in the Matched Cohort

In the matched cohort, SMM prevalence increased over the six-month delivery intervals from March 2016 to August 2019 (1-7 six-month timepoints; **Table 2.9**). From March 2016 to August 2019, SMM increased from 72 (12.9%) to 100 (17.9%). Despite the observed increase in SMM over time, six-month delivery timepoints were not found to be significantly associated with SMM. An unexpected decrease in SMM (n= 70 [12.5%]) in those with an SRD was identified from September 2017 to March 2019 (Figure 3.4).

SMM Over Time in the Unmatched and Matched Cohort

During this time period, 558 (5.5%) were diagnosed with an SMM. The overall prevalence rate of SMM stayed about the same from 58.6 per 1,000 deliveries in 2016 to 59.0 per 1,000 deliveries in 2019 (P for trend is 0.9789).

In the trend analysis for all women, the Cochran and Armitage test did not show a significant increase in SMM by delivery month (n= 10,125, Z-value = -0.1019, p-value = 0.9188), 3-months (n= 10,125, Z-value = -0.0958, p-value = 0.9237), or 6-months (n= 10,125, Z-value = -0.1019, p-value = 0.9155) from March 2016-August 2019.

In the trend analysis for those with an SRD, the Cochran and Armitage test did not show a significant increase in SMM by delivery month (n= 692, Z-value = 0.4089, p-value = 0.6826), 3-months (n= 10,125, Z-value = 0.3505, p-value = 0.7260), or 6-months (n= 692, Z-value = 0.3128, p-value = 0.7544) from March 2016-August 2019.

In the trend analysis for those without an SRD, the Cochran and Armitage test did not show a significant increase in SMM by delivery month (n= 9,433, Z-value = -0.2359, p-value = 0.8135), 3-months (n= 10,125, Z-value = -0.2079, p-value = 0.8353), or 6-months (n= 9,433, Z-value = -0.2135, p-value = 0.8309) from March 2016-August 2019.

DISCUSSION

SRD and SMM

Using a large healthcare system-based pregnancy cohort, this retrospective study evaluated whether there is an association between an SRD and SMM among women who presented for delivery and assessed the prevalence rate of SRD and SMM from 2016-2019. In the matched adjusted regression, having an SRD was found to be associated with SMM. These findings are consistent with a recently published study investigating SMM hospitalizations in the United States, England, and Australia from 2008-2013. The study found that advanced maternal age, substance use, hypertension, and diabetes were strongly associated with SMM in all three countries.

Although blood transfusions represented the largest proportion of SMM in the current study sample, it was not found to be independently associated with SRD. This finding differs from the significant relationship between substance use and hemorrhaging identified in a study conducted in Iran, which found that hemorrhaging was more likely in those who reported substance use (7.5%; opium (63.0%), crack (20.0%), poly-substances (7.5%), heroin (3.9%), methamphetamines (3.9%), and cannabis (1.7%)) compared to those who did not report substance use (2.5%).[19] The observed differences in the relationship between SRD and blood transfusions in our study may be due to

regional differences in substance use and access to care between California and Iran.[19] The absence of a significant relationship in our study may also be related to the way ICD-10 disorders and procedure codes are used to classify hemorrhaging and blood transfusions in the EMR (e.g., procedures vs. clinical diagnoses). Future studies should investigate how different types of substances such as alcohol or stimulants impact hemorrhaging and identify methods for detecting pregnant women who may be at risk during clinical visits.

The associations observed between an SRD and SMM in this study may be related to other types of SMMs that were found to be more common in the SRD group. For example, the most common SMMs in this sample in order of prevalence after blood transfusions included sepsis, acute renal failure, disseminated intravascular coagulation, pulmonary edema/acute heart failure, puerperal cerebrovascular disorders, air and thrombotic embolism, shock, acute myocardial infarction, eclampsia, and hysterectomy. This ordered list differs from the CDC's national findings in 2014 which listed hysterectomies, ventilation, and temporary tracheostomies as the most common in the national sample. These differences may be due to improvements in assessments and prevention for hysterectomies, ventilation and temporary tracheostomies in the United States since 2014. Because the CDC did not account for SRD in their study, it is not clear how substance use impacted SMM nationally.

Differences in SMM type likely vary by SRD type (e.g., stimulants, nicotine). When the relationship between the SRD type and any SMM was examined in the bivariate analysis, alcohol, stimulant, nicotine, and non-specific and other (hallucinogens/inhalants) substance related diagnoses were significantly associated with SMM in the unmatched and matched cohorts. A similar association between alcohol and maternal morbidity was observed in a study that identified alcohol use as a predictor of vaginal bleeding in the first trimester of pregnancy.[20] Alcohol is one of the most commonly used substance in pregnant women and it is often used with other substances such as nicotine and cannabis.[21]

Stimulant use (i.e., cocaine, methamphetamines, ecstasy, prescription stimulants) has been increasing in the United States, and is now the second most common SRD in pregnant women.[22] A newly published study investigating the impact of amphetamine and opioid use on trends in incidence and maternal outcomes from 2005-2015 found that a higher incidence of SMM, preterm delivery, preeclampsia, and mortality was observed in the stimulant-related deliveries compared to the opioid-related deliveries.[23] Future research should investigate how stimulant use directly impacts maternal morbidity and if the impact differs by stimulant type (i.e., cocaine vs methamphetamines).

Earlier and ongoing studies have provided a rich understanding of adverse fetal and delivery outcomes associated with nicotine use in the perinatal period.[24] However, less is known about the direct impact of nicotine use on SMM. Smoking has been found to be associated with placental abruption (premature separation of the placenta before delivery).[25] Maternal risks associated with placental abruption included SMM outcomes such as obstetric hemorrhage, need for blood transfusions, emergency hysterectomy, disseminated intravascular coagulopathy and renal failure.[25–27] As mentioned previously, blood transfusions were not found to be significantly associated with any SRD or nicotine in the unmatched or matched cohorts. As the popularity of electronic cigarettes (e-cigarettes) continues to increase in the United States, additional research on the direct effects of maternal nicotine use and SMM is needed.[28]

Andersen Model Covariates

This study found that the Andersen Model's *need* covariates such as SRD and pre-existing health conditions were the strongest predictors of SMM. It is not surprising the pre-existing conditions were significantly associated with SMM in all the unmatched and matched unadjusted and adjusted analyses. Rates of women with chronic health conditions such as hypertension, cardiac disease and diabetes in the United States are increasing.[29] These types of pre-existing conditions can be exacerbated during pregnancy. For example, chronic hypertension and coronary artery disease in pregnant women have been shown to increase the risk of pre-eclampsia, myocardial infarction, and

mortality.[29] Pregnant women with an SRD and pre-existing health conditions should be identified and monitored closely by healthcare providers to prevent a potential SMM outcome.

SMM Over Time

Overall, SMM has been increasing over time in our sample of pregnant women with and without an SRD from March 2016 to August 2019. There was not a significant difference in the observed increase in SMM prevalence over time in the SRD (12.9%-17.9%) and non-SRD (12.2%-16.7%) groups. There was an observed decrease in SMM in those with an SRD and an increase in SMM in those without an SRD in mid-2018 (Figure 3.3-3.4). This unexpected decrease in SMM in the SRD group may be related to missing diagnoses for substance use in the SMM group. For example, it is possible that patients may have omitted their substance use or providers did not know how to appropriately diagnose an SRD at the time of the clinical visit. Assessments of trends in SMM in those with and without an SRD over a longer period of time would help researchers and healthcare providers monitor change over time and respond accordingly.

Study Strengths and Limitations

The research presented in this study addressed significant gaps in the literature on the relationship between an SRD and SMM in pregnant women who presented for delivery. This study is strengthened by the large sample size of women who presented for delivery with (n= 692 [6.8%]) and without (n= 9,433 [93.2%]) an SRD over 3.5 years of EMR data. Having access to a large health record dataset allows for in-depth review of the prevalence and correlates of SRDs and SMM. By using propensity score matching, we were able to control for confounding in the unstructured EMR data used in this study. As such, by matching on age at delivery, parity, pre-existing health condition, and delivery year, a greater portion of potential bias was eliminated when estimating the effects of SRD.

Because providers are required to enter all of the medical data in the EMR directly, a large amount of data (e.g., ICD-10 codes for diagnoses and procedures) can be captured over a long period

of time. Using EMR data allows for a unique perspective on maternal morbidities among a large sample of women with and without an SRD, which is focused on accurate diagnoses and outcomes instead of self-report. However, ICD-10 codes are designed to identify diagnoses and procedures for billing purposes which can lead to unspecified diagnosis coding. For example, some health-related diagnoses (e.g., SRD) may be missing or not adequately assigned in the EMR due to provider and patient reporting. This limitation is clearly observed in the way many SRDs are identified in the EMR as "non-specified substance related disorder" instead of a designated substance type (alcohol, opioids, etc.). Further exploration of the factors contributing to a clinical provider's decision to classify a patient with an SRD in this ambiguous category instead of a designated substance type would be helpful to improve code classification in the EMR. It would also be advantageous to clearly identify the severity of the SRD and other mental illnesses in the EMR.

The absence of a significant relationship between SRD and blood transfusions in our study may be related to the way ICD-10 disorders and procedure codes are used in the EMR. The procedure codes for blood transfusions used by the CDC to create the 21 SMM indicators were not made available in the EMR until a couple years after the EMR's inception. As such, there may be some discrepancies in the classification of blood transfusions and the subsequent SMM grouping variable. It would be beneficial to compare the specific codes for hemorrhaging and blood transfusions in the EMR to assess how they are coded and monitored and if the relationship between and SRD and hemorrhaging is observed. Generalizability of the relationship between SRD and SMM in this study is limited by the restriction to Southern California and to one healthcare system.

CONCLUSION:

Findings from this study show that having an SRD or a pre-existing health condition are strong predictors for SMM among pregnant women in Southern California. When stratified by substance type in the bivariate analysis, alcohol, stimulants, nicotine, and non-specific substance type

and other (hallucinogens/inhalants) were significantly associated with SMM in the unmatched and matched cohorts. Additional research on the type of substance (e.g., alcohol, opioids, stimulants) and how maternal health service utilization impacts SMM is needed to develop new interventions that can be applied in clinical settings. Additional research on role of SRDs on SMM is also needed to develop new interventions that identify the need covariates such as SRD and pre-existing conditions early in pregnancy to reduce the risk of SMM. Interventions should be tailored to meet the needs of this vulnerable population and inform future improvements in maternal health and clinical care.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contributions to this research by the Altman Clinical and Translational Research Institute's Virtual Research Desktop (VRD) analytics team and collaborators at University of California San Diego (supported by the National Institute of Health, Grant UL1TR001442 of CTSA Funding). This research is funded by Dr. Carla Marienfeld’s research funds through the department of Psychiatry at the University of California San Diego School of Medicine.

Table 2.1: Unmatched unadjusted analysis of factors associated with a severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

Parameter	Total n (%)/ Mean (SD)	Severe Maternal Morbidity n (%)/ Mean (SD)	No Severe Maternal Morbidity n (%)/ Mean (SD)	Odds Ratio 95% (CI)	X^2/F	P
All	10,125 (100.0)	558 (5.5)	9,567 (94.5)			
Predisposing Variables						
Age at delivery (range 18-44)	31.3 (5.3)	31.2 (5.4)	31.3 (5.3)	1.00 (0.98-1.01)	0.07	0.7808
Race/ethnicity						
Hispanic/Latino	961 (9.7)	55 (10.0)	906 (9.7)	1.32 (0.97-1.80)	0.14	0.7131
Non-Hispanic/Latino Black	584 (5.9)	46 (8.4)	538 (5.7)	1.86 (1.33-2.60)	6.00	0.0144
Other	4,147 (41.7)	261 (47.5)	3,886 (41.4)	1.46 (1.20-1.77)	0.66	0.4167
Non-Hispanic/Latino White	4,248 (42.7)	187 (34.1)	4,061 (43.2)	__		
Marital status						
Single	2,733 (27.0)	193 (34.7)	2,540 (26.6)	1.53 (1.27-1.83)	0.36	0.5477
Divorced, separated, widowed	200 (2.0)	24 (4.3)	176 (1.8)	2.74 (1.77-4.26)	12.86	0.0003
Married	7,175 (71.0)	340 (61.0)	6,835 (71.6)	__		
BMI at delivery (range 17.2-83.5)	31.1 (6.6)	32.3 (7.4)	31.1 (6.5)	1.03 (1.01-1.04)	17.82	<0.0001
Parity						
No previous pregnancies	8,243 (81.4)	482 (86.4)	7,761 (81.1)	1.48 (1.15-1.89)	9.52	0.0020
≥ 1 previous pregnancy	1,882 (18.6)	76 (13.6)	1,806 (18.9)	__		
Enabling Variables						
Health insurance						
Public	2,157 (21.3)	137 (24.6)	2,020 (21.1)	1.21 (0.99-1.47)	3.15	0.0761
No insurance	413 (4.1)	19 (3.4)	394 (4.1)	0.86 (0.54-1.38)	1.06	0.3042
Private	7,555 (74.6)	402 (72.0)	7,153 (74.8)	__		
Need Variables						
Substance related diagnosis						
Yes	692 (6.8)	64 (11.5)	628 (6.6)	1.84 (1.40-2.42)	19.35	<0.0001
No	9,433 (93.2)	494 (88.5)	8,939 (93.4)	__		
Severe mental illness						
Yes	229 (2.3)	19 (3.4)	210 (2.2)	1.57 (0.97-2.53)	3.43	0.0638
No	9,896 (97.7)	539 (96.6)	9,357 (97.8)	__		
Non-SMI						
Yes	2,243 (22.2)	182 (32.6)	2,061 (21.5)	1.76 (1.47-2.12)	36.64	<0.0001
No	7,882 (77.9)	376 (67.4)	7,506 (78.5)	__		
Pre-existing health condition						
Yes	3,472 (34.3)	334 (59.9)	3,138 (32.8)	3.06 (2.57-3.64)	157.23	<0.0001
No	6,653 (65.7)	224 (40.1)	6,429 (67.2)	__		

Age at delivery by SMM: n = 558, median = 31, range = 18-44. Age at delivery by non-SMM: n = 9,567, median = 32, range = 18-44. BMI at delivery by SMM: n = 548, median = 30.5, range = 17.2-71.5. BMI at delivery by non-SMM: n= 9,404, median = 29.7, range = 18.0-83.5

Table 2.2: Unmatched unadjusted analysis of substance related diagnoses associated with having severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

Parameter	Total n (%)	Severe Maternal Morbidity n (%)	No Severe Maternal Morbidity n (%)	Odds Ratio 95% (CI)	X^2/F	P
Any substance related diagnosis						
Yes	692 (6.8)	64 (11.5)	628 (6.6)	1.84 (1.40-2.42)	19.35	<0.0001
No	9,433 (93.2)	494 (88.5)	8,939 (93.4)	—		
Alcohol						
Yes	77 (0.8)	14 (2.5)	63 (0.7)	3.88 (2.16-6.97)	20.62	<0.0001
No	10,948 (99.2)	544 (97.5)	9,504 (99.3)			
Opioids						
Yes	147 (1.5)	9 (1.6)	138 (1.4)	1.12 (0.57-2.21)	0.11	0.7436
No	9,978 (98.6)	549 (98.4)	9,429 (98.6)			
Cannabis						
Yes	249 (2.5)	19 (3.4)	230 (2.4)	1.43 (0.89-2.30)	2.18	0.1399
No	9,876 (97.5)	539 (96.6)	18,015 (97.6)			
Stimulants						
Yes	204 (2.0)	25 (4.5)	179 (1.9)	2.46 (1.60-3.77)	17.03	<0.0001
No	9,921 (98.0)	533 (95.5)	9,388 (98.1)			
Nicotine						
Yes	268 (2.7)	30 (11.2)	238 (2.5)	2.22 (1.51-3.29)	16.22	<0.0001
No	9,857 (97.4)	528 (94.6)	9,329 (97.5)			
*Non-specific substance and other**						
Yes	180 (1.8)	21 (3.8)	159 (1.7)	2.31 (1.46-3.68)	12.60	0.0004
No	9,945 (98.2)	537 (96.2)	9,408 (98.3)			

*Other substances only include sedatives only (ICD-10 F13.xx), hallucinogens/inhalants only (ICD-10 F16.xx/F18.xx), and other psychoactive substance related disorders (F19.xx). SD = standard deviation, CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data. Variable totals may not sum to column totals due to missing data.

