

MATERNAL PSYCHOSOCIAL ADVERSITY AND PREGNANCY AND DELIVERY COMPLICATIONS ASSOCIATED
WITH PERINATAL DEPRESSION AND ANXIETY: A CUMULATIVE INDEX APPROACH

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2021

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ABSTRACT

Yasmin Viviana Barrios: Maternal Psychosocial Adversity and Pregnancy and Delivery Complications Associated with Perinatal Depression and Anxiety: A Cumulative Index Approach
(Under the direction of Joanna Maselko)

Background. Despite current screening practices and known risk factors, perinatal mental health is a leading public health concern. Several key gaps remain in the perinatal mental health literature. First, despite the higher prevalence of anxiety, anxiety and its comorbidity with depression during pregnancy receives less clinical and research attention. Second, the accumulation of psychosocial factors in relation to antepartum mental health has been understudied. Third, research of postpartum mental health has infrequently focused on new-onset symptoms. Fourth, while psychosocial and obstetric risk factors don't necessarily occur in isolation, exposure to the cumulative occurrence of these factors and mental health is understudied.

Methods. Using cross-sectional data from pregnant women (n=1,797), we examined the association between eight psychosocial factors and antepartum mental health. Specifically, we estimated the association between a psychosocial adversity index on 1) the persistence of depression and anxiety, individually, and on 2) the comorbid occurrence, throughout the second and third trimesters of pregnancy. In our second analysis, we utilized longitudinal data from women (n=378) without elevated mental health symptoms in pregnancy to estimate the relationship between nine pregnancy and delivery complications and the new onset symptoms of depression and/or anxiety at 3 or 12 months postpartum.

Results. Compared to women with a low psychosocial adversity index score, women reporting a high level of psychosocial adversities (43% of sample) had 2.06 (95% Confidence Interval:1.51-2.82)

times higher adjusted odds of endorsing only depressive symptoms or anxiety, and 5.57 (95% Confidence Interval:3.95-7.85) times higher the odds of endorsing comorbid symptoms at either the second or third trimester. The associations for persistent symptoms of depression and anxiety were of similar direction and magnitude. Women with high pregnancy and delivery complications (23% of sample) had 1.71 (95% Confidence Interval:1.13-2.59) times the risk of incident mental health symptoms postpartum, compared to women with low complications.

Conclusion. Women with high psychosocial adversities during pregnancy may be at higher risk of elevated depressive symptoms and anxiety in pregnancy. Even in absence of mental health symptoms in pregnancy, women with an accumulation of pregnancy and delivery complications may be at higher risk of mental health symptoms during postpartum.

I dedicate this dissertation to the matriarchs in my life. Specifically, my abuelita Tomasa and abuelita Maria del Refugio, who's prayers from afar and from heaven accompany me at every step. Their strength, ingenuity, and tenderness are my foundation and inspiration.

ACKNOWLEDGEMENTS

Completing this dissertation was indeed a marathon and there are so many individuals that helped me make it across the finish line. I would like to take this opportunity to wholeheartedly express my gratitude to them.

First, to my dissertation committee members, Joanna Maselko, Brian Pence, Andy Olshan, Samantha Meltzer-Brody, Stephanie Engel, who dedicated their time and contributed their expertise to answering my questions, all of which helped guide and shape this work.

To, Joanna 'Asia' Maselko, thank you for being my dissertation chair these last two years. Although we worked separated by oceans, across time zones, and through a pandemic it never felt like we were anything other than a team. Due to the circumstances of pandemic life, it would have been easy to see our weekly meetings as a burden, but your enthusiasm reminded me that you were as excited as I was to see progress. Thank you for giving me the space to struggle and rest but never abandoning me when I needed the encouragement to push harder and the guidance to persevere.

To Brian Pence and Andy Olshan, thank you both for being great professors during coursework. Your courses were the foundation of my analysis and interpretation. Thank you for the feedback on my analysis plan and for asking questions that stretched my skills and improved the overall quality of my work. To Samantha, your substantive area contributions pushed me to further explore the potential impact of my findings and I thank you for the enthusiasm you showed for my research questions. I appreciate the encouragement you three provided and your flexibility as the pandemic turned my timeline upside down.

To Stephanie, thank you for so much for taking on the role of my advisor when I was left without one. You helped me craft my research questions and helped me form a wonderful dissertation committee with your guidance. I appreciate your help on so many levels. Thank you for getting to know me well enough to understand what approaches would be most useful in getting me over hurdles during my training. Thank you for always listening and having kind words that motivated me to use my resources and think outside of the box to solve any problems that came along. I also want to thank you for demonstrating how to be a good mentor and for connecting me with opportunities where I could act as a mentor. Thank you for not giving up on me and for not letting me give up on myself.

I also appreciate the incredible programming support from Kim Ludwig and Chris Weisen, without their trouble shooting and help I would not have quickly overcome some obstacles in my analysis.

Second, to the many important mentors who helped me carve out my educational path. Karlotta Rosebaugh, you became my advisor my freshman year of college and have done everything in your power to ensure that I completed my PhD, including 5 am wakeup calls to remind me to start writing. Thank you for never accepting my self-doubt as truth and for all of your help editing my work and with problem solving. Dr. Michelle A. Williams and Dr. Bizu Gelaye, thank you both for introducing me to epidemiology and allowing me to work with you on intimate partner violence and mental health research. You've always demonstrated impressive work ethic and an unshakable determination to do high quality and meaningful research; I aim to follow your example in all my work.

To my science fair teacher Joyce 'Starkey' Stark and her husband Dr. Richard Stark, thank you for being the first to teach me about the magic of science and the scientific method. Dr. Stark, you taught me how to remain composed while answering the difficult questions and I am saddened that you left this world before you could ask me questions at my defense. Mr. Neubauer my fourth grade teacher,

Ms. Mckeith my English language teacher, and Mr. Rounds my high school math teacher, made a meaningful impact in my early education and I am grateful to them.

Third, to UNC and the Epidemiology Department, especially Valerie Hudock and Jennifer Moore, who are amazing and handling the problems and concerns of all the students and always have a kind word, solution, or reminder to keep you enrolled. Chandra Caldwell, thank you for helping me find study spaces and for your help in preparing my grant applications. I am even more grateful for the motivating conversations. Dr. Karin Yates, thank you for allowing me to teach with the best TA team ever (Monica Jimenez, Kam Reynolds, Sydney Thai) and for showing me how fulfilling teaching can be. Dr. Charlie Poole, thank you for the many hours spent discussing epi methods and answering my questions without judgement. Additionally, I would like to thank my Co-Chairs (LB Klein, Hannabeth Franchino-Olsen, Josie Caves) Gender Based Violence Research Group and Agnieszka McKort, for working to bring together the researchers and practitioners working on Gender Based Violence to engage in important discussions.

A special thank you to all of my writing groups created over Zoom. As the Covid-19 pandemic eliminated the ability to study and write at coffee shops (Market Street Coffee) or form study groups, we used Zoom to create virtual study sessions for accountability and support. Dirk Davis, Venita Embry, Jennifer Richmond, Cherrel Manley, Brook Staley, Andrea Negrete, Laura Crystal Magana, and many others became my working buddies at different times and all were incredibly instrumental to helping me finish my dissertation during the pandemic.

Additionally, my time as a doctoral student was enriched by my fellow students. I learned so much from them and consider myself lucky to have such thoughtful and intelligent classmates. Alex Breskin and Paul Zivich, thank you for always engaging with me in such interesting discussions about difficult epi concepts. Thank you, Samatha Drover, Shahar Shmuel, Josie Caves, Lauren Graybill, Jessica Islam, and Nidia Rodriguez-Ormaza, you were a constant support and great study partners. Nidia, you are forever my epi-sister, forged in the fires of Ridgewood and anointed by Mahoney.

Fifth, to the friends who never faltered and knew when I needed a cheering squad to motivate me. Thank you for keeping me grounded in the real world and for helping me make memories outside of the classroom when I was overwhelmed.

To my UNC “Squad,” thank you for welcoming me into your lives and passing down all of your hard learned lessons and brilliant insight on everything from negotiating in academia to proper brunching. Thank you for doing everything at a PhD level. Thank you, Dr. Yesenia Merino and Dr. Deshira Wallace for simultaneously challenging me and accepting.

To my Boston Strong crew, thank you for helping me find my voice. Especially, Thalia Cordon, thank you for sharing your strength. To my Seattle Sisters, thank you for reminding me that I was working hard to complete this stage of my education so that I could come home, especially Ruthy Gonzales, who convinced me that I can do anything I set my mind to.

Monica Castro, thank you for always having time to talk about my dissertation, for keeping me focused and sane, and for your support at every stage of my pursuit of this degree. As you prepare to follow your dreams, I hope to be a light on your path, as you were in mine. If they awarded doctorates for friendship, you’d be granted a PhD.

Finally, to my family. To my father, Miguel Barrios, gracias por su sacrificios y por darme la oportunidad de hacer de mi vida lo que yo sueño. To my mother Juliana Herrera, usted es la razón por la cual tengo fuerza y felicidad en mi vida. Puedo hacer todo lo que me propongo porque usted me tiene fe. To my brother, Miguel A., thank you for being an inspiration and for always making me laugh when I least expect it with your clever humor. To my sister Brenda, thank you for your hugs and for making me feel like you look up to me. Thank you for my nephew as well, Milo Julian is my absolute joy and my motivation to finish my dissertation so that I can spend time just being Tia Yasmin.

PREFACE

Funding information:

The Pregnancy, Infection, and Nutrition study was supported by The National Institute of Child Health and Human Development, National Institutes of Health Grants HD37584, HD39373, and The National Institute of Diabetes and Digestive and Kidney Diseases Grant DK61981. The General Clinic Research Center was supported by the National Institutes of Health General Clinical Research Centers program of the Division of Research Resources Grant RR00046.

Approvals:

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All procedures of this study were approved by The University of North Carolina Institutional Review Board. Informed consent was obtained from all individual participants included in the study.

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LIST OF ABBREVIATIONS

ACE	Adverse Childhood Experiences
AP	Antepartum
C-section	Cesarean-section
GA	General Anxiety
GDM	Gestational Diabetes
IPV	Intimate Partner Violence
LBW	Low Birth Weight
PDC	Pregnancy and Delivery Complications
PIH	Pregnancy Induced Hypertension
PP	Postpartum
PRF	Psychosocial Risk Factor
PTD	Preterm Delivery
SES	Socioeconomic Status
SLE	Stressful Life Events
SS	Social Support

CHAPTER 1. BACKGROUND AND SPECIFIC AIMS

1.1 Public Health Burden

Although the burden of perinatal depression is high for women in both AP and PP, prevalence estimates vary widely.¹ It is accepted that one in ten mothers will experience postpartum (PP) depression, with rates reaching up to 13% in the first three months and then declining to 6.5% after seven months PP.² Prevalence estimates for antepartum (AP) depression range from 7-38%³⁻¹⁰ and, in the US, minor depression has been found in 16.6% of pregnant women compared to 11.4% of their non-pregnant counterparts.⁶ Depression includes feelings of guilt or worthlessness, difficulty concentrating, sleeping too much or too little, loss of interest in activities, and can include recurring thoughts of death, suicide or hopelessness.¹¹ When depression is evaluated at different trimesters, it has ranged from 7-15%.⁹ A meta-analysis of 21 studies reported the prevalence of depression at first, second, and third trimester was 7.4%, 12.8%, and 12.0%, respectively⁵ and while some studies show symptoms remain constant from the 2nd to the 3rd trimester,³ others report the highest prevalence is actually in the third.⁸ In terms of incidence, a longitudinal study beginning in early pregnancy and through a year PP, found that of the 7.3% women who reported a new occurrence of perinatal depression, 1.6% of them had their first episode during pregnancy and 5.7% had the onset in the first 12 months PP.¹² A separate study, reported the incidence of PP depressed mood to be similar, at 6.6%¹³ and demonstrates that pregnancy is a vulnerable period not only for the recurrence, but the onset of depression.

Perinatal anxiety is even more prevalent than depression, and yet has received less clinical and research attention.¹⁴ Symptoms of general anxiety (GA) affect anywhere from 25-45% of perinatal women^{4,15} and estimates of diagnosed generalized anxiety disorders are higher in PP women than the

general population.¹⁶ In one systematic review the prevalence of anxiety in AP ranged from 13-21%^{17,18} and from 11-17% in PP¹⁹ demonstrating the wide range in estimates. Some level of anxiety is expected in the perinatal period but GA symptoms are concerning and include excessive worrying, feeling irritable or agitated, uncontrollable sense of anxiousness, and an inability to concentrate or sleep well.²⁰ Additionally, pregnancy specific anxiety, a separate and distinct condition surrounding worries and fears about pregnancy and childbirth, is found to occur more often among women with high GA levels.²¹ GA symptoms have been reported to have a U-shaped pattern in pregnancy, driven by worries surrounding the start and end of pregnancy,²² with **severe anxiety** reported to be as high as 48% in the first trimester, 11% in the second, and 30% in the third.²³ Similarly, a systematic review of 102 studies covering 34 countries found anxiety symptoms in the third trimester to be highest at 24.6%.¹⁹ **One study evaluating the severity of GA found that all of the women reported either moderate (71%) to severe (29%) levels of anxiety in the 3rd trimester.**²³ Anxiety has a mean age of onset at 20 years which coincides with reproductive age²⁴ and although incidence in the perinatal period is not often assessed, one study reported the onset of anxiety in the PP to be 2.2%.¹⁸

The comorbid occurrence of depression and anxiety is understudied in the perinatal period.²⁵

In a nationally representative sample of the U.S., it was estimated that half of depressed patients also experience symptoms meeting the criteria for one or more mood and anxiety disorders.²⁶ A small study of a community sample of women showed that 10-50% of those with anxiety symptoms also reported depressive symptoms.²⁰ However, a recent meta-analysis reported lower estimates of comorbid occurrence of depression and anxiety to be 9.5% during pregnancy and 7.6% in the PP period.¹⁹ In a study of women diagnosed with major depressive disorder, the severity of anxiety seemed to play a role in depressive symptoms; at 8-weeks PP it was 13% and the authors noted that depressive symptoms differed by state anxiety status with women who reported high state anxiety showing significantly elevated depressive scores as well.²⁷ Although anxiety disorders do occur in the absence of depression,

the identification and management of comorbidity in the perinatal period are important given the adverse effects of anxiety and depression on maternal and child outcomes. **Continued efforts to describe the symptoms across the perinatal period remain important for understanding maternal mental health.**

1.2 Maternal and Child Outcomes

Untreated depression and anxiety in AP negatively affect maternal health, pregnancy outcomes, and child development. Depressed and anxious mothers are more likely to engage in substance use (drug, alcohol, smoking),²⁸ have inadequate diets²⁹ or suffer from eating disorders,^{30,31} all of which impact the progression of a healthy pregnancy. There is also a reduction in overall quality of life³² and in cases of severe depression, an increase in suicide ideation and attempts.³³ Women with anxiety have decreased effective coping strategies, perceive a greater risk during pregnancy, have increased fear of difficult delivery^{34,35} and for some, an increased preference for Cesarean-section (C-section).³⁵⁻³⁷ Women with depressive symptoms face difficulties in carrying out normal daily activities and are more likely to delay receiving prenatal care, which can prevent managing or identifying pregnancy complications.²⁹

Complications consistently linked with depression and anxiety range from pregnancy induced hypertension syndrome,³⁸ pregnancy anemia,³⁴ low birth weight,^{39,40} small for gestational age, shorter gestation,⁴¹ less optimal obstetric complications scores⁴² and increased frequency of neonatal intensive care unit admission^{43,44} for the newborn, and spontaneous preterm delivery, which is a leading cause of infant morbidity and mortality.⁴⁵ Diego et. al., reported that depressed women had a 13% greater incidence of premature delivery and a 15% greater incidence of low birthweight,⁴⁶ which in turn, are linked with morbidity in adulthood.^{47,48,49} The prenatal origins theory posits that fetal programming explains the relationship between these birth outcomes and later disease states.⁵⁰

Maternal depression and anxiety affect fetal development, newborn functioning,⁵¹ and psychological development of offspring.⁵² It is hypothesized that depression and anxiety increase maternal stress hormones, such as cortisol, which cross the placental barrier and may restrict fetal brain development and fetal growth^{42,53,54} resulting in smaller fetuses at lower birth weight.⁴⁶ Higher fetal activity has also been seen among women with high levels of anxiety⁵⁵ and it is believed that this increased fetal activity interferes with adequate fetal growth.⁴² Newborns of depressed and anxious mothers exhibit more stress behaviors, spend more time fussing and crying,⁴⁶ and show less optimal performance on the Brazelton assessment.⁵⁶ Additionally, reduced quality of maternal bonding and responsiveness impacts cognitive development.⁵⁷

Mothers with higher levels of anxiety during pregnancy report more problem behavior, hyperactivity or inattention, emotional symptoms, peer relationship and conduct problems, and less pro-social children.⁵⁸ Maternal depression and anxiety in the PP are associated with more distress to novelty and emotional problems in 3-8 month olds¹⁸ and with increased negativity, poor fear regulation, and reduced social engagement at 9 months.⁵⁹ O'Connor et. al., found that high levels of perinatal anxiety and depression more than doubled the rate of behavioral and emotional problems seen in children at 4 years of age.⁶⁰ The long term impact is seen as increased behavioral problems in adolescence for children of depressed and anxious mothers.^{61,62} Longitudinal studies have reported that children of perinatally depressed mothers have an increased risk of depression among 16 year-old adolescents (OR: 4.99, 95% CI: 1.68-14.70)⁶³ and a risk of depression among 18 year-olds.⁶⁴

Comorbid occurrence, severity, and persistence of depression and anxiety symptoms have stronger associations with maternal and child outcomes.⁶⁵ Field et. al., reported that chronic levels of prenatal depression were associated with shorter gestational age and lower birthweight of newborns, and also highlighted that comorbid depression was prevalent with other conditions including chronically high anxiety.^{42,66} In an observational pregnancy cohort, depression combined with anxiety increased the

risk of spontaneous preterm birth but not for birthweight.⁶⁷ There remains a need to study comorbid depression and anxiety symptoms across pregnancy and PP.¹⁸

1.3 Risk Factors of Interest

The past 40 years of research has identified demographic, psychosocial, and obstetric risk factors for perinatal depression and anxiety. Increased risk has been associated with factors such as younger or older age,^{36,68,69} minority race, immigrant status, unemployment,⁶⁸ low education,⁷⁰ low income or socioeconomic status⁶⁸ and facing financial difficulties.⁷¹ Smoking, alcohol use, and substance abuse⁷² have also been shown as associated with increased risk of depression^{73,74} and anxiety,³⁶ but the direction of the relationship is often not clear. Women who report unplanned or mistimed pregnancies⁷³ tend to endorse higher levels of anxiety. However, constructs such as higher levels of religiosity, high self-esteem locus of control,⁷⁵ and having positive coping styles⁷⁶ have been found to be inversely associated with anxiety and therefore these factor are seen as protective or offering a buffer for managing and reducing symptoms. The most often cited risk factor for current depression is having a history of depression or anxiety symptoms, either diagnosed, self-reported, or a family history of mental health problems.^{74,77}

Efforts to differentiate risk factors for depression and anxiety by trimester⁷⁸ and for comorbid occurrences⁷⁶ often result in varying factors identified across studies. Van de Look et al, evaluated both depression and anxiety during early and late pregnancy and identified that being foreign born, not living with partner and having an unplanned pregnancy were only associated with depression and anxiety symptoms in early pregnancy, but that history of depression, low level education, negative life events, and severe nausea, extreme fatigue, and lack of exercise were associated with overall depression and anxiety.⁷⁹ Whereas, Bunvicus et al., reported trimester specific risk factors included low education, previous history of depression, and the occurrence of psychosocial stressors at the end of pregnancy.⁷⁸ A longitudinal study evaluating chronic depression and anxiety symptoms across pregnancy found that

women with less optimism had a four-fold increased risk of developing chronic symptoms, and that partner tension was an exclusive predictor of chronic anxiety but, poor physical health, unplanned pregnancy and infertility treatments predicted chronic depression.⁷⁶ These studies demonstrate that efforts to identify numerous risk factors may depend upon the factors available in the study and whether depression or anxiety is measured by trimester or by chronicity. **Few studies have evaluated the important well-established risk factors in relation to severity, pattern, and comorbidity in a single study for the AP period.**⁸⁰⁻⁸³

1.4 Psychosocial Factors

The psychosocial factors that consistently emerge as relevant include: intimate partner abuse, serious life events, economic stressors, and low social support.^{10,70,84,85} The impact of neighborhood safety and gender discrimination on depression have been shown in the general population but are understudied factors in the AP period. Therefore, these risk factors will be considered for Aim 1 and are described below:

Intimate Partner Violence (IPV) occurs frequently and has a strong association with AP⁸⁶ and PP depression.^{87,88} One in four women in the US will experience abuse from an intimate partner in their lifetime, this is similar for women in North Carolina, where 35% of women over 18 years old report lifetime physical, sexual, and psychological abuse.⁸⁹ A Boston-based study reported that lifetime violence was associated with AP depression and that recent abuse showed a stronger association, with an Odds Ratio of 1.77 (95% CI: 1.14–2.74).⁹⁰ A systematic review of 70 studies reported that abuse was associated with AP depression and moderate effect sizes were seen for any abuse and for type of abuse (physical abuse, sexual abuse, and emotional).⁹¹ One longitudinal study of pregnant women also reported that partner tension was an exclusive predictor of anxiety⁷⁶ and since pregnancy has been demonstrated as a vulnerable period for abuse,⁹² IPV constitutes an ongoing psychosocial exposure of importance.

