MATERNAL ADVERSE CHILDHOOD EXPERIENCES AND INFANT OUTCOMES

by

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Abstract

Background Adverse childhood experiences (ACEs) are common among women of child bearing age and associated with numerous negative health outcomes for both mothers and infants. Minimal research to date has examined relationships between maternal ACEs and the adverse birth outcomes of low birth weight (LBW) and small for gestational age (SGA).

Objectives a) To examine the relation between maternal ACEs and delivering an infant with LBW b) to examine the relation between maternal ACEs and delivering an infant with SGA c) to evaluate if the relation between maternal ACEs and LBW or SGA is moderated by prenatal cigarette smoking or illicit drug use.

Design and Methods A cross-sectional, secondary data analysis of a population-based data set from the Pregnancy Risk Assessment Monitoring System (PRAMS). Multiple logistic regressions were used to examine the relationships between the first two objectives, and multiple logistic regressions with interaction terms were used for the third objective.

Sample 78,153 (weighted sample) respondents from North Dakota and South Dakota, who had recently given birth and answered ACE questions through the PRAMS survey between the years of 2016 and 2020.

Findings No significant associations between maternal ACEs and LBW or SGA were detected. Moderation by prenatal smoking: respondents who smoked during pregnancy with a history of 1-3 ACEs (OR 2.08 95% CI 1.15, 3.77) or 4 or more ACEs (OR 1.88 95% CI 1.06, 3.34) were found to have greater odds of having a LBW infant than respondents with no history of ACEs who did not smoke while pregnant. Respondents who smoked during pregnancy with 4 or more ACEs had twice the odds of having a SGA infant (OR 2.08 95% CI 1.23, 3.28).

Moderation by prenatal illicit drug use: respondents who used illicit drugs during pregnancy with a history of 4 or more ACEs had greater odds of having a SGA infant (OR 1.76 95% CI 1.07, 2.89).

Conclusion This study provides insight into understanding the moderating role that prenatal smoking and illicit drug use play in the relationship between maternal ACEs and the infant outcomes of LBW and SGA. The study highlights the need for population-based surveys to include questions about ACEs in order to further understand the important relationships between maternal ACEs and the infant outcomes of LBW and SGA.

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Chapter One: Introduction

In the United States, 61% of adults have experienced at least one adverse childhood experience (ACE), and 16% have experienced 4 or more ACEs.[1] Women and several racial and ethnic minority groups are at greater risk for experiencing a higher number of ACEs.[2] The greater the number of ACEs, the greater the risk is for negative outcomes.[2,3] Adverse childhood experiences include exposures, in the first 18 years of life, to various forms of childhood abuse, childhood neglect and family dysfunction.[4] There is a strong dose-response relationship between ACE exposure and a broad range of negative health outcomes throughout an individual's entire lifespan.[1] Negative outcomes associated with ACEs include many chronic diseases, depression, anxiety, substance abuse, and premature death.[1,4] The impact of ACEs on health outcomes extends to the perinatal period and to the health of offspring. Maternal ACE exposure is associated with increased risk of perinatal mental illness (depression, anxiety, post-traumatic stress disorder (PTSD), suicidal ideation), risky health behaviors during pregnancy (alcohol use, smoking, illicit drug use) and increased risk of negative birth outcomes including low birth weight (LBW), preterm birth (PTB), and small for gestational age (SGA).[5–14] A large body of research has made clear that ACEs are a critical public health issue. Adverse childhood experiences have wide-spread, lasting negative effects that reach across the lifespan and may be passed down to future generations.[4,15]

Adverse Childhood Experiences

The term adverse childhood experiences was originally coined by Felitti and colleagues in their seminal study published in 1998.[4] The foundational ACE study was conducted from 1995-1997 at Kaiser Permanente's San Diego Health Appraisal Clinic. Through two waves of data, over 17,000 participants completed surveys regarding their childhood experiences, current

health status and current behaviors.[4] The participants in the ACE study were 75% White, 11% Hispanic, 7.5% Asian and Pacific Islander and 5% Black.[4] All participants were members of Kaiser Permanente through their employment. The average age of participants was 57, and 76% of participants had some college education or higher.[4]

Felitti et al.,[4] undertook the ACE study in order to begin to understand the relationships between childhood abuse and adult medical problems. Prior to the ACE study, there was a body of evidence that childhood abuse was common and led to long-term consequences, but little researching exploring the relationships between childhood abuse and adult disease and lifestyle factors.[4] The ACE study was one of the first to examine multiple types of childhood abuse and consider the cumulative effects of different categories of abuse on lifetime health outcomes.[4]

Adverse childhood experiences occur in the first 18 years of life and are categorized into three main groups including abuse, neglect and household dysfunction/challenges. Abuse is further divided into the categories of emotional abuse, physical abuse and sexual abuse. Neglect is divided into emotional neglect and physical neglect. Household dysfunction/challenges include the categories of mother treated violently, substance abuse in the household, mental illness in the household, parental separation or divorce, and incarcerated household member. Table 1 describes ACE categories and definitions from the ACE study.[16]

Table 1

Adverse Childhood Experience Categories and Definitions

Abuse (in first 18 years of life)	
Emotional	A parent, stepparent, or adult living in your home swore at you, insulted you, put you down, or acted in a way that made you afraid that you might be physically hurt.

Table 1 (continued.)

Physical	A parent, stepparent, or adult living in your home pushed, grabbed, slapped, threw something at you, or hit you so hard that you had marks or were injured.
Sexual	An adult, relative, family friend, or stranger who was at least 5 years older than you ever touched or fondled your body in a sexual way, made you touch his/her body in a sexual way, attempted to have any type of sexual intercourse with you.
Neglect (in first 18 years of life)	
Emotional	Someone in your family never or rarely helped you feel important or special, you never or rarely felt loved, people in your family never or rarely looked out for each other and felt close to each other, or your family was never or rarely a source of strength and support.
Physical	There was never or rarely someone to take care of you, protect you, or take you to the doctor if you needed it, you did not have enough to eat, your parents were too drunk or too high to take care of you, or you had to wear dirty clothes.
Household Challenges/ Family Dysfunction (in first 18 years of life)	
Mother treated violently	Your mother or stepmother was pushed, grabbed, slapped, had something thrown at her, kicked, bitten, hit with a fist, hit with something hard, repeatedly hit for over at least a few minutes, or ever threatened or hurt by a knife or gun by your father (or stepfather) or mother's boyfriend.
Substance abuse in the household	A household member had a substance abuse problem or drinking problem.
Mental illness in the household	A household member was depressed or mentally ill or a household member attempted suicide.
Parent/guardian separation	Your parents/guardians were ever separated or divorced.
Incarcerated Household member	A household member went to prison.

Note: Adapted from Felitti et al.[4]
Abbreviations: ACE, adverse childhood experiences

In the original ACE study, over 50% of participants reported at least one ACE, and a little over one-fourth of participants reported 2 or more different types of ACEs.[4] Findings from the study were extensive. Participants reporting 4 or more ACEs, as compared to those reporting no ACEs, had a 4 to 12 fold increased risk of alcoholism, drug abuse, depression and suicide attempt; a 2 to 4 fold increased risk of smoking and sexually transmitted disease; and a 1.4 to 1.6 fold increased risk of severe obesity.[4] The results demonstrated a graded relationship between the increasing number of ACEs and the presence of the following adult diseases: ischemic heart disease, cancer, chronic lung disease, skeletal fractures and liver disease.[4] The potential far-reaching, severe implications of the findings from Felitti, et al.,[4] has led to a large, accumulating body of research examining relationships between ACEs, disease, behaviors and premature death.

Maternal ACEs and Mental Health During Pregnancy

Perinatal Depression

Adverse childhood experiences are associated with a wide array of negative mental health outcomes for women during the perinatal period. There is a strong association between maternal ACEs and perinatal depressive symptomology.[7–9,12,17–20] Depressive symptoms include, but are not limited to, the following: persistent sad mood, feelings of hopelessness, pessimism, irritability, worthlessness, frustration, helplessness, loss of interest in hobbies or activities, decreased energy, fatigue, difficulty sleeping, difficulty concentrating, changes in appetite, thoughts of death.[21] Depression is diagnosed when an individual experiences depressive symptoms most of the time for at least 2 weeks.[21] Perinatal depression may include prenatal depression, postpartum depression or both.

The etiology of perinatal depression is not fully understood, but thought to occur from the

interaction of genetic, hypothalamic-pituitary-adrenal (HPA) axis, environmental and social factors.[22] Risk factors for perinatal depression include previous mood disorder, family history of depressive disorders, multiple birth, unwanted pregnancy, difficult or traumatic pregnancy, history of abuse or domestic violence, on-going health problems, lack of social support, and financial difficulties.[22]

Perinatal depression is common and when untreated can lead to severe consequences for both mom and baby. In the United States, more than 500,000 women/year or 1 in 7 pregnant women and 1 in 5 postpartum women develop depression.[22] Women with perinatal depression report worse health than perinatal women without depression, likely because of a lack of reaching out for help, complying with medical visits, and decreased self-care.[23,24] Mothers with perinatal depression are at increased risk of illicit drug use, smoking, relationship problems, breastfeeding problems, attachment with baby difficulties, parenting difficulties, and persistent depression.[24,25]

Babies born to mothers with untreated perinatal depression experience more physical concerns such as greater amounts of childhood illnesses, more diarrheal episodes, more colic, and more difficult sleep patterns as compared to babies of mothers without depression or those with treated depression.[25] In addition, research has found that children born to untreated mothers with perinatal depression continue to suffer consequences throughout childhood such as decreased cognitive functioning, behavioral inhibition, internalizing/externalizing disorders, emotional problems and psychiatric disorders in adolescence.[25,26] Pathways from mothers perinatal depression to childhood and adolescent emotional and psychiatric disorders may differ for prenatal versus postpartum depression[27] and may involve limited early cognitive stimulation from depressed mothers, limited parent-child interaction, lack of an enriching early environment,

and influence of a depressed mother's increased cortisol passing to fetus while in utero.[27–29]

Many studies have found associations between perinatal depression and the negative birth outcomes of preterm birth (PTB) and low birth weight (LBW), however consensus is inconclusive.[30–32] One recent meta-analysis[33] of 23 studies reported significant associations between prenatal depression and PTB (RR 1.35 95% CI 1.19, 1.52) and LBW (RR 1.86 95% CI 1.32, 2.62), however a previous meta-analysis reported that only about a fourth of the 50 studies examined found a significant association between perinatal depression and PTB, and about half found a significant association between perinatal depression and LBW.[31] Due to the important public health implications of PTB and LBW further research is needed to understand the relationships between perinatal depression and infant birth outcomes. One possible explanation for the different results may be due to the use of different depression screening tools, some of which are short in nature and may not be adequate to assess depression. Other explanations may include inconsistent timing of when depression screening occurs (various trimesters, postpartum), not accounting for severity of depressive symptoms and potentially not controlling for confounders such as race and previous relevant medical conditions. Perinatal depression is common, associated with ACEs, and contributes to serious negative outcomes for both mother and baby.