Table 2.3: Severe maternal morbidity indicators identified in women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

	Yes n (%)	No n (%)
Severe Maternal Morbidity	558 (5.5)	9,567 (94.5)
Blood transfusion	227 (2.24)	9,898 (97.76)
Sepsis	111 (1.10)	10,125 (98.90)
Acute renal failure	84 (0.83)	10,041 (99.17)
Disseminated intravascular coagulation	79 (0.78)	10,046 (99.2)
Pulmonary edema/Acute heart failure	40 (0.40)	10,085 (99.60)
Puerperal cerebrovascular disorders	38 (0.38)	10,087 (99.62)
Air and thrombotic embolism	36 (0.36)	10,089 (99.64)
Shock	29 (0.29)	10.096 (99.71)
Acute myocardial infarction	24 (0.24)	10,101 (99.76)
Eclampsia	19 (0.19)	10,106 (99.81)
Hysterectomy	17 (0.17)	10,108 (99.83)
Adult respiratory distress syndrome	13 (0.13)	10,112 (99.87)
Ventilation	13 (0.13)	10,112 (99.87)
Cardiac arrest/ventricular fibrillation	10 (0.10)	10,115 (99.910
Conversion of cardiac rhythm	9 (0.09)	10,116 (99.91
Aneurysm	4 (0.04)	10,121 (99.96)
Amniotic fluid embolism	2 (0.02)	10,123 (99.98)
Sickle cell disease with crisis	1 (0.01)	10.124 (99.99)
Heart failure/arrest during surgery or procedure	0 (0.00)	10,125 (100.00)
Severe anesthesia complications	0 (0.00)	10,125 (100.00)
Temporary tracheostomy	0 (0.00)	10,125 (100.00)

Table 2.4: Unmatched unadjusted analysis of pregnancy outcomes in those with and without a blood transfusion among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

Parameter	Total n (%)	Blood Transfusion Yes n (%)	Blood Transfusion No n (%)	Odds Ratio 95% (CI)	X^2	P
All	10,125 (100.0)	227 (2.2)	9,898 (97.8)			
Substance related diagnosi						
Yes	692 (6.8)	19 (8.4)	673 (6.8)	1.25 (0.78-2.02)	0.86	0.3543
No	9,433 (93.2)	208 (91.6)	9,225 (93.2)			

CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data.

Table 2.5: Matched unadjusted analysis of factors associated with a severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 1,346).

Parameter	Total n (%)/Mean (SD)	Severe Maternal Morbidity n (%)/Mean (SD)	No Severe Maternal Morbidity n (%)/Mean (SD)	Odds Ratio 95% (CI)	X^2/F	P
All	1,346 (100.0)	94 (7.0)	1,252 (93.0)			
Predisposing Variables						
Age at delivery (range 18-44)	29.9 (5.6)	29.9 (5.0)	29.9 (5.7)	1.00 (0.96-1.04)	0.00	0.9675
Race/ethnicity						
Hispanic/Latino	148 (11.2)	7 (7.5)	141 (11.5)	0.73 (0.31-1.67)	1.76	0.1841
Non-Hispanic/Latino Black	128 (9.7)	12 (12.8)	116 (9.45)	1.51 (0.76-3.00)	1.66	0.1977
Other	482 (36.5)	39 (41.5)	443 (36.1)	1.29 (0.81-2.06)	0.85	0.3575
Non-Hispanic/Latino White	563 (42.6)	36 (38.3)	527 (93.6)	__		
Marital status						
Single	625 (46.6)	50 (53.2)	575 (46.1)	1.49 (0.96-2.32)	0.07	0.7952
Divorced, separated, widowed	62 (4.6)	8 (8.5)	54 (4.3)	2.54 (1.13-5.75)	3.44	0.0636
Married	654 (48.8)	36 (38.3)	618 (49.6)	__		
BMI at delivery (range 17.2-83.5)	32.3 (7.2)	33 (8.6)	32.2 (7.1)	1.01 (1.00-1.04)	0.79	0.3750
Parity						
No previous pregnancies	1,214 (90.2)	85 (90.4)	1,129 (90.2)	1.03 (0.50-2.01)	0.01	0.9380
≥ 1 previous pregnancy	132 (9.8)	9 (5.6)	123 (9.8)	__		
Enabling Variables						
Health insurance						
Public	330 (24.5)	18 (19.2)	312 (24.9)	1.22 (0.37-4.03)	0.63	0.4262
No insurance	48 (3.6)	3 (3.2)	45 (3.6)	0.87 (0.25-3.06)	0.37	0.5287
Private	968 (71.9)	73 (77.7)	895 (71.5)	__		
Need Variables						
Substance related diagnosis						
Yes	673 (50.0)	61 (64.9)	612 (48.9)	1.93 (1.26-3.00)	8.71	0.0032
No	673 (50.0)	33 (35.1)	640 (51.1)	__		
Severe mental illness						
Yes	114 (8.5)	11 (11.7)	103 (8.2)	1.48 (0.76-2.86)	1.35	0.2459
No	1,232 (91.5)	83 (88.3)	1,149 (91.8)	__		
Non-SMI						
Yes	490 (36.4)	45 (47.9)	445 (35.5)	1.67 (1.09-2.54)	5.64	0.0175
No	856 (63.6)	49 (52.1)	807 (64.5)	__		
Pre-existing health condition						
Yes	698 (51.9)	72 (76.6)	626 (50.0)	3.27 (2.00-5.34)	22.47	<0.0001
No	648 (48.1)	22 (23.4)	626 (50.0)	__		

Age at delivery by SMM: n = 94, median = 30, range = 19-42. Age at delivery by non-SMM: n = 1,252, median = 30, range = 18-44. BMI at delivery by SMM: n = 94, median = 31, range = 20.4-71.5. BMI at delivery by non-SMM: n= 1,252, median = 30.8, range = 18.8-66.5.

Table 2.6: Matched unadjusted analysis of substance related diagnoses associated with having severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 1,346).

Parameter	Total n (%)	Severe Maternal Morbidity n (%)	No Severe Maternal Morbidity n (%)	Odds Ratio 95% (CI)	X^2/F	P
Any substance related diagnosis						
Yes	673 (50.0)	61 (64.9)	612 (48.9)	1.93 (1.26-3.00)	8.71	0.0032
No	673 (50.0)	33 (35.1)	640 (51.1)	—		
Alcohol						
Yes	75 (5.6)	13 (13.8)	62 (5.0)	3.08 (1.63-5.84)	11.91	0.0006
No	1,271 (94.4)	81 (86.2)	1,190 (95.0)	—		
Opioids						
Yes	142 (10.6)	9 (9.6)	133 (10.6)	0.89 (0.44-1.81)	0.10	0.7497
No	1,204 (89.5)	85 (90.4)	1,119 (89.4)	—		
Cannabis						
Yes	241 (17.9)	19 (20.2)	222 (17.7)	1.18 (0.70-1.99)	0.37	0.5454
No	1,105 (82.1)	75 (79.8)	1,030 (82.3)	—		
Stimulants						
Yes	193 (14.3)	22 (23.4)	171 (13.7)	1.93 (1.17-3.20)	6.56	0.0105
No	1,153 (85.7)	72 (76.6)	1,081 (86.3)	—		
Nicotine						
Yes	258 (19.2)	27 (28.7)	231 (18.5)	1.78 (1.11-2.85)	5.82	0.0159
No	1,088 (80.8)	67 (71.3)	1,021 (81.6)	—		
*Non-specific substance and other**						
Yes	175 (13.0)	20 (21.3)	155 (12.4)	1.91 (1.14-3.22)	5.94	0.0148
No	1,171 (87.0)	74 (87.7)	1,097 (87.6)	—		

*Other substances only include sedatives only (ICD-10 F13.xx), hallucinogens/inhalants only (ICD-10 F16.xx/F18.xx), and other psychoactive substance related disorders (F19.xx). SD = standard deviation, CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data. Variable totals may not sum to column totals due to missing data.

Table 2.7: Unmatched and matched adjusted logistic regression analysis of factors associated with a severe maternal morbidity among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019.

	Unmatched cohort (n=9,757)				Matched cohort (n = 1,341)			
Parameter	*B*	SE (β)	Adjusted Odds Ratio (95% CI)	X^2	*B*	SE (β)	Adjusted Odds Ratio (95% CI)	*P*
Race/ethnicity								
Hispanic/Latina	-0.01	0.12	1.19 (0.87-1.64)	0.01				
Non-Hispanic/Latina Black	0.10	0.13	1.33 (0.93-1.89)	0.57				
Other	0.10	0.08	1.33 (1.08-1.63)	1.70				
Non-Hispanic/Latina White	—							
Marital status								
Single	-0.12	0.09	1.19 (0.98-1.46)	1.90				
Divorced, separated, widowed	0.43	0.15	2.10 (1.33-3.32)	8.08*				
Married	—							
BMI at delivery	0.01	0.01	1.01 (1.00-1.02)	1.44	0.01	0.01	1.01 (0.98-1.04)	0.33
Parity								
No previous pregnancies	0.17	0.65	1.42 (1.10-1.83)	7.35***				
≥ 1 previous pregnancy	—							
Substance related diagnosis								
Yes	0.17	0.08	1.16 (0.85-1.57)	0.88	0.30	0.12	1.81 (1.14-2.88)	6.25**
No								
Non-SMI								
Yes	0.22	0.05	1.56 (1.28-1.90)	19.9***	0.12	0.11	1.28 (0.82-2.01)	1.70
No	—							
Pre-existing health condition								
Yes	0.51	0.05	2.76 (2.30-3.31)	117.91***	0.58	0.13	3.21 (1.96-5.26)	21.46***
No								

β = standardized betas, SE(β) = standard errors, CI = confidence interval, P-value significance * = P ≤ 0.05, ** = P ≤ 0.01, *** = P ≤ 0.001

Table 2.8: Unmatched unadjusted analysis of delivery six-month timepoint and substance related diagnosis among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

Parameter	Total n (%)	Severe Maternal Morbidity n (%)	No Severe Maternal Morbidity n (%)	Odds Ratio 95% (CI)	X^2	P
Delivery six-month timepoint						
March 2016 — August 2016	1,240 (12.3)	72 (12.9)	1,168 (12.2)	0.98 (0.72-1.34)	0.26	0.6072
September 2016 — March 2017	1,337 (13.2)	74 (13.3)	1,263 (13.2)	0.94 (0.69-1.27)	0.00	0.9525
March 2017 — August 2017	1,434 (14.2)	78 (14.0)	1,356 (14.2)	0.92 (0.68-1.24)	0.01	0.9125
September 2017 — March 2018	1,401 (13.8)	70 (12.5)	1,331 (13.9)	0.84 (0.61-1.15)	0.81	0.3673
March 2018 — August 2018	1,440 (14.2)	79 (12.5)	1,361 (14.2)	0.93 (0.68-1.25)	0.00	0.9793
September 2018 — March 2019	1,578 (15.6)	85 (14.2)	1,493 (15.6)	0.91 (0.67-1.22)	0.05	0.8312
March 2019 — August 2019	1,695 (15.6)	100 (17.9)	1,595 (16.7)	—		

SD = standard deviation, CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data and analysis of variance (ANOVA) for continuous data. Variable totals may not sum to column totals due to missing data.

Table 2.9: Matched unadjusted analysis of delivery six-month timepoint and substance related diagnosis among women with a documented delivery from a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 1,346).

Parameter	Total n (%)	Severe Maternal Morbidity n (%)	No Severe Maternal Morbidity n (%)	Odds Ratio 95% (CI)	X^2	P
Delivery six-month timepoint						
March 2016 — August 2016	167 (12.4)	12 (12.8)	155 (12.4)	0.86 (0.40-1.84)	0.04	0.8444
September 2016 — March 2017	182 (13.5)	9 (9.6)	173 (13.8)	0.58 (0.25-1.32)	1.23	0.2666
March 2017 — August 2017	176 (13.1)	13 (13,8)	163 (13.0)	0.89 (0.42-1.86)	0.10	0.7535
September 2017 — March 2018	187 (13.9)	11 (11.7)	176 (14.1)	0.69 (0.32-1.51)	0.32	0.5743
March 2018 — August 2018	207 (15.4)	13 (13.8)	194 (15.5)	0.75 (0.36-1.56)	0.12	0.7343
September 2018 — March 2019	209 (15.4)	18 (19.2)	191 (15.3)	1.05 (0.53-2.07)	1.13	0.2869
March 2019 — August 2019	218 (16.2)	18 (19.2)	200 (16.0)	—		

SD = standard deviation, CI = confidence interval, P-values based on Chi-square (X^2) tests of significance for categorical data and analysis of variance (ANOVA) for continuous data. Variable totals may not sum to column totals due to missing data.