According to the weathering hypothesis, stressful life events (SLE) can lead to an accumulation of stress and increase vulnerability⁹³ to depression and anxiety. Instruments used to evaluate SLE measures stress related to events such as: family death or serious illness, moving, homelessness, divorce, and trouble paying bills that have accumulated over a life time or a specific period.⁹⁴ An evaluation of nationally representative data collected in 27 states, found approximately 70% of US women in 2010 reported experiencing one or more SLE in the year before their infant's birth.⁹⁵ In a separate nationally representative study of Swedish pregnant women, those with two or more SLE within the past year, were 3 times as likely to have elevated depression scores.⁹⁶ In addition to the individual events, researchers have assessed whether the events are perceived as positive or negative and have found the negative events to remain significantly associated depression.⁸⁴ SLE, when evaluated individually or cumulatively, find that as the number of events increase so does risk for perinatal depression.⁹⁷

Stress related to economic hardships has been associated with an increase in mental health symptoms. This has been demonstrated at the population level when examining mental health during economic recessions, even if the mechanism has not been confirmed.⁹⁸ At the individual level and among pregnant women, the association of socioeconomic status (SES) with depression and anxiety has been inconsistent and varies by the indicator or aspect of SES that is measured.⁸⁴ For example, in a Hungarian study of women, those who were unemployed and were in the lowest socio-economic stratum, as measured by the Family Income Scale, exhibited higher levels of depression and anxiety during the first trimester of pregnancy compared to the other categories (low and middle stratum).⁶⁸ In a Canadian study examining whether symptoms of anxiety were sustained 8 weeks into the PP period, it was found that women who reported difficulty in managing their household income had persistent symptoms into the PP period, although this association did not reach statistically significant levels after adjustment for confounders.⁹⁹ Struggling financially was strongly and independently associated with a 2-

fold increased risk for worse mental health across all racial and ethnic groups in a study of pregnant women living in a low income United Kingdom city.¹⁰⁰ This study also concluded that financial concerns were the most important and independently associated factor with mental health symptoms overall, and that for some groups, the specific items (employment and education) were more important.¹⁰⁰ Overall, this may indicate that capturing economic stress rather than these markers of SES may be more useful for assessing depression and anxiety risk among pregnant women.

Experiencing or witnessing neighborhood violence has been associated with depression in adolescents,¹⁰¹ older adults,¹⁰² and urban women,¹⁰³ but few studies include pregnant women. One study that did evaluate the role of neighborhood safety among pregnant African American women reported that high levels of perceived crime were associated with psychological distress, which included depression and anxiety.¹⁰⁴ In a pregnancy cohort based in New Orleans that evaluated both intimate partner violence and neighborhood safety, it was found that indicators of neighborhood crime and safety were significantly associated with probable depression and Post-Traumatic Stress Disorder.¹⁰⁵ Finally, a study carried out among pregnant women living in Durham, North Carolina, evaluated various aspects of the built environment (external physical conditions of the home, infrastructures, and resources that are created or modified by people, including schools, workplaces, parks/recreations areas, business areas, roads) and psychosocial outcomes. After adjusting for appropriate covariates, their results showed that perceived stress was reported more frequently among residents with a less hospitable residential environment, characterized by more housing damage, property disorder, vacancy, and violent crime.¹⁰⁶ They also found that depression was more frequently reported among women who resided in areas with property damage, violent crime, and nuisances.¹⁰⁶ Neighborhood safety is an important and understudied contributor to poor mental health among pregnant women.

Discrimination is a type of stressor that, inherently is not experienced equally across gender, race, or SES.¹⁰⁷ Findings from studies in the general population indicate that discrimination is associated

with mental and physical health.¹⁰⁸ Discrimination may contribute to the disparities seen in the prevalence of depression¹⁰⁹ since women experience depression at twice the rate that men do.¹¹⁰ When evaluating PP depression among father and mother dyads, depressive symptoms were greater among mothers (10% vs 6%) than fathers, even after controlling for SES and social support.¹¹¹ Among pregnant women, racial discrimination and discrimination based on nationality, immigration status, and acculturation level have been linked with depressive symptoms.¹¹² Among low-income, inner city women, every day discrimination due to any cause was reported by both African American and white women.¹¹³ Also, discrimination specific to gender and economic status among both groups of women was found to be positively associated with depressive symptoms.¹¹⁴ Based on self-reported experience of gender discrimination, a Michigan-based study found similar proportions of white women and African American women reported 'Some' (~33%) and 'High' (~17%) levels of gender discrimination.¹¹⁴ Gender discrimination and neighborhood safety, while understudied in the context of perinatal depression, address broader constructs of psychosocial adversity and merit continued attention in maternal mental health.

Lack of social support (SS) can increase a pregnant woman's risk of depression and anxiety by limiting her ability to cope with stressful events and changes related to pregnancy.¹⁰ Evaluating SS objectively (instrumental and emotional support) received from friends, family and partners, may be challenging because it has been noticed that depressed women tend to feel less supported than they objectively are,¹¹⁵ therefore, it is important to also measure perceived support.¹¹⁶ Adequate SS has been consistently shown to be a protective factor in the risk for major depression,¹¹⁷ whereas a perceived lack of total SS leads to increased levels of depression,⁸⁴ In a study of immigrants in Canada, they showed that pregnant women with higher scores on the depression screener reported less satisfaction with SS and also had fewer individuals (friends, relatives and people from their own ethnic group) in their network.¹¹⁸ Two pathways have been used to describe how SS works to reduce the risk of depression;

the first is a direct protective pathway that improves maternal health behavior, increases positive feelings and enhances emotional regulation, the second is an indirect mediating pathway that helps attenuate the negative effects¹¹⁷ of stress.^{119,120} One study evaluating the causal relationship between SS and depression during early pregnancy in a Peruvian cohort found that having a low number of people to provide support (OR:1.62, 95% CI: 1.12, 2.34) and a low satisfaction with the support received (OR:1.41, 95% CI: 0.99, 1.99) prior to pregnancy and in early pregnancy were associated with an increased risk of depression.¹²¹ Considering that SS can be explored as a risk factor when it is perceived as low, it can be considered as part of the psychosocial adversity faced in the AP period.

1.5 Pregnancy and Delivery Complications

Few studies evaluate the cumulative impact of being exposed to multiple complications across pregnancy and delivery, especially in relation to both depression and anxiety. Symptoms of Post-traumatic stress (an anxiety disorder) are common among women who report having experienced a traumatic birth with severe childbirth pain or fear for her or her child's life.¹²² The trauma experienced may represent a more extreme example of the psychosocial impact of complications faced during pregnancy and delivery. However, to a lesser degree, having a mismatch between expectations and how the pregnancy and delivery actually progresses, may increase maternal vulnerability to depression and anxiety.¹²³ Unexpected PDC may include: preeclampsia, hyperemesis, premature labor, as well as delivery related complications, like emergency C-section, instrumental delivery, and excessive bleeding intrapartum.

In a 2004 synthesis of the literature, Robertson et. al., reported on results from 16 large-scale studies of 9,500 women and concluded that these pregnancy and delivery complications have a small but significant effect on the development of PP depression^{115,124,125} and anxiety.¹²⁶ Additionally, in a population-based study of Danish registries, the authors found women with the conditions of hyperemesis gravidarum, gestational hypertension, pre-eclampsia, and C-section were associated with

an increased risk for the onset of postpartum depression.¹²⁷ Since these PDC may not necessarily occur in isolation (e. g., emergency cesarean section may be a consequence of preeclampsia) it is possible that as these events accumulate, the risk for PP depression and anxiety also increases. Further exploration of the psychosocial burden of experiencing multiple complications across pregnancy and delivery, especially in relation to anxiety, can help us to better understand the cumulative impact on PP mood and anxiety disorders. The risk factors considered for Aim 2 include pregnancy induced conditions and events related to delivery and newborn outcomes that are considered to produce worry and stress for mothers.

Gestational Diabetes Mellitus (GDM) and Pregnancy Induced Hypertension (PIH) can cause significant concern for mothers throughout pregnancy. A small cross sectional study found that depression symptoms were reported more often by women with GDM than those without, 20% and 13%, respectively¹²⁸ and that women with GDM were 3.79-times more likely to have a history of depression (OR: 3.79; 95% CI:1.07, 13.45).¹²⁸ A retrospective cohort using data from New Jersey Medicaid administrative data included 11,024 women who gave birth from 2004-2006 and compared their depression status with gestational diabetes status. Adjusted estimates showed that women with diabetes had nearly double the odds (OR: 1.85; 95% CI: 1.45-2.36) of experiencing depression during the perinatal period (6 months prior to and up to 1 year following delivery) compared to women without gestational diabetes. Specific to PP depression, women with GDM and no prenatal indication of depression had higher odds (OR: 1.69; 95% CI: 1.27-2.23) compared to women without GDM, to receive a PP depression diagnosis or use antidepressant medication in the 12 months following delivery.¹²⁹

Pregnancy-induced hypertension (PIH) complicates 6-10% of pregnancies and is defined as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg.¹³⁰ PIH refers to one of four conditions: a) pre-existing hypertension, b) gestational hypertension and preeclampsia (PE), c) pre-existing hypertension plus superimposed gestational hypertension with proteinuria and d)

unclassifiable hypertension. PIH is a major cause of maternal, fetal and newborn morbidity and mortality. A cross-sectional study evaluated women with depressive symptoms and compared their previous diagnosis with hypertensive disorders of pregnancy, and found that women with PIH were more likely to have depressive symptoms than their normotensive counterparts.¹³¹ **Also, nausea and vomiting in pregnancy that is severe to become a concern can interrupt the routine and overall quality of life for women.** In a case-control study of women who were hospitalized for severe nausea and vomiting, there was a significant difference in scores of depression and anxiety. Higher scores for both depression and anxiety were reported by the women with severe nausea and vomiting compared to their counterparts.¹³² **A strength of this dissertation is that depression and anxiety status is evaluated during pregnancy and can be controlled for when trying to better understand these PDC, which are often studied in cross-sectional or retrospective studies.**

The above conditions may result in a need to deliver through emergency Caesarian-section, which can cause significant stress for mothers.¹³³ In 2017, the percentage of all live births that were delivered via C-section in NC was 29.2%.¹³⁴ In a large (n=5,000), nationally representative study in England, depression, anxiety and PTSD (at 1 and 3 months PP) were evaluated in relation to the mode of delivery and whether it was forceps-assisted. Although the associations failed to reach statistical significance, the women who had a forceps-assisted vaginal birth had a somewhat greater risk of symptoms of anxiety at 1 month after birth (OR: 1.30; 95%CI: 0.90-1.89) compared to women with unassisted vaginal births, they also found the increased risk of PTSD-type symptoms remained at 3 months (OR: 1.86; 95%CI: 1.06-3.24).¹³³ It is thought that the association between C-section and depression may be stronger for women who strongly preferred a vaginal delivery¹³⁵ this aspect of having emergency C-sections was found to be more relevant for early PP depression symptoms.¹³⁶

Preterm Delivery (PTD) and low birth weight (LBW) are also linked with depression in the postpartum period. In 2017, the percentage of babies born PT (prior to completing 37 weeks' gestation)

in NC was 10.5%.¹³⁴ In a study considering depression among low income women who delivered preterm found that 42% of the women reported PP depression and an increase in depressive symptoms was identified for women who also reported state anxiety symptoms.¹³⁷ Similar rates of PP depression were found in a systematic review which reported that depression 40% in the early PP period was 40% among women who delivered prematurely and that ongoing depressive symptoms were associated with an earlier gestational age, infant illness and having lower birth weight infant.¹³⁸ In 2017, the percentage of babies born LBW (weighing less than 2,500 grams or 5 lbs. 8oz) in North Carolina was 9.2%.¹³⁴ A small (n=230) Germany-based study compared PP depression among mothers of very LBW (<1500 grams) and normal weight infants, and found that the risk of being depressed at one-month PP was 4 to 18 times higher among mothers of very low weight infants.¹³⁹ This same research group also examined state anxiety and clinical diagnosis of anxiety disorders, and reported the risk for minor/major anxiety symptoms were higher among parents who had a very LBW infant compared to normal term infants. They also evaluated the mode of delivery and stress experienced during pregnancy, but did not find statistically significant associations with these other factors.¹³⁹

Having an extended hospital stay or returning to the hospital within the first three days may be a marker of the above complications or may be unrelated to them, but is still a stressful experience. In a small study (n=126) in Turkey, researchers found that 35% of women reported PP depressive symptoms and that having a baby stay in the incubator was predictive of PP depression, additional items that were predictive included history of mental health problems, domestic abuse, and not breastfeeding.¹⁴⁰ Since this proposed study does not contain information regarding the perceived traumatic experience of delivery, evaluating the number of these PDC provides an indirect way to measure the level of adversity faced. As the number of events increase, it may be possible to see the association with PP depression and anxiety.

1.6 Cumulative Risk Scoring Approach

The primary aim of most of the studies that evaluate multiple psychosocial factors has been to identify the most relevant or most predictive factor of depression and anxiety. This approach has been useful and necessary to identify the above described risk factors, in turn, influencing screening recommendations and interventions.¹⁴¹ It is recommended that practitioners pay close attention to women who present with one or more of these risk factors and to make certain they are screened for depression during their prenatal care visits.¹⁴² However, these risk factors don't occur in isolation, and yet when making these recommendations, **these studies rarely provide information on the cumulative effect of experiencing two or more of these risk factors on depression and anxiety.**¹⁴³

Despite some shortcomings cumulative scores, the value of considering the accumulation of risk factors has been demonstrated in the cumulative stress literature.¹⁴⁴ The Adverse Childhood Experiences (ACEs) literature consistently shows that the cumulative impact (count of events) is important for predicting future risk of multiple physical and mental health outcomes in adulthood.¹⁴⁵ The ACEs literature demonstrates consistent findings across study populations; higher count of events equates to increased risk for mood disorders,^{146,147} suicide,¹⁴⁸ and multiple health risk factors later in life.¹⁴⁵ This literature takes the life course approach and uses the cumulative stress theoretical framework¹⁴⁹ to posit that stress from events increase vulnerability to subsequent adversities.¹⁵⁰ For example, women who experience childhood abuse, have been shown to be at increased risk to experience subsequent physical and sexual abuse by an intimate partner.^{151,152}

Similarly, the number of Stressful Life Events (SLE) is a marker for the accumulation of stress over the life course and have been important predicting future risk of depression in the PP period (see Risk Factor section 1.3). Although the number of SLE also show that as the events accumulate the risk for depression increases, the draw-back of the SLE checklist is the narrow window of time may not allow for multiple events to occur, such as the time surrounding pregnancy. The concern is that the SLE

checklist doesn't allow for a thorough evaluation of a higher number of events or of more proximal events.¹⁵³ Therefore, incorporating the evaluation of additional well-defined PRF can help better characterize the current psychosocial adversity experienced by perinatal women.

Additionally, efforts to examine psychosocial factors and pregnancy factors as a risk score or as an accumulation of endorsed items has been primarily done to predict PP depression.¹⁵⁴ A number of inventories (Antenatal Psychosocial Health Assessment,¹⁵⁵ Antenatal Risk Questionnaire,^{156,157} Predictive Index of Postnatal Depression¹⁵⁸) were designed specifically for practitioners to quickly review risk factors with perinatal women. These inventories include psychosocial factors, pregnancy complications, and demographic factors across the pregnancy. They have demonstrated that taking the risk score approach can be successful and many report that women who endorse multiple risk factors can be considered at higher risk for PPD.^{156,158} However, these have been designed specifically for assessing PP depression risk, and neglect to consider anxiety or the depression and anxiety in AP. These inventories don't typically evaluate PDC separately from the more well-established PRF.

1.7 Specific Aims

Aim 1. To estimate the association of a cumulative psychosocial adversity index on: 1) the presence of depression and anxiety symptoms at the second and third trimesters; 2) the pattern of depression and anxiety across the second and third trimesters; and 3) the comorbid occurrence of depression and anxiety during the antepartum period.

Hypothesis. *We hypothesized that high psychosocial adversity would be associated with increased odds of: 1) depression and anxiety at each trimester, 2) having a pattern of symptoms that persist across both trimesters, and 3) a comorbid occurrence of depression and anxiety in the antepartum period.*

Aim 2. To estimate the association of a cumulative pregnancy and delivery complications index with new-onset symptoms of mental health during the first year postpartum, among women with no pregnancy history of depression or anxiety.

Hypothesis. *We hypothesize that high pregnancy and delivery complications would be associated with increased risk for mental health symptoms (depression and/or anxiety) in the postpartum period, among women with no pregnancy history of depression or anxiety.*

CHAPTER 2. INNOVATION

An important innovation of this dissertation is the creation of a novel psychosocial adversity index for the antepartum period. The PIN study measured multiple psychosocial risk factors therefore, the number and type of psychosocial risk factors included in the psychosocial adversity index is novel. For example, poverty, income level or other markers of socioeconomic status are often proxy measures for economic stress, however they may not represent the burden or stress actually experienced by the participant. The PIN study does measure economic stress therefore we are able to include a subjective measure of economic stress. We also improve upon previous studies that evaluate psychosocial factors by including neighborhood safety and gender discrimination, two important but understudied factors in relation to antepartum mental health symptoms. Additionally, prior research of the psychosocial risk factors and mental health has focused on the association with postpartum mental health symptoms, whereas our focus is on the antepartum depressive and anxiety symptoms.

In this dissertation, we are able to examine the postpartum onset of symptoms among a subgroup of women who do not have a history of depression and anxiety symptoms during pregnancy. This new onset of symptoms will be evaluated in relation to a pregnancy and delivery complications index. While individual pregnancy and delivery complications have been shown to have moderate to weak associations with postpartum mental health symptoms, we will evaluate whether the accumulation of these complications has a more robust relationship.

This dissertation contributes to the mental health literature by describing the pattern (based on

the presence of symptoms at two time-points) of depression and anxiety and the comorbid experience of depression and anxiety during pregnancy, as well as the onset of new symptoms during the postpartum period.