Perinatal Anxiety

Adverse childhood experiences are associated with other mental health conditions including perinatal anxiety and PTSD.[5,12,14,18] Anxiety during the perinatal period is common and yet it is less screened for and less studied than perinatal depression. Perinatal anxiety and perinatal depression often occur together and can be difficult to distinguish from one another. Estimates of the prevalence of perinatal anxiety are difficult to determine, due to the

heterogeneity of screening tools and lack of screening in general, and range from 5-36% of pregnant women.[34,35] Risk factors for perinatal anxiety disorders include adverse circumstances around the pregnancy or birth, history of poor mental health, lack of quality support from partner and/or other social support, socioeconomic disadvantage and environmental stressors.[34,36] Perinatal anxiety can occur prenatally, postpartum or both and can present with different symptoms in different individuals. Common symptoms of perinatal anxiety include but are not limited to the following: feeling nervous, restless, tense, sense of impending danger, panic, increased heart rate, rapid breathing, trembling, fatigue, trouble sleeping or concentrating, having trouble controlling worry.[34]

Perinatal anxiety is associated with many negative outcomes for the mother and her baby. Mothers with perinatal anxiety are at increased risk for persistent anxiety beyond the perinatal period, co-morbid depression, parenting difficulties, and increased risk of harmful behaviors including cigarette smoking and illicit drug use.[34,37] Prenatal anxiety effects the fetus and neonate through increased maternal cortisol levels, pro-inflammatory cytokines, increased risk of cesarean section and potential increased risk of LBW and PTB.[37] Perinatal anxiety is associated with more illnesses in the first two years of life and reduced gray matter in the childhood brain.[37] Perinatal anxiety is further associated with negative outcomes throughout childhood and into adolescence including lower mental development/scores, more internalizing problems, and more negative emotionality.[37]

Post-traumatic stress disorder during the perinatal period is associated with maternal ACEs and falls under the umbrella of anxiety disorders. Perinatal PTSD occurs in about 3% to 15% of perinatal women and is often not detected and not treated.[38] It is defined as a psychiatric condition that occurs in a person who has experienced or witnessed a traumatic event or series of

events. Common symptoms include intrusive thoughts such as repeated, involuntary memories, dreams or flashbacks, avoidance of reminders, alterations in cognition or mood, and alterations in arousal and reactivity.[39] Perinatal PTSD includes onset of symptoms during pregnancy and also prior to pregnancy and continuing during pregnancy. Risk factors for perinatal PTSD are history of abuse and trauma, severe fear of childbirth, depression in early pregnancy, and low socioeconomic status.[38,40,41]

Untreated PTSD during the perinatal period can lead to maternal and infant morbidity. As compared to women without PTSD or treated PTSD, women with untreated perinatal PTSD have higher risk of increased symptom severity during the pregnancy and postpartum, increased risk of postpartum depression, and they are at risk for poor bonding with their infants.[12,42,43] Studies have found perinatal PTSD to be associated with the negative birth outcomes of PTB and LBW.[44–47] The overwhelming majority of studies examining relationships between maternal ACEs and mental health conditions during pregnancy including depression, anxiety and PTSD, found significant relationships, highlighting the critical role maternal ACEs confer on mental health in pregnancy.

Low Birth Weight and ACEs

A small, but growing body of literature has found associations between maternal ACEs and LBW.[5,48,49] Low birth weight is an adverse neonatal outcome defined as birth weight less than 2500g regardless of gestational age.[50] Low birth weight is caused by prematurity (baby born prior to 37 weeks gestation), and/or intrauterine growth restriction (IUGR). Intrauterine growth restriction occurs when fetal growth unexpectantly slows or stops in utero. Globally, between 15%- 20% of all babies born/year have LBW, and in the United States, about 8% of all babies born/year have LBW.[51,52] Risk factors for having a LBW infant include certain chronic health

conditions such as hypertension or diabetes, certain infections during pregnancy, complications with the placenta, history of having a previous infant with LBW, being pregnant with multiples, history of domestic violence, being a teenager or >35, exposure to lead or high levels of air pollution, living in poverty, and being a member of a group that experiences the effects of racial discrimination and health disparities.[52] Potential pathways in which racial discrimination may contribute to having a LBW or SGA neonate include factors such as personal and institutional discrimination both in accessing and during prenatal care, and maternal physiologic alterations from chronic stress that effect fetal development and growth.[53]

Low birth weight is a valuable public health indicator of maternal health, nutrition, healthcare delivery, and poverty.[54] Infants with low birth weight have greater than 20 times the risk of dying than infants with birth weight of >2500 g.[50] Low birth weight infants are at increased risk of respiratory distress, sepsis, intracranial hemorrhage and gastrointestinal disorders due to immature organ systems.[54] Long term consequences of LBW include neurologic disability, decreased academic achievement, and increased risk of chronic diseases such as cardiovascular disease and diabetes.[50,54] The burden of LBW is substantial to the family, the health care system and society.

Small for Gestational Age and ACEs

Limited studies have found an association between maternal ACEs and the adverse birth outcome SGA.[6,55] Small for gestational age is defined as birth weight that is less than the 10th percentile adjusted for gestational age by sex.[56] Infants that are SGA, typically, suffer from in utero fetal growth problems, or IUGR. Intrauterine growth restriction can occur at any stage of pregnancy and is commonly caused by placental problems where blood flow bringing nutrients and oxygen to the fetus is diminished.[56] In low and middle income countries, 1 in 5 babies born

are SGA.[57] In the United States, about 11.1% of live births are SGA.[58] Risk factors for having a SGA infant include placenta problems, infection, chromosomal anomalies, multiple births, maternal disease such as diabetes, hypertension, kidney disease, malnutrition, anemia, living in poverty, being a member of a group that experiences the effects of racial discrimination and health disparities, and maternal behaviors such as smoking and drug use.[53,56]

Small for gestational age neonates are at increased risk of respiratory depression, jaundice, polycythemia, hypoglycemia, hypothermia, neonatal infections and neonatal mortality.[56] Long term consequences include physical disability, cognitive disability, diabetes mellitus and cardiovascular disease in adulthood.[56] Small for gestational age is a common, serious adverse birth outcome with increased risk of stillbirth, neonatal mortality and childhood morbidity.[59]

Prenatal Cigarette Smoking and Birth Outcomes

About 7% of women in the United States report smoking during pregnancy.[60] Prevalence of smoking varies by state with some estimates as high as 1 in 14 pregnant women.[61] Smoking during pregnancy is associated with a host of serious adverse outcomes for both women and babies. During the pregnancy, prenatal smoking is associated with an increased risk of gestational diabetes, ectopic pregnancy, placental abruption, placenta previa and premature rupture of the membranes.[62] Nicotine and other chemicals found in cigarettes are able to cross the placental barrier and may affect fetal development.[63] Prenatal smoking increases the risk of abnormal in utero lung development, and contributes to long-lasting structural lung changes in childhood, along with increased risk of respiratory illnesses, and asthma.[62,64]

It is well documented that prenatal smoking is associated with the negative birth outcomes of PTB, LBW, SGA and perinatal mortality.[62] According to the World Health

Organization (WHO), PTB is considered the leading cause of neonatal morbidity and mortality.[65] Globally, 15 million births/year are preterm and 10.5% of births in the United States are preterm.[62,66] A recent study with a sample size of over 9 million found a 1.39 (95% CI 1.35, 1.43) increased risk of PTB to mothers who smoke.[67]

One in five babies born to mothers who smoke during pregnancy has LBW. A recent review reported that mothers who smoked during pregnancy gave birth to infants, on average, weighing 174g less than infants of mothers who did not smoke.[68] Even light smoking (<5 cigarettes/day) during pregnancy is associated with elevated rates of LBW.[69] It is estimated that about 13.1%-19% of LBW infants are attributable to prenatal smoking.[70]

Small for gestational age has also been linked to prenatal cigarette smoking.[67,71] Infants born SGA, often suffer from placenta complications. Prenatal smoking can inhibit placental growth and development.[72] Smoking can contribute to vasoconstriction and impaired placental perfusion thereby decreasing nutrients and oxygen to the fetus.[72] Maternal smoking in all trimesters is associated with increased risk of SGA, with risk of SGA increasing in a dose response pattern as number of cigarettes/day increases.[72] Even non-daily smoking during pregnancy is associated with elevated risk of SGA.[73] Prenatal smoking contributes to many pregnancy complications and the serious birth outcomes of PTB, LBW and SGA.

Prenatal Illicit Drug Use and Birth Outcomes

In the United States in 2020, between 8% and 11% of pregnant women used illicit drugs, tobacco or alcohol.[74] The most commonly used illicit drug among pregnant women is marijuana. The use of marijuana during pregnancy more than doubled in the United States between 2010 and 2017.[75] The use of opioids during pregnancy has also increased in recent years. In 2019, about 7% of pregnant women reported using opioids while pregnant, and 1 in 5 of those reported

obtaining opioids from a non-healthcare source and/or using them for a reason other than pain.[76] Other common illicit drugs include cocaine, methamphetamine, heroine and methlenedioxymethamphetamine (MDMA). Polysubstance abuse during pregnancy is common, making it difficult to sort out effects of individual drugs on maternal and fetal outcomes. In addition, women who use illicit drugs during pregnancy are more likely to have poor nutrition or not attend prenatal visits, which may further contribute to adverse outcomes.[75]

Illicit drug use during pregnancy is associated with many, serious negative outcomes for infants including neonatal abstinence syndrome (NAS), miscarriage, stillbirth, PTB, LBW, sudden infant death syndrome (SIDS), and cognitive and behavioral problems in childhood.[77–81] A study by Hon[82] found commonly abused drugs (CAD) including methadone, ketamine, methamphetamine, morphine, codeine, heroin and midozalam in the urine of about 25% of a sample of 190 neonates. Low birth weight was found to be independently associated with CAD ($p < .0001$).[82] Maternal cocaine use during pregnancy has been significantly associated with PTB, LBW and SGA.[79,83] A recent review[80] including 16 studies evaluating prenatal marijuana use and birth outcomes found increases in several adverse birth outcomes among infants whose mothers were exposed to marijuana as compared to infants whose mothers were not exposed to marijuana. Low birth weight was 2.06 times more likely (95% CI 1.25, 3.42), SGA was 1.61 times more likely (95% CI 1.44-1.79), PTB was 1.28 times more likely (95% CI 1.16, 1.42), NICU admission was 1.38 times more likely (95% CI 1.18, 1.62) and mean infant head circumference decreased by -0.34 (95% CI -0.63, -0.06).[80] While further study will add to an understanding of specific illicit drugs, birth outcomes and potential confounders, there are solid significant studies reporting associations between prenatal illicit drug use and negative birth outcomes including LBW and SGA.

Purpose

The purpose for this study is to contribute to a better understanding of the relationship between how a mother's ACE exposure affects her offspring's birth outcomes, specifically as it relates to LBW and SGA. The objectives of this study are to evaluate the association between maternal ACEs and the negative birth outcomes of LBW and SGA, and to evaluate potential moderation of these relationships by risky behaviors during pregnancy including smoking cigarettes and illicit drug use.

The specific aims are as follows:

AIM 1: examine the relation between maternal ACEs and delivering an infant with LBW.
AIM 2: examine the relation between maternal ACES and delivering an infant with SGA.
AIM 3: evaluate if the relation between maternal ACEs and LBW or SGA is moderated by prenatal smoking or prenatal illicit drug use.

Significance

Limited research with community studies have found relationships between maternal ACEs and neonatal outcomes of LBW and SGA. Further research is imperative to better understand the associations between widespread maternal ACEs and these adverse birth outcomes whose negative effects are serious and far reaching. This study utilizes population data from multiple states from the Pregnancy Risk Assessment Monitoring System (PRAMS)[84] to further examine these relationships.

In addition, maternal ACEs are known to contribute to an increase in risky behaviors during pregnancy including smoking and drug use.[85–87] This study investigates how engaging in prenatal cigarette use or prenatal illicit drug use may moderate the relationship between maternal ACEs and LBW and SGA.

Chapter Two: Review of the Literature

Decades of research have found significant relationships between ACEs and negative health outcomes that span entire lifetimes and beyond. This review of the literature will begin by exploring factors that place individuals at risk of exposure to ACEs and then move on to an overview of how ACEs impact specific areas of disease such as cardiovascular disease, autoimmune disease, mental health disorders, and premature death. The review will then specifically explore the perinatal period and relationships between ACEs and maternal mental health, maternal physical health, risky behaviors during pregnancy, pregnancy complications and birth outcomes. The review will conclude with a discussion of buffers or factors that may protect against ACEs and the conceptual framework of the study.

ACE Risk Factors

While ACEs are common across populations they are not equally distributed. Risk factors for ACEs include having a parent with history of trauma, living in a family with high stress, living in a community with high rates of violence, unstable housing, limited educational and employment opportunities, living in poverty, being a member of certain minority groups, and suffering from individual and systemic racism.[1,86,88–92]

A history of parental trauma has been linked to adverse parenting outcomes including increased likelihood of child maltreatment, increased parenting stress, and less responsive and/or less stimulating parent-child interactions.[93–96] In a systematic review of 12 studies, all with relatively small, community samples, there were significant associations between mothers with histories of emotional abuse and/or emotional neglect and increased parenting stress and self-reported increased risk of maltreatment to their children as compared to mothers without history of emotional abuse/neglect.[95] Another study with a community sample of 118 mothers found that

higher maternal ACE scores were significantly associated with parental stress even while controlling for socioeconomic status.[93]

Parenting stress may be one important pathway leading from both parental history of trauma as well as difficult family living conditions to adverse parenting outcomes, including ACEs. Parenting stress is distinct and has been defined as the stress that results when parent perception determines that the demands of parenting outweigh the available resources.[97] In a study utilizing data from the National Survey of Children's Health (NSCH) with a sample size of 48,831 by Crouch et al.,[98] children living with caregivers that reported "high parenting stress" were three times more likely to experience 4 or more ACEs (OR 3.05 95% CI 0.23, 4.15) than children living with caregivers who reported little to no parenting stress. Parenting stress is associated with history of parent ACEs/trauma and with ACEs in the offspring.