Table 2.10: Changes over time in the unmatched cohort assessed with the Cochran-Armitage test by delivery month, three-months, and six-months in pregnant women with and without a substance related diagnosis in a Southern California health system's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

Parameter	Total Sample	Z-value	P
Delivery by month			
Total	10,125 (100.0)	-0.1019	0.9188
SRD	692 (5.5)	0.4089	0.6826
No-SRD	9,433 (95.5)	-0.2359	0.8135
Delivery by three-months			
Total	10,125 (100.0)	-0.0958	0.9237
SRD	692 (5.5)	0.3505	0.7260
No-SRD	9,433 (95.5)	0.3128	0.7544
Delivery by six-months			
Total	10,125 (100.0)	-0.1019	0.9155
SRD	692 (5.5)	0.3128	0.7544
No-SRD	9,433 (95.5)	-0.2135	0.8309

SRD = substance related diagnosis

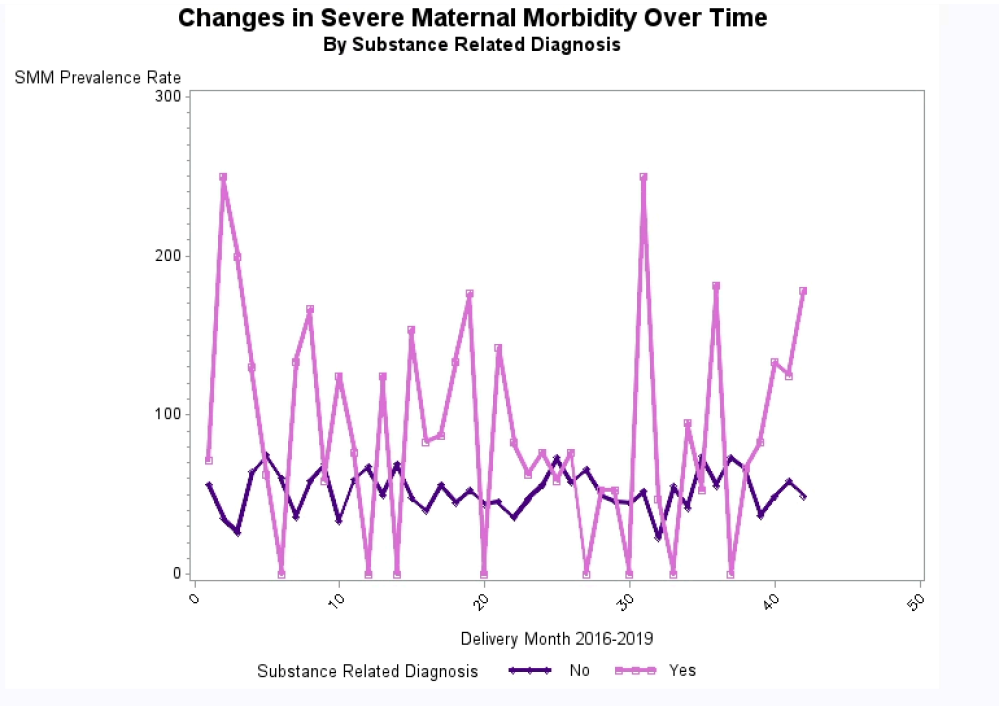

Figure 3.2: Prevalence rate of severe maternal morbidity (SMM; n = 558) by delivery month/year in 10,125 deliveries with (n= 692) and without (n=9,433) a substance related diagnosis (SRD) from a Southern California health system's electronic medical record (March 1st, 2016 - August 30th, 2019)

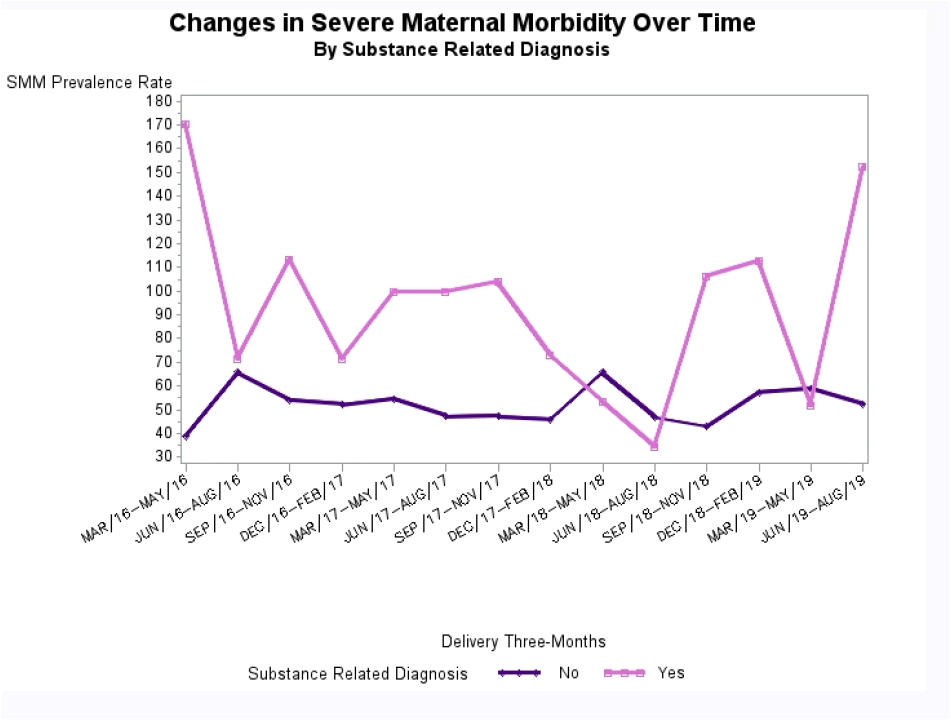

Figure 3.3: Prevalence rate of severe maternal morbidity (SMM; n = 558) by delivery month/year every three months in 10,125 deliveries with (n= 692) and without (n=9,433) a substance related diagnosis (SRD) from a Southern California health system's electronic medical record (March 1st, 2016 - August 30th, 2019)

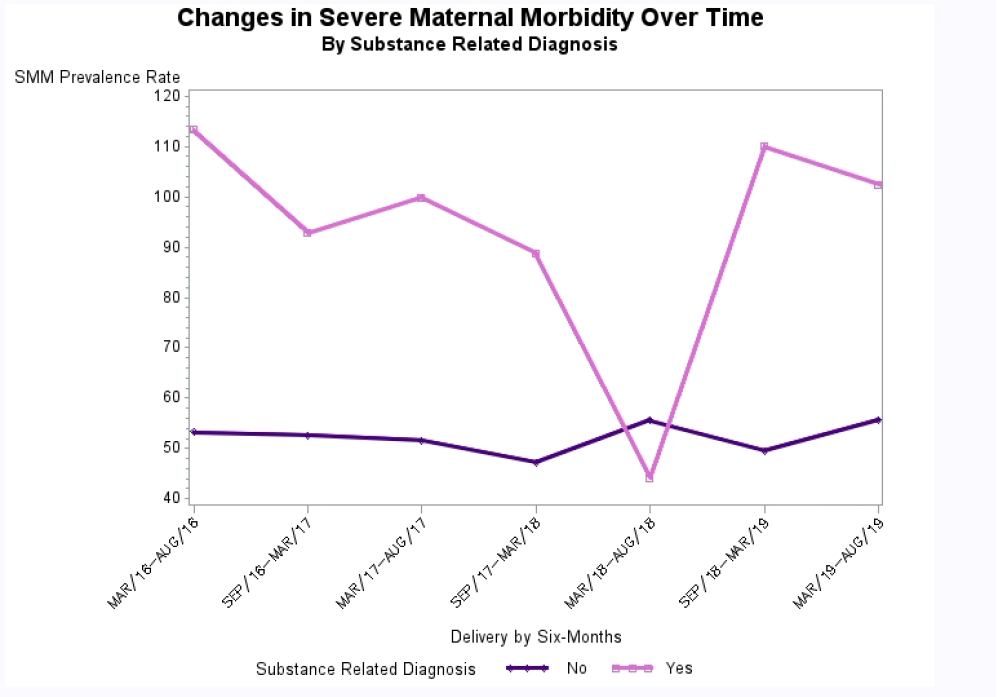

Figure 3.4: Prevalence rate of severe maternal morbidity (SMM; n = 558) by delivery month/year every six months in 10,125 deliveries with (n= 692) and without (n=9,433) a substance related diagnosis (SRD) from a Southern California health system's electronic medical record (March 1st, 2016 - August 30th, 2019)

REFERENCES

1. Division of Reproductive Health National Center for Chronic Disease Prevention and Health Propomotion Center for Disease Control and Prevention. *Severe Maternal Morbidity in the United States*.; 2017. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/severematernalmorbidity.html#anchor_References. Accessed May 9, 2019.

2. Center for Disease Control and Prevention, Hamilton BE, Osterman MJK, Driscoll AK, Rossen LM. Births : provisional data for 2017. 2018. https://stacks.cdc.gov/view/cdc/55172. Accessed May 9, 2019.

3. Campbell KH, Savitz D, Werner EF, et al. Maternal Morbidity and Risk of Death at Delivery Hospitalization. *Obstet Gynecol*. 2013;122(3):627-633. doi:10.1097/AOG.0b013e3182a06f4e

4. Small MJ, James AH, Kershaw T, Thames B, Gunatilake R, Brown H. Near-Miss Maternal Mortality. *Obstet Gynecol*. 2012;119(2, Part 1):250-255. doi:10.1097/AOG.0b013e31824265c7

5. Hinkle SN, Sharma AJ, Kim SY, et al. Prepregnancy Obesity Trends Among Low-Income Women, United States, 1999–2008. *Matern Child Health J*. 2012;16(7):1339-1348. doi:10.1007/s10995-011-0898-2

6. Fisher SC, Kim SY, Sharma AJ, Rochat R, Morrow B. Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003–2009. *Prev Med (Baltim)*. 2013;56(6):372-378. doi:10.1016/j.ypmed.2013.02.015

7. Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications Contributing to the Increasing Cesarean Delivery Rate. *Obstet Gynecol*. 2011;118(1):29-38. doi:10.1097/AOG.0b013e31821e5f65

8. Callaghan, W. M., Creanga, A. A., & Kuklina E V. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. *Obstet Gynecol*. 2012;120(5):1029-1036.

9. Priester MA, Browne T, Iachini A, Clone S, DeHart D, Seay KD. Treatment Access Barriers and Disparities Among Individuals with Co-Occurring Mental Health and Substance Use Disorders: An Integrative Literature Review. *J Subst Abuse Treat*. 2016;61:47-59. doi:10.1016/j.jsat.2015.09.006

10. Forray A. Substance use during pregnancy. *F1000Research*. 2016;5. doi:10.12688/f1000research.7645.1

11. Andersen R. A behavioral model of families' use of health services. *A Behav Model Fam use Heal Serv*. 1968;(25). https://www.cabdirect.org/cabdirect/abstract/19702701913. Accessed June 8, 2020.

12. Ivanov LL. Use of a Western Theoretical Model to Investigate the Relationships Among Characteristics of Pregnant Women, Utilization, and Satisfaction with Prenatal Care Services in St. Petersburg, Russia. *Public Health Nurs*. 2000;17(2):111-120. doi:10.1046/j.1525-

1446.2000.00111.x
13. LaVeist TA, Keith VM, Gutierrez ML. Black/white differences in prenatal care utilization: an assessment of predisposing and enabling factors. *Health Serv Res*. 1995;30(1):43-58. http://www.ncbi.nlm.nih.gov/pubmed/7721584. Accessed April 29, 2019.

14. Hatzenbuehler ML, Keyes KM, Narrow WE, Grant BF, Hasin DS. Racial/ethnic disparities in service utilization for individuals with co-occurring mental health and substance use disorders in the general population: results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry*. 2008;69(7):1112-1121. http://www.ncbi.nlm.nih.gov/pubmed/18517286. Accessed April 29, 2019.

15. ICD10Data.com. 2019 ICD-10-CM Codes. https://www.icd10data.com/ICD10CM/Codes. Accessed May 14, 2019.

16. eMDs. ICD 10 Code for Pregnancy: OB-GYN. http://www.e-mds.com/revenue-cycle-management-age-icd-10-primer-ob-gyn. Accessed May 9, 2019.

17. Ho DE, Imai K, King G, Stuart EA. Matching as Nonparametric Preprocessing for Reducing Model Dependence in Parametric Causal Inference. *Polit Anal*. 2007;15(3):199-236. doi:10.1093/pan/mpl013

18. Iacus SM, King G, Porro G. Causal Inference without Balance Checking: Coarsened Exact Matching. *Polit Anal*. 2012;20(1):1-24. doi:10.1093/pan/mpr013

19. Gargari SS, Fallahian M, Haghighi L, Hosseinnezhad-Yazdi M, Dashti E, Dolan K. Maternal and Neonatal Complications of Substance Abuse in Iranian Pregnant Women. *Acta Med Iran*. 2012;50(6):411-416. http://acta.tums.ac.ir/index.php/acta/article/view/3922. Accessed May 23, 2019.