CHAPTER 3. METHODS

3.1 Overview

This dissertation used data from the Pregnancy, Infection, and Nutrition (PIN) Study, a longitudinal cohort designed to study risk factors for preterm birth among women living in North Carolina. The first analysis addressed aim 1 (presented in chapter 4, referred to as analysis 1) and focused on the antepartum mental health symptoms. Specifically, this was a cross-sectional examination of a cumulative index of psychosocial adversity with the pattern and comorbid occurrence of depression and anxiety in the antepartum. The second analysis addresses aim 2 (presented as chapter 5, referred to as analysis 2) and is focused on postpartum mental health symptoms, specifically among women with no history of mental health symptoms during pregnancy. It was a longitudinal analysis assessing a cumulative index of pregnancy and delivery complications with new-onset mental health symptoms in the postpartum period. This chapter presents an overview of the PIN study and additional details not contained in chapter 4 and chapter 5 including a discussion of the Directed Acyclic Graph and a priori power analysis. Table 1 summarizes the main details for each analysis.

Table 1. Summary of analysis 1 and analysis 2

	Analysis 1 Chapter 4	Analysis 2 Chapter 5
Study design	Cross-Sectional	Longitudinal
Sample	1,797 pregnant women, less than 20 weeks gestation	378 postpartum women with no elevated mental health symptoms in pregnancy
Exposure	Antepartum Psychosocial adversity index (composite of 8 items)	Pregnancy and delivery complications index (composite of 9 items)
Outcome(s)	Antepartum (2 nd , 3 rd trimester) depression pattern Antepartum (2 nd , 3 rd trimester) anxiety pattern Comorbid depression and anxiety	Postpartum mental health symptoms (either depression or anxiety at 3 and 12-months postpartum)
Estimate(s)	Prevalence Ratio, Odds Ratio	Risk Ratio

3.2 Parent Study

The Pregnancy, Infection, and Nutrition (PIN) Study was a longitudinal pregnancy cohort designed to study risk factors for preterm birth among women living in North Carolina. The antepartum wave, referred to as PIN3, was carried out from January 2001 to June 2005 and included women who were less than 20 gestational weeks pregnant and were receiving their prenatal care at the University of North Carolina Hospitals. During the second trimester (spanning 17-22 gestational weeks) and third trimester (spanning 27-30 gestational weeks) women attended a clinic visit, completed a self-administered questionnaire (SAQ) returned via mail, and had a telephone interview (TPI). In total there were 6 data-collection points in PIN3 and the women were also followed to delivery to ascertain birth outcomes.

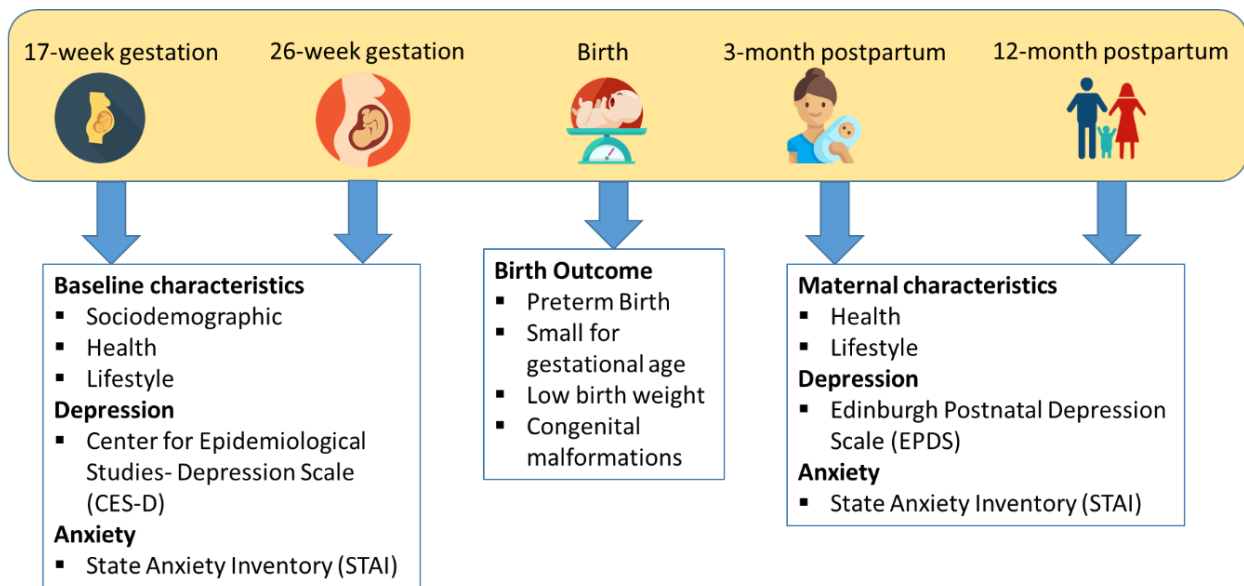
Beginning in 2003, a subset of eligible women participating in PIN3 were recruited for the PIN-Postpartum Study, referred to as PIN-Post, which was designed to study maternal diet, weight, infant feeding, physical activity, psychosocial factors, and health behaviors during PP. Participants from PIN3 that agreed to participate in the PIN-Post and were interviewed during home visits by trained

interviewers using a standardized questionnaire at 3-months and at 12-months postpartum. Follow up continued through 2007. Details of the PIN study are available at: <http://epidpin.web.unc.edu/>

3.3 Parent Study Timeline

Data collected during the antepartum phase of the study (PIN3) was used to conduct analysis 1. Pregnancy data collected in the PIN3 phase of the study and through the postpartum follow up (PIN-Post) was used to conduct analysis 2. Figure 1 presents an overview of the study timeline of data collection from pregnancy to postpartum.

Figure 1. Timeline of data collection across perinatal period in the Pregnancy, Infection, and Nutrition Study 2003-2007



3.4 Analytic Sample and Data Collection

Analysis 1 sample and data collection. The initial cohort (n=2,006) for analysis 1 consisted of women receiving prenatal care at the University of North Carolina who were recruited into the PIN3 study from January 2001 to June 2005. Exclusion criteria included; age less than 16 years, non-English speaking, not planning to continue care or deliver at the study site, carrying multiple gestations, or not having a telephone for phone interviews. After recruitment and informed consent, women provided basic demographic information. In the second trimester, and again in the third trimester, women were

interviewed via telephone interview and completed self-administered questionnaires. The instruments used to measure psychosocial factors, depression, and anxiety were collected across these four data collection methods. A more detailed summary of the data collection, timing and instruments used in the antepartum, is presented in Table 2. Of the 2,006 women who consented to participate, 1,797 provided follow-up data.

Table 2. Description of data collection method, timing, and instruments across the antepartum period in the PIN study used for analysis 1

Data Collection		Instruments Administered		
Method	Timing	Exposure	Outcome	Covariates
Phone Interview #1	Second Trimester (17-22 weeks gestation)	*Sarason's Life Experiences Survey	-----	*Demographic Survey
Mailed in Self-administered Questionnaire #1	Second Trimester (<20 weeks gestation)	*MOS Social Support Scale: -Economic Stressors	*State Anxiety Inventory *CES-D Depression Scale	-----
Phone Interview #2	Third Trimester (27-30 weeks gestation)	*Gender Discrimination *Neighborhood Safety	-----	-----
Mailed in Self-administered Questionnaire #2	Third Trimester (24-29 weeks gestation)	*Emotional Abuse *Physical Abuse *Sarason's Life Experiences Survey update	*State Anxiety Inventory *CES-D Depression Scale	-----

Analysis 2 study sample and data collection. Analysis 2 evaluates the pregnancy and postpartum experience of mental health symptoms and will utilize data from women from PIN3 and continued into the PIN-Post study (n=688). Data was collected during pregnancy at phone interviews at the second and third trimester. After women delivered, birth outcomes were abstracted from medical records. Women in the PIN-Post study had an in-home interview at 3 and 12-months postpartum. Information regarding data collection, timing, and instruments for analysis 2 is summarized in Table 3. Because recruitment for PIN-Post began in 2003, two years after the start of PIN3, only 1,169 women were eligible to be recruited to participate in the post-partum portion of the study. Women were assessed in person during in-home interviews by trained study personnel at 3 and 12-month postpartum. We excluded 215 women who reported elevated symptoms of depression and anxiety at either the second or third trimester of

pregnancy and 187 women that had no information about mental health symptoms during pregnancy. An additional 258 women were lost to follow-up and did not provide information on depression and anxiety status at either 3 or 12-months postpartum period, resulting in an analytical sample of 378 women.

Table 3. Description of data collection method, timing, and instruments in the PIN study and used for analysis 2

Data Collection		Instruments Administered		
Method	Timing	Exposure	Outcome	Covariates
Phone Interview 1 Phone Interview 2	Second Trimester (17-22 weeks' gestation) Third Trimester (27-30 weeks gestation)	-Vaginal bleeding -Pregnancy Nausea	-----	-Demographic Information
Medical Abstraction	After delivery/Prenatal care records/-Need to verify what data comes from this	-Gestational Diabetes -Pre-eclampsia/ Gestational Hypertension -Low birth weight -Preterm delivery -C-Section -Extended hospital stay	-----	-----
In-home interview	3 months postpartum	-----	-State-Trait Anxiety Inventory (STAI) -Edinburg Postnatal Depression Scale (EPDS)	-----
In-home interview	12 months postpartum	-----	-State-Trait Anxiety Inventory (STAI) -Edinburg Postnatal Depression Scale (EPDS)	-----

3.5 Measures of Psychosocial Risk Factors

The exposure of interest for analysis 1 was the psychosocial adversity index which included the psychosocial factors measured by the instruments described below and summarized in Table 4.

- 1) *Serious life events:*** The Life Experiences Survey (LES)¹⁵⁹ examines acute and chronic life stresses. Women are asked if events occurred since the start of pregnancy and if so, to report the impact of as positive, negative, or neutral. LES was modified by eliminating item asking whether the respondent experienced a pregnancy, and combining husband and boyfriend (details of marital status, cohabitation, and relation with the father are obtained elsewhere), resulting in 39 items from the original 57 in the LES. Test-retest reliability studies were conducted with reliability coefficients of 0.53 for the positive impact score, 0.88 for the negative impact score, and 0.64

for the total score.¹⁶⁰ This instrument was administered at TPI #1 and updated at SAQ#2 and asked about the time 'since the start of pregnancy.'

- 2) **Verbal aggression:** Aggression¹⁶¹ was assessed with a subset of questions from the Revised Conflict Tactics Scales 2 (CTS2) to assess psychological aggression. It measures “psychological and physical attacks on a partner in a marital, cohabiting, or dating relationship, and also use of negotiation.” Included in the PIN3 administration are the four “minor” items for the psychological/verbal aggression. These items are the most pertinent to a general population and will yield an adequate prevalence to examine these areas of abuse in the PIN population. This was administered at SAQ#2 and asked about the 'time since becoming pregnant.'
- 3) **Physical aggression.** Five “minor” items for the Physical Assault Scale from the RCTS2 were also used to assess physical assault, and injury. These items are the most pertinent to a general population and will yield an adequate prevalence to examine these areas of abuse in the PIN population. This was administered at SAQ#2 and asked about the 'time since becoming pregnant.'
- 4) **Neighborhood safety:** Perceptions of Neighborhood Safety¹⁶² uses seven questions to assess the woman's perception of safety in and stress from living in her neighborhood. This provided a subjective assessment of the contextual environment and is a proxy of how stressful she perceives her environment to be. Questions were also included to measure the perceptions of neighborhood disorder and victimization¹⁶³. This was measured at TPI #2 and asks about 'current neighborhood.'
- 5) **Economic stress:** Economic stress was measured with seven questions about whether she felt able to afford: a suitable home, furniture, car, medical care, clothing, leisure activities. Two questions used a Likert scale to assess the difficulty of paying bills and amount of money left at the end of the month.¹⁴⁹ This was applied at SAQ #1 and asked about her feelings 'at this time.'

6) **Gender discrimination:** Gender Discrimination¹⁶⁴ was measured by a discrimination scale developed to focus on African Americans. The questions used to evaluate gender discrimination participants were asked if they have ever experienced discrimination because you are a woman on the job or in public; and a Likert scale was used to assess the degree of frustration, anger, sadness, hopeless and powerless due to gender discrimination. This was measured at TPI #2 and asked 'have you ever.'

7) **Functional social support:** The MOS Social Support Scale assesses the availability of perceived SS in four categories. The instrument's developers selected response items based on current theory about the most important dimensions of SS, primarily the perceived availability, if needed, of functional support.¹⁶⁵ It uses a five-category Likert response for 19 items. The instrument focuses on perceived support because report of received support can be confounded by the need for support, and as a result might not reflect the amount of support available in times of need. Reliability measures for 14 definitions of health concepts were in the 0.74 to 0.93 range using Cronbach's alpha.¹⁶⁵ The items are scaled into an overall score of tangible or instrumental support, and a combination category of emotional/informational support, including love and empathy, and providing feedback and guidance. This was measured at SAQ #1 and asked about the time 'since becoming pregnant.'

8) **Structural social support:** This was measured by asking a separate question about the number of relatives and friends she feels close to and can talk to or ask for help. The sum of both friends and relatives was calculated (range: 0-60). This was measured at SAQ #1 and asked about the time 'since becoming pregnant.'

Psychosocial adversity index. The exposure of interest for **analysis 1** was the **psychosocial adversity score** and is a numerical cumulative score based on the Centers for Disease Control (CDC)/Kaiser Permanente model for assessing Adverse Childhood Experiences.¹⁴⁵ A 'yes' (or other

affirmative response) to any of the questions within the psychosocial constructs counts as one point.

The total score was the sum the potential points. Based on the distribution of the continuous index, an appropriate grouping for a categorical variable was determined to represent high psychosocial adversity.

Table 4. Description of each complication used to develop the Psychosocial Adversity Index for analysis 1

Psychosocial Risk Factors		Cumulative Index	
Measure	Factor Questions/Description	Response	Points If Yes
Stressful life events	The sum of life events (range 0-13) with a negative impact was calculated. Those with no negative events were categorized as such. Those who reported 1 or more events with a negative impact were categorized as: <i>'Yes- experienced negative life events'</i>	0= None 1= Yes	1pt
Verbal abuse	The frequency of events occurring was summed. Those with all events reported as 'never' occurring were categorized as having experienced 'No Verbal Abuse' all others were categorized as: <i>'Yes-Experienced Verbal Abuse'</i>	0= None 1= Yes	1pt
Physical abuse	The frequency of events occurring was summed. Those with all events reported as 'never' occurring were categorized as having experienced 'No Physical Abuse' all others were categorized as: <i>'Yes-Experienced Physical Abuse'</i>	0= No 1= Yes	1pt
Neighborhood Safety	A composite score (range: 8-35) was created and a score of 0-10 indicated the neighborhood was perceived as safe. A score of 11 or greater was categorized as: <i>'Yes-neighborhood perceived somewhat/very unsafe'</i>	0= No 1= Yes	1pt
Economic stress	Responses of 'no difficulty' or 'little difficulty' were combined to indicate no economic stress and responses of 'some difficulty' or 'great difficulty' were combined to indicate: <i>'Yes-experienced economic stress'</i>	0= No 1= Yes	1pt
Gender discrimination	A 'No' response indicated that woman never felt she experienced discrimination because she was a woman at either a job or in public. Those responding Yes, were categorized as: <i>'Yes- experienced gender discrimination'</i>	0= No 1= Yes	1pt
Functional social support	The 19 items are scaled into a combination category for an overall score of Functional Support (range: 21-95). Those with a score of 89 and had adequate social support and those with a score less than 89 (0-88) were categorized as: <i>'Yes-experienced low social support'</i>	0= No 1= Yes	1pt
Structural social support	The sum of both friends and relatives was calculated (range: 0-60). Those with 5 or more people were considered to have adequate structural support and those with less than 5 were categorized as: <i>'Yes- experienced low structural support'</i>	0= No 1= Yes	1pt

3.6 Measures of Pregnancy and Delivery Complications

Pregnancy and delivery complications index included the following complications:

- 1) **Severe vaginal bleeding:** Women were asked if they experienced bleeding during pregnancy, asked to report the number of bleeding episodes and for each episode they were asked to describe the severity. This was assessed at during phone interview #1 and updated at phone interview #2.
- 2) **Severe nausea and vomiting:** Women were asked if they: Felt nausea during pregnancy and whether nausea caused her to eat less, avoid doing normal activity, or caused her not to take prenatal vitamins. Women were also asked whether they vomited because of nausea, vomited more than 4x on a week for at least 1 week, saw a doctor because of vomiting or took medication to help stop vomiting. Nausea was assessed during phone interview #1 and updated at phone interview #2.
- 3) **Gestational diabetes:** Medical records were used to identify whether women had presented with gestational diabetes. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.
- 4) **Gestational hypertension/pre-eclampsia:** Medical records were used to identify if women presented with gestational hypertension or pre-eclampsia. Gestational hypertension is diagnosed when blood pressure readings are higher than 140/90 mm Hg in a woman who had normal blood pressure prior to 20 weeks and has no proteinuria (excess protein in the urine). Pre-eclampsia a condition in pregnancy characterized by high blood pressure/fluid retention and proteinuria.
- 5) **Caesarean-section:** Pregnancy information from prenatal care visits, triage visits, and admissions to the hospital, including delivery admission, medical history, pregnancy history was collected from medical record. Type of delivery, vaginal or caesarian, was identified.

- 6) Preterm delivery:** Pregnancy outcome information was abstracted from the medical record following delivery. Gestational age at delivery was assigned by early ultrasound or last menstrual period date if ultrasound was unavailable. Preterm (delivery prior to completing 37 weeks' gestation) was determined by obstetrician review and classified as preterm birth (PTB).
- 7) Low birth weight:** Pregnancy information from prenatal care visits, triage visits, and admissions to the hospital, including delivery admission, medical history, pregnancy history was collected from medical record. Birth weight was assessed (LBW) was <2500g).
- 8) Mother extended hospital stay:** Pregnancy information from prenatal care visits, triage visits, and admissions to the hospital, including delivery admission, medical history, pregnancy history was collected from medical record. Extended hospital stays past 48 hours for vaginal deliveries and past 96 hours for C-section deliveries.
- 9) Baby hospitalized after delivery:** Pregnancy information from prenatal care visits, triage visits, and admissions to the hospital, including delivery admission, medical history, pregnancy history was collected from medical record. Information about whether the baby was hospitalized after delivery was identified.

Pregnancy and delivery complications index: The exposure of interest for **analysis 2** is the **pregnancy/delivery adversity score** that will be a numerical cumulative score is based on the Centers for Disease Control (CDC)/Kaiser Permanente model for assessing Adverse Childhood Experiences.¹⁴⁵ A 'yes' (or other affirmative response) to any of the nine pregnancy and obstetric complications counts as one point (Table 5). The total pregnancy and delivery complication score ranges will be determined (possible range: 0 to 9) Based on the distribution of the continuous score, an appropriate grouping for a categorical variable was determined.

Table 5. Description of each complication used to develop the Pregnancy and Delivery Complications index for analysis 2

Pregnancy/Delivery Complication		Cumulative Index	
Measure	Factor Questions/Description	Response	Points If Yes
Severe vaginal bleeding	Number of bleeding events and severity at 2 nd and 3 rd trimester; endorsed severe	0=None 1=Yes	1pt
Severe Nausea	Yes/no questions: -nausea prevented eating, taking prenatal vitamins -Vomited more than 4x/week for a 1 week	0=None 1=Yes	1pt
Gestational Diabetes	Any degree of glucose intolerance with onset during pregnancy.	0=No 1=Yes	1pt
Gestational hypertension/ Pre-eclampsia	BP > 140/90 mm Hg in a woman who had normal blood pressure prior to 20 weeks and has no proteinuria (excess protein in the urine). OR A condition in pregnancy characterized by high blood pressure, sometimes with fluid retention and proteinuria.	0=No 1=Yes	1pt
Caesarean-section	Type of delivery, vaginal or caesarian, was identified.	0=No 1=Yes	1pt
Preterm Delivery	Gestational age at delivery. Preterm birth was defined as delivery prior to completing 37 weeks' gestation; defined as term or preterm.	0=No 1=Yes	1pt
Low Birth Weight	Low birth weight was newborn weight <2500g	0=No 1=Yes	1pt
Baby hospitalized	Baby was hospitalized after delivery	0=No 1=Yes	1pt
Extended hospital stay	Extended hospital stay (past 48 hours for vaginal delivery and 96 hours for C-section delivery)	0=No 1=Yes	1pt

3.7 Antepartum Measurement of Mental Health Symptoms

Participants completed self-administered questionnaires during the second and third trimesters.