Poverty is known to be one of the most important predictors of all forms of child maltreatment.[99–102] In the United States, poverty status (also referred to as low socioeconomic status (SES)) is determined by income thresholds and size of family. In 2021, a family of 4 with 2 children under the age of 18 would be considered impoverished if the household income was $\leq$ 27,479 dollars/year.[103] In the Fourth National Incidence Study of Child Abuse and Neglect by Sedlack et al.,[99] with a nationally representative sample from 122 United States counties, children with low SES were three times more likely to be abused and seven times more likely to be neglected than children in higher SES categories. Another study, by Kim & Drake,[104] utilizing national maltreatment data at the county level linked to census data reported that as county poverty rates increased, total child maltreatment rates significantly increased for all race/ethnicity groups studied (Black, White, Hispanic).

There is evidence that poverty is a risk factor for ACEs.[1,89,105] In a nationally representative sample of 94,520 with data from the National Survey of Children's Health (NSCH), Halfon et al.,[105] found that children in families below the federal poverty level (FPL) were 3 times as likely to report ≥ 2 ACEs compared to families at or above 400% of the FPL, and that children below the FPL are 5 times more likely to experience ≥ 4 ACEs then children who live 400% above the FPL. In the highest income group, about ¾ of children reported no ACEs, while only ¼ of children in the lowest income group reported no ACEs.[105]

Poverty also affects living conditions. Neighborhoods characterized by poverty place children at risk for childhood maltreatment, including ACEs.[101,106,107] A child living in a neighborhood with a high level of poverty (>20% living under the FPL) at the time of birth, has an increased risk of experiencing 4 or more ACEs as compared to children living with low levels of poverty.[107]

Poverty leads to material hardships and deficits that can impact family functioning and living conditions.[102,108] Low SES can lead to food insecurity, poor health care, inadequate or dangerous housing situations, low-quality schools, and limited recreation activities.[108–110] Impoverished parents are at greater risk of depression and inadequate or negative coping strategies including substance abuse and child neglect.[108,111] Poverty causes material deficits which in turn may contribute to impaired parenting, impaired family functioning, dangerous environments, and ACEs.

An individual's race/ethnicity, gender or sexual preferences may increase the likelihood of experiencing ACEs.[1,112–114] The Behavioral Risk Factor Surveillance System (BRFSS) is a nationally representative yearly survey. From 2011-2014, BRFSS data, with a sample size of 248,934 adults from 23 states, reported that ACE scores were significantly higher for participants

identifying as Black (mean score 1.69; 95% CI 1.62, 1.76), Hispanic (mean score 1.80; 95% CI 1.70, 1.91), and multi-racial (mean score 2.52; 95% CI 2.3, 2.67) as compared to those identifying as White. Individuals identifying as gay/lesbian reported ACE scores significantly higher (mean score 2.19; 95% CI 1.95, 2.43) that individuals identifying as straight.[1] Mean ACE scores were higher for women as compared to men.[1]

The relationship between poverty and race/ethnicity with respect to ACEs is complex. Black children typically have the highest rates of abuse and neglect among Hispanic and White children.[1,99,114–116] Black children also have the highest rates of living in poverty. According to United States Census data from 2020, 19.5% of Black families live at or below the FPL compared to 17.0% of Hispanic families and 8.2% of White families.[117] In addition, 75% of Black children spend at least 1 year in poverty, compared to 30% of White children, and Black children experience severe poverty (income below 50% of FPL) at 3 times the rate of White children.[118,119] As child poverty rates increase, child maltreatment rates (all categories) also increase for all race/ethnicity groups.[104]

In the United States, a root cause of unequal distribution of poverty among races, or racialized poverty, is systemic racism.[120] Systemic racism is pervasive and embedded in societal structures, systems, laws, policies, and "entrenched practices and beliefs that produce, condone, and perpetuate widespread unfair treatment and oppression of people of color".[121,122] Systemic racism leads to racialized poverty by limiting access to educational and employment opportunities.[123] Further examples of how systemic racism contributes to low SES include barriers to home ownership and accumulating wealth, environmental injustice, biased policing and sentencing of men and boys of color, and voter suppression policies.[122] In addition, systemic racism also has been associated with parenting stress, an additional risk factor for ACEs.[98]

Contact with child protective services (CPS) occurs at higher rates among Black families than White families.[107,124] Black children are more than 2 times as likely to be investigated by CPS for assessment and intervention regarding cases of child abuse and neglect as White children.[125,126] One possible explanation for inequitable contact with CPS is the potential bias by caseworkers and mandated reporters, who may systematically over-evaluate the evidence or risk to a Black child. [107,124] Another explanation is that racialized poverty, driven by systemic racism, places proportionally more Black families in impoverished living situations that are higher risk for impaired family functioning, dangerous conditions and childhood maltreatment.[108,120]

ACEs Effect on Health Throughout the Lifetime

Adverse childhood experiences are common and have been strongly associated with long-term health risk behaviors, health status, diseases and premature death.[4] Negative sequelae include increased rates of developing mental and physical disorders, such as depression, PTSD, drug addiction, obesity, and cardiovascular, metabolic and autoimmune diseases.[127–133] It has been estimated that if ACEs were eradicated from North America there would be reduced rates of the following: depression by 40%, anxiety by 30%, respiratory disease by 28%, cardiovascular disease (CVD) by 20%, cancer by 10% and diabetes by 8%.[134]

Cardiovascular Disease

Adverse childhood experiences are associated with CVD as an adult.[127,134–138] Cardiovascular disease is the leading cause of death in the US and refers to disease of the heart or blood vessels including heart attack, heart failure, stroke, arrhythmias, and other heart complications.[139] The CDC Kaiser-ACE study found that individuals with a history of 4 or more ACEs had an increased risk of ischemic heart disease (IHD) with a hazard ratio (HR) of 2.2 (95% CI 1.3, 3.7).[4] A recent nationally representative sample of 14,425 young adults from

BRFSS data found that exposure to 5 or more ACEs is associated with a 62% increase in low CVD risk and 339% increase in high CVD risk (p <0.01).[136] Multiple studies have found a dose-response relationship between ACEs and CVD; as the number of ACEs increase the risk of CVD also increases in a step-wise fashion.[4,127,136,137] The pathways from ACEs to CVD as an adult are not well understood. A plausible pathway starts with ACEs contributing to chronic stress and adverse mental health outcomes which in turn increase risk of CVD.[136]

Hypertension (HTN) has been associated with ACEs in many studies[128,132,140] but not all.[141,142] In a review by Suglia et al.,[140] all five of the studies addressing HTN found a significant association between ACEs and HTN, including a study with a sample of 68,505 women from the Nurses' Health Study II (NHS II).[143] The ACEs of sexual abuse (SA) and physical abuse (PA) were each broken down into mild-moderate and severe according to the following specifications: mild- moderate PA (hit, pushed, shoved); severe PA (kicked, bitten, punched, choked, burned, attacked); mild-moderate SA (touched in sexual way); severe SA (forced sexual activity). As compared to individuals with no ACEs, the risk of HTN rose in a dose-response pattern for cumulative abuse exposure with a range of 4% (95% CI 1%, 8%) among women with mild-moderate abuse, to 59% (95% CI 42%, 78%) among individuals with severe abuse.[143] In contrast, a study with a nationally representative sample of 15,701 young adults from the Add Health Study[144] did not find an association between ACEs and rates of HTN. A few studies have found an inverse relationship; as ACEs increase the risk of HTN decreases.[141,145] Inconsistencies in research findings may be due to objective measure of blood pressure (BP) compared to self-report of BP by participants, different types of ACEs, gender, or age of BP measurement. Further research is needed to clarify the complexities of associations between ACEs and HTN.

Autoimmune Disease

There is a growing body of research addressing the relationships between ACEs and certain autoimmune diseases including diabetes mellitus (DM) and multiple sclerosis (MS). Similar to CVD, chronic stress has been highlighted as a potential mechanism between ACEs and autoimmune disease.[146] Excessive stress is associated with inflammation, negative mental health outcomes, and increased susceptibility to infections, all of which are risk factors for autoimmune disease.[129,146]

Diabetes is a disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood and urine. Globally, in 2019, about 463 million were affected by DM.[147] Multiple studies have found significant associations, between ACEs and DM.[148–150]As the number of ACEs increase, the risk of DM increases in a step-wise gradient.[148,150] A recent meta-analysis of 49 studies reported that the odds of an individual having DM increased ranging from 1.22 (95% CI 1.16, 1.28) for any one ACE to 1.44 (95% CI 1.27, 1.63) for $\geq$ 4 ACEs, compared to individuals with no ACEs.[148] The specific ACEs of sexual/verbal/physical abuse and incarceration were significantly associated with DM while neglect, emotional abuse, parental divorce/death and family member with substance abuse/mental disorder were not.[148] It is unclear why certain ACEs and not others would impact DM later in life. More research is needed in this area.

Multiple Sclerosis is an immune-modulated demyelinating inflammatory disease of the central nervous system that globally affects about 2.8 million people.[129] The amount of studies addressing ACEs and MS are few, but growing. Some studies have found significant associations with childhood trauma/ACEs and development of MS.[129,151] Individuals with MS may have

higher rates of specific types of ACEs such as sexual and emotional abuse than individuals without MS.[151] There are also studies that show no evidence of an association between ACEs and risk for MS.[129,152] As the body of research continues to grow, a better understanding of the role of ACEs in autoimmune disease will result.

ACEs and Premature Death

There is a relationship between ACEs and premature death. Brown et al.,[153] from the original CDC-Kaiser ACE study reported that compared to individuals with no ACE exposure, those with six or more ACEs died nearly 20 years earlier. Other studies have found that exposure to 4 or more ACEs nearly doubled the likelihood of premature mortality.[135,154,155] The greater the number of ACE exposures the greater the risk increases for many of the leading causes of death including CVD disease, drug overdose and cancer.[153,156] Certain ACE clusters, referred to as high adversity clusters, have been found to increase risk of premature mortality more than other ACE clusters, referred to low adversity clusters. High adversity clusters include exposure for the same individual to both poverty and crowded housing, or poverty and parental separation, or parental instability.[156] Further study is necessary to tease out associations between different combinations of ACEs and premature mortality.

Mental Health

A very large body of research supports the link between ACEs and mental health disorders throughout life.[157–159] One of the most studied mental health disorders in relation to ACEs is depression followed by anxiety. Many reviews and meta-analyses have demonstrated a strong association between ACEs and depression and anxiety throughout the lifecourse.[157–160] An example of a recent meta-analysis including 37 studies found that those with ACE histories were 4.4 times more likely to develop depression (95% CI 3.54, 5.46), and 3.7 times more likely to

develop anxiety (95% CI 2.62, 5.22) as compared to individuals without ACE histories.[161] Another recent meta-analysis of 68 reviews by Sahle et al.,[160] reported a pooled odds ratio of 2.01 (95% CI 1.86, 2.32) for ACEs and depression and 1.94 for ACEs and anxiety (95% CI 1.82, 2.22). In addition to the most commonly studied ACEs, described in Table 1, other ACEs including bullying, reported racial discrimination and exposure to violence/war have all been found, by at least one review and/or meta-analysis, to be significantly associated with both depression and anxiety.[160] ACEs, and especially emotional abuse, are associated with early onset depression, or depression before the age of 18, and also with decreased lack of response to treatment for depression.[157,158] Individuals with ACE exposure have chronic stress and inflammation which have both been associated with recurrent depressive episodes and poor treatment response.[158]

Significant relationships have also been found between ACEs and PTSD, suicidality and suicidal ideation.[133,160,162,163] A meta-analysis by Sahle et al.,[160] reported a greater than 2 fold increase in odds (OR 2.27 95% CI 2.06, 2.49) of suicidality for individuals exposed to ACEs compared to individuals with no ACE exposure. Bullying, both traditional and cyberbullying, was the most frequently reported ACE associated with suicidality.[160]