20. Hasan R, Baird DD, Herring AH, Olshan AF, Jonsson Funk ML, Hartmann KE. Patterns and Predictors of Vaginal Bleeding in the First Trimester of Pregnancy. *Ann Epidemiol*. 2010;20(7):524-531. doi:10.1016/J.ANNEPIDEM.2010.02.006

21. Huizink AC. Moderate use of alcohol, tobacco and cannabis during pregnancy: New approaches and update on research findings. *Reprod Toxicol*. 2009;28(2):143-151. doi:10.1016/J.REPROTOX.2009.04.010

22. SMID MC, METZ TD, GORDON AJ. Stimulant Use in Pregnancy: An Under-recognized Epidemic Among Pregnant Women. *Clin Obstet Gynecol*. 2019;62(1):168-184. doi:10.1097/GRF.0000000000000418

23. Admon LK, Bart G, Kozhimannil KB, Richardson CR, Dalton VK, Winkelman TNA. Amphetamine- and Opioid-Affected Births: Incidence, Outcomes, and Costs, United States, 2004–2015. *Am J Public Health*. 2019;109(1):148-154. doi:10.2105/AJPH.2018.304771

24. McEvoy CT, Spindel ER. Pulmonary Effects of Maternal Smoking on the Fetus and Child: Effects on Lung Development, Respiratory Morbidities, and Life Long Lung Health. *Paediatr Respir Rev*. 2017;21:27-33. doi:10.1016/J.PRRV.2016.08.005

25. TIKKANEN M. Placental abruption: epidemiology, risk factors and consequences. *Acta Obstet Gynecol Scand*. 2011;90(2):140-149. doi:10.1111/j.1600-0412.2010.01030.x

26. Bodelon C, Bernabe-Ortiz A, Schiff MA, Reed SD. Factors Associated With Peripartum Hysterectomy. *Obstet Gynecol*. 2009;114(1):115. doi:10.1097/AOG.0B013E3181A81CDD

27. Tikkanen M, Gissler M, Metsäranta M, et al. Maternal deaths in Finland: Focus on placental abruption. *Acta Obstet Gynecol Scand*. 2009;88(10):1124-1127. doi:10.1080/00016340903214940

28. Mark KS, Farquhar B, Chisolm MS, Coleman-Cowger VH, Terplan M. Knowledge, Attitudes, and Practice of Electronic Cigarette Use Among Pregnant Women. *J Addict Med*. 2015;9(4):266-272. doi:10.1097/ADM.0000000000000128

29. Hirshberg A, Srinivas SK. Epidemiology of maternal morbidity and mortality. *Semin Perinatol*. 2017;41(6):332-337. doi:10.1053/J.SEMPERI.2017.07.007

CHAPTER 4: LATENT CLASSES OF SUBSATNCE RELATED DIAGNOSIS, MENTAL ILLNESS, PHYSICAL HEALTH CONDITIONS, AND SEVERE MATERNAL MORBIDITY AMONG PREGANT WOMEN

ABSTRACT:

Background: Pregnant women may be experiencing different patterns of substance related diagnoses (SRD), mental illness, physical health conditions, and severe maternal morbidity (SMM). The **primary goal** of this study is to characterize the patterns of SRD, mental illness, and physical health conditions by SMM and examine pattern correlates among women who presented for delivery from 2016-2019.

Methods: Data on women (ages ≥ 18 and ≤ 44 years) who delivered a single live or stillbirth at ≥ 20 weeks of gestation from March 1st, 2016-August 30th, 2019 was retrieved from the electronic medical record. Using latent class analysis (LCA), meaningful classes of SRDs, serious mental illness (SMI), non-SMI (e.g., depression), and pre-existing health conditions (e.g., cardiovascular disease) were identified to understand if discrete classes of co-morbidities would emerge in women with and without a SMM.

Results: A two-class solution for those with and without SMM best fit the data producing clinically distinct classes. In those with SMM, Class 1 represented high prevalence of co-occurring SRD, mental illness, and physical health conditions (11.5%) and Class 2 represented high prevalence of pre-existing health conditions (88.5%). In those without SMM, Class 1 represented moderate prevalence of co-occurring SRD, mental illness, and physical health conditions without SMM (6.0%) and Class 2 represented low prevalence of co-occurring mental illness and physical health conditions (94.0%). Compared to those with SMM in Class 2, Class 1 membership was associated with single marital status (adjusted odds ratio (AOR) = 5.19 [95% CI, 2.71-9.96], p-value = 0.0320) and inversely associated with Hispanic/Latina ((AOR) = 0.18 [95% CI, 0.05-0.64], p-value = 0.0445) or other race/ethnicity (AOR = 0.23 [95% CI, 0.12-0.47], p-value = 0.0123).

Conclusion: In those with and without SMM, SRDs were common in the groups with high and moderate co-occurring mental illness and physical health conditions. The proportion of SRD was higher in the those who had a SMM. Those with high co-occurring SRD, mental illness, and physical health conditions and SMM were more likely to be non-Hispanic/Latina White and single or divorced/separated/widowed.

INTRODUCTION:

Pregnant women with co-occurring substance related diagnoses (SRD), mental illness (e.g., depression), and physical health conditions (e.g., cardiovascular disease) may be experiencing different patterns of severe maternal morbidity (SMM) compared to pregnant women without these morbidities. SMM is a term that refers to adverse labor and delivery outcomes that result in significant short- or long-term consequences to a woman's health (e.g., hemorrhaging/blood transfusions, eclampsia). The Center for Disease Control and Prevention (CDC) and other clinical and public partners developed a list of 21 SMM diagnoses or procedures during delivery hospitalizations and their associated 10th revision of the International Classification of Diseases (ICD-10) codes.[1] From 1993-2014, SMM increased 200% in the United States (49.5 to 144.0 per 10,000 delivery hospitalizations) and affected more than 50,000 women in 2014.[1] These increases in SMM may be due to the changes in the population of women giving birth (e.g., maternal age,[2] chronic conditions [e.g., hypertension],[3,4] obesity,[5,6] and cesarean delivery[2,7]). Chronic hypertension and pregestational diabetes are also common during pregnancy and can lead to the development of preeclampsia or eclampsia (a type of SMM).[3] Increasing rates of SMM lead to increased adverse outcomes for women, increased medical costs, and longer hospital stays.[8]

SRD, serious mental illness (SMI; e.g., bipolar, severe major depressive disorder, schizophrenia) and non-SMI (e.g., mild/moderate major depressive disorder, anxiety) in pregnant women have been well documented in the literature.[9] One study found that pregnant women with co-occurring psychiatric symptoms (e.g., mood disorder, anxiety disorder, suicidal thinking, major depressive disorder, dysthymia, and symptoms consistent with a hypomanic episode) showed more severe impairment on the Addiction Severity Index compared to pregnant women without co-occurring symptoms.[10] In addition to co-occurring mental illness, co-occurring alcohol, opioid, cannabis, or stimulants related diagnoses may be occurring and impacting pregnant women

differently.[11] Co-occurring SRDs and mental illness in pregnant women are interrelated risk factors that that may lead to maternal morbidity.[12,13]

The prevalence of co-morbidities (e.g., hypertension, diabetes, asthma, thyroid disorders, obesity, mental illness, substance use, and tobacco use) among pregnant women has been increasing over time.[14] Rates of women with chronic health conditions such as hypertension, cardiac disease and diabetes in the United States are also increasing.[15] These types of pre-existing conditions can be exacerbated during pregnancy. For example, chronic hypertension and coronary artery disease in pregnant women have been shown to increase the risk of pre-eclampsia, myocardial infarction, and mortality.[15] One study found that pregnant women with chronic pre-existing conditions were two times more likely to develop SMM compared to those without a pre-existing condition.[16]

The independent relationships between mental illness, physical health conditions, and SMM have been established in earlier and ongoing studies[1,17,18] However, limited data are available on the patterns of co-occurring SRD, mental illness, and physical health conditions in pregnant women who develop SMM to characterize the heterogeneity of these health conditions. The current study provides a person-centered approach, using latent class analysis (LCA), to analyze co-occurring SRD, mental illness, and physical health conditions by SMM to identify groups of pregnant women who share similar risk characteristics.

As a subset of structural equation modeling (SEM), LCA is helpful to assess groups or subgroups of cases in complex multivariable categorical data.[19] This person-centered analysis places similar individuals in groups based on their similarities.[20] Latent variables are variables that are not directly observed but are inferred from other observed variables. These variables are error-free constructs and they show the shared variance among the measured variables in the analysis. As such, this type of analysis allows for the simultaneous evaluation of causal hypotheses from correlational, nonexperimental data and the effects of independent variables.[21] First, the probability that a person chosen at random will be in each class (i.e., prevalence of each latent class) and the probability of a

response to a given indicator (i.e., conditional on the latent class) is assessed. These classes are then categorized based on the prevalence of the unique latent classes and are assumed to be mutually exclusive and exhaustive.[22] As such, LCA identifies an individual's one true class. LCA was chosen to decrease the possible measurement error, oversimplification, or bias that may occur when definitions are developed to categorize complex behaviors and outcomes.[23] Other advantages of using LCA include the inclusion of covariates that may impact class membership.[19]

To address the current gap in knowledge of patterns of health conditions in pregnant women with and without SMM, the **primary goal** of this study is to characterize the extent and patterns of co-occurring SRD, mental illness, and physical health conditions by SMM and examine pattern correlates among women who presented for delivery.

To accomplish this goal, the **Andersen Model** was applied to guide and structure the analysis using **predisposing** (age, race/ethnicity, marital status, body mass index at delivery, parity (>1 previous pregnancy ending in livebirth or stillbirth), **enabling** (health insurance type), and **need** (SRD, SMI, non-SMI, pre-existing health conditions) covariates. The predisposing factors reflect characteristics that may impact an individual's ability to attain healthcare services. The enabling factors represent the resources that may facilitate access to health services. Finally, the need factors reflect potential needs such as chronic health conditions or self-perceived health. By assessing the predisposing, enabling, and need covariates, this model can identify which of these levels have the greatest impact on maternal health. This model has been used to investigate hospitalizations of homeless women, utilization of prenatal care services,[24] racial/ethnic differences in prenatal care utilization,[25] and racial/ethnic differences in health service utilization for individuals with co-occurring mental health and SRDs.[26]

This study used LCA to create meaningful latent classes based off the Andersen Model's *need* covariates (SRD, SMI, non-SMI, pre-existing health condition). The latent classes were stratified by SMM (yes/no) to identify how these *need* covariates were grouped in those with and

without SMM. It was hypothesized that having an SRD would strongly influence SMM class membership among pregnant women (Hypothesis 3a (**H3a)**).

METHODS

Study Participants and Procedures

Deidentified electronic medical record (EMR) data on any woman (age 18 – 44) who delivered a single live or stillbirth at ≥ 20 weeks of gestation was collected from a large health system in Southern California from March 1st, 2016 (42 weeks after the procedure codes for blood transfusions (the largest SMM indicator) became available in the EMR at the study site) through the date the data was requested from the EMR team (August 30th, 2019; 3 years and 6 months). Because deidentified EMR data was requested without direct patient consent, ages ≥ 18 have been selected to protect adolescents under the age of 18 who are considered an especially vulnerable population that may be identifiable due to small sample sizes.

Because pregnancy may be identified at various stages of the woman's pregnancy (1st, 2nd, 3rd, trimester or at delivery), only women with an International Classification of Diseases, 10th edition (ICD-10) code for delivery (Z37.xx) for a single live or stillborn after ≥ 20 weeks of gestation were used in the dataset for analysis. Deliveries of multiple gestation (e.g., twins) were omitted due to potential differences in maternal morbidity related to gestation. Medical record data was collected from the antepartum (conception to ≤42 weeks), intrapartum (labor and delivery), and postpartum (4 weeks from delivery) periods. Based on the CDC's recommendations, data was requested for the 4 weeks after delivery to capture maternal morbidity-related ICD-10 codes. When an individual record had more than one delivery carried to a gestational age of ≥ 20 weeks over the 3.5 years of data, each patient identification (PID) number and its unique delivery date represented one subject. The number

of previous pregnancies for each delivery by PID was identified by delivery codes that appear before the most recent delivery in the dataset.

All medical diagnoses and procedures were identified using ICD-10 Clinical Modification (CM) and Procedure Coding System (PCS) codes. A full list of the codes used to meet the aim of this study can be found in Table A-B in the appendix. ICD-10 CM codes are assigned to prenatal encounters and at labor and delivery.[27] ICD-10 CM uses "Z" codes to identify reasons for encounters (Z3A.xx for specific week of gestation, Z34.xx for supervision/routine prenatal visit of normal pregnancy by trimester). Each trimester is counted from the first day of the patient's last menstrual period: first trimester (0-13 weeks), second trimester (14-28 weeks), and third trimester (28-42 weeks).[28] Therefore, a Z3A.40 code would indicate 40 weeks' gestation and Z34.03 would indicate an encounter for supervision of normal first pregnancy, third trimester.[28] A code for Z37.xx represents the outcome of delivery (e.g., single live birth, single still birth, twins' live birth etc.) and should be included on every maternal record when a delivery has occurred. Complications in pregnancy and childbirth are identified using "O" codes and include a routine visit for high-risk pregnancy (O09.xx), full-term normal delivery without complications (O80), and complications in labor and delivery (O67.xx-O77.xx). ICD-10 PCS codes are used to identify procedures such as blood transfusions (e.g., 30233H1). These codes were used to create the SMM variable outlined in Table B.

ICD-10 codes for SRDs and other mental illness diagnoses correspond with the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), which provides a more detailed description of each diagnosis. An SRD and other mental illness diagnoses may be included in a patient chart during any outpatient visit (e.g., prenatal visit with their obstetrician, psychiatric visit), inpatient visit (e.g., hospitalization), emergency department visit (e.g., delivery), or during one of the many other types of healthcare related visits.

The Human Research Protection Program (HRPP) and the Institutional Review Board (IRB) approved the study protocol. All of the data was collected from the health center's biomedical informatics team through their standardized data request process. Data was provided in a secured Health Insurance Portability and Accountability Act (HIPAA) approved Virtual Research Desktop (VRD; supported by the National Institute of Health, Grant UL1TR001442 of CTSA Funding). The VRD interface is protected by multi-factor authentication and is managed and monitored by the biomedical informatics team. Servers are behind firewalls configured to allow access only to credentialed personnel within the network. No removable media services were used with this data. All of the data was electronic and was not accessible to the internet.

Measures

Outcome measure: The **primary outcome** is any of the CDC's 21 SMM indicators identified by ICD-10 CM and PCS codes during the perinatal period (conception to 4 weeks post-delivery; yes/no; Table B). SMM may be included in a patient chart during any clinical outpatient visit (e.g., primary, obstetric, psychiatric), emergency department visit (e.g., delivery), or inpatient (e.g., hospitalization).

Andersen Model Variables

Predisposing variables: **age** (18-44) and **race/ethnicity** (Hispanic/Latina, non-Hispanic/Latina Black, non-Hispanic/Latina White, and other race/ethnicity [American Indian/Alaskan Native, Asian/Pacific Islander, and other race or mixed]) at delivery were included in the predisposing category. On intake, patients are asked to include their race (e.g., Black, White) and ethnicity (e.g., African American, Caucasian) as separate categories. In the race and ethnicity categories, the EMR has the option of "other race or mixed" and "unknown" respectively. If neither of the race or ethnicity selections were listed as Hispanic/Latina, non-Hispanic/Latina Black or non-Hispanic/Latina White then they were grouped into the "other" category. Other predisposing variables include **marital status** (single, divorced/separated/widowed, or married), and **body mass**

index (BMI; calculated as weight in kilograms divided by height in meters squared) at delivery [Figure 2.1]). **Parity** (no previous pregnancies or ≥ 1 previous pregnancy carried to a gestational age of ≥ 20 weeks and ending in livebirth or stillbirth) was identified to assess the impact of previous pregnancies on maternal morbidity.