The Center for Epidemiologic Studies Depression (CES-D) Scale was used to screen for depressive symptoms and the State-Trait Anxiety Inventory (STAI) was used to screen for anxiety symptoms. The screening tools are described below.

Depressive symptoms. Measured using the CES-D Scale¹⁶⁶ which is designed as a short, structured self-administered instrument and includes 20-item scale has Likert response categories assessing feelings and activities the respondent experienced during the past week. She is asked how frequently she is experiencing symptoms (been able to laugh, felt sad or miserable, thought of harming

myself). A composite score is calculated with a total score range of 0-60. A cutoff score of >16 indicates moderate to severe depression and women with a score >16 were considered as screening positive for depression. The CES-D was administered at the SAQ #1 and #2.

Anxiety symptoms. The STAI,¹⁶⁷ a 20-item scale assessed state anxiety during pregnancy. STAI asks about immediate feelings ("right now") and because responses can vary over time, it can be administered repeatedly to assess changes in anxiety. The State scale uses a 4-point response from which a composite score is generated with the following categories: low/mild anxiety (0 to <29); moderate anxiety (>29 to <39); severe anxiety (39+). Based on the three categories, anxiety was further collapsed to a binary variable with the low/mild and moderate categories combined, resulting in the dichotomous anxiety variable: low to moderate anxiety (0-39) vs. severe anxiety (39+). Women with a severe score (39+) were considered as endorsing anxiety because a cut-point of 39/40 has been suggested to detect clinically significant symptoms for the State-Anxiety scale and is the cut-point used among perinatal women.^{168,169} STAI was administered as part of the SAQ #1 and #2.

Operationalization of antepartum mental health outcomes. Screening results for depression and anxiety from each trimester were used to define each of the outcomes of interest. The operationalization of each variables is described below and summarized in Table 6.

- a) Second trimester depressive symptoms:** Based on the CES-D administration at the second trimester, a dichotomous variable was created based on the cut-point (score >16).
- b) Third trimester depressive symptoms:** Based on the CES-D administration at the third trimester, a dichotomous variable was created based on the cut-point (score >16).
- c) Second trimester anxiety symptoms:** Based on the STAI-State administration at the second trimester a dichotomous variable was created based on the cut-point for severe anxiety (39+).
- d) Third trimester anxiety symptoms:** Based on the STAI-State administration at the third trimester a dichotomous variable was created based on the cut-point for severe anxiety (39+).

- e) *Antepartum depression pattern***: Based on screening results from the second and third trimester, the three level variable for antepartum depression pattern was created: No symptoms (women who did not screen positive for depression at either trimester); Symptoms only at second or third trimester (screened positive (CES-D score >16) for depression at either the second or third trimester); and Symptoms at both trimesters (screened positive (CES-D score >16) for depression at both the trimesters).
- f) *Antepartum anxiety pattern***: Based on symptoms at the second and third trimester, the three level variable for antepartum anxiety pattern was: No symptoms (women who did not screen positive for severe anxiety at either trimester); Symptoms at only at second or third trimester (screened positive for severe anxiety at either trimester); and Symptoms at both trimesters (screened positive at both trimesters).
- g) *Antepartum comorbid depression and anxiety***: Based on symptoms at the second and third trimester, the three level variable for comorbid depression and anxiety was: No Symptoms (did not screen positive for depression or anxiety at any trimester); Depression or Anxiety only (screened positive for only depression or only anxiety at the second and third trimester); Comorbid depression and anxiety (positive for depression and anxiety at the same time, at either the second or third trimester).

3.8 Postpartum Measurement of Mental Health Symptoms

Postpartum depression and anxiety were assessed with the following instruments:

- 1) *Edinburgh Postnatal Depression Scale (EPDS)***: Depression during the postnatal period was measured using the EPDS.¹⁷⁰ The EPDS depression screening questionnaire was developed to be used in health care settings and has been used extensively for research and has been validated for use during PP. The 10-item scale assesses the woman's mood during the past week with 4-point response categories. A composite score is calculated after reverse coding and summing across

items to create the categories of Depressed (No: 0 to <10); (Possible depression: 10+). Item 10 of the EPDS indicates whether suicidal ideation was endorsed. Additionally, the score will be evaluated and using a tertile cut-off, a three level variable will be created to represent the severity of depression. The EPDS was administered at the 3 and 12-month in-home interview.

2) The State-Trait Anxiety Inventory (STAI): The STAI¹⁶⁷ was used to assess state anxiety PP and the following categories are generated: low/mild anxiety (0 to <29); moderate anxiety (>29 to <39); severe anxiety (39+). Based on the three categories, anxiety was further collapsed to a binary variable with the low/mild and moderate categories combined, resulting in the dichotomous anxiety variable: low to moderate anxiety (0-39) vs. severe anxiety (39+). The State anxiety scale was administered at the 3 and 12-month in-home interview.

Operationalization of outcome: The outcome variables of interest for analysis 2 was the presence of postpartum depression or anxiety at either 3 month or the 12-month postpartum screening. Women who screened positive for either depression or anxiety, based on the above described cut-points were considered to have elevated mental health symptoms (Table 6).

Table 6. Summary of outcome variable operationalization for analysis 1 and analysis 2

Analysis	Outcome Label	Operationalization
Analysis 1 Outcomes	2 nd Trimester Depressive Symptoms	0=No Symptoms 1=Moderate/severe Symptoms
	3 rd Trimester Depression Symptoms	0=No Symptoms 1=Moderate/severe Symptoms
	2 nd Trimester Anxiety Symptoms	0=No Symptoms 1=Severe Symptoms
	3 rd Trimester Anxiety Symptoms	0=No Symptoms 1=Severe Symptoms
	Antepartum Depression Pattern	0=No symptoms 1=Depression only at 2 nd or 3 rd Trimester 2=Depression at both trimesters
	Antepartum Anxiety Pattern	0=No symptoms 1=Depression only at 2 nd or 3 rd Trimester 2=Depression at both trimesters
	Antepartum Comorbid Depression and Anxiety	0=No symptoms 1=Depression or Anxiety only 2=Comorbid depression/anxiety
Analysis 2 Outcome	Postpartum Elevated Mental Health Symptoms (depression/anxiety)	0=No elevated mental health symptoms 1=Elevated mental health symptoms

3.9 Covariates and Adjustment Sets

Using a Directed Acyclic Graph¹⁷¹ (DAG) and based on the review of existing literature, an a priori adjustment set was established for each analysis. The DAG was restricted to variables that met at least one of the following criteria: 1) there is evidence that the variable affects both the exposure (psychosocial adversity) and the outcome (AP Depression and Anxiety); 2) the variable is a strong predictor of the outcome or 3) there is evidence that the variable is part of a confounding path.

Covariates of interest were assessed during baseline interviews.

Covariates of interest for analysis 1 (DAG Figure 2.)

- 1) **Maternal age.** Age (16-50 years) was examined for the appropriate functional form.
- 2) **Race/ethnicity:** White non-Hispanic, Black non-Hispanic, and other.
- 3) **Education:** Years of schooling categorized as 8-12 years, 13-16 years, 17-20 years of education.
- 4) **Employment:** Employment status at the start of pregnancy.
- 5) **Poverty level:** Based on reported income and number in household, the % below poverty level was established based on 2001 statistics.
- 6) **Marital status:** Status was evaluated as Married, Cohabiting, or Single
- 7) **Parity:** The number of live births
- 8) **Smoking:** The woman was asked whether she was a current smoker or not.

In addition to covariates 1-8, the following covariates were of interest for analysis 2 (DAG Figure 3.)

- 9) **Body mass index:** BMI Categories for underweight, normal, and overweight/obese at baseline
- 10) **Anxiety/depression during pregnancy:** Screening results at second and third trimester will determine mental health status during pregnancy.

11) Psychosocial Adversity Index: The psychosocial adversity index created for analysis 1 will be included as overall psychosocial adversity during pregnancy.

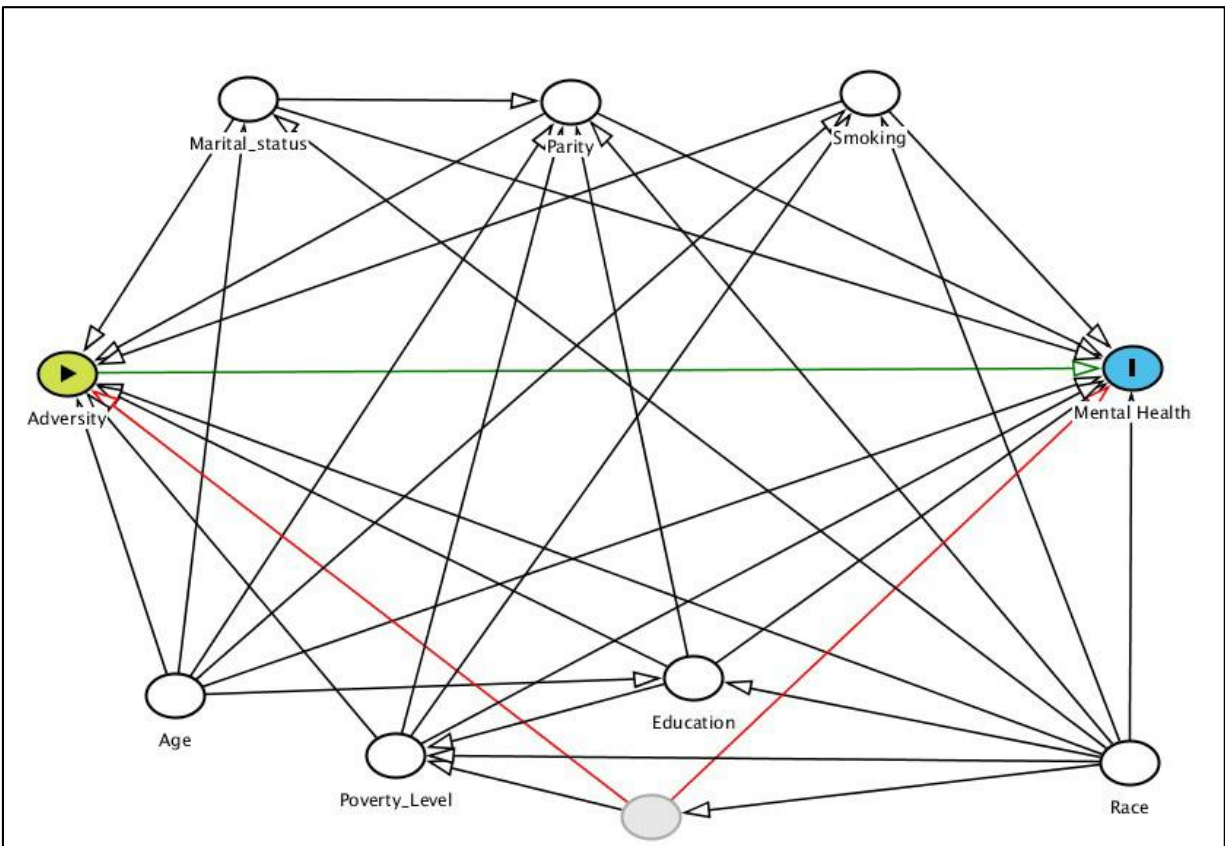


Figure 2. Analysis 1. Directed Acyclic Graph (DAG) of the hypothesized causal associations between psychosocial adversity and mental health outcomes (depression and anxiety) in the antepartum period. History of mental health was not measured in this study and therefore it is included in the DAG, as the gray shaded node, and represents unmeasured confounding.

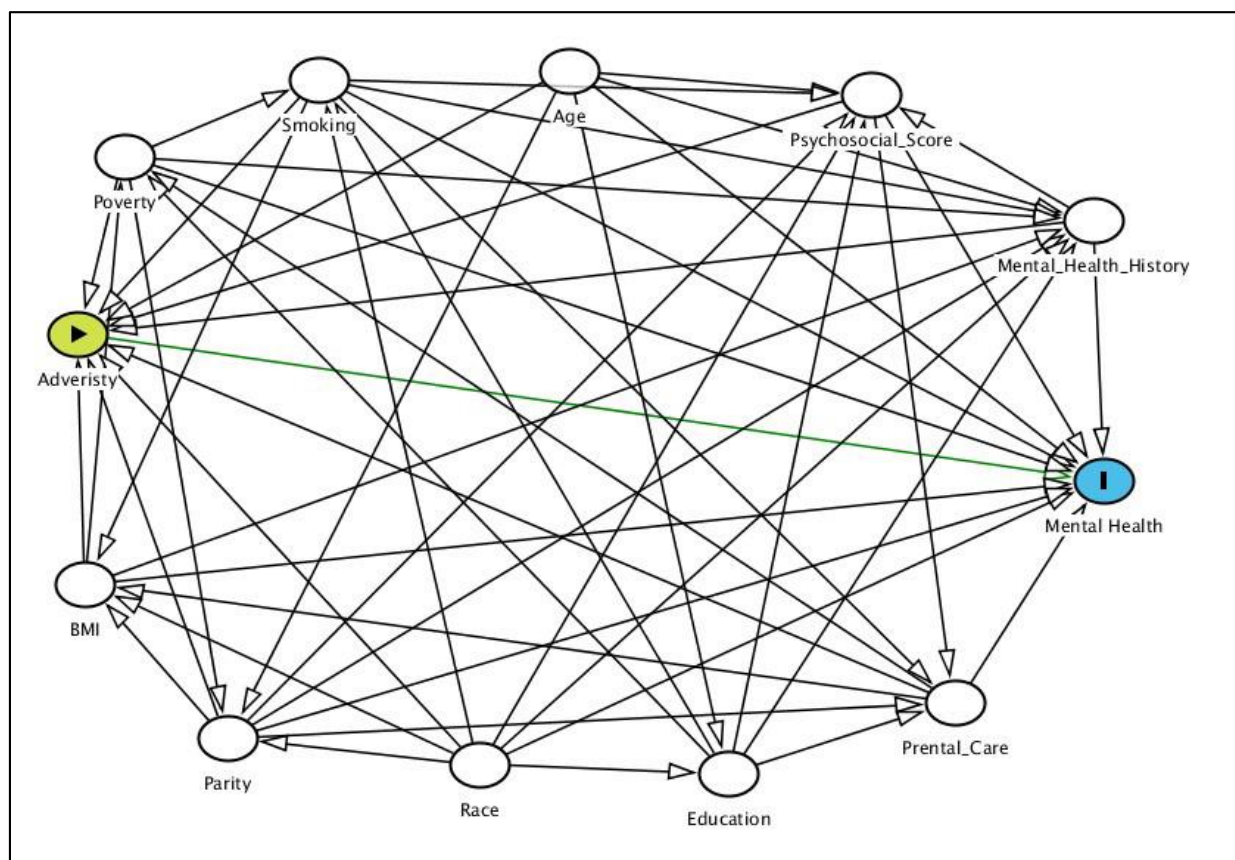


Figure 3. Analysis 2. Directed Acyclic Graph (DAG) of the hypothesized causal associations between pregnancy/ delivery adversity and mental health outcomes (depression and anxiety) in the postpartum period. History of mental health was not measured in this study and therefore it is included in the DAG, as the gray shaded node, and represents unmeasured confounding.

3.10 A Priori Power Estimation

A priori we used a categorical exposure (exposed/unexposed) and categorical outcomes (no symptoms/symptoms) across varying prevalence levels and preliminary data on case and control sample sizes. Table 7 summarizes the analysis 1 inputs used in Quanto statistical program to determine the Odds Ratio (OR) we could estimate. There is 80% power to detect main effects of OR:1.4-2.3, under the different scenarios summarized in Table 8. Table 9 summarizes the analysis 2 inputs used in Quanto and Table 10 shows there is 80% power to detect main effects of OR:1.6-3.2. These are the most conservative estimates.

Table 7. Estimating the size of the effect detectable at 80% power of psychosocial factors on outcomes for analysis 1: Inputs for Quanto

Description of Parameter		Input	Rationale
Design	Case-Control	'unmatched'	This is an unmatched study
	Controls per case	1=2 2=4	Number of available controls per case, varied to reflect controls available for each level 1 and 2 of the three category variable. (1=One time point, 2=Both time points, 0=Never)
Exposure	Population prevalence	0.05-0.3	Varied based on the range of the prevalence of each exposure of interest
Outcome	Baseline risk	1=0.30 2=0.20	Prevalence of severe perinatal anxiety for level 1 and 2 of the three category variable (1=One time point, 2=Both time points)
Power	Power	0.80	The required study power
	Confidence level	0.95	Based on 95% confidence intervals, or an alpha of 0.05.
	Sided test	2	Conduct a two sided test
Sample size	Total sample	1702	The total number of subjects in the study
	Cases	1=471 2=243	The number of cases for level 1 and 2 of the three category variable(1=One time point, 2=Both time points)
	Controls	988	The number of controls (0=Never)

Table 8. The main effect size (Odds Ratio) in analysis 1 at 80% power by baseline prevalence

Exposure: Population Prevalence Inputs	Outcome: Baseline Risk Inputs	Odds Ratio Detected at 80% power
0.05	0.30	2.0
	0.20	2.3
0.10	0.30	1.7
	0.20	1.9
0.15	0.30	1.6
	0.20	1.7
0.20	0.30	1.5
	0.20	1.6
0.30	0.30	1.4
	0.20	1.5

Table 9. Estimating the size of the effect detectable at 80% power of pregnancy-related experiences on postpartum depression for analysis 2: Inputs for Quanto

Description of Parameter		Input	Rationale
Design	Case-Control	'unmatched'	This is an unmatched study
	Controls per case	2	Number of available controls per case
Exposure	Population prevalence	0.05-0.3	Varied based on the potential range of the prevalence of the exposure of interest
Outcome	Baseline risk	0.35	Prevalence of postpartum depression
Power	Power	0.80	The required study power
	Confidence level	0.95	Based on 95% confidence intervals, or an alpha of 0.05.
	Sided test	2	Conduct a two sided test
Sample size	Total sample	576	The total number of subjects in the study
	Cases	157	The number of cases
	Controls	419	The number of controls

Table 10. The main effect size (Odds Ratio) of analysis 2 at 80% power by baseline prevalence.

Exposure: Population Prevalence Inputs	Odds Ratio Detected at 80% power
0.05	3.2
0.15	2.1
0.25	1.8
0.40	1.6

CHAPTER 4. ANALYSIS 1: THE RELATIONSHIP OF CUMULATIVE PSYCHOSOCIAL ADVERSITY WITH ANTEPARTUM DEPRESSION AND ANXIETY¹

4.1 Chapter Overview

Exposure to multiple psychosocial risk factors may increase vulnerability for mental health conditions during pregnancy. This analysis examined the relationship of a novel psychosocial adversity index with the co-occurrence and persistence of depression and anxiety throughout pregnancy. The index included measures for neighborhood safety and gender discrimination, two important but understudied psychosocial factors in pregnant populations. This cross-sectional analysis included 1,797 pregnant participants. Women were screened for depression and anxiety symptoms and for eight psychosocial factors in the second and third trimester. The eight factors were summed for a psychosocial adversity index; reporting 4+ factors indicated high adversity. Elevated symptoms in both trimesters indicated persistent depression/anxiety and elevated symptoms at the same trimester indicated comorbid symptoms. The associations between psychosocial adversity index and mental health were estimated.