While the link between ACEs and mental health has been well established, the mechanisms that underlie these pathways are still poorly understood. Several factors, presented briefly below, have been found to play a role in the pathway from childhood maltreatment to mental health disorders. ACEs are associated with an atypical development of the hypothalamic-pituitary-adrenal (HPA) axis stress response which may predispose individuals to mental disorders later in life. Another factor that may contribute to the pathway from ACEs to negative mental health outcomes is anxious attachment by the child to the primary caregiver.[164]

Attachment style is developed through interactions between the infant and caregiver.[165] Secure attachment occurs when the caregiver is reliable, responsive and the infant feels secure. Insecure attachment can be anxious-insecure or avoidant-insecure and is characterized by the child's uncertainty about whether the caregiver is dependable, consistent and able to meet the child's needs.[165,166] Other factors that have been found to contribute to the pathway include a decrease in self-esteem,[167] maladaptive coping strategies[164] and emotional dysregulation.[162]

ACEs Effect on Health During Pregnancy

Research suggests that the long-term consequences of ACE exposure may not just affect the exposed woman throughout her lifetime, but may also be transmitted to her children.[168–170] The perinatal period, conception to postpartum, is an important time for the developing fetus, neonate and mother, and maternal ACEs may confer additional vulnerability on both mother and child.[169] Adverse childhood experiences are associated with a wide array of negative health outcomes for women during the perinatal period including perinatal depressive symptomology, [7–9,12,17–19] perinatal anxiety, PTSD and suicidal ideation.[5,12,14] Somatic symptomatology during pregnancy associated with ACEs include high blood pressure, migraines, headache, body pain, and subclinical hypothryodism.[171–174]

Mental Health in Pregnancy

Adverse childhood experiences are strongly associated with depression in adulthood, and a growing body of research has focused on depression during pregnancy.[7,8,11–13,18,175–178] Many studies have examined the relationship between total numbers of ACEs and prenatal depression or depressive symptoms with significant positive results.[8,11,20,176,179] A recent meta-analysis of 12 included studies with sample sizes ranging from 25-1,994 women, reported a significant pooled effect size between total maternal ACEs and prenatal depressive symptoms (r = 0.19 95% CI

0.13, 0.24).[179] As the amount of total ACEs increased the risk of depression/depressive symptoms also increased in a step-wise fashion.[8,11,20]

A few studies have begun to look at individual ACEs, groups of ACEs, or timing of ACEs in relation to prenatal depression.[8,18,179,180] Exposure to certain types of ACEs may increase risk of prenatal depression more than other types of ACEs. Some studies have compared maltreatment ACEs (abuse, neglect) to family dysfunction ACEs (mother treated violently, substance abuse in household, parental separation/divorce, incarcerated household member, mental illness in household).[7,18,176] A study with a community sample of 101 women, looked at maltreatment ACEs and family dysfunction ACEs as independent groups, controlled for poverty, and found the maltreatment ACE group was significantly associated with prenatal depressive symptoms (ß = 0.25 $p<0.05$) while the family dysfunction ACE group was not significantly associated with prenatal depressive symptoms.[18] Two other studies with community sample sizes of 303 and 398 women, found both maltreatment ACEs and family dysfunction ACEs to significantly predict higher levels of prenatal depressive symptoms.[7,176] The discrepancy in findings may be due in part to differences in sample characteristics or covariates. Timing of ACEs (early childhood, middle childhood or adolescent) may play a role in the relationship between maternal ACEs and perinatal depression. Emerging evidence suggests that early age of ACEs may predict prenatal mental health symptoms such as PTSD and possibly depression, although more research is needed.[18]

There is evidence of associations between ACEs and prenatal anxiety, prenatal PTSD and suicidal ideation during pregnancy.[14,40,179,181–184] In a meta-analysis of 7 studies, the significant pooled effect size of the association of ACEs and prenatal anxiety symptoms was r = 0.14 (95% CI 0.07, 0.21).[179] Higher total ACE scores were associated with greater risk of anxiety

symptoms during pregnancy.[178,182,184] Timing of measurement of anxiety symptoms may be important to assess associations. In a meta-analysis taking into account 5 studies with community samples, the association between maternal ACEs and prenatal anxiety was highest when measured at 18 weeks gestation and decreased by an effect size of 0.06 (95% CI = −0.11, −0.01) for every week after until the end of study measurement at 23 weeks gestation.[179] It is unclear why anxiety symptoms may be higher earlier in the pregnancy; women may seek treatment or develop effective coping mechanisms as pregnancy continues.

Several studies have associated ACEs and PTSD during pregnancy.[18,185–187] High levels of total ACE scores have been associated with PTSD symptoms in pregnancy[18] as well as certain specific ACEs including sexual abuse and physical abuse.[185,186] In a review of 5 studies examining the relationship between childhood sexual abuse (CSA) and PTSD in pregnancy, with sample sizes ranging from 44 to 1,586 pregnant women, all 5 studies found an increase in the prevalence of PTSD symptoms among women with CSA exposure, although only findings from two of the studies reached statistical significance.[186] Other individual or clusters of ACEs found to be independently associated with PTSD during pregnancy include physical abuse[185] and maltreatment ACEs (abuse and neglect).[18] Age of ACE exposure may affect the association between ACEs and PTSD. One study found that early childhood onset of maltreatment ACEs significantly predicted increased prenatal PTSD symptoms, while onset of maltreatment ACEs during middle childhood or adolescence did not.[18] There is still much to unpack from a research standpoint in terms of individual ACEs, timing of exposure and strength of association.

Suicide ideation during pregnancy has been associated with ACEs in a small and growing body of research.[14,188,189] Leeners et al.,[188] in a sample of 85 women specifically addressed CSA and reported that women with CSA were more likely to report suicidal ideation during pregnancy

than women without CSA (p <0.0001). A study by Zhang et al.,[189] found that women with a history of any ACEs had a 2.9 fold increase in odds of reporting suicidal ideation (95% CI 2.12, 3.97) during pregnancy. Research supports associations between maternal ACEs and depression, anxiety, PTSD and suicidal ideation during pregnancy. Possible explanations may include the unique stress of pregnancy adding to already elevated stress levels resulting in potential allostatic overload.[190] Another possible explanation is that early traumatic experiences may resurface during pregnancy bringing with them the emotional responses from childhood.[191]

Physical Health in Pregnancy

Limited research has investigated relationships between ACEs and physical symptoms and conditions during pregnancy. ACEs of abuse were found to be associated with increased common complaints and pain during pregnancy in a couple of studies.[173,192] In a cohort study with a sample size of 55,776 pregnant women, those with histories of exposure to sexual, physical and emotional abuse had greater than 3 times the odds (OR 3.5 95% CI 3.0, 4.0) of reporting 7 or more common complaints during pregnancy as compared to women with no history of abuse.[192] Common complaints during pregnancy refer to heartburn, nausea/vomiting, leg cramps, tiredness, pelvic girdle relaxation, braxton hicks, backache, fear of labor, edema, pruritus gravidarum, constipation, headache, urine incontinence, urinary tract infection, candidiasis and leukorrhea.[192] As women increased in number of abuse categories, the amount of common complaints also increased in a dose-response pattern.[192] In another study with a sample size of 232, women with physical abuse exposure reported a higher prevalence of sacral and pelvic pain (p = 0.0003 and p = 0.02, respectively). As the total number of ACEs increased there was a significant association with increased numbers of pain locations reported in late pregnancy (r = 0.19, p = 0.02).[173] Mechanisms by which ACEs may affect pain and common complaints

during pregnancy are unknown but may be linked to increased prevalence of obesity and smoking in the ACE exposed population or due to sensitization of stress.[193] ACEs are associated with sustained stress overtime which promotes changes in neural circuits and potential increases in response to stimuli. Sensitization has been linked to increase in reports of pain and somatic complaints.[193]

Gelaye et al.,[174] and Moog et al.,[171] examined the associations ACEs have with conditions such as migraine headaches and hypothyroidism during pregnancy. In a sample of 2,970 pregnant women, those who experienced any childhood abuse had a 38% increase in odds of any migraine compared to women with no history of childhood abuse (OR 1.38; 95% CI 1.15, 1.64). Moog et al.,[171] with a sample size of 146, examined the relationship between thyroid function and maternal ACEs, finding that women exposed to moderate to severe childhood ACEs were 4-7 times more likely to exhibit subclinical hypothyroidism across the course of the pregnancy (ß = 0.70, 95% CI 0.3, 1.1). Pathways from ACEs to migraines and thyroid disease during pregnancy are unclear, but stress is likely to be implicated. In addition, ACE exposure may influence thyroid function through alterations in the HPA axis.[171,194]

The relationship between maternal ACEs and HTN during pregnancy is somewhat unclear. A few studies have shown a positive association between ACEs and hypertension during pregnancy[6,172] but not all.[195] A study of 127 women by Bublitz et al.,[172] found that pregnant women with higher ACE scores had higher night-time blood pressure (BP) as compared to women with lower ACE scores (night-time systolic ß = 0.23 $p = 0.13$; night-time diastolic ß = 0.22 $p = 0.028$). There was no significant association between ACEs and day-time BP.[172] Further, women with $\geq$ 4 ACEs were less likely to display nocturnal BP dipping than women with no ACEs (ß = 0.18 $p = 0.018$).[172] Nocturnal HTN is associated with cardiovascular disease

and preeclampsia.[172] Miller et al.,[6] in a sample of 1,274 women from the Collaborative Care Model for Perinatal Depression Support Services (COMPASS), reported that women with high ACE scores had a 1.55 fold (95% CI 1.06, 2.26) increase in odds of having hypertensive disorder of pregnancy (HDP). A study with a sample size of 2,329 utilizing the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) data found no significant association between ACEs and HTN during pregnancy.[195] Differences among studies may be due in part to differences in the study populations.

Risky Health Behaviors During Pregnancy

Research supports associations between maternal ACEs and increased engagement in risky health behaviors during pregnancy. As cumulative ACEs increase, risk of prenatal smoking, prenatal alcohol use and prenatal illicit drug use also increase in a dose-response pattern.[87] Several studies have found an increase in cigarette smoking in pregnant women with ACE exposure as compared to pregnant women with no ACE exposure.[12,86,87,181,196,197] A study by Racine[198] with a sample of 1,994 women, explored associations between specific sub-groups of ACEs and prenatal smoking and found that the sub-groups of family violence and household dysfunction both significantly predicted smoking in pregnancy. Another study with a sample of 201 explored associations between maternal ACEs and levels of nicotine dependence among pregnant smoking women.[196] Nicotine dependence has been correlated with increased difficulty with smoking cessation and can be estimated by time to first cigarette upon waking.[196] Individuals who self-report smoking within 5 minutes or less from waking have been found to significantly differ from those who smoke within 6 or more minutes in numbers of cigarettes/day and ability to abstain from smoking.[199] Significant associations were found between exposure to all types of abuse/ neglect ACEs and smoking within 5 minutes of waking, with the greatest

associations between emotional abuse (OR 2.69 95% CI 1.32, 5.47) and physical neglect (OR 2.68 95% CI 1.29, 5.47).[196]

Maternal ACE exposure is also associated with increased prenatal alcohol use. A study by Currie et al.,[200] with a sample size of 1,663, found that maternal ACE exposure to ≥4 ACEs resulted in an almost 3 fold increase in the odds of binge drinking during pregnancy (OR 2.71 95% CI 1.62, 4.52). In a sample of 1,987 pregnant women, Frankenberger et al.,[201] reported a significant graded relationship between ACEs and alcohol use during pregnancy. Women with one reported ACE had nearly three times the odds of using alcohol (OR 2.92, 95% CI 1.08, 7.87) as compared to women with no history of ACEs. Women reporting ≥4 ACEs had nearly 5 times the odds of using alcohol as compared to those reporting no ACEs (OR 4.79, 95% CI 2.14, 10.72).[201]

Engagement in the risky behavior of prenatal drug use is associated with ACE exposure in women.[87,202,203] Kors et al.,[202] in a sample of 93 pregnant women reported that the presence of childhood sexual abuse was significantly associated with opioid misuse in pregnancy (p >0.05). A study by Hemady et al.,[203] with a sample of 1,189 mother-infant dyads, created 4 classes of groupings of ACEs that had high homogeneity in ACEs: class 1 included intra-familial violence, and physical/emotional/sexual abuse, class 2 included intra-familial violence and emotional and physical abuse, class 3 included emotional abuse, and class 4 included household dysfunction.[203] Significantly higher probabilities of prenatal drug use were found in classes 1 and 2 than classes 3 and 4.[203]