Enabling variable: Health insurance type at delivery was the enabling variable of interest. **Health insurance** was defined as private (e.g., commercial, managed care), public (e.g., Medicaid) and no insurance. Those with private insurance could also have public insurance. However, those with public insurance did not have private insurance.

Need variables used in the LCA: Pre-existing and/or new **SRD** (yes/no) during the antepartum and intrapartum period was the primary need variable of interest. Maternal exposure to substance use was identified with ICD-10 codes for SRDs, which includes substance use, abuse, dependence, and substance use disorders (F10.xx-F19.xx).

A summary variable for **non-SMI** included persistent mood disorder (F39), major depressive disorder mild or moderate (F32.0-F32.1, F32.4-F32.9, F33.0-F33.1, F33.4-F33.9), delusional disorders (F22), brief psychotic disorders (F23), other psychotic disorder not due to a substance or known physiologic condition (F28), unspecified psychosis (F29), reaction to severe stress, and adjustment disorders (includes post-traumatic stress syndrome (PTSD; F43-F43.9), obsessive compulsive disorder (F42-F42.9), phobic anxiety disorder (F40-F40.9), other anxiety disorder (F41-F41.9), eating disorder (F50-F50.9), specific personality disorder (F60-F60.9), or impulse disorder (F63-F63.9; a full list can be found in the Table A in the appendix).

A summary variable for **pre-existing health condition** included cardiovascular disease, diabetes (non-gestational), anemia, kidney failure, hypertension, lupus, epilepsy, pulmonary disease, cancer, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hepatitis c virus (HCV), and tuberculosis (TB; ICD-10 codes supplied on request).

Statistical Analysis

A summary variable for SMM (yes/no) was created for any record with an ICD-10 code SMM during the perinatal period (≥ 20 weeks of gestation to 4 weeks after delivery). The Andersen Model *need* variables (SRD, SMI, non-SMI, and pre-existing health conditions) were identified and grouped into dichotomous variables (yes/no). The *need* variables were then included in the LCA, to understand if discrete classes of mental and physical co-morbidities would emerge in women with and without a SMM during the perinatal period. The Andersen Model's *predisposing* and *enabling* variables were also identified and grouped into dichotomous or continuous variables for analysis.

Modeling approach:

The LCA model was developed using any women with an ICD-10 code for a live or stillbirth delivery regardless of whether they have an SMM. A simple unadjusted model was built followed by a more complex adjusted model. A sequence of 1-5 models were fitted using SAS PROC LCA package to identify an optimal baseline model.[29,30] The G^2 deviance statistic, Akaike Information Criterion (AIC), Bayesian information criterion (BIC), and the entropy value (a measure that conveys classification quality) were used as the principal indices of best fit.[31] We aimed to minimize the G^2, AIC, BIC and maximize entropy to identify the ideal number of latent classes, the optimal fitted model, and produce interpretable latent classes of >1% prevalence.[32] The differences by SMM were then tested in the model.[22] The best-fitted model was identified and reported. Once the appropriate latent model was identified, the latent classes of SRD, mental illness, and physical health conditions and their predictions of the Andersen Model's predisposing and enabling variables (expressed as probabilities, %) were calculated and reported.

Unadjusted analyses of the Andersen Model predisposing and enabling covariates and the SMM Class 1-2 were then conducted using analysis of variance (ANOVA) for continuous data and Chi-square (X^2) tests of significance for categorical data. To determine the effect/magnitude of the

associations, unadjusted odds ratios (ORs) were calculated and reported. Two-sided tests with p-values significant at ≥ 0.05 and OR 95% CIs that cross 1 indicating that there was no significant difference were used to determine whether a covariate would be included in the final adjusted regression model in both the unmatched and matched cohorts.

Multivariable logistic regression was conducted to determine the Andersen Model predisposing and enabling covariates that were associated with SMM class assignment. Standardized betas (β), standard errors (SE(β)), adjusted odds ratios (AOR) and the respective confidence intervals and p-values were reported. All analyses were conducted with SAS 9.4 (SAS Institute, Cary, North Carolina). The PROC LCA statistical package was retrieved from the Pennsylvania State University Methodology Center.[29]

RESULTS

Sample Characteristics

There was a total of 10,129 deliveries with an ICD-10 code for a single delivery at ≥ 20 weeks' gestation from March 1, 2016 to August 30, 2019. Four individuals were diagnosed with an SRD after delivery and were removed from the full dataset. In the final cohort of 10,125 deliveries, most were non-Hispanic/Latina White (42.7%) or other race/ethnicity (41.7%) with a mean age of 31.2 (standard deviation [SD]) =5.3, range 18-44 years of age; **Table 3.3**). Most were married (71.0%), had a mean BMI of 31.1 ([SD= 6.6], range = 17.2-83.5), had no previous pregnancies (81.4%), and had private health insurance (74.6%).

An SRD was documented in 692 (6.8%) deliveries. Of these, any SRD for alcohol (0.8%), opioids (1.5%), cannabis (2.5%), stimulants (2.0%), nicotine (2.7%), or non-specific and other (1.8%) were identified (data not shown in tables). SMI and non-SMIs (e.g., depression anxiety) were documented for 2.3% and 22.2% respectively. Of those with a non-SMI, 12.8% (n=1,298) had mild

or moderate depressive disorder and 14.2% (n=1,436) had an anxiety disorder (data not shown in tables). Pre-existing health conditions were documented for 34.3%. An SMM diagnosis was documented for 558 (5.5%) deliveries.

SMM-specific Latent Classes

Using the Andersen Model's need variables (SRD, SMI, non-SMI, pre-existing health condition), the LCA identified a 2-class model stratified by SMM to be the most parsimonious (AIC 2- class = 50.6 vs. AIC- 3 = 65.1, BIC 2- class=180.6 vs. BIC 3-class=267.3, Entropy 2-class = 0.75 vs. Entropy 3-class = 0.40; **Table 3.1**). This model was clinically interpretable and resulted in relevant patterns of maternal mental and physical health.

Among those with SMM, Class 1 included 64 (11.5%) women with a documented delivery and was labeled ***High prevalence of co-occurring SRD, mental illness, and physical health condition with SMM*.** Class 1 included SRDs (82.8%), non-SMI (67.2%), SMI (29.7%) and pre-existing health conditions (84.4%) (**Table 3.2**). Almost every covariate was represented in ≥ 50% of this group except SMI, making this the group with the highest proportion of morbidity in those with SMM**.** Among those with SMM, Class 2 included 494 (4.9%) women with a documented delivery and was labeled ***Moderate pre-existing health conditions with SMM***. Class 2 was made up of mostly pre-existing health conditions (56.7%). The remaining co-occurring conditions that accounted for a small proportion in this category were non-SMI (28.1%), and SRD (1.2%).

Among those without SMM, Class 1 included 577 (5.7%) women with a documented delivery and was labeled ***Moderate prevalence of co-occurring mental illness and physical health conditions.*** Class 1 was made up of mostly SRD (73.8%), non-SMI (67.9%), and pre-existing health conditions (62.9%). The remaining co-occurring condition that accounted for a small proportion in this category was SMI (36.4%). Almost every covariate was represented in ≥ 50% of this group except SMI, making this the group with the highest proportion of morbidity without SMM**.** Among

those without SMM, Class 2 included 8,990 (88.8%) women with a documented delivery and was labeled ***Low prevalence of co-occurring mental illness and physical health conditions.*** The contribution of pre-existing health conditions (30.9%), non-SMI (18.6%), and SRD (1.7%) were all ≤ 50% and no one had SMI. As such, this was the healthiest group.

Sample Characteristics by Latent Classes

The Andersen Model's predisposing and enabling variables (expressed as probabilities, %) from the two-class LCA model stratified by SMM can be found in **Table 3.3**. Age at delivery remained consistent in all of the classes from 30.0-31.5. In each of the classes stratified by SMM, most were non-Hispanic/Latina White (32.3%-47.6%) or other race/ethnicity (27.0%-50.2%). Among Class 1 in the SMM group, a higher proportion of non-Hispanic/Latina Black race/ethnicity (20.6%) was observed compared to the other classes. The proportion of single marital status was higher in the high and moderate SRD mental and physical health with and without SMM (Class 1 with SMM = 60.9%; Class 1 without SMM: 58.4%). The mean and SD of BMI at delivery was slightly higher in the Class 1 with SMM group (33.6 (10.6)) compared to the other SMM and non-SMM classes (Class 2 with SMM = 32.1 (6.9); Class 1 without SMM = 32.8 (6.9); Class 2 without SMM = 31.0 (6.5)). The number of those with no previous pregnancies remained relatively consistent in Classes 1 (87.5%) and 2 (86.2%) with SMM and Class 1 (89.4%) without SMM. In the non-SMM Class 2 group, a lower proportion of no previous pregnancies (80.6%) was observed. The majority of the sample had private health insurance (71.7%-75.5%) or public health insurance (20.9%-25.0%).

SMI was only observed in the classes with high and moderate prevalence of co-occurring SRD, mental illness, and physical health conditions with and without SMM (Class 1 with SMM = 29.7%; Class 1 without SMM = 36.4%). The proportion of non-SMI was higher in the high co-occurring SRD, mental illness, and physical health conditions with SMM and the moderate prevalence of co-occurring mental illness, and physical health conditions without SMM classes

(Class 1 with SMM= 67.2%; Class 1 without SMM = 67.9%) compared to the moderate pre-existing health conditions and low prevalence of co-occurring mental illness and physical health conditions (Class 2 with SMM = 29.7%; Class 2 without SMM: 18.7%). Pre-existing health conditions were higher in the Class 1 (84.4%) and 2 (56.7%) with SMM, and Class 1 (62.9%) without SMM compared to the Class 2 (30.9%) without SMM.

Prevalence and Correlates of Co-Occurring SRD, Mental Illness, and Physical Health

In the unadjusted analysis comparing Class 1 (high prevalence of co-occurring SRD, mental illness, and physical health conditions in those with SMM) to Class 2 (moderate prevalence of pre-existing conditions in those with SMM; reference), Class 1 membership was associated with being non-Hispanic/Latina Black (OR = 2.06 [95% CI, 1.00-4.37], p-value = 0.0002) and inversely associated with other race/ethnicity (OR = 0.37 [95% CI, 0.20-0.68], p-value = 0.0134). Class 1 membership was associated with divorced/separated/widowed marital status (OR = 5.63 [95% CI, 2.00-15.83], p-value = 0.0426). Class 1 membership was also marginally associated with single marital status (OR = 4.28 [95% CI, 2.39-7.65], p-value = 0.0645); **Table 3.4**).

In the adjusted analysis comparing Class 1 to Class 2 (reference), Class 1 membership was associated with Hispanic/Latina race/ethnicity (adjusted odds ratio (AOR) = 0.19 [95% CI, 0.05-0.66], p-value = 0.0455), other race/ethnicity (AOR = 0.23 [95% CI, 0.11-0.45], p-value = 0.0123), and single marital status (AOR = 5.59 [95% CI, 2.93-10.67], p-value = 0.0238; **Table 3.4**). Class 1 membership was also marginally associated with divorced/separated/widowed marital status (OR = 6.35 [95% CI, 2.14-18.81], p-value = 0.0584).

DISCUSSION

This study used LCA to discover subpopulations of SRD, mental illness, and physical health conditions through the Andersen Model's *need* variables (SRD, SMI, non-SMI, pre-existing health condition) in those with and without SMM. These findings show that the need variables are stronger

predictors of SMM compared to the predisposing and enabling variables. SRDs were common in the groups with high and moderate co-occurring SRDs, mental illness, and physical health outcomes in both the SMM and non-SMM classes. However, proportions of SRD were higher in the those who had a SMM compared to those who did not have a SMM. Similarly, non-SMIs were common in the groups with high and moderate co-occurring SRD, mental illness, and physical health conditions in both the SMM and non-SMM classes respectively. SMI was only observed in those with high to moderate prevalence of co-occurring SRD, mental illness, and physical health in the SMM and non-SMM classes respectively.

Studies show similar relationships between co-occurring SRDs, SMI, and non-SMIs.[33,34] One study found that those with SMI were less likely to report being diagnosed with co-occurring medical conditions such as heart disease, arthritis, cancer, diabetes, back pain, congestive heart failure, and hypertension compared to those with non-SMI.[33]

Having a pre-existing health condition was common in almost all of the latent classes. This finding is consistent with findings from the current literature on maternal morbidity. For example, a study investigating obstetric outcomes in pregnant women found that women with multiple chronic conditions such as chronic respiratory disease, chronic hypertension, substance use disorders, pre-existing diabetes, chronic heart disease, chronic renal disease, chronic liver disease, and HIV were at a significantly higher risk than women with one chronic condition.[35] The aforementioned study found that preterm delivery, cesarean delivery, and SMM were significantly higher among women with multiple chronic conditions compared to women with no chronic condition or one chronic condition.

High and moderate co-occurring SRD, mental illness, and physical health outcomes in women with SMM were observed in mostly non-Hispanic/Latina Whites, non-Hispanic/Latina Blacks, and those in the other race/ethnicity category. In the adjusted regression of those with SMM, women who are Hispanic/Latina or other race/ethnicity were less likely to have high co-occurring morbidity compared to non-Hispanic/Latina Whites. This association demonstrates that non-Whites

in this study are more likely to have moderate prevalence of pre-existing health conditions compared to high prevalence of co-occurring morbidity. This finding differs from existing literature which shows that racial/ethnic minorities tend to experience higher rates of SRD and non-SMI. It is possible that misdiagnosis or misclassification of SRDs and mental illness in the EMR may account for this unexpected association. Studies have shown that racial/ethnic minority pregnant women may be less likely to report substance use or mental illness due to stigma and fear of prosecution or removal of their child.[36] One study found that compared to White women, Black women reported more stigma related depression (regardless of whether they had depression) and were more likely to agree that depression should be kept secret.[37] Another study found that non-Hispanic White pregnant women with depressive symptoms had the highest rates of mental health services use compared to Mexicans and other Hispanics.[38]

The lower proportion of non-Whites with a SMM observed in this study may also be due to misclassification of other non-White race/ethnicity categories that were captured in the EMR during a healthcare visit. For example, mixed race/ethnicity is common and may consist of a large number of non-White women grouped into the "other" category. Similarly, when patients are asked to include their race/ethnicity at a healthcare visit they may choose to select "other" because they do not fit in the limited race/ethnicity categories provided.

High and moderate co-occurring mental and physical health outcomes in those with and without SMM were observed in mostly those who were single (not married). In the adjusted regression of those with SMM, women who were single or divorced/separated/widowed were more likely to have high prevalence of co-occurring morbidity compared to women who were married. A similar relationship between marital status and substance use has been documented in the literature. For example, a systematic review and metanalysis on maternal marital status and birth outcomes found that the odds of preterm birth, low birth weight, and small for gestational age were higher

among single mothers compared to married mothers.[39] This shows that having marital support may be protective for adverse maternal outcomes.