Compared to a low psychosocial adversity index, women reporting a high level of psychosocial adversities had 2.06 (95% Confidence Interval:1.51-2.82) times higher adjusted odds of only depressive or anxiety symptoms, and 5.57 (95% Confidence Interval:3.95-7.85) times higher adjusted odds of comorbid symptoms. The associations for persistent symptoms were of similar direction and magnitude. Women at higher risk of elevated depressive symptoms and anxiety can be identified with early

¹ **Note:** Tables and figures for this chapter are in section 4.7

assessments of psychosocial adversities. Identifying women at risk who may benefit from targeted interventions may help improve mental health outcomes.

4.2 Introduction

Appropriate and tailored interventions for perinatal mental health problems require early identification of women at increased risk for these conditions. Despite growing clinical and research attention, antepartum mental health disorders remain prevalent. Elevated depression and anxiety symptoms during pregnancy affect an estimated 15% to 30% of women and approximately 10% experience comorbid symptoms.^{19,25,172} Mental health negatively impacts maternal physical health, birth-related outcomes, and future child development^{10,28,51,52,173-175} and deleterious impacts are strongest for women who experience more severe, persistent, or comorbid symptoms.^{42,60,66} A limited number of studies measure symptoms of both depression and anxiety more than once during pregnancy, therefore continued research describing risk factors for persistence and comorbid occurrence in the antepartum is warranted.^{19,25,176}

The high public health burden of antenatal depression and anxiety has prompted research into risk factors that increase vulnerability to these problems.⁹³ Besides prior history of psychiatric illness, psychosocial factors such as significant life events, intimate partner violence (IPV), economic stress,^{84,85} neighborhood safety,¹⁰³ gender discrimination,¹¹¹ and low social support,^{10,84} have emerged as individual predictors of perinatal mental health. Given the prevalence of adversities, such as physical and verbal abuse⁸⁷ and poverty,¹⁷⁷ are not low, the contribution of these adversities to the overall mental health burden in the perinatal period may be significant. While each of these factors independently contributes to increased risk, there is growing evidence that the accumulation of multiple factors is independently linked with depression and anxiety.^{96,97} Such findings led to the creation of inventories designed for practitioners to quickly review risk factors.^{155,157,158} However, these inventories tend to focus on individual-level risks, such as low social support, with less focus on contextual factors, such as

neighborhood safety. Which specific psychosocial factors should be included in such inventories is still a matter of debate.

While research on the impact of cumulative exposures to multiple psychosocial factors on perinatal mental health has grown, most studies focus on the postpartum period.¹⁷⁸ Research on risk factors for depression and anxiety throughout the pregnancy period is limited, even though the burden of mental health problems is as high, or maybe higher, when compared to the postpartum period.^{19,176} Although mental health varies over time, few studies measure symptoms more than once during pregnancy and even fewer evaluate the comorbid occurrence of depression and anxiety in the antepartum period.²⁵ Having such information is key to a better understanding of how exposures such as psychosocial adversities impact women differentially throughout the pregnancy period.

This study aimed to contribute to the literature by defining a measure of cumulative psychosocial adversity that combines both individual and contextual level factors, and by examining the association between this cumulative index and patterns of depression and anxiety during pregnancy.

4.3 Methods

Data source and sample. Data were obtained from the Pregnancy, Infection, and Nutrition (PIN) Study, a pregnancy cohort in North Carolina carried out from January 2001 to June 2007.^{179,180} Women were eligible if they were receiving prenatal care at University of North Carolina Hospitals and were less than 20 weeks pregnant. Exclusion criteria included: age less than 16 years, non-English speaking, not planning to continue care/deliver at the study site, carrying multiple gestations, or did not have access to a telephone. Because the PIN study spanned five years, women with repeat pregnancies could participate more than once. Details of the PIN study are available at: <http://epidpin.web.unc.edu/>

Of the 3,203 women invited to participate, 2,006 provided written informed consent. The University of North Carolina Institutional Review Board approved this study. Data were collected at baseline and via phone interviews and self-administered questionnaires during the second and third

trimesters. This analysis was restricted to individuals who completed interviews at the second or third trimesters and did not become ineligible (n=108) or request to withdraw (n=101) participation, resulting in a sample of 1,797 pregnancies. Loss to follow-up resulted in varying sample sizes for each outcome: second-trimester depression (n=1,585); second-trimester anxiety (n=1,586); third-trimester depression (n=1,418); third-trimester anxiety (n=1,413); depression pattern (n=1,357); anxiety pattern (n=1,345), and comorbid pattern (n=1,341).

Measures for Psychosocial Adversity Index. We created a novel psychosocial adversity index as a composite score based on eight psychosocial risk factors that have been shown to contribute to mental health symptoms. In addition to individual-level factors more frequently studied (stressful life events and low social support), we included contextual factors such as neighborhood safety and gender discrimination. These two factors capture the potential stress of a woman's experience of existing in the public sphere. Our approach was based on the Centers for Disease Control (CDC)/Kaiser Permanente model for assessing Adverse Childhood Experiences.¹⁴⁵

The specific domains available in the PIN data were not assessed at a single timepoint. They were measured over the course of two phone interviews and two self-administered questionnaires in the second and third trimesters. For this analysis, we do not distinguish across the method of measurement or timepoints and treat the exposure data as cross-sectional. Each factor is described below and in more detail in Table 11.

Stressful life events, measured with the Life Experiences Survey,¹⁵⁹ asked whether 39 life stressors occurred since the start of pregnancy. If an event occurred, participants reported whether the impact was positive, negative, or neutral. Women reporting 1 or more negative events indicated: '*Yes- Experienced negative life events.*' Verbal abuse was measured using questions from the Revised Conflict Tactics Scales 2 (CTS2)¹⁶¹ which asked about the frequency of four acts of verbal aggression since the start of pregnancy. Women reporting all events as 'never' having occurred were categorized as '*No*

Verbal Abuse' while all others indicated: *'Yes-experienced verbal abuse.'* Physical abuse was measured with questions from the CTS2 as well,¹⁶¹ and asked about the frequency of five physical aggression acts occurring during pregnancy. Women with all events reported as 'never' having occurred were categorized as *'No physical abuse'* all others indicated: *'Yes-experienced physical abuse.'* The Perceptions of Neighborhood Safety instrument¹⁶² included seven questions about the frequency of events witnessed and feelings about neighborhood safety. This subjective assessment of the contextual environment was a proxy for how safe the participant perceived her current neighborhood environment¹⁶³. Based on the composite score (range:8-35) a score 11 or greater indicated: *'Yes-Neighborhood perceived somewhat/very unsafe.'* The Economic Strain instrument included the item: "How difficult is it to pay bills?"¹⁴⁹ Responses of 'some difficulty' or 'great difficulty' indicate: *'Yes-experienced economic stress.'* Women were asked if they had ever experienced discrimination because of being a woman on the job or in public¹⁶⁴. Those responding Yes, were categorized: *'Yes- experienced gender discrimination.'* Perceived social support was measured using the Medical Outcomes Study Social Support Scale¹⁶⁵ assessing availability of perceived social support "since becoming pregnant." The 19 Likert-scaled items measured four categories (tangible or instrumental support; affectionate; positive social interaction; emotional/informational support) that are summed for an overall score. The score was standardized to a 0-100 scale and tertile categories corresponding to 1=low support with a score of <78, 2=middle with a score of 79-88, and 3=adequate support at 89+ were created.¹⁶⁵ For the current analysis, a score of 88 or lower represented: *'Yes- experienced low social support.'* Structural social support¹⁶⁵ was measured by asking about the number of relatives and friends she feels close to and can talk to or ask for help. The sum of both friends and relatives was calculated (range: 0-60). Based on the distribution and theoretical understanding, having five or more friends/relatives to count on was considered adequate structural support and fewer than five indicated: *'Yes- experienced low structural support.'*

Table 11. Description of instruments used and operationalization of each psychosocial factor included in the psychosocial adversity index

Psychosocial Factor/ Instrument	Description	Example of Items	Operationalization of Each Factor
Stressful life events/The Life Experiences Survey	Examines 39 distinct acute and chronic life stresses since the start of pregnancy. If an event occurred, women were asked to report the impact as positive (+1 to +3), negative (-1 to -3), or no impact (0).	-getting married -partner died -started new job	The sum of life events (range 0-13) with a negative impact was calculated. Those with no negative events were categorized as such. Those who reported 1 or more events with a negative impact were categorized as: <i>'Yes- experienced negative life events'</i>
Verbal abuse/ Revised Conflict Tactic Scale 2 (CTS)	The CTS measures “psychological and physical attacks on a partner in a marital, cohabiting, or dating relationship.” The verbal aggression questions measure the frequency of 4 acts during pregnancy on a Likert scale.	-Insulted/sworn at -Shouted/yelled at -Showed spite	The frequency of events occurring was summed. Those with all events reported as ‘never’ occurring were categorized as having experienced ‘No Verbal Abuse’ all others were categorized as: <i>'Yes-Experienced Verbal Abuse'</i>
Physical abuse/ CTS	The physical aggression questions of the Revised CTS2 measure the frequency of 5 acts occurring during pregnancy on a Likert scale.	-Threw things -Twisted arm -Grabbed/Slapped	The frequency of events occurring was summed. Those with all events reported as ‘never’ occurring were categorized as having experienced ‘No Physical Abuse’ all others were categorized as: <i>'Yes-Experienced Physical Abuse'</i>
Neighborhood Safety/ Perceptions	Includes seven question to assess the frequency of events such as drug dealings, violent crimes, and property crimes.	-Feel safe at night -Drug deals happen -Violent crimes	A composite score (range: 8-35) was created and a score of 0-10 indicated the neighborhood was perceived as safe. A score of 11 or greater was categorized as: <i>'Yes-neighborhood perceived unsafe'</i>
Economic stress/ Economic Stress	Measures with one of the questions from the Economic Strain instrument on a Likert scale (no difficulty to great difficulty).	-How difficult is it to pay bills?	Responses of ‘no difficulty’ or ‘little difficulty’ were combined to indicate no economic stress and responses of ‘some difficulty’ or ‘great difficulty’ were combined to indicate: <i>'Yes- economic stress'</i>
Gender discrimination/ Sex discrimination	Discrimination based on sex measured with one of the questions from a discrimination scale developed to focus on African American women.	-Experience discrimination because at job?	A ‘No’ response indicated that woman never felt she experienced discrimination because she was a woman at either a job or in public. Those responding Yes, were categorized as: <i>'Yes- experienced gender discrimination'</i>
Perceived social support/ MOS Social Support Scale	Assesses the availability of perceived social support with 19 items and summed in a composite score covering four categories (tangible or instrumental support; affectionate; positive social interaction, emotional/informational support).	-have someone to take me to doctor -shows love -gives information	The 19 items are scaled into a combination category for an overall score of Functional Support (range: 21-95). Those with a score of those with a score less than 89 (0-88) were categorized as: <i>'Yes- experienced low social support'</i>
Structural support/MOS SS scale	Structural support was measured by asking about the Number of relatives and friends she feels close to and can talk to or ask for help.	- # of relatives - # of close friends	The sum of both friends and relatives was calculated (range: 0-60). Those with less than 5 were categorized as: <i>'Yes-experienced low structural support'</i>

A Psychosocial Adversity Index was constructed by summing the dichotomous categories of the eight risk factors (range: 0-8). Based on prior literature, the distribution of the index score and a sensitivity analysis, we defined a score of 4+ psychosocial adversities as having 'High psychosocial adversity' and a score of 0-3 as 'Low psychosocial adversity'.^{95,97}

Antepartum depression and anxiety. The outcomes of interest are elevated depression, anxiety symptoms, or both, assessed during the second and third trimesters through the self-administered questionnaires. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression (CES-D) Scale,¹⁶⁶ consisting of 20 items assessing how frequently symptoms occurred in the last week. A three-level outcome variable for antepartum depressive symptoms was defined as: 'No symptoms' and included women not screening positive at either trimester; 'Symptoms in only one trimester' included women who screened positive (CES-D score >16) for depression at either trimester; and 'Symptoms in both trimesters' which included women who screened positive for depression in both trimesters.

Anxiety was measured using the State portion of the State-Trait Anxiety Inventory (STAI)¹⁶⁷ a 20-item scale inquiring about current feelings of anxiety (range: 0-80). We used the outpoint of 39/40 suggested in the literature to detect clinically significant levels of anxiety symptoms.¹⁶⁸ Similar to the depression variable, a three-level outcome variable for antepartum anxiety patterns was defined as: 'No symptoms'; 'Symptoms in only one trimester'; and 'Symptoms in both trimesters' for those who screened positive for anxiety in both trimesters.

Comorbid depression and anxiety was indicated with a three-level variable defined as: 'No Symptoms' for women who did not report depression or anxiety symptoms in either trimester; 'Either depression or anxiety only' for women who reported only depression or only anxiety at one or both trimesters, but never reported both simultaneously; and 'Comorbid depression and anxiety' for women who screened positive for depression and anxiety at the same time, in either trimester.

Maternal sociodemographic characteristics. Maternal characteristics were collected at baseline and included: maternal age, race/ethnicity (White non-Hispanic, Black non-Hispanic, other), years of education completed (8-12, 13-16, 17-20), marital status (married/cohabitating, single), parity (number live births), employment status at the start of pregnancy, a dichotomous indicator of being below poverty level (based on household income, number of adults and children in household and dichotomized at being below 100% of the official poverty level for 2001),¹⁸¹ and smoking status.

Data analysis. Censoring weights¹⁸² were applied to account for loss to follow-up attributable to missing outcome information on depression and anxiety in the second trimester (11%), the third trimester (21%), and their patterns and comorbidity (25%). Multiple Imputation (MI) was used to impute missing covariate data (0.4%-10%), and psychosocial measures (10%).¹⁸³ One hundred iterations were created with imputed values and the final index was created in each imputed dataset. The PROCMIANALYZE procedure in SAS was used to read parameter estimates and associated standard errors or covariance matrices to derive valid parameter estimates.

We estimated the cross-sectional association between psychosocial adversity and depression and anxiety symptoms during the second and third trimesters using log-binomial regression to calculate prevalence ratios (PR) and 95% confidence intervals (CI). The COPY Method was used when the log-binomial regression model did not converge.¹⁸⁴ To estimate the association between psychosocial adversity and the three-level outcomes (depression pattern, anxiety pattern, and comorbid occurrence) we used generalized logistic regression procedures (multinomial logistic regression analysis for nominal variables) to calculate odds ratios (OR) and 95% CIs. Based on a Directed Acyclic Graph, each model was adjusted for possible confounding by including the maternal sociodemographic variables.¹⁸⁵ Additionally, we used generalized estimating equation methods (PROC GENMOD with GEE in SAS) that adjust estimates and standard errors to account for women (n=233) who participated in the PIN study more

than one time for subsequent pregnancies and were therefore not independent observations. All analyses were carried out with SAS 9.4 (Cary, NC).

4.4 Results

Maternal characteristics by mental health symptoms. Maternal characteristics of the analytic sample by depression and anxiety levels by trimester are presented in Table 12. Women were on average 29 years old and 70% identified as white. Participants had an average of 15.4 years of education, with 26% unmarried and 20% unemployed. At the second trimester, 21% of women had elevated depression symptoms and 30% had elevated anxiety symptoms. At the third trimester, the proportion of women with elevated depression symptoms remained the same (20%) while the proportion of women with elevated anxiety symptoms decreased to 21%.

Multiple sociodemographic variables were correlated with the presence of elevated depression and/or anxiety symptoms. As an example, in the second trimester women with elevated symptoms were younger (age 27 vs. age 29 among those with none/low symptoms), less educated (14 completed years vs. 16), not married (46% vs. 16%), or lived below the poverty line (24% vs. 7%). Elevated depression symptoms were also more prevalent among Black women, where 12% had elevated symptoms compared to 9% of white women.

Table 13 shows the pattern of depression (panel A) and anxiety symptoms (panel B) across pregnancy by categorizing them as either no symptoms in either trimester (column 1), having symptoms in only one trimester, either the second or third trimester (column 2), or having symptoms in both trimesters (column 3). Screening results for anxiety found that 44% of women had no symptoms, while 50% had no depression symptoms. Persistent symptoms of depression and anxiety were reported by 11% and 13% of women, respectively. Nineteen percent of women experienced the comorbid depression and anxiety pattern during at least one trimester (panel C, column 3). Compared to women with no symptoms and to women with symptoms at only one trimester, women with persistent or

comorbid symptoms tended to be younger, with fewer years of education, unmarried, multiparous, unemployed, smoked, Black or other race/ethnicity, and below the poverty level.

Psychosocial adversity and mental health patterns. The psychosocial adversity index had a normal distribution and a mean and standard deviation of 3.24 ± 1.50 . Ninety-seven percent of women reported at least one factor, while 42% reported four or more factors (Table 14). The most prevalent (>50%) factors were serious negative life events (68%), lack of structural social support (57%), unsafe neighborhood (55%), and verbal aggression (51%). Conversely, gender discrimination (28%), economic stress (16%), lack of perceived social support (10%), and physical aggression (4%) were experienced by fewer women.

Compared to the reference group with low psychosocial adversity, those reporting high psychosocial adversity had 2.39 (95% CI: 1.95-2.92) times the prevalence of screening positive for depression symptoms in the second trimester, and 2.17 (95% CI: 1.74-2.71) times the prevalence of screening positive for depression in the third trimester (Table 15). Compared to women with low psychosocial adversity, those with high psychosocial adversity had 2.16 (95% CI 1.83-2.54) times the prevalence of screening positive for anxiety in the second trimester and 2.11 (95% CI: 1.73-2.57) times the prevalence of screening positive in the third trimester.

Psychosocial adversity was associated with increased odds of persistent and comorbid symptoms. The OR estimates for persistent symptoms were greater than for symptoms at only one trimester (Table 16). For example, compared to low adversity, high psychosocial adversity was associated with 2.70 (95% CI: 1.95-3.73) times the odds of experiencing depressive symptoms once during pregnancy and with 6.67 (95% CI: 4.31-10.33) times the odds of persistent depressive symptoms in both trimesters. A similar pattern was observed for psychosocial adversity and anxiety. Regarding comorbidity, women with high psychosocial adversity had 2.06 (95% CI: 1.51-2.82) times the odds of having symptoms of either depression or anxiety at the second or third trimester (not comorbid)

compared to women with low adversity. Women with high psychosocial adversity had 5.57 (95% CI: 3.95-7.85) times the odds of having comorbid symptoms at either trimester, compared to women who had low psychosocial adversity.

4.5 Discussion

This analysis evaluated the association of cumulative psychosocial adversity with prevalence, chronicity, and comorbidity of mental health symptoms during the antepartum period. We found that higher psychosocial adversity was associated with overall increased odds of depression and anxiety, as well as a persistent and comorbid pattern throughout pregnancy.