ACEs may increase the risk of substance use during pregnancy through several interconnected psychosocial and systemic mechanisms. Substance use may be conceptualized as an attempt at coping with chronic stress, mental health difficulties, family dysfunction and

exposures to conflict and violence.[204] Pregnancy itself can be an additional source of stress, making it increasingly difficult for women entering pregnancy already using substances to quit, and may lead to feelings of guilt and shame that further undermine efforts to quit.[205,206] Inadequate or absent social support may contribute to substance abuse as well, and make cessation efforts less effective.[10] Low SES adds stressors and may contribute to an inability to access prenatal care or available resources.[204]

Maternal ACEs and Birth Outcomes

Research shows that the long-term consequences of ACE exposure may not just affect the exposed woman throughout her lifetime, but may also be transmitted to her children.[168–170] A growing body of research has found significant associations between maternal ACEs and infant birth outcomes including preterm birth (PTB), fetal loss or miscarriage, LBW infants, and SGA infants.[5,48,207–209] A recent systematic review found that all 9 included studies found a significant association between ACEs and PTB.[207] Limited studies have found positive associations between LBW[5,48,49] and SGA.[5,48]

A small number of studies have investigated the association between maternal ACEs and LBW infants.[5,48,49] A study by Smith et al.,[5] with a community sample size of 2,303 pregnant women found, after controlling for race/ethnicity and other mediators, that with every additional maternal ACE, infant birth weight decreased by 13.71 grams (95% CI 21.86, 6.91). Mersky & Lee[48] analyzed birth outcomes in a community sample of 1,848 low-income women and found that higher amounts of maternal ACEs were significantly associated with LBW (OR 1.08; 95% CI 1.03, 1.15). Each additional maternal ACE was associated with an 8% increase in the odds of delivering a LBW infant.[48] A study in Tunisia with a community sample size of 593 reported that history of the specific ACE of "witnessing community violence" was associated with a decrease

in infant birth weight by 456.1 grams (95% CI 629.5, 282.7) as compared to women who did not report "witnessing community violence".[49] Research examining the relationship between maternal ACEs and LBW are limited and all use community level data. Further research with population data is essential to understand the role of ACEs in LBW.

Very few studies have addressed the relationship between maternal ACEs and SGA.[6,55] A study with a community sample of 2,303 women, after controlling for race/ethnicity, found that with each additional ACE a woman reported, the gestational age decreased by 0.041 weeks (95% CI 0.07, 0.02).[5] In contrast, a study of 1,274 women from the COMPASS study reported no significant association between ACEs and SGA.[6] The serious long-term consequences of SGA for infants and the limited research makes it essential for further study.

Causal pathways between maternal ACEs and negative birth outcomes are unclear, although a growing body of research suggests, as touched on in above sections, that early life adversity promotes chronic, cumulative stress in women throughout their lifetimes. Chronic stress alters the hypothalamic-pituitary-axis (HPA) pathway which in turn contributes to negative birth outcomes.[19,210–212] In tandem with an altered HPA mediated pathway, ACEs promote use of risky health behaviors in order to cope with the negative neurobiological, emotional, and social consequences of ACEs.[4,213] These risky health behaviors also contribute to an increased risk of negative birth outcomes.

Protective Factors

Demonstrated associations between maternal ACEs and poor mental and physical outcomes for mother and baby make it critical to understand existing research regarding factors that may be protective against the effects of ACEs during the perinatal period. A protective factor is one that serves to buffer an individual from the negative impact of ACEs on health

outcomes. Despite a growing body of research showing the negative effects of maternal ACEs on health, less understood are protective factors which may counteract or lessen the effects of ACEs.

Social Support

Social support is one factor that may offer protection from ACEs. Social support is defined in multiple ways and can be conceptualized as the structural and functional ways that different people behave supportively in the social environment.[214] It includes both structural components (existing social relationships), and functional components (resources that individuals within a social network provide). [214] Research has shown that social support in non-pregnant, ACE exposed women can mitigate risks for depression, substance abuse, and poor physical health. [215] During pregnancy, there is evidence that social support may buffer the negative effects of prenatal depression and that low social support during pregnancy is associated with an increased risk of PTB.[216] A meta-analysis[216] of 8 studies, demonstrated a pooled odds ratio of 1.22 (95% CI 0.84, 1.76) for PTB in women with low social support as compared to women with high social support.

There is a small, but growing body of literature investigating the role social support may play on pregnancy and birth outcomes for ACE exposed women.[23,175,217–221] Some studies have found significant mediation or interaction effects of social support in pregnant ACE-exposed women with the outcome of perinatal depression.[8,23,218] Muzik et al.,[23] reported that the interaction between social support and income significantly predicted postpartum depression symptoms ($p < 0.001$). Social support provided buffering of the relationship between ACEs and postpartum depression symptoms, while income only provided a protective effect when accompanied by social support (model accounted for 29% variance). [23] Wajid et al.[8] found that

when social support was added to the multivariable analysis the interaction between maternal ACEs and depression in pregnancy was no longer significant suggesting that social support may be protective against depressive symptoms. Nidey et al.[218] reported that perceived social support during pregnancy indirectly influenced depression, suggesting prenatal social support was a mediator. Two studies found the influence of social support on the association between maternal ACEs and perinatal depression to not be significant .[222,223]

Racine et al.,[219] assessed the moderating role of social support between maternal ACEs and antepartum risk scores (scores based on past medical history and current health). Among pregnant women with high ACEs (3-4) and high levels of social support no association between ACEs and antepartum health risk was found, while among pregnant women with high ACEs and low levels of social support there was an association. Specifically, those women with low levels of social support were at an increased risk of higher antepartum health risk scores (ß = 0.17, $p<0.001$).[219] Social support may buffer ACE exposed pregnant women from antepartum health risks.

Studies by Appleton et al.,[220] and Thomas et al.,[221] investigated whether social support during the perinatal period played a role in moderating the effects of maternal ACEs on infants. Thomas et al.,[221] found evidence to support the hypothesis that maternal hypothalamic-pituitary-adrenal (HPA) axis function during pregnancy mediated the effects of maternal ACEs on infant HPA reactivity. Further, prenatal social support moderated the association between ACEs and maternal HPA axis function during pregnancy ($\beta = -0.36$, $p = .04$) and postpartum social support moderated the association between maternal HPA axis function and infant HPA axis function, or specifically, infant cortisol reactivity ($\beta = 0.02$, $p = .02$).[221] Social support may help buffer maternal childhood adversity in infants via maternal and infant HPA axis function. Appleton et

al.,[220] assessed the association between maternal ACEs, infant birth size and social support during pregnancy. The authors evaluated birth size by cephalization index scores which are a marker of asymmetric fetal growth. Higher numbers of ACEs were associated with higher cephalization scores, while higher social support was associated with lower cephalization scores.[220] A significant interaction was observed in that cephalization scores of infants of women with no ACEs or moderate ACEs (1-3) were buffered by social support (p <0.05).[220] Taken together, this research suggests that maternal social support may confer advantages on infant health.

Resilience

Resilience is a complex construct made up of biological, psychological, social and cultural factors that interact and determine an individual's response to a stressful experience. [224] Resilience encompasses individual factors including self-agency and cognitive ability as well as social-ecological factors such as family and community support and resources.[225] Research supports resilience as a buffer between ACEs and depression, psychological distress and substance abuse in populations other than pregnant women.[226–229]

Given its demonstrated benefits, resilience may serve to modify the relationship between ACEs and negative mental and physical outcomes during the perinatal period. Howell et al.,[230] investigated 101 pregnant women and found that resilience mediated the relationship between ACEs and prenatal depression. With resilience as a mediator, the effect of ACEs on depression was no longer significant.[230] Similarly, pregnant and postpartum ACE exposed women categorized as having high levels of resilience had significantly less depression compared to women categorized as having low levels of resilience.[231,232] In a study of 355 pregnant women, a significant association between ACE exposure and prenatal anxiety, depression, intimate partner

violence and substance abuse was seen in women with low resilience, yet a significant relationship was not found in women with high resilience.[231] Postpartum women with high resilience were significantly less likely to meet the criteria for PTSD as compared to women with low resilience.[232] More research is needed with compatible constructs and measures of resilience to further understand the relationships between maternal ACEs, pregnancy outcomes and resilience.

Positive Influences in Childhood

Positive Influences in Childhood (PICs) or Benevolent Experiences in Childhood (BCEs) are those early life experiences including positive parenting behaviors, attachment bonds to parents or mentors and other community experiences that may protect against childhood adversity.[233] Positive Influences in Childhood may buffer the effects of ACEs during the perinatal period.

In ACE exposed pregnant women PICs/BCEs are associated with a lower likelihood of exhibiting depressive symptoms during pregnancy.[20,234] Chung et al.,[20] reported that as the number of PICs increased, the risk of depressive symptoms in ACE exposed pregnant women decreased. Specific associations of note include pregnant women with a history of a parent in trouble with the law who were often given hugs as children (PIC) had less odds of having depressive symptoms than women with history of a parent in trouble with the law and limited to no hugs (OR 0.19; 95% CI 0.07, 0.53), and pregnant women with history of sexual abuse and a positive maternal relationship (PIC) had lower odds of having depressive symptoms than an exposed woman without a positive maternal relationship (OR 0.39; 95% CI 0.18, 0.85).[20] In a study by Narayan et al.,[234] high levels of BCEs in pregnant women with a history of ACEs, were significantly inversely associated with depression symptoms ($r = -.24$, $p < 0.05$), PTSD

symptoms (r = -0.37, $p < 0.01$), perceived stress (r = -0.26, $p < 0.01$) and total number of stressful life events (r = -0.37, $p < 0.01$). Merrick et al.,[235] examined timing of BCEs and found that early age onset of BCEs was negatively associated with prenatal stressful life events ($ß = -20\ p < .05$). Positive childhood experiences may offset or protect against the effects of childhood adversity during pregnancy, however more studies are needed, with comparable measures and outcomes.

Framework

The guiding conceptual framework for the study is the ACEs study pyramid developed by Felitti et al.,[4] and depicted in Figure 1. The ACE pyramid takes into account certain, specific types of ACEs, that occur before the age of 18 including abuse (physical, sexual, emotional) and household dysfunction/challenges. [4]

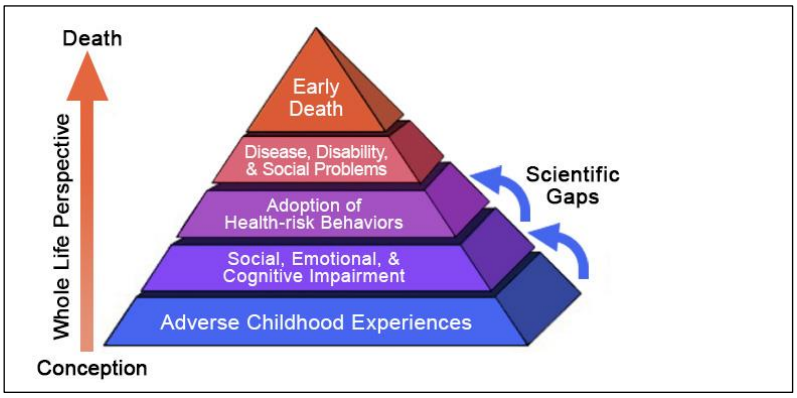
The ACE pyramid posits that ACEs establish a foundational layer in an individual's life. As an individual's life progresses the negative experiences from childhood (ACEs) contribute to social, emotional and/or cognitive impairments.[236–239] Exposure to ACEs also increases the likelihood of developing risky health behaviors such as smoking, illicit drug use, and alcohol use throughout an individual's life when compared to individuals without ACE exposure.[85,154,201,240–242] These impairments and/or adoption of risky health behaviors may in turn contribute to disease and early death.[4,135,236,243(p),244] The ACE pyramid points out that there are scientific gaps in understanding the causal pathways that lead from one step of the pyramid to the next.

The pyramid serves as a guide for this study in that maternal ACEs are the foundational layer, with risky health behaviors during pregnancy further up the pyramid and negative birth outcomes (LBW, SGA) near the top of the pyramid.

Figure 1

ACE Study Pyramid

Note: From Felitti et al.[4]



Limitations of the Framework

There are several limitations to the ACE pyramid. The pyramid takes into account only specific categories of childhood adversity including abuse (physical, sexual, emotional) and household dysfunction (household member with a substance abuse, or drinking problem, household member with mental illness, household member incarcerated, mother treated violently, parental separation/divorce).[4] These particular ACEs may not account for all of a woman's childhood adversity. Additional ACEs may include childhood poverty, death of a household member, child bullying, witnessing violence, food insecurity.[245–247] The ACE pyramid limits the conceptualization of what makes up childhood adversity.