The mean BMI was found to be slightly higher in the SMM group with high prevalence of co-occurring SRD, mental health, and physical health compared to the other classes, indicating that this group may be at an increased risk for SMM. The lowest mean BMI was identified in the low prevalence of co-occurring SRD, mental health, and physical health class with no SMM. Among those with SMM in the current study, BMI was found to be higher in women with high prevalence of co-occurring morbidity compared to those with moderate pre-existing conditions in only the unadjusted regression. Studies have found lower and higher BMI to be associated with maternal morbidity. For example, one study found that pregnant women with low and high weight gain during pregnancy were more likely to have SMM compared to women with normal-weight gain, however the absolute increase in SMM was small.[40] Another study found that those with increased BMI had an increased incidence of pre-eclampsia, macrosomia, gestational hypertension, and induction of labor and cesarean delivery.[41] In addition, women who were underweight demonstrated better outcomes than women with a normal BMI.[41] BMI was not found to be significantly associated with class membership in the adjusted regression, showing that race/ethnicity and marital status are stronger predictors of high prevalence of co-occurring SRD, mental illness, and physical health in those with SMM.

Study Strengths and Limitations

The use of LCA strengthens this study, as it provides a novel person-centered approach to understanding distinct groups of maternal morbidity based on the individuals in the dataset. The use of LCA is also beneficial because it decreases possible measurement error, oversimplification, or bias that may occur when definitions are developed to categorize complex behaviors and outcomes.[23] This is helpful when using EMR data that is not designed for research purposes and is dependent on billing categories. Other advantages of using LCA include the inclusion of covariates that may

impact class membership.[19] When the data is assumed to be missing at random, all of the available data can be used in the analysis because a full information maximum likelihood approach is employed. As such, it is possible to use all of the available data instead of deleting those with missing data.

This study is also strengthened by the large sample size of women who presented for delivery (n= 692 [6.8%]) and without (n= 9,433 [93.2%]) an SRD over 3.5 years of EMR data. Because providers are required to enter all of the medical data in the EMR directly, a large amount of data can be captured over a long period of time. However, some health-related diagnoses (e.g., SRD, SMI) may be missing or not adequately assigned in the EMR. It is possible that patients may have omitted their substance use or providers did not know how to appropriately diagnose an SRD at the time of the clinical visit. Providers may also be reluctant to enter diagnoses such as SRDs or a SMIs into the permanent medical record if it is not the focus of the encounter.

Another limitation includes the classification of race/ethnicity in the EMR. Patients are asked to list their race/ethnicity during a clinical visit intake, emergency department visit, or hospitalization. By requiring patients to select pre-determined categories that include options such as Asian/Pacific Islander, patients are forced to put themselves in a single category that may not capture the unique experiences related to their race or ethnicity. For example, studies have shown that there are health related differences between Asian and Pacific Islanders that would not be captured when they are grouped together into one category.[42]

Because maternal morbidity varies over time and across regions, generalizability is limited by the restriction to Southern California and to one healthcare system.

CONCLUSION

Results from this study show that the majority of women with a documented delivery have low prevalence of co-occurring mental and physical health conditions. SRDs were common in the

groups with high and moderate co-occurring mental and physical health outcomes in both the SMM and non-SMM classes. However, the prevalence of SRD was higher in the those who had a SMM compared to those who did not have a SMM. In those with SMM, women with high co-occurring SRD, mental illness, and physical health conditions were more likely to be non-Hispanic White and single or divorced/separated/widowed compared to those with only pre-existing health conditions. Based on these latent classes, a more significant predictor of SMM across each class include pre-existing health conditions. These conditions include cardiovascular disease, diabetes (non-gestational), anemia, kidney failure, hypertension, lupus, epilepsy, pulmonary disease, cancer, HIV/AIDS, HCV, and TB.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contributions to this research by the Altman Clinical and Translational Research Institute's Virtual Research Desktop (VRD) analytics team and collaborators at University of California San Diego (supported by the National Institute of Health, Grant UL1TR001442 of CTSA Funding). This research is funded by Dr. Carla Marienfeld's research funds through the department of Psychiatry at the University of California San Diego School of Medicine.

Table 3.1 Comparison of baseline models for the latent classes of substance related diagnosis, mental illness, and physical health among women with a documented delivery from a Southern California's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

No. of Classes	Likelihood Ratio G^2	Degrees of Freedom	AIC	BIC	Entropy
2	14.59	13	50.59	180.60	0.75
3	9.06	3	65.06	267.29	0.40
4	8.68	-7	84.68	359.15	0.28

Boldface type indicates the selected model. AIC D Akaike's Information Criterion; BIC D Bayesian Information Criterion.

Table 3.2 The latent classes of substance related diagnosis, mental illness, and physical health conditions among women with a documented delivery and their predictions of the Andersen Model's need variables (expressed as probabilities, %) from the two-class LCA model stratified by severe maternal morbidity. Data collected from a Southern California hospital's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

		Severe Maternal Morbidity n = 558 (5.5%)		No Severe Maternal Morbidity n = 9,567 (94.5%)	
Parameter	Total n (%)/ Mean (SD)	Class 1: High prevalence of co-occurring SRD, mental illness, and physical health conditions n (%)	Class 2: Moderate pre-existing health conditions n (%)	Class 1: Moderate prevalence of co-occurring mental illness and physical health conditions n (%)	Class 2: Low prevalence of co-occurring mental illness and physical health condition n (%)
All	10,125 (100.0)	64 (11.5)	494 (88.5)	577 (6.0)	8,990 (94.0)
Need Variables					
Substance related diagnosis					
Yes	641 (6.3)	53 (82.8)	6 (1.2)	426 (73.8)	156 (1.7)
No	9,484 (93.7)	11 (17.2)	488 (98.8)	151 (26.1)	8,834 (98.3)
Serious mental illness					
Yes	229 (2.3)	19 (29.7)	0 (0.0)	210 (36.4)	0 (0.0)
No	9,896 (97.7)	45 (70.3)	4974(100.0)	367 (63.6)	8,990 (100.0)
Non-SMI					
Yes	2,243 (22.2)	43 (67.2)	139 (28.1)	392 (67.9)	1,669 (18.6)
No	7,882 (77.9)	21 (31.8)	355 (71.9)	185 (32.1)	7,321 (81.4)
Pre-existing health condition					
Yes	3,472 (34.3)	54 (84.4)	280 (56.7)	363 (62.9)	2,775 (30.9)
No	6,653 (65.7)	10 (15.6)	214 (43.3)	214 (37.1)	6,215 (69.1)

Variable totals may not sum to column totals due to missing data.

Table 3.3 The latent classes of substance use related diagnosis, mental illness, and physical health among women with a documented delivery and their predictions of the Andersen Model's predisposing and enabling variables (expressed as probabilities, %) from the two-class LCA model stratified by severe maternal morbidity (four classes). Data collected from a Southern California hospital's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

		Severe Maternal Morbidity n = 558 (5.5%)		No Severe Maternal Morbidity n = 9,567 (94.5%)	
Parameter	Total n (%)/Mean (SD)	Class 1: High prevalence of co-occurring SRD, mental illness, and physical health conditions n (%)/Mean (SD)	Class 2: Moderate pre-existing health conditions n (%)/Mean (SD)	Class 1: Moderate prevalence of co-occurring mental illness and physical health conditions n (%)/Mean (SD)	Class 2: Low prevalence of co-occurring mental illness and physical health condition n (%)/Mean (SD)
All	10,125 (100.0)	64 (11.5)	494 (88.5)	577 (6.0)	8,990 (94.0)
Predisposing Variables					
Age at delivery	31.2 (5.3)	30.4 (5.3)	31.5 (5.5)	30.0 (5.9)	31.3 (5.2)
Race/ethnicity					
Hispanic/Latino	961 (9.7)	3 (4.8)	52 (10.7)	58 (10.3)	848 (9.6)
Non-Hispanic/Latino Black	584 (5.9)	13 (20.6)	33 (6.8)	71 (12.5)	467 (5.3)
Other	4,147 (41.7)	17 (27.0)	244 (50.2)	181 (32.0)	3,705 (42.0)
Non-Hispanic/Latino White	4,248 (42.7)	30 (47.6)	157 (32.3)	256 (45.2)	3,805 (43.1)
Marital status					
Single	2,733 (27.0)	39 (60.9)	154 (31.2)	335 (58.4)	2,205 (24.6)
Divorced, separated, widowed	200 (2.0)	6 (9.4)	18 (3.6)	41 (7.1)	135 (1.5)
Married	7,175 (71.0)	19 (29.7)	321 (65.1)	198 (34.5)	6,637 (73.9)
BMI at delivery	31.1 (6.6)	33.9 (10.6)	32.1 (6.9)	32.8 (6.9)	31.0 (6.5)
Parity					
No previous pregnancies	8,243 (81.4)	56 (87.5)	426 (86.2)	516 (89.4)	7,245 (80.6)
≥ 1 previous pregnancy	1,882 (18.6)	8 (12.5)	68 (13.8)	61 (10.6)	1,745 (19.4)
Enabling Variables					
Health insurance					
Public	2,157 (21.3)	14 (21.9)	123 (24.9)	144 (25.0)	1,876 (20.9)
No insurance	413 (4.1)	2 (3.1)	17 (3.4)	17 (3.0)	377 (4.2)
Private	7,555 (74.6)	48 (75.0)	354 (71.7)	416 (72.1)	6,737 (74.9)

All age at delivery: n =10,125, median = 32, range = 18-44, SMM LCA 1 age at delivery: n =61, median = 31, range = 20-43, SMM LCA 2 age at delivery: n =553, median = 30, range = 18-44, no SMM LCA 1 age at delivery: n =486, median = 32, range = 18-44, no SMM LCA 2 age at delivery: n =9,442, median = 32, range = 18-44, All BMI at delivery: n = 9,952, median = 29.7, range = 17.2-83.5, SMM LCA 1 BMI at delivery: n = 62, median = 29.7, range = 20.4-71.5, SMM LCA 2 BMI at delivery: n = 565, median = 31.6, range = 20.3-57.3, no SMM LCA 1 BMI at delivery: n = 486, median = 30.7, range = 17.2.-62.3, no SMM LCA 2 BMI at delivery: n = 8,839, median = 29.6, range = 18.0-83.5. Variable totals may not sum to column totals due to missing data.

Table 3.4 Unadjusted and adjusted relationship between high prevalence of co-occurring substance use related diagnosis, mental health, and physical health by the Andersen Model's predisposing and enabling variables among women with serious maternal morbidity and a documented delivery. Data collected from a Southern California's electronic medical record from March 1st, 2016 - August 30th, 2019 (n= 10,125).

	Unadjusted Cohort with Severe Maternal Morbidity (SMM) n = 558 (5.5%)			Adjusted Cohort with Severe Maternal Morbidity (SMM) n = 538 (5.3%)		
Parameter	Class 1: High prevalence of co-occurring SRD, mental illness, and physical health conditions OR (95% CI)* n= 64 (11.5%)	X^2/F	P	Class 1: High prevalence of co-occurring SRD, mental illness, and physical health conditions AOR (95% CI)* n= 61 (10.9%)	X^2/F	P
Total						
Predisposing Variables						
Age at delivery	1.03 (0.98-1.08)	1.61	0.2034			
Race/ethnicity						
Hispanic/Latina	0.30 (0.89-1.03)	3.23	0.0721	0.19 (0.05-0.66)	4.00	0.0455
Non-Hispanic/Latina Black	2.06 (1.00-4.37)	13.50	0.0002	1.19 (0.52-2.75)	8.68	0.0032
Other	0.37 (0.20-0.68)	6.12	0.0134	0.23 (0.11-0.45)	7.78	0.0053
Non-Hispanic/Latina White	—					
Marital status						
Single	4.28 (2.39-7.65)	3.32	0.0645	5.59 (2.93-10.67)	5.10	0.0238
Divorced, separated, widowed	5.63 (2.00-15.83)	4.11	0.0426	6.35 (2.14-18.81)	3.58	0.0584
Married	—					
BMI at delivery	0.97 (0.94-1.00)	3.30	0.0691			
Parity						
No previous pregnancies	1.12 (0.51-2.45)	0.08	0.7814			
≥ 1 previous pregnancy	—					
Enabling Variables						
Health insurance						
Public	1.15 (0.26-5.14)	0.14	0.7112			
No insurance	0.97 (0.20-4.63)	0.05	0.8265			
Private	—					

*Reference is Class 2 with SMM: Moderate prevalence of co-occurring mental health and physical health. SRD = substance related diagnosis, OR = odds ratio, AOR = adjusted odds ratio, CI = confidence interval.

REFERENCES

1. Division of Reproductive Health National Center for Chronic Disease Prevention and Health Propomotion Center for Disease Control and Prevention. *Severe Maternal Morbidity in the United States*.; 2017. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/severematernalmorbidity.html#anchor_References. Accessed May 9, 2019.

2. Center for Disease Control and Prevention, Hamilton BE, Osterman MJK, Driscoll AK, Rossen LM. Births : provisional data for 2017. 2018. https://stacks.cdc.gov/view/cdc/55172. Accessed May 9, 2019.

3. Campbell KH, Savitz D, Werner EF, et al. Maternal Morbidity and Risk of Death at Delivery Hospitalization. *Obstet Gynecol*. 2013;122(3):627-633. doi:10.1097/AOG.0b013e3182a06f4e

4. Small MJ, James AH, Kershaw T, Thames B, Gunatilake R, Brown H. Near-Miss Maternal Mortality. *Obstet Gynecol*. 2012;119(2, Part 1):250-255. doi:10.1097/AOG.0b013e31824265c7

5. Hinkle SN, Sharma AJ, Kim SY, et al. Prepregnancy Obesity Trends Among Low-Income Women, United States, 1999–2008. *Matern Child Health J*. 2012;16(7):1339-1348. doi:10.1007/s10995-011-0898-2

6. Fisher SC, Kim SY, Sharma AJ, Rochat R, Morrow B. Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003–2009. *Prev Med (Baltim)*. 2013;56(6):372-378. doi:10.1016/j.ypmed.2013.02.015

7. Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications Contributing to the Increasing Cesarean Delivery Rate. *Obstet Gynecol*. 2011;118(1):29-38. doi:10.1097/AOG.0b013e31821e5f65

8. Callaghan, W. M., Creanga, A. A., & Kuklina E V. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. *Obstet Gynecol*. 2012;120(5):1029-1036.