We assessed symptoms during the second and third trimesters and found that about 20% of women were depressed at each timepoint. The prevalence of elevated anxiety symptoms decreased across the two points, from 30% to 21%. These estimates are higher than prevalence estimates previously reported by trimester for depression (7%-13%) and similar for anxiety prevalence estimates by trimester in the United States (18%-25%).^{5,19} Among women who reported elevated depression or anxiety symptoms at least once during pregnancy, roughly half reported elevated symptoms at both trimesters, indicating a chronic course of mental health problems. The resulting proportion of women with persistent symptoms was similar to the those reported in the Lee study.¹⁸⁶ Finally, a fifth of women had comorbid depression and anxiety during at least one timepoint, a slightly higher estimate than the 14% reported by Lee et al.¹⁸⁶

In our cohort, over two-thirds of women reported experiencing at least one psychosocial adversity and just under half experienced a high level of adversity (four or more factors). A direct comparison across studies is difficult due to variations in specific psychosocial factors assessed, the reference time period, and the underlying populations.^{187,188} However, the CDC nationally representative Pregnancy Risk Assessment Monitoring System (PRAMS) that assessed four broad life stressor categories

reported that 71% of women experienced at least one life stressor in year prior to pregnancy, an estimate not very different from ours.¹⁷⁸

Consistent with our hypothesis, we found that an increased number of psychosocial adversities was associated with increased odds of depression and anxiety. While there is diversity in the number and types of adversities considered in the existing literature, our findings are consistent with other studies that have examined the accumulation of psychosocial adversities in relation to perinatal mental health problems. Glazier et al.¹²⁰ evaluated cumulative psychosocial adversity as the number of life events, social support, socioeconomic status in the second trimester and showed an association with symptoms of both depression and anxiety. Westdahl and colleagues¹⁸⁹ used information on social support, interpersonal and partner conflict to define psychosocial adversity and found a dose-response relationship, with each increase of a risk factor resulting in consequent risk for depression symptoms. We did not observe a consistent dose-response association with outcomes which, in turn, guided our decision to dichotomize our psychosocial adversity index score. Other studies focused on specific types of adversities such as violence-related domains and generated aggregate exposures relying on items such as intimate partner violence and crime indicators.¹⁰⁵ The consistency of findings across types of measures further supports the idea that gathering information on a wide range of possible adversities experienced by women provides insights into mental health risks. The utility of measuring the accumulation of a range of psychosocial factors has been demonstrated on outcomes beyond mental health, including cardiovascular disease¹⁹⁰ and youth behavior,¹⁹¹ further reinforcing the idea that their assessment is key in multiple clinical settings. Our index is unique in combining both individual factors such as low social support with additional factors, such as perceived neighborhood safety and experiences of gender discrimination, that take into account a broader context of their experience during pregnancy.

Several limitations should be noted. First, exposure and outcome were measured simultaneously. The cross-sectional nature of this analysis limited the potential to infer causal directions in the trimester-specific relations between psychosocial risk factors and mental health symptoms. However, this design may be reflective of clinical practice where practitioners evaluate women for risk factors and screen for depression and anxiety in the same clinical visit. Second, the generalizability of these results may be limited since PIN participants, who were more affluent, with higher education and low poverty levels, and may not be representative of the North Carolina pregnant population. Participants were recruited at less than 20 weeks pregnant, eliminating the inclusion of women who started prenatal care later in pregnancy and those women who may have different psychosocial risk profiles. Additionally, loss to follow-up and nonresponse to questionnaires resulted in missing information. We addressed limitation in our models by using censoring weights for outcomes and multiple imputation for missing covariates. A final limitation was unmeasured confounding due to the lack of information on psychotropic medication use or a history of mental health symptoms.

A strength of our study was the novel index we used to define psychosocial adversity. In addition to assessing widely studied factors, we included measures for perceived neighborhood safety and gender discrimination which are relevant but understudied. Factors were assessed with questionnaires that measure objective and subjective information resulting in an index that may represent a more accurate experience of the range of psychosocial adversity in the women in this study. Additionally, we used screening tools with established cutpoints to define elevated symptoms of depression and anxiety in pregnant populations. Finally, depression and anxiety symptoms were measured at two timepoints during pregnancy, which allowed examination of persistent symptoms over time and their comorbid occurrence.

4.6 Conclusion

Women who reported high psychosocial adversity had an increased prevalence of depression and anxiety, and increased odds of experiencing a persistent and comorbid pattern of symptoms throughout pregnancy. Clinically, women at higher risk of elevated depression and anxiety can be identified with early assessments of psychosocial adversities during routine antenatal visits. Identifying women at risk for persistent and comorbid depression and anxiety can lead to targeted interventions and improve maternal and child outcomes.

4.7 Tables for Analysis 1

Table 12. Maternal characteristics for analytic sample and by second and third trimester mental health symptoms screening in the Pregnancy, Infection, and Nutrition Study, North Carolina, 2001-2005 (N=1,797)

Characteristics	Depression screening ^a					Anxiety screening ^b			
	All N=1,797 (100%)	Second trimester n=1,585		Third trimester n=1,418		Second trimester n=1,586		Third trimester n=1,413	
		Low/mild n=1,201 (67%)	Moderate/seve re n=384 (21%)	Low/mild n=1,054 (59%)	Moderate / severe n=364 (20%)	Low/ moderate n=1,041 (58%)	Severe n=545 (30%)	Low/ moderate n=1,041 (58%*)	Severe n=372 (21%)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Maternal age (years)	29.01±5.6 2	29.84±5.2 1	26.99±6.01	29.92±5.2 6	27.70±5.7 2	29.76±5.2 9	28.03±5.8 0	29.92±5.2 6	27.70±5.7 2
Education (years)	15.43±2.9 3	16.13±2.7 2	13.98±2.78	16.2±2.71	14.29±2.8 8	16.15±2.7 3	14.54±2.8 8	16.09±2.7 3	14.64±3.0 0
Race/ethnicity									
White	1264 (70.34)	864 (76.66)	125 (65.79)	805 (76.38)	241 (66.21)	800 (76.85)	354 (64.95)	792 (76.08)	252 (67.74)
Black	365 (20.31)	168 (14.91)	44 (23.16)	155 (14.71)	81 (22.25)	149 (14.31)	139 (25.50)	158 (15.18)	80 (21.51)
Other	168 (9.35)	95 (8.43)	21 (11.05)	94 (8.92)	42 (11.54)	92 (8.84)	52 (9.54)	91 (8.74)	40 (10.75)
Not married	471 (26.21)	193 (16.07)	180 (46.88)	171 (16.22)	136 (37.36)	170 (16.33)	201 (36.88)	188 (18.06)	121 (32.53)
Multiparous	970 (53.98)	607 (50.54)	229 (59.64)	526 (49.91)	210 (57.69)	525 (50.43)	315 (57.80)	509 (48.90)	227 (61.02)
Not employed	375 (20.87)	234 (19.48)	100 (26.04)	199 (18.88)	89 (24.45)	215 (20.65)	117 (21.47)	192 (18.44)	96 (25.81)
Below poverty level	224 (12.47)	87 (7.24)	93 (24.22)	74 (7.02)	72 (19.78)	75 (7.20)	104 (19.08)	77 (7.40)	69 (18.55)
Smoke	202 (11.24)	87 (7.24)	80 (20.83)	65 (6.17)	79 (21.70)	67 (6.44)	97 (17.80)	74 (7.11)	68 (18.28)

Note: Percent may not add up to 100 due to missing.

^a Center for Epidemiologic Studies Depression Scale: A CES-D score of 0-16 indicates low/mild depression symptoms. A cutoff score of ≥ 17 indicates moderate to severe depression and participants with a score ≥ 17 were considered as screening positive for depression.

^b State Trait Anxiety Inventory: A score ≥ 39 on the STAI indicates severe anxiety. A cutoff score of ≥ 39 was considered as screening positive for anxiety.

Table 13. Maternal characteristics by antepartum patterns of depression, anxiety and comorbid symptoms[#] in the Pregnancy, Infection, and Nutrition Study, North Carolina, 2001-2005 (N=1,797)

Characteristics	Panel A: Depression pattern n=1,357			Panel B: Anxiety pattern n=1,345			Panel C: Comorbid symptoms n=1,341		
	Column 1	Column 2	Column 3	Column 1	Column 2	Column 3	Column 1	Column 2	Column 3
	No symptoms	2 nd or 3 rd trimester	Persistent symptoms	No symptoms	2 nd or 3 rd trimester	Persistent symptoms	No symptoms	Depression or anxiety	Comorbid symptoms
	n=902 (50%) n (% ^{**})	n=253 (14% [*]) n (% ^{**})	n=202 (11% [*]) n (% ^{**})	n=791 (44% [*]) n (% ^{**})	n=320 (18% [*]) n (% ^{**})	n=243 (13% [*]) n (% ^{**})	n=692 (38% [*]) n (% ^{**})	n=313 (17% [*]) n (% ^{**})	n=336 (19% [*]) n (% ^{**})
Age (years)*	30.21±5.07	28.65±5.59	26.77±5.97	29.96±5.16	29.29±5.54	27.78±5.85	30.18±5.02	29.73±5.46	27.51±5.81
Education (years) *	16.44±2.59	14.98±2.95	13.67±2.68	16.33±2.66	15.61±2.81	14.12±2.90	16.53±2.54	15.76±2.86	14.21±2.85
Race/ethnicity									
White	713 (79.05)	173 (68.38)	126 (62.38)	625 (79.01)	228 (71.25)	158 (65.02)	558 (80.64)	228 (72.84)	220 (65.48)
Black	114 (12.64)	55 (21.74)	50 (25.75)	103 (13.02)	57 (17.81)	61 (25.10)	80 (11.56)	57 (18.21)	78 (23.21)
Other	75 (8.31)	25 (9.88)	21 (12.87)	63 (7.96)	35 (10.94)	24 (9.88)	54 (7.80)	28 (8.95)	38 (11.31)
Not married	122 (13.53)	68 (26.88)	95 (47.03)	118 (14.92)	74 (23.13)	94 (38.68)	87 (12.57)	65 (20.77)	129 (38.39)
Multiparous	438 (48.56)	145 (57.31)	117 (57.92)	377 (47.66)	179 (55.94)	147 (60.49)	328 (47.66)	164 (52.40)	202 (60.12)
Not employed	169 (18.74)	51 (20.16)	59 (29.21)	152 (19.22)	61 (19.06)	64 (26.34)	129 (18.64)	60 (19.17)	84 (25.00)
Below poverty level	55 (6.10)	34 (13.44)	49 (24.26)	51 (6.45)	30 (9.38)	56 (23.05)	37 (5.35)	31 (9.90)	66 (19.64)
Smoke	45 (4.99)	41 (16.21)	48 (23.76)	41 (5.18)	40 (12.50)	49 (20.16)	27 (3.90)	40 (9.58)	72 (21.43)

Note: Percent may not add up to 100 due to missing.

Panel A: Depression pattern was based on 2nd and 3rd trimester screening. A score ≥ 17 on the CES-D were considered as screening positive for depression. Those who did not screen positive at either trimester were considered as having no symptoms and those who screened positive at both trimesters were considered as persistent depression.

Panel B: Anxiety pattern was based was based on 2nd and 3rd trimester screening. A score ≥ 39 on the STAI was considered as screening positive for anxiety. Those who did not screen positive at either trimester were considered as having no symptoms and those who screened positive at both trimesters were considered as persistent anxiety.

Panel C: Based on depression and anxiety symptoms at the 2nd and 3rd trimester, women who endorsed depression and anxiety at the same time, at either the 2nd or 3rd trimester were considered to be experiencing comorbid depression and anxiety. Women who endorsed only depression or only anxiety at either trimester were not considered as experiencing comorbid symptoms.

Table 14. Prevalence of individual psychosocial factors endorsed and psychosocial adversity index in the Pregnancy, Infection, and Nutrition Study, North Carolina, 2001-2005 (N=1,797)

Psychosocial factor^a	Prevalence	
	n	%
Experienced negative life events	1,231	68.50
Lacked structural social support	1,027	57.15
Perceived neighborhood as unsafe	1,006	55.98
Experienced verbal aggression	932	51.86
Experienced gender discrimination	520	28.94
Experienced economic stress	301	16.75
Lacked perceived social support	195	10.85
Experienced physical aggression	74	4.12
Psychosocial adversity index* (mean+SD)	3.24±1.50	
Low Psychosocial Adversity (index: 0-3)	699	57.06
High Psychosocial Adversity (index: 4+)	526	42.99

Note: Factor ranked from highest prevalence to lowest.

^aPsychosocial adversity index calculated only for those with completed data (n=1,225).

Table 15. Prevalence Ratios for the association between Psychosocial Adversity Index* (Low: 0-3 vs High:4+) and Depression and Anxiety status during the Second and Third Trimester in the Pregnancy, Infection, and Nutrition Study, 2001-2005

	Second trimester				Third trimester			
	Moderate/severe depression (n=1,585)		Severe anxiety (n=1,586)		Moderate/severe depression (n=1,418)		Severe anxiety (n=1,413)	
	aPR	95% CI**	aPR	95% CI**	aPR	95% CI	aPR	95% CI
Psychosocial adversity								
Low (0-3)	1.00	---	1.00	---	1.00	---	1.00	---
High (4+)	2.39	1.95-2.92	2.16	1.83-2.54	2.17	1.74-2.71	2.11	1.73-2.57

Note: Psychosocial adversity index: Reference category is Low (0-3).

Note: Generalized estimating equation methods were used to account for women who repeated participation in the study with subsequent pregnancies.

Note: Models adjusted for: Maternal age, Race/ethnicity, Marital status, Parity, Education, Smoking, Poverty, Employment.

Abbreviation: aPR, adjusted prevalence ratio, CI, confidence interval

Table 16. Multinomial logistic regression evaluating the association between the psychosocial adversity index (Low: 0-3 vs. High: 4+) and mental health patterns during antepartum in the Pregnancy, Infection, and Nutrition Study, 2001-2005

	Depression pattern (n=1,357)		Anxiety pattern (n=1,345)		Comorbid pattern (n=1,341)	
	Symptoms at only one trimester	Persistent symptoms	Symptoms at only one trimester	Persistent symptoms	Symptoms of either depression or anxiety	Comorbid symptoms at either trimester
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Psychosocial adversity index						
Low (0-3)	1.00	1.00	1.00	1.00	1.00	1.00
High (4+)	2.70 (1.95-3.73)	6.67 (4.31-10.33)	2.36 (1.74-3.19)	5.32 (3.67-7.71)	2.06 (1.51-2.82)	5.57 (3.95-7.85)

Note: Psychosocial adversity index: Reference category is Low (0-3).

Note: Generalized estimating equation methods were used to account for women who repeated participation in the study with subsequent pregnancies.

Note: Models adjusted for: Maternal age, Race/ethnicity, Marital status, Parity, Education, Smoking, Poverty, Employment.

Abbreviation: aOR, adjusted odd ratio, CI, confidence interval

CHAPTER 5. ANALYSIS 2: THE EFFECT OF CUMULATIVE PREGNANCY AND DELIVERY COMPLICATIONS ON POSTPARTUM MENTAL HEALTH²

5.1 Chapter Overview

Women experiencing multiple obstetric complications may be at increased risk for postpartum depression and anxiety. We examined cumulative pregnancy and delivery complications on incident mental health symptoms during the first year postpartum. This longitudinal analysis included mothers without elevated depression or anxiety symptoms during pregnancy (n=378). An index based on nine complications was created; reporting two or more or more complications on the index was defined as 'high number of pregnancy and delivery complications'. Women who screened positive for depression or anxiety symptoms at 3 or 12-months postpartum were categorized as 'elevated mental health symptoms'. Log-binomial regression was used to estimate adjusted risk ratios and 95% confidence intervals for the relationship between the complication index and incident mental health symptoms.

Eighteen percent of women reported postpartum mental health symptoms. Women with a high pregnancy and delivery complication index had 1.71 (95%CI 1.13-2.59) times the risk of incident mental health symptoms postpartum, compared to women with low complication index. Even in the absence of mental health symptoms in pregnancy, women with a high number of pregnancy and delivery complications may benefit from increased mental health screening and targeted interventions to address postpartum mood disorders.

² **Note:** Tables and figures for this chapter are in section 5.7.

5.2 Introduction

Postpartum mental health is a significant public health concern, with the prevalence of major/minor depression ranging from 13-19%^{2,124} and anxiety from 11-17%.¹⁹ Postpartum mental health conditions are linked with decreased well-being, negative health behaviors, and in severe cases, higher risk for suicide.³³ Depression and anxiety interfere with maternal-infant bonding, potentially impairing cognitive development^{52,192} and increasing behavioral problems.⁵⁸ Children of depressed mothers are also at increased risk of mental health problems as teenagers⁶³ and young adults themselves,⁶⁴ pointing to the intergenerational impact of depression. Although there are no universal screening practices, it is recommended that practitioners assess established sociodemographic and psychosocial risk factors to identify women who may benefit from additional screening for postpartum mental health problems,^{193,194} especially among those who reported symptoms during pregnancy.¹⁴²

Although having a history of mental health disorders is one of the most predictive factors for future depression and anxiety episodes,^{77,74} a subset of women who are first diagnosed with major depression or generalized anxiety during the postpartum period. Fewer studies focus on the unique risk factors for incident mental health problems in this group of women. Importantly, the impact of individual and cumulative pregnancy and delivery complications on the risk of developing postpartum depression^{115,124,125} and anxiety¹²⁶ is not well understood. The small number of studies in this area have reported an association between severe nausea and vomiting, gestational diabetes, pre-eclampsia, and Cesarean-section¹⁹⁵ with an increased risk of incident postpartum depression.¹²⁷ Conditions such as gestational diabetes or pre-eclampsia may be burdensome and stressful to manage,¹⁹⁶ while the psychological impact of a difficult delivery (Cesarean-section, preterm delivery, newborn needing emergency medical care) may further contribute to mental health problems postpartum.¹²⁶ Importantly, since complications may not occur in isolation, women with multiple complications may be at even greater risk.^{124,141}

According to the Center for Disease Prevention and Control, there is evidence that rates of pregnancy complications, such as preterm birth and gestational diabetes, are increasing.¹⁹⁷⁻¹⁹⁹ Given this increase, there is a need to understand the role of cumulative complications on postpartum mental health symptoms, especially among who do not experience mental health problems during pregnancy and who experience their first episode of depression or anxiety in the postpartum period. Accordingly, the objective of this study was to evaluate the association of cumulative pregnancy and delivery complications with new-onset symptoms of depression or anxiety during the first year postpartum using data from a well-characterized prospective cohort study.

5.3 Methods

Population and study design. Data for this longitudinal analysis come from the Pregnancy, Infection, and Nutrition (PIN) Study (<http://epidpin.web.unc.edu/>). The PIN study was originally designed to study risk factors for preterm birth among women living in North Carolina, with recruitment occurring between 2001 and 2005. Beginning in 2003, a subset of eligible women (n=1,038) were recruited to participate in the post-partum portion of the study. Women were assessed in person during in-home interviews by trained study personnel at 3 and 12 months postpartum. We excluded 215 women who reported elevated symptoms of depression and anxiety at either the second or third trimester of pregnancy and 187 women that had no information about mental health symptoms during pregnancy. An additional 258 women were lost to follow-up and did not provide information on depression and anxiety status at either 3 or 12-months postpartum period, resulting in an analytical sample of 378 women. The University of North Carolina Institutional Review Board approved this study.

Measures. Data for this analysis were gathered in several phases including the baseline prenatal in-person screenings, telephone and self-administered interviews during the second and third trimesters, medical records, and in-home interviews at 3 and 12 months postpartum.

Pregnancy and delivery complications. Nine separate pregnancy and delivery experiences were used to define a pregnancy and delivery the complications index. At the second and third trimester telephone interviews, women were asked to report the number of vaginal bleeding episodes, if any, during pregnancy. If women reported two or more episodes at either trimester, they were categorized as *“Yes- vaginal bleeding.”* Additionally, women were asked to report if they experienced nausea which caused them to eat less or avoid doing normal activities since becoming pregnant. Those who reported they had experienced such nausea at either interview were categorized as *“Yes- severe nausea.”*

Medical records were used to identify whether women had gestational diabetes, defined as any degree of glucose intolerance with onset or first recognition occurring during pregnancy. Those with glucose intolerance were categorized as *“Yes- gestational diabetes.”* Medical records were also used to identify women with gestational hypertension or pre-eclampsia. Gestational hypertension is diagnosed when blood pressure readings are higher than 140/90 mm Hg in a woman who had normal blood pressure prior to 20 weeks and has no proteinuria (excess protein in the urine).²⁰⁰ Pre-eclampsia is a condition in pregnancy characterized by high blood pressure/fluid retention and proteinuria. Women with either gestational hypertension or pre-eclampsia in their medical records were categorized as *“Yes- gestational hypertension or pre-eclampsia.”* Medical records were also used to abstract information regarding type of delivery and preterm delivery. Vaginal or C-section, was extracted from medical records. C-section deliveries included both planned and emergency C-sections. C-section delivery were categorized as *“Yes- C-section delivery.”* Gestational age at delivery was assigned by early ultrasound or last menstrual period date if ultrasound was unavailable. Preterm (delivery prior to completing 37 weeks’ gestation) was determined by obstetrician review and abstracted from medical record. Women who delivered prior to 37 weeks were categorized as *“Yes- preterm delivery.”* Birth weight was also abstracted from medical records and newborns weighing <2500g were considered to be low birth weight (LBW). Mothers of those newborns were categorized as *“Yes- LBW newborn.”* Women with

newborns who were hospitalized, as extracted from medical record, were categorized as “*Yes- baby hospitalized.*” Mothers with hospital stays beyond 2 days for vaginal deliveries, and beyond 4 days for C-section deliveries, are considered to be extended hospital stays. At the 3-month postpartum interview, women were asked for the number of days of their hospital stay. Those with vaginal deliveries and stays longer than 2 days and those with C-section deliveries with stays longer than 4 days were categorized as “*Yes- extended hospital stay.*”

Pregnancy and delivery complications index. Each ‘yes’ to the nine pregnancy and delivery complications counted as one point and the total sum represented the cumulative pregnancy and delivery complications index. We dichotomized the pregnancy and delivery complication index at 2 complications based on a preliminary examination of the bivariate association with mental health symptoms. Women with 0 to 1 complications were considered to have low pregnancy and delivery complications and women with 2 or more were considered to have high pregnancy and delivery complications.