Another methodological limitation is that the pyramid model lends itself most readily to be incorporated into studies in a retrospective design. Asking participants, at the middle or top of the pyramid, to self-report events that happened during childhood may introduce recall bias into the study results.[246,247] It may be difficult to accurately remember events that happened in the recent or distant past.

Recent critiques in the literature have referred to foundational ACE studies as being overly simplified.[246,247] In the pyramid approach from the original ACE study[4] the idea of

association, causality and impact, from one step up to another, seem to be interchangeable.[246] The authors refer to childhood exposures and negative health outcomes in adulthood as associations and yet within the model it is implied that the exposures "cause" adult disease and premature death.[246] It is important to conceptualize the steps as associations and note the authors understanding that there are scientific gaps in causality between the steps.

Chapter Three: Methodology

This chapter describes the design and methods for an investigation of the relationship between ACEs and the birth outcomes of LBW and SGA, with possible moderation of the relationship by prenatal smoking or illicit drug use, through data collected by an on-going, population-level dataset from PRAMS, a surveillance system managed by the Centers for Disease Control and Prevention (CDC).[84] Previous research has demonstrated an association between ACEs and adverse birth outcomes including PTB[207], however, the associations between ACEs, LBW[5,48,49] and SGA[6,48,55] are less well examined. It is hypothesized that cumulative ACE exposure will be positively associated with increased odds of both LBW and SGA infants. Further, it is hypothesized that the association is impacted by cigarette smoking and illicit drug use during pregnancy. The study sought to address the following specific aims: (1) examine the relation between maternal ACEs and delivering an infant with LBW; (2) examine the relation between maternal ACES and delivering an infant with SGA; (3) evaluate if the relation between maternal ACEs and LBW or SGA is moderated by prenatal smoking or prenatal illicit drug use.

Design

The study is a cross-sectional, secondary data analysis of a population-based data set from the Pregnancy Risk Assessment Monitoring System (PRAMS). The Pregnancy Risk Assessment Monitoring System, started in 1987, is a joint project between state, territorial, local health departments and the CDC's division of reproductive health. The Pregnancy Risk Assessment Monitoring System is an ongoing, population-based surveillance system created to reduce infant morbidity/mortality by influencing maternal perinatal behaviors, to identify groups of women and infants at high risk for health problems, to observe health status changes, and to measure progress towards positive outcomes.[84] Data from PRAMS are used by researchers,

federal agencies, nonprofit health organizations, and state health departments to help develop new programs and policies, to evaluate existing programs, to create educational materials for health care providers, and to contribute to general health knowledge.[248] The Pregnancy Risk Assessment Monitoring System provides estimates of certain maternal/infant health indicators that are not available from any other source such as infant sleep position over time, unintended births and patterns of insurance coverage during and after pregnancy.[248]

Insights obtained from PRAMS data are vast and of great public health significance. At the state level, PRAMS data has been used to develop health education/promotion campaigns with some examples including the following: the importance of folic acid during pregnancy, need for flu vaccination during pregnancy, importance of a tobacco-free pregnancy and education to promote safe sleeping practices of infants.[84] At the national level, PRAMS data has been used to monitor maternal/infant health targets put forth in Healthy People 2020, Title V performance measures for safe sleep and preventative dental visits, and National Quality Forum performance measures for postpartum contraception and preconception health.[248] Study results using PRAMS data have been used to influence legislative decisions regarding the health issues of increasing breastfeeding support in the workplace, expanding dental coverage to pregnant women, improving access to contraception, and others.[84] Numerous researchers have utilized PRAMS data to investigate relationships among maternal/infant indicators and advance the understanding of issues in the field of maternal and child health.[84]

PRAMS Sampling

The Pregnancy Risk Assessment Monitoring System is a mixed-mode mail and telephone survey, based on the Tailored Design Method developed by Dillman.[84,249] The mail/telephone methodology used by the CDC and developed by Dillman, incorporates many

techniques to improve participant response including personalized mailing packages, use of incentives, rewards, and repeat yet varied contact attempts.[248] Survey questionnaires are first sent to participants by mail as a paper survey; up to three times. Individuals who do not respond to the mailed survey attempts are contacted via telephone by trained interviewers (up to 15 times) who attempt to gather answers to the survey questions.[84] Phone calls are made at various times in the day over a period of 3-5 weeks. Mixed-mode design decreases likelihood of mode bias (when participants respond differently according to the mode in which the questions are asked), and increases the likelihood of response by variations in timing of contact, mode of contact and incentives and personalization.[84,249]

Each state's vital records birth certificate file serves as the source of the sampling frame representing live-born infants.[248] Women who delivered a live-born infant within the past 2-6 months are the target population for the PRAMS survey.[84] Women who experienced fetal death, stillbirth, or induced abortion were excluded from the sample, while women whose infants died after being born alive were not excluded.[84] Monthly, each state or jurisdiction randomly selects a stratified sample of 100-330 (about 1000-3000/year). The Pregnancy Risk Assessment Monitoring System uses a stratified sample in order to permit estimates of subgroups (strata) of interest and permit comparisons across these subgroups (strata).[248] Certain subgroups of interest may not make up a sizable portion of the state's overall population and, therefore, these subgroups may need to be oversampled or sampled at a higher rate than other subpopulations.[248] In order to account for the complexities in PRAMS sampling design, a weighting system is used. Weighting contributes to unbiased population parameter estimates. Weights were developed by CDC to adjust for sample design, nonresponse patterns and omissions from the sampling frame.[250]

State sample sizes range from approximately 1000 to 3000 women.[250] The Pregnancy Risk Assessment Monitoring System establishes minimum overall response rate threshold policies for release of data. In 2006 and prior, the response threshold was 70%. The threshold decreased to 65% in 2007, 60% in 2012, 55% in 2015, and 50% in 2018 to present.[250] States that meet established response rate thresholds are included in multistate analytic sets. PRAMS data is for public use and available to researchers by request from the CDC after approval of an application and proposal summary.[250]

PRAMS Instrument

The original PRAMS questionnaire was developed in 1987 and was used through the end of Phase 1 in 1988. Since then, the questionnaire has been revised several times and has evolved into the current questionnaire used in the most recent phase of PRAMS, Phase 8.[84] The questionnaire is made up of core questions and standard questions. Core questions are asked by all participating states and comprise questions about the following topics: attitudes and feelings about pregnancy, preconception care, prenatal care, Medicaid and WIC participation, breastfeeding, cigarette smoking, alcohol use, health insurance, physical abuse, infant health care, and contraceptive use.[84] Standard questions are additional questions chosen from a list of pretested questions from the CDC or developed by individual states or jurisdictions, and therefore each state's questionnaire may be unique.[84] The topical list of all questions relevant to this study is provided in Appendix A.

Study Sample

Prior to Phase 8, no states or jurisdictions included ACE questions in their questionnaires. Starting in Phase 8 (2016-2020), some states began asking ACE questions to participants. Of the states asking ACE questions, South Dakota and North Dakota were the only states to reach the

established minimum response threshold (50%) for the ACE questions in order to be included in PRAMS data sets.[84] The sample for Aims 1, 2 and 3 include 78,153 (weighted) / 6,534 (unweighted) respondents who answered ACE questions from SD or ND and recently gave birth between 2016 and 2020.

Study Variables

Independent Variables

The independent variables for all three aims are maternal ACEs. Maternal ACEs are measured retrospectively by participant self-report responses to 10 questions asking about forms of adversity before the age of 18. The 10 questions are similar to the widely used ACE questionnaire developed by the Kaiser ACE Study.[4] Questions are answered either yes or no and coded as binary variables (1 = yes; 0 = no). Consistent with previous research using PRAMS data, ACE question responses are combined to form a cumulative ACE score with the categories of 0 ACEs, 1 ACE, 2 ACEs, 3 ACEs and 4 or more ACEs.[5,251,252] In order to promote model stability due to small numbers of ACEs in the individual categories, and similar to previous research, numbers of ACE were collapsed into groups of 0 ACEs, 1-3 ACEs and 4 or more ACEs.[253–255]

Dependent Variables

The dependent variables for all three aims are the birth outcomes of LBW and SGA. Data on gestational age at delivery and birth weight come from birth certificates. Low birthweight is defined as infant birthweight < 2,500 g. In PRAMS, LBW is grouped into 250 gram intervals.[84] Low birthweight will be dichotomized with 1 = LBW; 0 = not LBW. In PRAMS, SGA is defined as birthweight below the 10th percentile of the population for infants of the same sex and

gestational age and adjusted for maternal race.[250] SGA is coded as a binary variable (SGA_10) with 1 = yes infant is SGA; 0 = infant is not SGA.

Moderation Variables

Aim 3 explores whether prenatal cigarette smoking or prenatal illicit drug use moderate the relationship between maternal ACEs and the birth outcomes of LBW and SGA. The variable of cigarette smoking during pregnancy (SMOKING) was coded dichotomously as 0 for respondents who answered never smoked or stopped for pregnancy and 1 for respondents who smoked prior to pregnancy and during pregnancy, or just during pregnancy. The drug use variable during pregnancy includes the drugs of heroin, methadone, amphetamines, cocaine, marijuana, tranquilizers, hallucinogens, LSD, Adderall/stimulants, sniffing/huffing gas or glue. Drug use during pregnancy (DRUGUSE) is dichotomized as 0 = no drug use during pregnancy and 1 = any of above drugs used during pregnancy.

Control Variables

Consistent with prior research assessing adverse infant health outcomes with PRAMS data, control variables include maternal age, maternal race/ethnicity, maternal education, Medicaid status, pre-pregnancy body mass index (BMI), and gestational weight gain during pregnancy.[252,256] Maternal age will be controlled for as research indicates that both mothers at the older and younger ends of the of the child-bearing age continuum are at higher risk for having a LBW or SGA infant than women in the middle.[257–259] Maternal age is coded as MAT_AGE_NAPHSIS and grouped into 4 categories: (< 20, 20-24, 25-34, $\geq$ 35). Maternal race/ethnicity is important to control as certain races are consistently found to be at higher risk for adverse pregnancy outcomes including LBW and SGA. Black infants are about 2 times more likely to be LBW as compared to White infants, and American Indians consistently have higher

rates of LBW and SGA infants than White infants.[260] The race/ethnicity of mothers is coded as MAT_RACE and includes the categories of Black, White, American Indian and other. There is a separate variable for Hispanic (HISPANIC).

Socioeconomic status is considered an important predictor of health inequalities, including discrepancies in infant birth outcomes. There is evidence that lower maternal income level is associated with higher risk of adverse infant outcomes. A graded association between income and LBW has been documented in the United States.[261] Medicaid provides health insurance to low income Americans and Medicaid recipients have been found to be high risk for adverse birth outcomes, including LBW and SGA.[262,263] Medicaid is a dichotomous variable and coded as MEDIC. Maternal education level also plays a role in health inequalities and influences LBW and SGA. Higher maternal education is associated with higher infant birth weights as compared to infants of mothers with low education.[264,265] Maternal education is coded as MAT_ED and divided into four categories (less than high school, high school graduate, some college, college degree or higher).

Mother's pre-pregnancy weight status may influence weight of the infant. Mothers whose BMI prior to pregnancy is considered underweight (< 18.5) have increased risk of delivering a LBW or SGA infant.[266,267] Mothers with pre-pregnancy BMI considered overweight (25.0-29.9) or obese ($\geq$ 30) have increased risk of both PTB as well as macrosomia.[266–268] Maternal obesity may have multidirectional and opposing effects on infant birth weight.[268] In addition, gestational weight gain (GWG) below the recommended guidelines by the Institute of Medicine (IOM) is associated with increased risk of PTB, LBW and SGA.[269] Guidelines provide a suggested gestational weight gain of 28-40 pounds for underweight women, 25-35 pounds for normal weight women, 15-25 pounds for overweight women and 11-20 pounds for obese women.[270] Pre-

pregnancy BMI is coded as MOM_BMI_BC and divided into the categories of underweight (< 18.5), normal weight (18.5-24.9), overweight (25.0-29.9) and obese (≥ 30). Gestational weight gain is coded as MOMLBS and divided into the categories of (< 25lbs, 25-35lbs, > 35lbs).