9. Gonzalez G, Rosenheck RA. Outcomes and Service Use Among Homeless Persons With Serious Mental Illness and Substance Abuse. *Psychiatr Serv*. 2002;53(4):437-446. doi:10.1176/appi.ps.53.4.437

10. Benningfield MM, Arria AM, Kaltenbach K, et al. Co-occurring Psychiatric Symptoms Are Associated with Increased Psychological, Social, and Medical Impairment in Opioid Dependent Pregnant Women. *Am J Addict*. 2010;19(5):416-421. doi:10.1111/j.1521-0391.2010.00064.x

11. Forray A. Substance use during pregnancy. *F1000Research*. 2016;5. doi:10.12688/f1000research.7645.1

12. Abrams LS, Curran L. "And You're Telling Me Not to Stress?" a Grounded Theory Study of Postpartum Depression Symptoms among Low-Income Mothers. *Psychol Women Q*. 2009;33(3):351-362. doi:10.1177/036168430903300309

13. Bailey BA. Partner violence during pregnancy: prevalence, effects, screening, and management. *Int J Womens Health*. 2010;2:183-197. doi:10.2147/ijwh.s8632

14. Fridman M, Korst LM, Chow J, Lawton E, Mitchell C, Gregory KD. Trends in maternal morbidity before and during pregnancy in California. *Am J Public Health*. 2014;104 Suppl 1(Suppl 1):S49-57. doi:10.2105/AJPH.2013.301583

15. Hirshberg A, Srinivas SK. Epidemiology of maternal morbidity and mortality. *Semin Perinatol*. 2017;41(6):332-337. doi:10.1053/J.SEMPERI.2017.07.007

16. Gray KE, Wallace ER, Nelson KR, Reed SD, Schiff MA. Population-Based Study of Risk Factors for Severe Maternal Morbidity. *Paediatr Perinat Epidemiol*. 2012;26(6):506-514. doi:10.1111/ppe.12011

17. Creanga AA, Bateman BT, Kuklina E V., Callaghan WM. Racial and ethnic disparities in severe maternal morbidity: a multistate analysis, 2008-2010. *Am J Obstet Gynecol*. 2014;210(5):435.e1-435.e8. doi:10.1016/J.AJOG.2013.11.039

18. Howell EA, Egorova NN, Janevic T, et al. Race and Ethnicity, Medical Insurance, and Within-Hospital Severe Maternal Morbidity Disparities. *Obstet Gynecol*. 2020;135(2):285-293. doi:10.1097/AOG.0000000000003667

19. Muthén B. Latent variable analysis. In: *The Sage Handbook of Quantitative Methodology for the Social Sciences*. ; 2004:345(368), 106-109.

20. Jung, T., & Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Soc Personal Psychol Compass*. 2008;2(1):302-317.

21. Stein JA, Andersen R, Gelberg L. Applying the Gelberg-Andersen Behavioral Model for Vulnerable Populations to Health Services Utilization in Homeless Women. *J Heal Psychol www.sagepublications.com*. 2007;12(5):791-804. doi:10.1177/1359105307080612

22. Green TC, Kershaw T, Lin H, et al. Patterns of drug use and abuse among aging adults with and without HIV: A latent class analysis of a US Veteran cohort. *Drug Alcohol Depend*. 2010;110(3):208-220. doi:10.1016/J.DRUGALCDEP.2010.02.020

23. Kapadia F, Vlahov D, Donahoe RM, Friedland G. The role of substance abuse in HIV disease progression: reconciling differences from laboratory and epidemiologic investigations. *Clin Infect Dis*. 2005;41(7):1027-1034. doi:10.1086/433175

24. Ivanov LL. Use of a Western Theoretical Model to Investigate the Relationships Among

Characteristics of Pregnant Women, Utilization, and Satisfaction with Prenatal Care Services in St. Petersburg, Russia. *Public Health Nurs*. 2000;17(2):111-120. doi:10.1046/j.1525-1446.2000.00111.x

25. LaVeist TA, Keith VM, Gutierrez ML. Black/white differences in prenatal care utilization: an assessment of predisposing and enabling factors. *Health Serv Res*. 1995;30(1):43-58. http://www.ncbi.nlm.nih.gov/pubmed/7721584. Accessed April 29, 2019.

26. Hatzenbuehler ML, Keyes KM, Narrow WE, Grant BF, Hasin DS. Racial/ethnic disparities in service utilization for individuals with co-occurring mental health and substance use disorders in the general population: results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry*. 2008;69(7):1112-1121. http://www.ncbi.nlm.nih.gov/pubmed/18517286. Accessed April 29, 2019.

27. ICD10Data.com. 2019 ICD-10-CM Codes. https://www.icd10data.com/ICD10CM/Codes. Accessed May 14, 2019.

28. eMDs. ICD 10 Code for Pregnancy: OB-GYN. http://www.e-mds.com/revenue-cycle-management-age-icd-10-primer-ob-gyn. Accessed May 9, 2019.

29. University Park: The Methodology Center PS. PROC LCA & PROC LTA (Version 1.3.2) [Software]. 2015. http://methodology.psu.edu.

30. Lanza, S. T., Dziak, J. J., Huang, L., Wagner, A., & Collins LM. Proc LCA & Proc LTA users' guide (Version 1.3. 2). *Penn State Univ Park PA Methodol Center*. 2015.

31. Berglund PA. Latent Class Analysis Using PROC LCA. *Univ Michigan*. Paper 5500.

32. Muthen, LK.; Muthen B. *Mplus User's Guide.* Los Angeles, CA: Muthen & Muthen; 2007.

33. Kilbourne AM, McCarthy JF, Welsh D, Blow F. Recognition of Co-Occurring Medical Conditions Among Patients With Serious Mental Illness. *J Nerv Ment Dis*. 2006;194(8):598-602. doi:10.1097/01.nmd.0000230637.21821.ec

34. Peters EN, Schwartz RP, Wang S, O'Grady KE, Blanco C. Psychiatric, psychosocial, and physical health correlates of co-occurring cannabis use disorders and nicotine dependence. *Drug Alcohol Depend*. 2014;134:228-234. doi:10.1016/J.DRUGALCDEP.2013.10.003

35. Admon LK, Winkelman TNA, Moniz MH, Davis MM, Heisler M, Dalton VK. Disparities in Chronic Conditions Among Women Hospitalized for Delivery in the United States, 2005-2014. *Obstet Gynecol*. 2017;130(6):1319-1326. doi:10.1097/AOG.0000000000002357

36. Acevedo A, Garnick DW, Lee MT, et al. Racial and Ethnic Differences in Substance

Abuse Treatment Initiation and Engagement. *J Ethn Subst Abuse*. 2012;11(1):1-21. doi:10.1080/15332640.2012.652516

37. O'Mahen HA, Henshaw E, Jones JM, Flynn HA. Stigma and Depression During Pregnancy. *J Nerv Ment Dis*. 2011;199(4):257-262. doi:10.1097/NMD.0b013e3182125b82

38. Chang JJ, Tabet M, Elder K, Kiel DW, Flick LH. Racial/Ethnic Differences in the Correlates of Mental Health Services Use among Pregnant Women with Depressive Symptoms. *Matern Child Health J*. 2016;20(9):1911-1922. doi:10.1007/s10995-016-2005-1

39. Shah PS, Zao J, Ali S. Maternal Marital Status and Birth Outcomes: A Systematic Review and Meta-Analyses. *Matern Child Health J*. 2011;15(7):1097-1109. doi:10.1007/s10995-010-0654-z

40. Lisonkova S, Muraca GM, Potts J, et al. Association Between Prepregnancy Body Mass Index and Severe Maternal Morbidity. *JAMA*. 2017;318(18):1777. doi:10.1001/jama.2017.16191

41. Bhattacharya S, Campbell DM, Liston WA, Bhattacharya S. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. *BMC Public Health*. 2007;7(1):168. doi:10.1186/1471-2458-7-168

42. Choi K-H, Paul J, Ayala G, Boylan R, Gregorich SE. Experiences of discrimination and their impact on the mental health among African American, Asian and Pacific Islander, and Latino men who have sex with men. *Am J Public Health*. 2013;103(5):868-874. doi:10.2105/AJPH.2012.301052

CHAPTER 5: DISCUSSION

OVERVIEW

This dissertation research was conducted to evaluate the relationships between maternal SRDs and preterm delivery, cesarean delivery, and SMM in a large Southern Californian healthcare system. The following aims were addressed by this research, **Aim 1**) Evaluate whether there are associations between an SRD and preterm or cesarean delivery among women who presented for delivery from 2012-2019; **Aim 2)** Evaluate whether there is an association between an SRD and SMM among women who presented for delivery and assess trends of SRD and SMM from 2016-2019; **Aim 3)** Characterize the patterns of SRD, mental illness, and physical health conditions by SMM and examine pattern correlates among women who presented for delivery from 2016-2019. This research contributes a better understanding of how SRDs are associated with preterm delivery, cesarean delivery, and SMM.

Broadly, results indicate three main findings. First, among women with a documented delivery, having an SRD is associated with preterm delivery and cesarean delivery. Second, among women with a documented delivery, having an SRD is associated with SMM and increase in SMM over time is not associated with an SRD. Third, SRDs were common in the groups with high and moderate co-occurring mental illness and pre-existing health conditions in both the SMM and non-SMM classes.

In **Chapter 2 (Aim 1)**, findings show that having an SRD or pre-existing health condition are strong predictors for preterm delivery among pregnant women in Southern California. This indicates that these Andersen Model need covariates are stronger predictors of preterm delivery than the predisposing or enabling covariates. When stratified by substance type, alcohol, opioids, and stimulant related diagnoses remained associated with preterm delivery in the matched unadjusted analysis. Findings also show that having an SRD, older age at delivery, higher BMI at delivery, and pre-existing health condition are strong predictors for cesarean delivery. When stratified by substance

type, stimulants, nicotine, and non-specific or other substance related diagnosis were associated with cesarean delivery in the matched unadjusted analysis.

In **Chapter 3 (Aim 2)**, having an SRD and pre-existing conditions were significantly associated with SMM. This indicates that these Andersen Model need covariates are stronger predictors of SMM than the predisposing or enabling covariates. When stratified by substance type in the bivariate analysis, alcohol, stimulants, nicotine, and non-specific substance type and other (hallucinogens/inhalants) remained significantly associated with SMM in the unmatched and matched cohorts. Additional Andersen Model covariates that may impact SMM include divorced/separated/widowed marital status, having no previous deliveries, and non-SMI. Overall, SMM has been increasing over time from 2016-2019 in pregnant women with and without an SRD. There was not a significant difference in the observed increase in SMM prevalence over time in the SRD and non-SRD groups.

In **Chapter 4 (Aim 3)**, SRDs were common in the SMM and non-SMM groups with high and moderate co-occurring mental illness and physical health conditions. The proportion of SRD was higher in the those who had a SMM. Those with high co-occurring SRD, mental illness, and physical health conditions and SMM were more likely to be non-Hispanic White and single or divorced/separated/widowed. The majority of women with a documented delivery had low prevalence of co-occurring mental and physical health. Based on these classes, a more significant predictor of SMM across each latent class is pre-existing health conditions. These conditions include cardiovascular disease, diabetes (non-gestational), anemia, kidney failure, hypertension, lupus, epilepsy, pulmonary disease, cancer, HIV/AIDS, HCV, and TB. These findings indicate that these Andersen Model need covariates are strong predictors of SMM and the interrelated predisposing covariates include race/ethnicity and marital status. The enabling covariate had no significant impact on these results.

STRENGTHS AND LIMITATIONS

The research presented in this dissertation addressed significant gaps in the literature on the relationship between an SRD and preterm delivery, cesarean delivery, and SMM in women who presented for delivery. Aim 1 is strengthened by the large sample size of women who presented for delivery with (n= 1,111 [5.8%]) and without (n= 18,192 [94.2%]) an SRD over 8.5 years of EMR data. Similarly, Aims 2-3 are strengthened by the large sample size of women who presented for delivery with (n= 692 [6.8%]) and without (n= 9,433 [93.2%]) an SRD over 3.5 years of EMR data. Because healthcare providers are required to enter all of the medical data in the EMR for monitoring and billing purposes, a large amount of data can be captured over a long period of time. As such, using EMR data provides focused and accurate diagnoses and outcomes instead of relying on patient self-report. This allows for a unique perspective on maternal morbidities among a large sample of women with and without an SRD.

This study was also strengthened by the use of propensity score matching to control for confounding in the unstructured EMR data used in this study in Aim 1-2. By matching by age at delivery, parity, pre-existing health condition, and delivery year, a greater portion of potential bias was eliminated when estimating the effects of SRD on SMM.[1] The use of LCA in Aim 3 also strengthens this study, as it provides a novel person-centered approach to understanding distinct groups of maternal morbidity based on the individuals in the dataset. Finally, using longitudinal data from 2012-2019 (Aim 1) and 2016-2019 (Aim 2-3) allows for the detection of developments or changes over time.

This research is not without its limitations. Some health-related diagnoses (e.g., SRD, SMI) may be missing or not adequately assigned in the EMR. For example, it is possible that patients may have omitted their substance use or providers did not know how to appropriately diagnose an SRD at the time of the clinical visit. Providers may also be reluctant to enter diagnoses such as SRDs or a SMIs into the permanent medical record if it is not the focus of the encounter. Conversely, patients

who have an assigned SRD in their chart but are in treatment (e.g., therapy, medication assisted treatment) and are not using substances may distort results related to maternal morbidity. In an effort to mitigate this concern, only the current SRD ICD-10 code diagnoses from the 42 weeks before delivery that are found on the active problem list were selected.

As mentioned, ICD-10 codes in the EMR are designed to identify diagnoses and procedures for billing purposes. This limitation is clearly observed in the way many SRDs are sometimes identified in the EMR as "non-specified substance related disorder" (n= 358). Further exploration of the factors contributing to a clinical provider's decision to classify a patient with an SRD in this ambiguous category instead of a designated substance type (alcohol, opioids, etc.) would be helpful to improve code classification in the EMR. It would also be advantageous to clearly identify the severity of the SRD in the EMR so that future studies who use this type of data can have a more accurate assessments of the impact of SRD on health outcomes.

Because we examined maternal outcomes over time, it is possible that patients could have changed their insurance and/or changed providers/services during their pregnancy. This could have led to missed diagnoses or procedures that could confound the relationships observed in these studies. In an effort to mitigate this concern, we retrospectively investigated data during the 42 weeks before delivery. We are optimistic that the large sample size and propensity score matching methods mitigated any potential confounding in the available data.