Assessment of postpartum mental health. Depression and anxiety symptoms were measured at the 3 and 12-month postpartum interviews. The Edinburgh Postnatal Depression Scale (EPDS),¹⁷⁰ validated for use during the postpartum period, was used for measuring depression. The 10-item scale assesses the woman’s mood during the past week with 4-point response categories. A summed score was generated and dichotomized at the recommended cut off of 10 or more to indicate possible minor depression (vs. 0 to 9 being considered ‘non-depressed’). The 20 item State-Trait Anxiety Inventory (STAI)¹⁶⁷ was used to assess current anxiety symptoms with a 4-point Likert scale. Items were summed for a total score ranging from 20-80. We used the cut-off score of >39 since it has been recommended to indicate severe anxiety among perinatal women.¹⁶⁸

Women who screened positive for either depression or anxiety symptoms at the 3 or 12-month screening were categorized as experiencing postpartum mental health symptoms. Due to the small

number of women with elevated anxiety symptoms, we combined information on depression and anxiety symptoms to create an indicator for elevated postpartum depression or anxiety symptoms called “mental health symptoms.” Data on pre-pregnancy mental health symptoms was not available for the PIN cohort.

Covariates. Baseline measures included maternal age, number of completed years of schooling, parity (number of live births), marital status (single or cohabitating/married), race/ethnicity (self-identified as white, black, other), current smoking status, and body mass index prior to start of pregnancy (calculated based on weight and height and categorized as underweight, normal, and overweight/obese). We also included a measure of antepartum psychosocial adversity. This was a composite index based on eight psychosocial factors: stressful life events, verbal abuse, physical abuse, neighborhood safety, economic stress, gender discrimination, low perceived social support, and low structural social support. The score (range:0-8) was dichotomized and a score of 4 or more psychosocial adversities indicated ‘high psychosocial adversity’ (*See section 4.3 for additional details*).

Statistical analysis. Due to the potential impact of bias due to loss to follow up, stabilized inverse probability for censoring weights were applied.¹⁸² The baseline covariates used for creating censoring weights included age, race/ethnicity, marital status, education level, and parity. The weights had a mean of 1.00 and a range of 0.81-2.22. Additionally, the Multiple Imputation (MI) method¹⁸³ was used to impute values missing values among covariates (0.4%-13% missing). One hundred iterations of the dataset were created with imputed values and the PROCMIANALYZE procedure in SAS was then used to read parameter estimates and associated standard errors or covariance matrices to derive valid parameter estimates.

To estimate the association between pregnancy and delivery complications and incident postpartum depression and anxiety symptoms, we used log-binomial regression procedures to calculate risk ratios (RR) and 95% confidence intervals (CI). The COPY method was used when the log-binomial

regression model did not converge.¹⁸⁴ An a priori adjustment set was determined using a Directed Acyclic Graph (DAG)¹⁷¹ and based on a review of existing literature. Variables that met at least one of the following criteria were included in the DAG: 1) evidence the variable affects both exposure (pregnancy and delivery complications) and outcome (postpartum depression/anxiety); 2) variable is a strong predictor of the outcome or 3) evidence the variable is part of a confounding path. The following covariates met the above-described criteria as possible confounders and were included in models: age, marital status, educational attainment, parity, race, BMI, smoking status, and antepartum psychosocial adversity. Women (n=7) who participated in the PIN study across different pregnancies were not independent observations, therefore we used generalized estimating equation methods (PROC GENMOD with GEE in SAS) to adjust both estimates and standard errors to account for these women. To evaluate the impact of shifting the cut point for the complications index to a higher value, we conducted a sensitivity analysis where women with 3 or more complications were considered to have high complications. All analyses were completed with SAS version 9.4 (Cary, NC).

5.4 Results

Maternal characteristics. Overall, the mean maternal age was 30 years and participants were primarily white (82%), married (88%), employed (78%), completed 13-16 years of education (48%), did not smoke (91%), and 60% reported 3 or fewer psychosocial factors, referred to as low levels of antepartum psychosocial adversity. Eighteen percent (n= 67) of participants who had no mental health symptoms during pregnancy screened positive for incident mental health symptoms at either 3 or 12 months postpartum. Of the 67 women with mental health symptoms, 55 (14.4% of total sample) screened positive for possible depression only, 6 (1.6%) for anxiety only, and 6 (1.6%) screened positive for both depression and anxiety during postpartum. The distribution of antepartum and maternal characteristics by the presence of mental health symptoms in the postpartum period is shown in Table 17. Women who were not white, not married/cohabitating, with lower education, who smoked, and

who had a higher level of psychosocial adversities were more likely to experience incident postpartum mental health symptoms.

A comparison of baseline maternal characteristics between women who were (n=258) and were not lost to follow up (n=636) are presented in Table 18. Women who did not complete the 12-month interview were more likely to be Black, not married, and experiencing high antepartum psychosocial adversity compared to women who were not lost to follow up.

Pregnancy and delivery complication index and postpartum mental health. The overall prevalence of pregnancy and delivery complications is shown in Table 19. Complications experienced during pregnancy included vaginal bleeding (10%), severe nausea (31%), gestational diabetes mellitus (3%), and either pregnancy-induced hypertension or pre-eclampsia (9%). Maternal experience of delivery-related factors included C-section (31%), preterm delivery (10%), baby hospitalized after delivery (6%), and mother's extended hospital stay after delivery (16%). Approximately 30% (n=112) of women did not experience any pregnancy and delivery complications, 43% (n=161) experienced only one complication, and the remaining 28% (n=105) experienced two or more complications. The pregnancy and delivery index had a range of 0-7, with a right-skewed distribution, and mean and standard deviation of 1.21 ± 1.22 . Based on a preliminary examination of the distribution of the index by presence of mental health that showed an increase in proportion of complications at 2 events (Table 19), the decision was made *post hoc* to set the cut-point of 2 complications or more as 'high number of pregnancy and delivery complications'.

The distribution of the frequency of pregnancy and delivery complications by presence of mental health symptoms is presented in Table 20. An increase in the burden of mental health symptoms is seen between women with one and two complications: Among women with only one complication, about 15% developed elevated mental health symptoms in the postpartum period, compared with 23% of women with 2 complications. Women with high pregnancy and delivery complications had 1.71

(95%CI: 1.13-2.59) times the risk of incident mental health symptoms in the first 12 months postpartum, compared to women who experienced low pregnancy and delivery complications (Table 21). Estimates without applied weights and multiple imputation are also presented in Table 21. The application of weights and imputation did not greatly impact the magnitude of estimates and width of the confidence intervals. Additionally, we carried out a sensitivity analysis to determine whether one item in the index was driving the association between the complications index and mental health status in the postpartum. We explored the strength of the association of each complication type with mental health status in the postpartum (Table 22) and also as well as removed each item from the index systematically (Table 23), results showed closely overlapping confidence intervals and therefore no one item was driving the association.

5.5 Discussion

The aim of the present study was to evaluate the relationship between cumulative pregnancy and delivery complications and the onset of postpartum mental health symptoms among women without elevated mental health symptoms during pregnancy. In our sample, 72% of women experienced 2 or more complications and 18% of women reported experiencing depression or anxiety in the first year postpartum. Consistent with our hypothesis, results showed that women who experienced a high number (2 or more) of complications were at greater risk of incident postpartum mental health symptoms.

Although for our main analysis we combined incident depression and anxiety, our estimate of incident depression is similar to those reported in a systematic review by Gavin et al.² They reported that, across studies reporting incidence, up to 14.5% of women had a new episode of major or minor depression during the first three months postpartum.² Several other studies have reported lower rates of incident depression and anxiety. For example, a longitudinal study in Germany examined diagnoses of depression and anxiety disorders among women with different histories of diagnosed disorders prior to

pregnancy and reported that among women with no prior diagnosed disorders, 7.3% had new onset anxiety and 0.9% had new onset depression in the first 16 months postpartum.²⁰¹ Another study that modelled trajectories of depression symptoms from pregnancy through 12 months postpartum concluded that about 1.7% of women belonged to a new postpartum onset category (although this study did use a slightly higher cutoff for the EPDS than we did in our study).¹

In our cohort, 29% of women did not experience any pregnancy and delivery complications. While a direct comparison to other studies in terms of the number of pregnancy and delivery complications is difficult, our findings are generally comparable to national estimates. For example, US estimates of C-section deliveries range from 28% to 31%, and our prevalence was 30%; it is also estimated that pregnancy hypertensive disorders complicated up to 10% of pregnancies nationally,²⁰² in our study sample, 8% of women reported gestational hypertension/pre-eclampsia. On the other hand, the proportion of women who had an extended hospital stay in our study (16%) is considerably lower than what has been reported from the North Carolina Pregnancy Risk Assessment Monitoring System Survey results, which was over 45%. Additionally, national estimates of gestational diabetes (8%),²⁰³ low-birth weight (6.5%),²⁰⁴ and preterm delivery (12.8%)¹⁹⁹ were also slightly higher than in our sample. However, these conditions have been steadily increasing over the last decade and if these trends continue a greater number of women will experience these complications during pregnancy.²⁰⁵

Although most prior studies have evaluated pregnancy and delivery complications individually rather than as a composite index and did not adequately identify incident (vs. prevalent) cases of postnatal depression²⁰¹ or anxiety,⁷⁰ our findings are consistent with the existing literature which has mostly shown a positive association between obstetric factors and postpartum depression or anxiety. For example, Verrault et al asked about the incongruence between the actual experience of delivery compared to the woman's expectations, and reported this factor to be a significant predictor of postpartum depression, even after adjusting for third-trimester depression.¹³ Clout *et al* reported a positive

association between C-sections and depression and anxiety at 4 to 6 months postpartum, but this was completely attenuated once prenatal mental health symptoms were controlled for.¹⁹⁵ Weak associations were also found by Johnstone et al who reported a positive, but not statistically significant, association between antepartum hemorrhage, having a delivery with forceps used, and C-section delivery.¹²⁵

Kettunen et al used a cumulative index of pregnancy and delivery issues, but it included mental health problems during pregnancy, making it impossible to tease out the independent effect impact of obstetric and antenatal mental health problems on postnatal mental health.¹⁵³ In contrast to these studies, Meltzer-Brody et al used Danish registry data to examine predictors of incident postpartum psychiatric disorders among women with no prior psychiatric history.¹²⁷ The authors reported that hyperemesis gravidarum, gestational hypertension, pre-eclampsia, and Caesarean-section were statistically significantly associated with postpartum depression in the first year postpartum.¹²⁷ We recognize that having a history of depression and anxiety prior to pregnancy is a strong predictor for experiencing symptoms during pregnancy and acknowledge that there is a diversity in the published literature as to how this information is collected (self-report, clinical records) and controlled for in analyses. Our results, focused on mental health symptoms during pregnancy and the postpartum, extends the literature by demonstrating there may be a subgroup of women who experience complications during pregnancy and delivery and are at higher risk of developing mental health problems in the postpartum period, even in the absence of mental health problems in the prenatal period

Strengths and limitations. An important strength of this study was our ability to account for a history of depression and anxiety during pregnancy, an often cited gap in the literature, by restricting our cohort to women who did not screen positive for depression or anxiety at either the second or third trimester. We also included antepartum psychosocial adversity in our models in order to control for this important confounder of postpartum mental health status and pregnancy and delivery complications.

The control of important confounders and the longitudinal nature of the study improved our ability to infer causality between the pregnancy and delivery complications and mental health symptoms. An additional strength of this study was the use of validated instruments for assessing depression and anxiety and recommended cut-points for the designation of elevated symptoms in the first 12 months postpartum.

Several limitations should be considered when interpreting our results. A significant limitation in our analysis was the lack of information on history of lifetime mental health. We restricted our analysis to women with no symptoms of depression or anxiety during pregnancy, but this does not fully eliminate potential confounding by lifetime history of mental health prior to pregnancy. While we included some of the most common pregnancy complications in our index, it is likely that additional complications of importance were not included. Additionally, the complications included were objective measures taken from medical charts and each item was assigned equal weight in our index. Research suggests that the subjective experience and burden of the complications may be the driver in the emergence of maternal morbidity and mental health problems.²⁰⁶ However, even with high quality data for some complications in this study, we didn't have measures for how stressful women found each of the complications. For example, since our measure for C-section included both planned and emergency C-section deliveries it did not capture the potential difference in impact, where the emergency C-section may be perceived as more stressful or burdensome than the planned C-section. In general, the PIN participants were more affluent, with higher education and low poverty levels, than the general North Carolina pregnant population, which may affect generalizability. Participants were initially recruited during their prenatal care visits at 20 weeks' gestation, eliminating the inclusion of women who started prenatal care later in pregnancy. Women who start prenatal care earlier in pregnancy may to some extent select for women who experienced complications, such as severe nausea and vaginal bleeding, requiring medical attention. Additionally, we had significant loss to follow up and nonparticipation in the

in-home interview at 3 months that resulted in missing depression and anxiety status. However, we addressed this in our models by including censoring weights and multiple imputation. A final limitation was our small sample size which prevented us from exploring the comorbid occurrence of depression and anxiety separately.

5.6 Conclusion

Women who experienced significant pregnancy and delivery complications were at risk for new onset mental health symptoms in the first 12 months postpartum. Current recommendations suggest screening women at least once in the postpartum and additional screening for those who experienced symptoms during pregnancy. However, practitioners should continue to monitor these mothers during the postpartum period, even if they did not have elevated symptoms of depression or anxiety during pregnancy. Additional screening or closer monitoring of this subgroup of women may be beneficial in identifying women who are at increased risk for new depression and anxiety symptoms in the postpartum period. Future studies should aim to better understand the biological and psychological mechanisms by which experience of multiple complications contribute to increased risk of postpartum mental health problems.

5.7 Tables for Analysis 2

Table 17. Distribution of antepartum and maternal characteristics by presence of postpartum mental health symptoms in the Pregnancy, Infection and Nutrition Study, North Carolina 2003-2007 (N=378)

Characteristics	No Symptoms (n=311)		Mental Health Symptoms ¹ (n=67)		p-value
	n	%	n	%	
Maternal age (mean±SD)	30.70±5.18		29.16±5.28		0.03
Maternal age (years)					
<25	39	12.42	11	16.42	0.33
25-29	84	26.80	23	34.33	
30-34	123	39.87	24	35.82	
35+	65	20.92	9	13.43	
Race/Ethnicity					0.09
White	266	85.62	50	74.63	0.09
Black	23	7.52	8	11.94	
Other	22	6.86	9	13.43	
Married					0.09
Yes	278	89.54	55	82.09	0.09
No	33	10.46	12	17.91	
Parity					0.65
Nulliparous	153	49.35	35	52.24	0.65
Multiparous	158	50.65	32	47.76	
Education (years)					0.03
≤12 (ref)	136	44.12	24	35.82	0.03
13-16	151	48.69	31	46.27	
17+	24	7.19	12	17.91	
Employed					0.39
Yes	247	79.41	50	74.63	0.39
No	64	20.90	17	25.37	
Smoke					0.08
No	289	93.14	57	85.07	0.08
Yes	14	4.24	5	7.46	
Psychosocial Adversity					0.03
Low	199	64.71	31	46.27	0.03
High	80	24.84	26	38.71	

¹ Based on depression and anxiety symptoms at 3 and 12-months postpartum, women who endorsed depression (EPDS) or anxiety (STAI) at either time point, were considered to be experiencing mental health symptoms. Mental Health Symptoms included: depression only (n=55), anxiety only (n=6), and both depression and anxiety (n=6).

Note: % may not add to 100 due to missing

Note: Chi-square Test was used for categorical variables and Two-Sample T-Test for continuous variables, significance level p <0.05

Table 18. Impact of loss to follow up on the distribution of maternal characteristics from the 3-month and 12-month postpartum visit in the Pregnancy, Infection and Nutrition Study, North Carolina 2003-2007

Characteristics	Lost to follow up (n= 258)		Not lost to follow up (n= 378)		p-value
	n	%	n	%	
Maternal age (mean±SD)	29.57±5.58		30.43±5.22		0.05
Maternal age (years)					0.45
<25	44	17.05	50	13.23	
25-29	78	30.23	107	28.31	
30-34	90	34.88	147	38.89	
35+	46	17.83	74	19.58	
Race/Ethnicity					<.0001
White	187	72.48	316	83.60	
Black	55	21.32	31	8.20	
Other	16	6.20	31	8.20	
Married					<.0001
Yes	192	74.42	333	88.10	
No	66	25.58	45	11.90	
Parity					0.46
Nulliparous	136	52.71	188	49.74	
Multiparous	122	47.29	190	50.26	
Education (years)					0.06
≤12 (ref)	90	34.88	160	42.33	
13-16	131	50.78	182	48.15	
17+	37	14.34	36	9.52	
Employed					0.17
Yes	214	82.95	297	78.57	
No	44	17.05	81	21.43	
Smoke					0.01
No	219	84.88	346	91.53	
Yes	27	10.4	19	5.03	
Psychosocial Adversity					0.01
Low	128	49.61	230	60.58	
High	92	35.66	106	28.04	

Note: % may not add to 100 due to missing
Note: Chi-square Test was used for categorical variables and Two-Sample T-Test for continuous variables, significance level p <0.05

Table 19. Prevalence of pregnancy and delivery complications included in the index (n=378)

Pregnancy and Delivery Complications	n	%
Severe Nausea	114	30.6
Cesarean Section	114	30.6
Mother Extended Hospital Stay	59	15.8
Preterm Delivery	37	9.9
Vaginal Bleeding	37	9.9
Pregnancy Induced Hypertension or Pre-Eclampsia	33	8.8
Baby Hospitalized after Delivery	23	6.2
Low Birth Weight Baby	21	5.6
Gestational Diabetes	12	3.3
Pregnancy and Delivery Complications Index		Mean:1.2 SD:±1.2
Low complications (0-1)	273	72.22
High complications (2+)	105	27.78

Table 20. Distribution of the frequency of the pregnancy and delivery complications index by presence of mental health symptoms in the Pregnancy, Infection, and Nutrition Study, North Carolina 2003-2007 (n=378)

Index*	No Symptoms		Mental Health Symptoms	
	n	%	n	%
0	96	85.7	16	14.3
1	136	84.5	25	15.5
2	43	76.8	13	23.2
3	20	76.9	6	23.1
4	8	57.1	6	42.9
5	5	83.3	1	16.7
6	2	100.0	0	0.0
7	1	100.0	0	0.0

Note: The index is a composite of the total number of pregnancy and delivery complications.