Analysis Plan

STATA Version 17 was used to clean the PRAMS dataset and conduct analysis of the variables for the study. Descriptive statistics and Pearson's chi-square were used to summarize respondent characteristics.

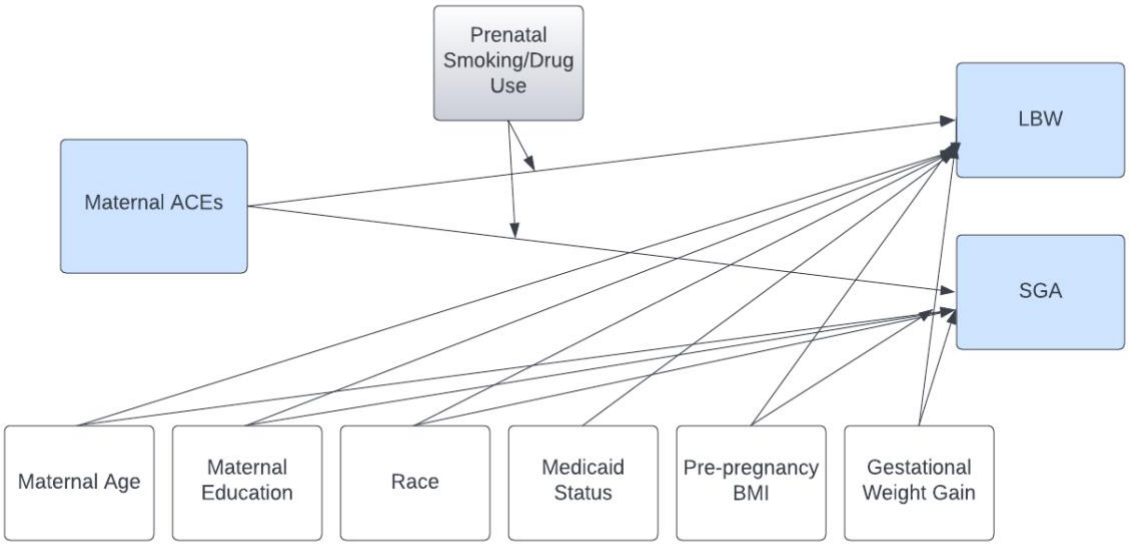
Regression is a statistical procedure that seeks to examine potential associations between a predictor variable(s) and outcome variables.[271] When there are two or more independent variables it is referred to as multiple regression. Logistic regression is used when the outcome variable of interest is a binary variable meaning there are only two possible scenarios (e.g. yes or no).[272] This study used logistic regression analysis to examine the predictive value of cumulative ACE exposure on the birth outcomes of LBW and SGA.

Moderating variables are those which affect the strength or nature of an association between the independent and dependent variables.[272,273] Moderating variables can strengthen, diminish, negate, or otherwise alter an association between the independent and dependent variables.[272] When both the predictor variable and moderator variable affect the outcome variable in the same direction, the moderator has an additive effect and the interaction between the predictor and moderator serves to strengthen the association. When the predictor variable and moderator variable affect the outcome in opposite directions the interaction results in a diminished association or potentially negated association.[272] Moderation was chosen for this study in that ACEs are hypothesized to be associated with adverse birth outcomes, and prenatal smoking and/or drug use may strengthen those associations.

Moderation effects can be assessed through the use of multiple regression analysis.[272,274] Moderating variables can be categorical or continuous and are constructed by the researcher by taking the product of two predictor variables and determining the joint impact of both independent variables on the dependent, or outcome, variables.[272,274] In this study the product of two predictor variables, either prenatal cigarette smoking and ACEs or prenatal illicit drug use and ACEs, were constructed and referred to as interaction terms. Logistic regression models were used to assess the impact of the interaction terms on LBW and SGA. Figure 2 provides a conceptual model of moderation of maternal ACEs and LBW/SGA by prenatal smoking/drug use with control variables.

Figure 2

Conceptual Model of Moderation of Maternal ACEs and LBW/SGA by Prenatal Smoking or Illicit Drug Use



Collinearity

Collinearity occurs when 2 or more independent variables in a regression model are correlated to each other. If collinearity is present in a regression model it will inflate the variance and standard error of coefficient estimates.[275] In order to determine if collinearity was present in the current study, variance inflation factors (VIFs) for each independent variable in the regression models were constructed and analyzed. It is common in research to consider a VIF of greater than 10 to indicate strong collinearity.[276] Analysis of VIFs in the regression models revealed that one variable, HISPANIC, was the only variable to have a VIF of >10. Due to the VIF > 10, the effects of being HISPANIC are understood to be captured by other variables in the model, and therefore, the HISPANIC variable was removed from the regression models.

Missing Data

Missing data is an important issue encountered in almost all research studies. Missing data is defined as a data value that is not available for a variable in the observation of interest.[277] Missing data can lead to reduced statistical power, cause bias and reduce the representativeness of the sample.[278] The best way to address potential missing data is to prevent it through a well planned and executed study to reduce nonresponse, survey fatigue and response bias.[278,279] This study utilized secondary data, and therefore was not able to address any design or data collection procedures.

Analyses of missing data was conducted through STATA 17 by determining amount of missing observations, frequencies, and determining patterns within the entire sample. The missing data approach is shown in Table 2. The analyses revealed that the missing data was very low across all study variables. For the majority of variables, missing data was less than 1% of cases, and for all but one of the variables, missing data was well below 5% of cases. The exception was maternal income, which had 6.3% of missing values. Due to the maternal income variable's relatively large number of cases with missing data and the availability of the maternal education variable and Medicaid status variables to serve as indicators of socioeconomic status, the decision was made to omit the maternal income variable from the regression analyses. Missing data on other variables was addressed by eliminating cases with missing data referred to as listwise deletion.[277] Listwise deletion is a traditional, frequently used method for missing data.[277,278] When missing data is less than 5% of data, biases and loss of power are both likely to be inconsequential and listwise deletion and other modern imputation techniques are likely to yield similar results.[277,280] Further analyses were conducted to ensure that the small percentages of observations missing from each variable were not compounded to lead to larger reductions in

the sample when using several variables in regression models. Analyses confirmed that 97.1% of total observations had no missing data, and therefore, would be suitable for listwise deletion.[277]

Table 2

Missing Data Approach

Variable	Approach	Missing n (%)
ACE: Parents separated	--	0 (0%)
ACE: Household with alcoholic	--	0 (0%)
ACE: Depressed household member	--	0 (0%)
ACE: Incarcerated household member	--	0 (0%)
ACE: Touched sexually	--	0 (0%)
ACE: Swear/insult	--	0 (0%)
ACE: Push/grab	--	0 (0%)
ACE: Not loved	--	0 (0%)
Table 2 (continued).		
ACE: Dirty clothes	--	0 (0%)
ACE: Violence to mother	--	0 (0%)
Maternal age	--	0 (0%)
Maternal education	deletion of missing data	42 (0.6%)
Maternal race/ethnicity	deletion of missing data	36 (0.55%)
Medicaid status	deletion of missing data	8 (0.0012%)
Pre-pregnancy BMI	deletion of missing data	80 (1.2%)
Gestational weight gain	deletion of missing data	102 (1.5%)
Smoking during pregnancy	recoded	--
Drug use during pregnancy	recoded	--

Abbreviations: ACE, adverse childhood experience; BMI, body mass index

Protection of Human Subjects

This study used secondary data provided by the CDC from PRAMS. All personally identifiable participant information including name, address, birthdate, IP address, and more was removed by the CDC prior to receipt of the data for this study. A CDC PRAMS agreement for sharing multi-state data with external researchers stating that the researcher would only use data for intended research and only share with collaborators of the specified project was completed on 2/25/21, when first PRAMS proposal was submitted, and again on 3/29/22 when second proposal was submitted for an additional phase of data. The Institutional Review Board for the Social and Behavioral Sciences at the University of Virginia approved research proposal #4982 for this study on 4/6/22.

Chapter 4: Results

This chapter reports the results of the analyses performed to address the specific aims of the study. Descriptive and bivariate analyses were conducted and presented to describe the sample characteristics. Multivariate analyses were performed using logistic regression models to explore the associations between the independent variables, ACEs and the dependent variable of either LBW or SGA. Moderation of the associations by prenatal smoking and illicit drug use were examined by including interaction terms into the regression models.

Respondent Characteristics

The weighted sample included n = 31,152 (39.86%) respondents who reported exposure to 0 ACEs, n = 30,003 (38.39%) respondents with exposure to 1, 2 or 3 ACEs, and n = 16,998 (21.75%) respondents with exposure to 4 or more ACEs. The unweighted sample included n = 2,305 (35.28%) respondents who reported exposure to 0 ACEs, n = 2,599 (39.78%) with exposure to 1, 2 or 3 ACEs, and n = 1,630 (24.94%) with exposure to 4 or more ACEs. Full characteristics of respondents are shown in Table 3. The groups differed significantly with respect to age, education, race/ethnicity, Medicaid status, pre-pregnancy BMI, gestational weight gain, prenatal smoking and drug use during pregnancy. In terms of age (p = 0.0001), younger respondents (< 20) were more likely to report exposure to either 1, 2, or 3 ACEs (1.77%) or 4 or more ACEs (1.39%) than 0 ACEs (0.72%), while older respondents (25-34) were more likely to report 0 ACEs (28.6%) than 1, 2, or 3 ACEs (24%) or 4 or more ACEs (12.32%). In regards to education (p = 0.0001), respondents with a college degree were more likely to report 0 ACEs (20.62%) as compared to 1, 2, or 3 ACEs (13.38%) or 4 or more ACEs (3.61%). With regards to race/ethnicity (p = 0.0001), respondents identifying as American Indian were more likely to report 4 or more ACEs (10.58%) than 1, 2, or 3 ACEs (4.13%) or 0 ACEs (1.55%), while

respondents identifying as White were more likely to report 0 ACEs (32.93%) as compared to 1, 2, or 3 ACEs (28.09%) or 4 or more ACEs (14.81%). In terms of Medicaid status ($p = 0.0001$), respondents with 1, 2, or 3 ACEs (8.31%) or 4 or more ACEs (7.91%) were more likely to have Medicaid than those reporting 0 ACEs (4.09%). In terms of pre-pregnancy BMI, about 19.06% of respondents with a pre-pregnancy BMI of 18.5-24.9 reported 0 ACEs as compared to about 7.11% reporting 4 or more ACEs ($p = 0.0001$). With regards to gestational weight gain ($p = 0.0001$), all three categories (<25, 25-35, >35) had higher percentages of 0 ACEs (13.81%, 12.85%, 13.37%) than 4 or more ACEs (8.20%, 5.37%, 8.15%). In regards to smoking during pregnancy, smoking increased as the number of ACEs increased with 1.26% of respondents with 0 ACEs, 4.29% with 1, 2 or 3 ACEs and 4.73% with 4 or more ACEs reporting smoking during pregnancy ($p = 0.0001$). Similar to smoking during pregnancy, drug use during pregnancy increased as ACEs increased with 0.30% of respondents with 0 ACEs, 2.04% with 1, 2, or 3 ACEs and 2.75% with 4 or more ACEs reporting drug use during pregnancy ($p = 0.0001$).

Table 3

Respondent Characteristics

Total Weighted N = 78,153				
Characteristic	0 ACEs reported n = 31,152 Column %	1,2,3 ACEs reported n = 30,003 Column %	4 or more ACEs reported n = 16,998 Column %	*p*-value
Age (years)				
< 20	0.72	1.77	1.39	
20 - 24	5.23	7.58	5.80	0.0001
25-34	28.6	24.0	12.32	
≥ 35	5.31	5.04	2.25	
Education level				
< High school	3.59	3.90	3.03	
High school	6.34	8.77	6.95	0.0001
Some college	9.23	12.38	8.19	
College degree	20.62	13.38	3.61	

Table 3 (continued).

Race/ Ethnicity				
White	32.93	28.09	14.81	0.0001
Black	1.83	2.00	0.66	
Am Indian	1.55	4.13	10.58	
Other	3.47	2.16	9.11	
Medicaid status				
Yes	4.09	8.31	7.91	0.0001
Pre-pregnancy BMI				
< 18.5	0.64	0.86	0.40	0.0001
18.5-24.9	19.06	15.04	7.11	
25-29.9	10.59	10.79	5.97	
≥ 30	9.70	11.58	8.26	
Gestational weight gain (pounds)				
< 25	13.81	14.49	8.20	0.0007
25-35	12.85	10.79	5.37	
> 35	13.37	12.97	8.15	
Smoking during pregnancy				
Yes	1.26	4.29	4.73	0.0001
Drug use during pregnancy				
Yes	0.30	2.04	2.75	0.0001

Abbreviations: ACE, adverse childhood experiences; BMI, body mass index.