Another limitation includes the classification of race/ethnicity in the EMR. Patients are asked to list their race/ethnicity during a clinical visit intake, emergency department visit, or hospitalization. By requiring patients to select pre-determined categories that include categories such as Asian/Pacific Islander, patients are forced to put themselves in a single category that may not capture the unique traits related to their race or ethnicity. For example, studies have shown that there are health related differences between Asian and Pacific Islanders that would not be captured when they are grouped together into one category.[2]

Because maternal morbidity varies over time and across regions, generalizability is limited by the restriction to Southern California and to one healthcare system. However, Southern California's close proximity to the Tijuana border, which is one of the busiest land border crossings in the world, and high number of racial/ethnic minorities and immigrant populations (69.2%) who may or may not be on Medi-Cal make it unique.[3]

POTENTIAL IMPACT AND FUTURE DIRECTIONS

This dissertation aimed to address a gap in knowledge on how SRDs impact maternal morbidity in pregnant women. This gap in knowledge was likely due to the focus on neonatal outcomes rather than maternal outcomes in the current literature. Preterm delivery, cesarean delivery, and SMM have been addressed in the literature.[4–6] However, the majority of the studies used data from the 1990's and early 2000's or investigating women outside of the United States.[7,8] More recently, some studies have included substance use as a covariate in their assessments of predictors related to maternal morbidity in small to moderate sample sizes.[9]

The findings in this current study reinforce the need to identify SRDs in pregnant women early to minimize potential harm through intervention and treatment. Using the EMR, robust SRD screening measures should be applied in all clinical settings and linked to longitudinal data. Because pregnant women with an SRD may be engaging with the health system in different capacities (pre-natal visit vs. emergency department), questions regarding substance use should be posed often. Providers should also strive to create safe and un-stigmatizing clinical environments for pregnant women who may have an SRD, mental illness, or pre-existing conditions. Questions related to substance use should be posed carefully and sensitively and should include questions specifically related to alcohol, opioids, cannabis, stimulants, and nicotine. Understanding how stigma impacts maternal morbidity in these settings could also lead to improvements in diagnoses and engagement in treatment.

Additional research on the type of substance (e.g., alcohol, opioids, stimulants) and how maternal health service utilization impacts maternal morbidity could lead to tailored interventions that can be applied in clinical settings.

This study assessed the relationships between SRDs and preterm delivery, cesarean delivery, and SMM separately. It is likely that these three types of maternal morbidities are interrelated. Future research should assess the relationship between these three types of morbidity and determine if SRDs play a role in preterm delivery or cesarean delivery that result in SMM.

Future studies should investigate differences in healthcare service utilization among pregnant women with and without an SRD to identify how this vulnerable population is engaging with the health care system (e.g., emergency department visits). Future studies should also investigate how providers feel about discussing substance use with pregnant patients and how they engage patients who reveal that they are actively using substances. This study was limited to pregnant women who were 18 years of age or older. Future studies should investigate how pregnant women under the age of 18 experience maternal morbidity as an exceptionally vulnerable population. Finally, future studies should identify the utility of training providers on how to better diagnose and engage pregnant women into treatment when appropriate to reduce the risk of maternal morbidity in this vulnerable population.

REFERENCES

1. Austin PC. Some Methods of Propensity-Score Matching had Superior Performance to Others: Results of an Empirical Investigation and Monte Carlo simulations. *Biometrical J*. 2009;51(1):171-184. doi:10.1002/bimj.200810488

2. Choi K-H, Paul J, Ayala G, Boylan R, Gregorich SE. Experiences of discrimination and their impact on the mental health among African American, Asian and Pacific Islander, and Latino men who have sex with men. *Am J Public Health*. 2013;103(5):868-874. doi:10.2105/AJPH.2012.301052

3. March of Dimes. Perinatal Stats 2013-2015.

4. Kilpatrick SJ, Abreo A, Gould J, Greene N, Main EK. Confirmed severe maternal morbidity is associated with high rate of preterm delivery. *Am J Obstet Gynecol*. 2016;215(2):233.e1-233.e7. doi:10.1016/J.AJOG.2016.02.026

5. Blanc J, Resseguier N, Goffinet F, et al. Association between gestational age and severe maternal morbidity and mortality of preterm cesarean delivery: a population-based cohort study. *Am J Obstet Gynecol*. 2019;220(4):399.e1-399.e9. doi:10.1016/J.AJOG.2019.01.005

6. Bhattacharya S, Campbell DM, Liston WA, Bhattacharya S. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. *BMC Public Health*. 2007;7(1):168. doi:10.1186/1471-2458-7-168

7. Kelly RH, Russo J, Holt VL, et al. Psychiatric and substance use disorders as risk factors for low birth weight and preterm delivery. *Obstet Gynecol*. 2002;100(2):297-304. doi:10.1016/S0029-7844(02)02014-8

8. Corsi DJ, Walsh L, Weiss D, et al. Association Between Self-reported Prenatal Cannabis Use and Maternal, Perinatal, and Neonatal Outcomes. *JAMA*. 2019;322(2):145. doi:10.1001/jama.2019.8734

9. Forray A, Foster D. Substance Use in the Perinatal Period. *Curr Psychiatry Rep*. 2015;17(11):91. doi:10.1007/s11920-015-0626-5

APPENDIX

Table A: International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes for pregnancy related diagnoses, substance use diagnoses, any mental illness, and severe mental illness

Condition/Diagnosis	Diagnosis (DX) or Procedure (PR)	ICD-10 Codes
Pregnancy related diagnosis		
Encounter for normal pregnancy	DX	Z34.xx
Outcome of delivery	DX	Z37.xx
Pregnancy with abortive outcome	DX	O00.xx - O08.xx
Edema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium	DX	O09.xx
Other maternal disorders predominantly related to pregnancy	DX	O10.xx - O16.xx
Maternal care related to the fetus and amniotic cavity and possible delivery problems	DX	O20.xx - O29.xx
Complications of labor and delivery	DX	O30.xx - O48.xx
Encounter for delivery	DX	O60.xx - O77.xx
Single spontaneous delivery	PR	O80.xx
Single delivery by Cesarean delivery	PR	O82.xx
Substance related diagnosis (SRD)		
Alcohol related disorders	DX	F10.xx
Opioid related disorders	DX	F11.xx
Cannabis related disorders	DX	F12.xx
Sedative, hypnotic, or anxiolytic related disorders	DX	F13.xx
Cocaine related disorders	DX	F14.xx
Other stimulant related disorders	DX	F15.xx
Hallucinogen related disorders	DX	F16.xx
Nicotine dependence	DX	F17.xx
Inhalant related disorders	DX	F18.xx
Other psychoactive substance related disorders	DX	F19.xx
Serious mental illness (SMI)		
Schizophrenia	DX	F20.xx
Schizotypal disorder	DX	F21.xx
Persistent delusional disorder	DX	F22.xx
Schizoaffective disorder	DX	F25.xx
Manic episode	DX	F30.xx
Bipolar disorder	DX	F31.xx
Major depressive symptom severe	DX	F32.2-F32.3, F33.2-F33.2
Non-Serious mental illness (Non-SMI)		
Delusional disorders	DX	F22
Brief psychotic disorders	DX	F23
Other psychotic disorder not due to a substance or known physiologic condition	DX	F28
Unspecified psychosis	DX	F29
Major depressive disorder mild or moderate	DX	F32.0-F32.1, F32.4-F32.9, F33.0-F33.1, F33.4-F33.9
Persistent mood disorder	DX	F39
Reaction to severe stress, and adjustment disorders (includes post-traumatic stress syndrome (PTSD)	DX	F43.xx
Obsessive compulsive disorder	DX	F42.xx
Phobic anxiety disorder	DX	F40.xx
Other anxiety disorder	DX	F41.xx
Eating disorder	DX	F50.xx
Specific personality disorder	DX	F60.xx
Impulse disorder	DX	

Table B: International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes for indicators for delivery hospitalizations with severe maternal morbidity (SMM).

Condition/Diagnosis	Diagnosis (DX) or Procedure (PR)	ICD-10 Codes
Indicators for delivery hospitalizations with severe maternal morbidity		
1. Acute myocardial infarction	DX	I21.xx, I22.x
2. Aneurysm	DX	I71.xx*, 179.0
3. Acute renal failure	DX	N17.x, O90.4
4. Adult respiratory distress syndrome	DX	J80, J95.1, J95.2, J95.3, J95.82x, J96.0x, J96.2x R09.2, J96.20, J96.21, J96.22, R09.2
5. Amniotic fluid embolism	DX	O88.1x * x=1st, 2nd and 3rd trimester
6. Cardiac arrest/ventricular fibrillation	DX	I46.x, I49.0x * Ventricular flutter
7. Conversion of cardiac rhythm	PR	5A2204Z, 5A12012
8. Disseminated intravascular coagulation	DX	D65, D68.8, D68.9, O72.3 *see comments for pregnancy related codes
9. Eclampsia	DX	O15.0x, O15.1, O15.2, O15.9, O14.22 – HELLP syndrome (HELLP), second trimester, O14.23 – HELLP syndrome (HELLP), third trimester, HELLP syndrome is not included currently (ranges in severity, more research is needed)
10. Heart failure/arrest during surgery or procedure	DX	I97.12x, I97.13x
11. Puerperal cerebrovascular disorders	DX	I60.xx- I68.xx, O22.51, O22.52, O22.53, I97.81x, I97.82x, O873, 674.0x – no crosswalk
12. Pulmonary edema / Acute heart failure	DX	J81.0, I50.1, I50.20, I50.21, I50.23, I50.30, I50.31, I50.33, I50.40, I50.41, I50.43, I50.9, (-) Add 5th character: 0=unspecified 1=acute 2=chronic 3=acute on chronic, 0=unspecified – keep since it is commonly used among health care providers terminology in medical records
13. Severe anesthesia complications	DX	O74.0 , O74.1 , O74.2, O74.3, O89.0x, O89.O89.2, *O89.01 Aspiration – decided to keep due to difficulties of separation from “Aspiration Pneumonitis”
14. Sepsis	DX	O85 T80.211A T81.4XXA or severity: R65.20 (or septic shock, see indicator “Shock”) or severity: R65.20 (or septic shock, see indicator “Shock”) or R65.20, A40.0, A40.1 , A40.3 , A40.8, A40.9, A41.0, A41.1, A41.2, A41.3, A41.4, A41.50, A41.51, A41.52, A41.53, A41.59, A41.81, A41.89, A41.9, A32.7 or A40.x, A41.x, A32.7
15. Shock	DX	O75.1, R57.x, R65.21, T78.2XXA, T88.2 XXA, T88.6 XXA, T81.10XA , T81.11XA, T81.19XA
16. Sickle cell disease with crisis	DX	D57.0x, D57.21x, D57.41x, D57.81x, (5th digit: unspecified, acute chest syndrome or splenic sequestration)

Table B continued: International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes for indicators for delivery hospitalizations with severe maternal morbidity (SMM)

Condition/Diagnosis	Diagnosis (DX) or Procedure (PR)	ICD-10 Codes
Indicators for delivery hospitalizations with severe maternal morbidity		
17. Air and thrombotic embolism	DX	I26.x, O88.0x, O88.2x, O88.3x, O88.8x, 673.3x, 673.8x, O88.011-O88.019, 088.02, O88.03, O88.211-O88.219, O88.22, O88.23, O88.311-O88.319, O88.32, O88.33, O88.81, O88.82, O88.83, O88.011-O88.019, 088.02, O88.03, O88.211-O88.219, O88.22, O88.23, O88.311-O88.319, O88.32, O88.33, O88.81, O88.82, O88.83, * I26.0- Pulmonary embolism with acute corpulmonale (acute right ventricle heart failure)
18. Blood transfusion	PR	30233H1′,’30233L1’, ‘30233K1’, ‘30233M1’,‘30233N1′,’30233P1′, ’30233R1′,’30233T1’, ‘30233H0′, ’30233L0’, ‘30233K0’, ‘30233M0’, ‘30233N0′,’30233P0′,’30233R0′, ’30233T0’,‘30230H1′,’30230L1’, ‘30230K1’, ‘30230M1’, ‘30230N1′,’30230P1′,’30230R1′, ’30230T1’, ‘30230H0′,’30230L0’, ‘30230K0’, ‘30230M0’, ‘30230N0′,’30230P0′,’30230R0′,’30230T0’, ‘30240H1′,’30240L1’, ‘30240K1’, ‘30240M1’, ‘30240N1′,’30240P1′,’30240R1′,’30240T1’, ‘30240H0′,’30240L0’, ‘30240K0’, ‘30240M0’, ‘30240N0′,’30240P0′,’30240R0′,’30240T0’, ‘30243H1′,’30243L1’, ‘30243K1’, ‘30243M1’, ‘30243N1′,’30243P1′,’30243R1′,’30243T1’, ‘30243H0′,’30243L0’, ‘30243K0’, ‘30243M0’, ‘30243N0′,’30243P0′,’30243R0′,’30243T0’, ‘30250H1′,’30250L1’, ‘30250K1’, ‘30250M1’, ‘30250N1′,’30250P1′,’30250R1′,’30250T1’, ‘30250H0′,’30250L0’, ‘30250K0’, ‘30250M0’,‘30250N0′,’30250P0′,’30250R0′,’30250T0’,‘30253H1′,’30253L1’, ‘30253K1’, ‘30253M1’, ‘30253N1′,’30253P1′,’30253R1′,’30253T1’, ‘30253H0′,’30253L0’, ‘30253K0’, ‘30253M0’, ‘30253N0′,’30253P0′,’30253R0′,’30253T0’, ‘30260H1′,’30260L1’, ‘30260K1’, ‘30260M1’, ‘30260N1′,’30260P1′,’30260R1′,’30260T1’, ‘30260H0′,’30260L0’, ‘30260K0’, ‘30260M0’, ‘30260N0′,’30260P0′,’30260R0′,’30260T0’, ‘30263H1′,’30263L1’, ‘30263K1’, ‘30263M1’, ‘30263N1′,’30263P1′,’30263R1′,’30263T1’, ‘30263H0′,’30263L0’, ‘30263K0’, ‘30263M0’, ‘30263N0′,’30263P0′,’30263R0′,’30263T0’
19. Hysterectomy	PR	0UT90ZZ, 0UT94ZZ, 0UT97ZZ, 0UT98ZZ, 0UT9FZZ
20. Temporary tracheostomy	PR	0B110Z, 0B110F, 0B113, 0B114
21. Ventilation	PR	5A1935Z, 5A1945Z, 5A1955Z