Table 21. Risk ratios and 95% confidence intervals for elevated mental health symptoms in relation to pregnancy and delivery complications in the Pregnancy, Infection, and Nutrition Study, 2003-2007 (n=378)

Pregnancy and delivery complications index			aRR (95% CI) ¹	aRR (95% CI) IPCW ²	aRR (95% CI) IPCW and MI ³
	n	%			
Low complications (0-1)	273	72.22	1.00	1.00	1.00
High complications (2+)	105	27.78	160 (1.01-2.52)	1.69 (1.09-2.63)	1.71 (1.13-2.59)

¹Adjustment for: Maternal age, Race/ethnicity, marital Status, parity, education level, smoking, Body Mass Index, and antepartum psychosocial adversity

²Inverse probability for censoring weights applied to account for missing outcomes (depression and anxiety status at 12 months)

³Multiple Imputation used to impute missing values for covariates

Note GEE methods used to account for women who repeated participation in PIN with subsequent pregnancies

Table 22. Prevalence and risk ratios for the association between each individual pregnancy and delivery complication and postpartum mental health symptoms in the Pregnancy, Infection, and Nutrition Study, 2003-2007 (n=378)

Pregnancy and Obstetric Factor [#]	Prevalence		Risk Ratio	
	n	%	aRR ¹	95% CI
Severe Nausea	114	30.56	0.81	0.35-1.88
Cesarean Section	114	30.56	1.24	0.97-1.96
Mother Extended Hospital Stay	59	15.82	1.61	1.03-2.49
Preterm Delivery	37	9.92	0.84	0.43-1.63
Vaginal Bleeding	37	9.92	1.52	1.00-2.31
Pregnancy Induced Hypertension/Pre-Eclampsia	33	8.85	1.69	0.97-2.93
Baby Hospitalized after Delivery	23	6.17	1.19	0.58-2.44
Low Birth Weight Baby	21	5.63	0.83	0.33-2.11
Gestational Diabetes	12	3.33	0.70	0.24-2.03

¹Adjustment for: Maternal age, Race/ethnicity, marital Status, parity, education level, smoking, Body Mass Index, and antepartum psychosocial adversity

Table 23. The impact of removing one item at a time on the risk ratios for the association between the pregnancy and delivery complications index and postpartum mental health (n=378)

Pregnancy and Delivery Complication removed from index	Risk Ratio	
	aRR ¹	95% CI
Severe Nausea–removed	1.53	0.97-2.42
Cesarean Section –removed	1.36	0.84-2.20
Mother Extended Hospital Stay–removed	1.78	1.20-2.69
Preterm Delivery–removed	1.85	1.24-2.77
Vaginal Bleeding–removed	1.67	1.10-2.54
Pregnancy Induced Hypertension/Pre-Eclampsia–removed	1.34	0.84-2.13
Baby Hospitalized after Delivery–removed	1.72	1.13-2.62
Low Birth Weight Baby –removed–removed	1.78	1.17-2.71
Gestational Diabetes	1.55	1.01-2.38

¹Adjustment for: Maternal age, Race/ethnicity, marital Status, parity, education level, smoking, Body Mass Index, and antepartum psychosocial adversity

CHAPTER 6. DISCUSSION

6.1 Overview of Study

The overarching objective of this dissertation was to explore maternal exposure to an accumulation of risk factors in relation to mental health symptoms across the perinatal period. The first analysis evaluated a cumulative index of psychosocial adversity with the pattern and comorbid occurrence of depression and anxiety in the antepartum period. The second analysis evaluated a cumulative index of pregnancy and delivery complications on the onset of mental health symptoms (depression/anxiety) in the postpartum period. Our study contributes to the maternal mental health literature by addressing some current gaps. Anxiety, and its comorbid occurrence with depression, in relation to psychosocial risk factors is understudied in the antepartum period. The onset of new symptoms of mental health in the postpartum period, especially among mothers who did not have symptoms in the antepartum, is also understudied. Importantly, we also explored the exposure to an accumulation of psychosocial adversity and of pregnancy and delivery complications, which have independently been associated with increased risk for mental health symptoms, but warrant improved understanding as cumulative exposures.

We used data from the Pregnancy, Infection, and Nutrition study, a longitudinal pregnancy cohort of women living in North Carolina from 2001-2007 to carry out these analyses. We demonstrated that women with an accumulation of psychosocial adversities during pregnancy may be at higher risk of elevated mental health symptoms in pregnancy and that women with an accumulation of pregnancy and delivery complications may be at higher risk of mental health symptoms in the postpartum.

6.2 Interpretation of Findings

Main findings. Results from our first analysis showed that women who reported high psychosocial adversity (4 or more psychosocial factors) had an increased prevalence of antepartum depression and anxiety, as well as increased odds of experiencing a persistent and a comorbid pattern of symptoms throughout pregnancy. These findings are consistent with prior research that evaluated these psychosocial risk factors individually (*see review of the background section 3.6*), as well as those that evaluated the cumulative impact of more than one psychosocial adversity. In our second analysis we found that even in the absence of mental health symptoms during pregnancy, women with an accumulation of pregnancy and delivery complications were at increased risk for incident mental health symptoms postpartum. In line with our hypothesis, we found that exposure to an accumulation of risk factors (psychosocial for antepartum and pregnancy and delivery for postpartum) was associated with an increased risk for mental health symptoms across in the perinatal period.

Antepartum mental health. Although the point prevalence at the second and third trimester of depression (20% and 20%) and anxiety (30% and 21%) was high, our estimates fall within the range of previously reported estimates for depression and anxiety.^{5,19} Based on screening at two time points, we defined the pattern of depression as three levels: ‘no symptoms’, ‘symptoms at only one time-point’, and ‘persistent symptoms’ for those who screened positive at both time points. We also defined the comorbid pattern as three levels: ‘no symptoms’, ‘symptoms of either depression or anxiety’, and ‘comorbid symptoms’ for those who screened positive for depression and anxiety at the same time point. We found that 19% of women had comorbid symptoms and 11% and 13% had persistent symptoms of depression and anxiety, respectively. While we did not make the assumption that these three level categories represent an ordinal distribution and worsening burden of mental health symptoms, we can say that these groupings represent subsets of women with differing experiences of symptoms. The description of the course and pattern of symptoms described in prior literature and

studies vary widely based on the population included, definition of persistence, and the number of time points measured across pregnancy.^{3,9} However, it has been shown that women with persistent symptoms and with comorbid symptoms experience a number of worse health outcomes compared to women without persistent or comorbid symptoms.²⁰⁷ Furthermore, we found that women who had more persistent or comorbid symptoms tended to be younger, with fewer years of education, not married, multiparous, not employed, smoked, Black or other race/ethnicity, and lived below the poverty level. Based on the existing literature, these characteristics are expected among women at risk for more severe mental health symptoms. The burden of depression and anxiety has been demonstrated to be high among vulnerable populations, including low-income women and Black or other racial/ethnic minority groups.^{68,70} It is important to understand these sociodemographic and maternal characteristics and how they differ across these subsets of women who have persistent or comorbid symptoms.

Postpartum mental health. Considering that having a history of depression or anxiety is the greatest predictor of postpartum or future mental health disorders, it is important to account for this history in analyses.²⁰⁸ We found that, even among women without pregnancy history of depression or anxiety, the incidence of new onset mental health symptoms in the postpartum year was 18%. Due to the small number of women with incident anxiety symptoms, we were unable to investigate anxiety symptoms independently and combined our depression and anxiety screening results to describe overall mental health symptoms. Although for our main analysis we combined incident depression and anxiety, our estimate of incident depression is similar to those reported in a systematic review which reported that, across studies reporting incidence, up to 14.5% of women had a new episode of major or minor depression during the first three months postpartum.²

Cumulative psychosocial adversity. In our cohort, almost all women reported experiencing at least one psychosocial adversity, and just under half experienced a high level of psychosocial adversity (4 or more factors). Consistent with our hypothesis, we found that an increased number of psychosocial

adversities was associated with increased odds of depression and anxiety. Our findings are consistent with other studies that have also examined the accumulation of psychosocial adversities in relation to perinatal mental health problems in the perinatal period.²⁰⁹ However, a majority of the studies typically limited their analysis to evaluating the cumulative impact of only two or three psychosocial risk factors. While using a cumulative measure such as psychosocial adversity index limits the ability to tease apart the individual contributions of each item, it nonetheless has potential to best identify vulnerable women²¹⁰ during pregnancy.¹⁵⁷

Cumulative pregnancy and delivery complications. In our cohort, 29% of women did not experience any pregnancy and delivery complications. While a direct comparison to other studies in terms of the number of pregnancy and delivery complications is difficult, our findings of the prevalence of each complication we included in the index are generally comparable to national estimates of each complication.^{202,204} Although most studies evaluated individual, rather than cumulative complications, and did not adequately address incident (vs. prevalent) cases of postnatal depression²⁰¹ or anxiety,⁷⁰ our findings are consistent with the existing literature. However, our focus on the relationship between the burden of pregnancy and delivery complications with mental health symptoms for those women with no mental health symptoms during pregnancy points to a potential pathway between complications and depression and anxiety. Further understanding of how accumulating complications, through psychological or biological mechanisms, may be linked to mental health in the postpartum is needed.^{211,212} There is growing evidence that women who experience difficult or traumatic deliveries are at increased risk of suffering from Post-Traumatic Stress, an anxiety disorder.²¹³

6.3 Methodological Considerations and Limitations

Temporality. For the analysis of psychosocial adversity and pregnancy mental health symptoms, we used a cross-sectional design which limited the potential to infer causal association in the trimester-specific relations between psychosocial adversity and mental health symptoms in the first analysis. The

outcome of prevalent mental health symptoms was measured in both the second and third trimesters for all women. Instruments measuring exposure to psychosocial adversities asked women to report on the time since the start of pregnancy, however, not all instruments were administered in both trimesters; meaning that mental health symptoms in the second trimester could have potentially influenced psychosocial adversity measured in the third trimester, hence, a scenario of reverse causation is possible. Nonetheless, the intervals at which the instruments were administered may reflect real-world clinical practice, in which practitioners are evaluating women for risk factors and screening for depression and anxiety during the same clinical visit(s).²¹⁴ The second analysis had a longitudinal design, making the temporality between pregnancy and delivery complications and postpartum incident mental health symptoms clear. However, it is still possible that some women in our sample experienced depression and anxiety symptoms in pregnancy, but they did not reach the cutoff level we used, therefore we may have missed including women who may have been included if we had used a different cut-point.

Outcome measurement. The specific research questions of this dissertation were not known to the participants or clinicians and did not influence the self-report of psychosocial adversity or documentation of pregnancy and delivery complications. Depression and anxiety were measured at two time points (second and third trimester) during pregnancy and at two time points (at 3 and 12-months) postpartum. The instruments (CES-D, EPDS, STAI) used to screen for mental health symptoms are validated and appropriate for use in perinatal populations. However, the instruments are not substitutable for a clinical interview and so misclassification is possible.^{166,215} Furthermore, antepartum screening was self-administered and the post-partum screening was completed during in-home visit interviews.

Results from depression and anxiety screenings at each trimester were used to define the persistence and comorbid occurrence of the outcome in participants and this was based on two

screening time points. Depression is an episodic disorder and, with only two time-points, it is possible that some women who were classified as not experiencing any symptoms actually did experience symptoms. More data points (screenings) across pregnancy could improve the differentiation of women who are experiencing persistent symptoms from those who are not. Although, small, there is potential for misclassification of women to no symptoms when they developed symptoms in the second trimester, even though they had already returned their questionnaire.

The indices for psychosocial adversity and the pregnancy and delivery complications included a breadth of psychosocial risk factors and pregnancy complications; it is possible that additional factors of importance were not included in these indices. Additionally, the complications included in the index were objective measures taken from medical charts, but research suggests that the subjective experience and burden of the complications may be the driver in the emergence of maternal mental health problems.²¹⁶ Therefore, it is crucial to incorporate subjective measures of complications,²¹⁷ as we did for the psychosocial index, which measured both subjective and objective aspects of adversity. Omitting the subjective experience of pregnancy and delivery women may underestimate the burden faced by the complications and this limits our ability to say that the cumulative burden of complications is associated with mental health symptoms.

Finally, a drawback of creating composite scores is that unless items are weighted based on their contribution or relative importance to the outcome, each item is assigned equal weight. This was the case for the psychosocial adversity index and the pregnancy and delivery complications index we created. Nonetheless, although the scoring system can be improved by adding weights, we are confident that these indices do measure each phenomenon (cumulative psychosocial adversity and cumulative complications) appropriately and reliably, allowing for the inclusion of more information on risk factors than an analysis of an individual risk factor would grant.

Unmeasured confounding. The use of a DAG helped us determine the set of minimally sufficient covariates needed to address confounding in each analysis.¹⁷¹ However, there remain several important confounders that were unmeasured such as lifetime of history of mental health episodes, childhood abuse, as well as intimate partner abuse. These life-course risk factors have been shown to be associated with future depression and anxiety, as well as with psychosocial adversity, pregnancy and delivery complications. However, this analysis was focused on more proximal components reflecting the perinatal experience of risk factors and mental health status. In order to investigate life-course confounders along with these more proximal measures, a mediation analysis would be necessary. An additional unmeasured confounder was medication use for mental health problems by participants. Medication use during pregnancy could impact the presence of mental health symptoms in our first analysis or the onset of new postpartum symptoms in our second analysis. Medication use may also be related to the number of psychosocial adversities, such as job loss due to worsening symptoms or pregnancy complications. Medication use specific to mental health conditions was not collected systematically enough in the PIN study to allow for controlling of this confounder.

Generalizability. There was significant loss to follow up and nonresponse to the self-administered questionnaires in the antepartum and nonparticipation at the 3-month postpartum in-home interview that resulted in missing information on depression and anxiety. However, we addressed this in our models by using censoring weights for missing outcomes and multiple imputation for missing covariates. These methods helped reduce selection bias due to missing information of covariates and improved the validity of the estimates. This dissertation also included data from women who participated in PIN during more than one pregnancy and this meant that their observations were not independent from one another. To account for this, we used generalized estimation equation methods to adjust estimates and standard errors. Additionally, the size for the second analysis did not allow for exploring anxiety on its own or with strict to comorbid occurrence of depression and anxiety, thus, we

were limited to evaluating any mental health symptoms (depression or anxiety) in the postpartum period.

Finally, the generalizability of our results may be limited since PIN participants, are more affluent, with higher education and low poverty levels, primarily white, and may not be representative of the general North Carolina perinatal population, since women in our study may have a different psychosocial risk profile or different pregnancy and delivery complications risk profiles.

6.4 Strengths

An important contribution of this dissertation was the demonstration that cumulative psychosocial adversity and cumulative pregnancy and delivery complications are associated with increased risk of mental health symptoms in the antepartum and postpartum, respectively. Across both analyses, we used depression and anxiety screening instruments that are validated for perinatal populations and we used recommended cut-points to define elevated symptoms.

A strength specific to the first analysis was the number and type of psychosocial adversities. The psychosocial factors included in this psychosocial adversity index are well-characterized and based on validated instruments for a pregnant population. The use of established instruments to measure both objective and subjective experience of psychosocial adversity resulted in an index representing a more accurate experience of the range of psychosocial adversity. It also included measures, such as neighborhood safety and gender discrimination that are not typically studied in pregnant populations. The psychosocial adversity measure created in the first analysis also contributed to an important strength in our second analysis. Psychosocial adversity is a strong predictor of mental health symptoms and pregnancy and delivery complications (e.g., preterm delivery). Because we created the index for psychosocial adversity in the antepartum period, we were able to control for potential confounding in models estimating the association between complications and postpartum mental health. Additionally, we restricted our second analysis to women who did not screen positive for depression or anxiety

during pregnancy to address confounding by history of mental health during pregnancy. The longitudinal nature of the second analysis and control for these significant confounders improved our ability to infer causality between the complications index and postpartum mental health.

6.5 Public Health Implications

Perinatal burden of mental health. While there are no evidence-based guidelines for nationwide screening practices with validated tools,²¹⁸ recommendations do suggest screening pregnant women at least once during the perinatal period.²¹⁹ We found that conducting more than one screening helped identify subgroups of women with differing patterns of symptoms. In line with existing literature, we found that depression and anxiety are prevalent, in both the antepartum and postpartum period. This was true for the single measures at the second or third trimester and when the two time points were used to define persistent symptoms of depression and anxiety across pregnancy. We also found that comorbid symptoms were prevalent, this is important to note since recommendations prioritize screening for depression and, only recently has screening for anxiety also been recommended.

Recommendations also suggest that practitioners screen women at least once in the first year postpartum and closely monitor those who screened positive for depression during pregnancy. However, we found that even among women who experienced no symptoms during pregnancy, new onset of symptoms in the postpartum were still prevalent. Recommendations may overlook this subgroup of women who will develop symptoms in the postpartum, especially if practitioners do not consider them high risk based on screening negative for symptoms during pregnancy. Our findings are supported by existing literature that demonstrates the course and pattern of mental health symptoms can vary across the perinatal period.^{9,220} The heavy burden of mental health symptoms in this population highlights the need to identify women who may benefit from interventions to manage symptoms starting during pregnancy.

Cumulative Index. We created an index using psychosocial risk factors that have demonstrated a strong relationship with mental health in the postpartum, but focused our analysis on the association with antepartum mental health symptoms. We found a positive association between antepartum psychosocial adversity and mental health symptoms during pregnancy. The psychosocial risk factors included in our index have been associated with mental health symptoms individually, but as an index, they could potentially help identify women who would benefit most from screening. Screening that thoroughly assesses psychosocial risk factors can be time consuming, especially if measuring both subjective and objective constructs but in intervention studies, practitioners have found them useful to identify women at risk for depression.^{209,221}

We also found there was a positive association between the pregnancy and delivery complications index and postpartum mental health symptoms. Practitioners should continue to monitor postpartum mothers who experienced multiple complications and our index could help identify women who may benefit from screening. This would be important, especially for women who didn't screen positive for depression in pregnancy, since they may be overlooked during the postpartum period. The specific complications that we used in this index represent some of the most common complications during pregnancy and delivery.

6.6 Future Studies

Future studies. Continued research is needed to fully understand the course and patterns of depression and anxiety, with a specific need to measure comorbidity of depression and anxiety, to determine the most appropriate number of screenings and the timing of screenings. Data from nationally representative studies and studies among vulnerable populations that screen for mental health symptoms at more frequent intervals can be used to better understand the course of mental health symptoms and the predictors of persistent, comorbid and new onset symptoms.

Appropriate and tailored interventions for perinatal mental health problems require the identification of women at increased risk of these conditions.²²² Developing a validated instrument to measure the number and breadth of psychosocial risk factors included in our study may be cumbersome so an important next step would be to explore whether an index with these specific items is useful. An important next step for the use of the pregnancy and delivery complications index would be to determine whether there is a weighting scheme for the complications that would improve the predictive ability of the index. An example of this approach is a comorbidity-based screening tool which applied weights to each of the complications in order to predict severe maternal morbidity at the time of delivery.²²³

Our results demonstrated that women with an accumulation of psychosocial adversities and with an accumulation of pregnancy and delivery complications may be at higher risk of mental health symptoms. Future studies should aim to better understand the biological and psychological mechanisms by which experience of multiple complications or multiple psychosocial risk factors contribute to increase risk of mental health problems. Additionally, interventions that improve management of pregnancy complications and psychosocial risk factors should be developed to reduce the risk of depression and anxiety, and in turn, improve maternal health.

6.7 Conclusion

In the antepartum, women with an accumulation of psychosocial adversities during pregnancy may be at higher risk for elevated depressive and anxiety symptoms. Those who experience an accumulation of pregnancy and delivery complications may be at increased risk for mental health symptoms in the postpartum, even when they had no history of mental health symptoms during pregnancy. Assessing the number of antepartum psychosocial adversities and the number of pregnancy and delivery complications during routine perinatal visits could help identify women at risk for mental health problems. Pregnant women who experience persistent or comorbid depression and anxiety

symptoms during the antepartum and those with the onset of symptoms in the postpartum may require different interventions to address the cumulative impact of psychosocial adversities or pregnancy and delivery complications.

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