Pearson Chi square p-value < .05

The prevalence of LBW and SGA by numbers of ACEs is shown in Table 4. The Pearson Chi-square test was performed to examine the relationship between numbers of ACEs (0, 1-3, 4 or more) and LBW and SGA. The relationship between numbers of ACEs and LBW was insignificant, x^2 (2, N = 78,153) = 1.29, p = 0.2743. Similarly, the relationship between numbers of ACEs and SGA was insignificant, x^2 (2, N = 78,153) = 1.01, p = 0.3645.

Table 4

Prevalence of Low Birth Weight and Small for Gestational Age by Number of Adverse Childhood Experiences Reported

LBW	**0 ACEs**	**1,2,3 ACEs**	**4 or more ACEs**	**Total**
No				
Frequency	29,816	28,666	16,052	74,534
Percent	38.15%	36.66%	20.54%	95.37%
Yes				
Frequency	1,336	1,337	946	3,618
Percent	1.71%	1.71%	1.21%	4.63%
p- value = 0.2743				
SGA	**0 ACEs**	**1,2,3 ACEs**	**4 or more ACEs**	**Total**
No				
Frequency	28,753	27,284	15,575	71,612
Percent	36.79%	34.91%	19.93%	91.63%
Yes				
Frequency	2,399	2,719	1,423	6,541
Percent	3.07%	3.48%	1.82%	8.37%
p- value = 0.3645				

Abbreviations: LBW, low birth weight; SGA, small for gestational age; ACE, adverse childhood experiences.

*Pearson Chi-square *p*-value < 0.05

Multivariate analyses

Multivariate analyses were performed using logistic regression models to explore the relationships between numbers of ACEs, and LBW or SGA. Table 5 presents the results from the multivariable logistic regression models. Covariates included in the models were age,

educational attainment, race/ethnicity, Medicaid status, pre-pregnancy BMI and gestational weight gain. The multivariable logistic regression models for LBW and SGA showed no significant relationships with any number of ACEs (1-3, 4 or more). The covariates significantly associated with LBW were age, Medicaid status, pre-pregnancy BMI and gestational weight gain. Respondents that were older (≥ 35), had Medicaid, or had a low pre-pregnancy BMI (<18.5) had greater odds of having a LBW infant as compared to younger respondents, those without Medicaid and those with a pre-pregnancy BMI >18.5, respectively. Covariates significantly associated with SGA were race/ethnicity, pre-pregnancy BMI and gestational weight gain. Respondents who identified as American Indian or Black had lower odds of having a SGA infant compared to White respondents. Respondents with a high pre-pregnancy BMI (≥ 30), or who gained over 26 pounds during pregnancy had lower odds of having a SGA infant as compared to respondents with a pre-pregnancy BMI of 18.5-24.9 and those with a gestational weight gain of < 25 lbs.

Table 5

Multivariable Logistic Regression Model for Low Birth Weight and Small for Gestational Age

Total N = 78,153 (weighted)						
	LBW			SGA		
Characteristics	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Numbers of ACEs (ref = No ACEs)						
1,2,3	0.97	(0.69, 1.37)	.8830	1.19	(0.92, 1.53)	.1910
4 or more	1.13	(0.75, 1.68)	.5540	1.11	(0.80, 1.53)	.5270
Educational attainment (ref = < High School)						
High school	1.05	(0.65, 1.69)	.8490	1.09	(0.73, 1.62)	.6890
Some college	1.04	(0.63, 1.71)	.8860	0.88	(0.58, 1.33)	.5510
College degree	0.80	(0.47, 1.38)	.4290	0.99	(0.69, 1.41)	.0400

Table 5 (continued).

Age (ref = < 20 years)						
20-24	0.88	(0.44, 1.78)	.7360	1.45	(0.77, 2.72)	.2410
25-34	1.42	(0.73, 2.75)	.3000	1.23	(0.66, 2.30)	.5110
≥ 35	2.10	(1.00, 4.40)	.0480	1.31	(0.65, 2.63)	.4450
Race/ethnicity (ref = White)						
Black	0.74	(0.39, 1.39)	.3500	**0.43**	**(0.23, 0.83)**	**.0120**
Am Indian	0.73	(0.51, 1.04)	.0800	**0.62**	**(0.46, 0.83)**	**.0010**
Other	0.85	(0.55, 1.32)	.4690	0.99	(0.69, 1.42)	.9780
Medicaid Status (ref = No Medicaid)						
Medicaid	**2.10**	**(1.01, 1.38)**	**.0001**	0.86	(0.62, 1.18)	.3510
Pre-pregnancy BMI (ref = 18.5-24.9)						
< 18.5	**2.22**	**(1.11, 4.45)**	**.0240**	**1.85**	**(1.02, 3.34)**	**.0430**
25.0-29.9	0.76	(0.53, 1.08)	.1310	0.78	(0.59, 1.02)	.0700
≥ 30	**0.62**	**(0.42, 0.91)**	**.0170**	**0.58**	**(0.43, 0.79)**	**.0001**
Gestational weight gain (ref = < 25 pounds)						
26-35	**0.38**	**(0.26, 0.54)**	**.0001**	**0.65**	**(0.49, 0.86)**	**.0020**
> 35	**0.22**	**(0.15, 0.34)**	**.0001**	**0.49**	**(0.38, 0.66)**	**.0001**

Bolded values are statistically significant.

Abbreviations: CI, confidence interval; LBW, low birth weight; SGA, small for gestational age; ACE, adverse childhood experiences; BMI, body mass index.

Moderation Analyses

Moderation analyses using multivariable logistic regression models were constructed with interaction terms. Table 6 presents the results from the multivariable logistic regression model for LBW and SGA with moderation by smoking during pregnancy. Smoking during pregnancy was defined as any cigarette smoking during the pregnancy. Respondents with the interaction of 1, 2, or 3 ACEs and smoking during pregnancy had significantly higher odds of LBW (OR 2.08; 95% CI 1.15, 3.77) as compared to respondents with no ACEs who did not smoke during pregnancy. Similarly, respondents who smoked during pregnancy with 4 or more

ACEs had higher odds of LBW (OR 1.88; 95% CI 1.06, 3.34). Other covariates significantly associated with LBW were Medicaid status, pre-pregnancy BMI, and gestational weight gain. Respondents with Medicaid or a low pre-pregnancy BMI (< 18.5) had greater odds of having a LBW infant, while respondents with a high pre-pregnancy BMI (≥ 30) or gestational weight gain less than 35 pounds had lower odds of having a LBW infant.

In terms of SGA, respondents with the interaction of 4 or more ACEs and smoking during pregnancy had significantly higher odds of SGA (OR 2.01; 95% CI 1.23, 3.28) as compared to respondents with no ACEs who did not smoke during pregnancy. Other covariates significantly association with SGA were race/ethnicity, pre-pregnancy BMI and gestational weight gain. Respondents identifying as Black or American Indian had lower odds of having a SGA infant as compared to respondents identifying as White. Respondents with a high pre-pregnancy BMI (≥ 30), or with gestational weight gain less than 35 pounds all had lower odds of having a SGA infant.

Table 7 presents the results from the multivariable logistic regression model for LBW and SGA with moderation by illicit drug use during pregnancy. No interaction between any numbers of ACEs and illicit drug use were significant for LBW. Covariates in the model significantly associated with LBW were age, Medicaid status, pre-pregnancy BMI and gestational weight gain. Older respondents (≥ 35), those with Medicaid, and those with a low pre-pregnancy BMI (< 18.5) all had increased odds of having a LBW infant.

In the model, respondents with 4 or more ACEs who used illicit drugs during pregnancy had 1.76 times the odds (95% CI 1.07, 2.89) of having a SGA infant as compared to respondents with no ACEs who did not use illicit drugs during pregnancy. Covariates significant for SGA were educational attainment, race/ethnicity, pre-pregnancy BMI and gestational weight gain.

Respondents with a college degree, and those identifying as Black or American Indian all had lower odds of having a SGA infant. Respondents with a low pre-pregnancy BMI (< 18.5) had greater odds of having a SGA infant, while those with a higher pre-pregnancy BMI (≥ 30) or who gained 35 pounds or less during pregnancy had lower odds of having a SGA infant.

Table 6

Multivariable Logistic Regression Model for Low Birth Weight and Small for Gestational Age with Interaction Term: Smoking During Pregnancy X Number of ACEs

	LBW			SGA		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Number of ACEs X Smoking (ref = No ACE X No Smoke)						
0 ACE X Smoke	1.89	(0.63, 5.68)	.2560	**4.24**	**(2.01, 8.96)**	**.0001**
1-3 ACE X NoSmoke	0.88	(0.61, 1.27)	.4990	1.26	(0.96, 1.65)	.0910
1-3 ACE X Smoke	**2.08**	**(1.15, 3.77)**	**.0160**	1.59	(0.94, 2.71)	.0810
4 ACE X NoSmoke	1.01	(0.64, 1.58)	.9660	1.04	(0.73, 1.49)	.8110
4 ACE X Smoke	**1.88**	**(1.06, 3.34)**	**.0310**	**2.01**	**(1.23, 3.28)**	**.0060**
Educational attainment (ref = < High School)						
High school	1.05	(0.65, 1.69)	.8440	1.10	(0.74, 1.65)	.6310
Some college	1.11	(0.68, 1.83)	.6680	0.93	(0.61, 1.41)	.7270
College degree	0.91	(0.53, 1.58)	.7460	0.70	(0.45, 1.09)	.1150
Age (ref = < 20 years)						
20-24	0.77	(0.38, 1.56)	.4780	1.34	(0.71, 2.52)	.3630
25-34	1.19	(0.62, 2.30)	.5990	1.12	(0.59, 2.09)	.7330
≥ 35	1.74	(0.83, 3.65)	.1400	1.18	(0.59, 2.39)	.6380
Race/ethnicity (ref = White)						
Black	0.82	(0.43, 1.55)	.5410	**0.46**	**(0.24, 0.88)**	**.0200**
Am Indian	0.71	(0.49, 1.01)	.0600	**0.60**	**(0.45, 0.81)**	**.0010**
Other	0.87	(0.56, 1.36)	.5550	0.99	(0.69, 1.43)	.9920
Medicaid Status (ref = No Medicaid)						
Medicaid	**1.91**	**(1.28, 2.83)**	**.0010**	0.79	(0.57, 1.09)	.1560

Table 6 (continued).						
BMI (ref = 18.5-24.9)						
< 18.5	**2.31**	**(1.17, 4.56)**	**.0160**	1.83	(1.00, 3.32)	.0490
25.0-29.9	0.75	(0.52, 1.07)	.1120	0.76	(0.78, 1.00)	.0530
≥ 30	**0.62**	**(0.42, 0.92)**	**.0170**	**0.566**	**(0.42, 0.77)**	**.0001**
Gestational weight gain (ref = > 35 pounds)						
< 25	**0.38**	**(0.26, 0.55)**	**.0001**	**0.65**	**(0.49, 0.85)**	**.0020**
25-35	**0.23**	**(0.15, 0.34)**	**.0001**	**0.49**	**(0.37, 0.66)**	**.0001**

Bolded values are statistically significant.

Smoke = prenatal smoking; NoSmoke = no prenatal smoking.

Abbreviations: CI, confidence interval; LBW, low birth weight; SGA, small for gestational age; ACE, adverse childhood experiences; BMI, body mass index.

N = 78,153 (weighted).

Table 7

Multivariable Logistic Regression Model for Low Birth Weight and Small for Gestational Age with Interaction Term: Drug Use in Pregnancy X Number of ACEs

	LBW			SGA		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Number of ACEs X Drug use (ref = No ACE X No Drug use)						
0 ACE X Druguse	1.04	(0.64, 1.70)	.8710	1.09	(0.75, 1.59)	.6460
1-3 ACE X NoDrug	1.05	(0.69, 1.59)	.8230	1.28	(0.94, 1.75)	.1150
1-3 ACE X Druguse	0.83	(0.45, 1.46)	.5270	1.06	(0.71, 1.59)	.7620
4 ACE X NoDrug	1.00	(1.00, 1.62)	.9900	0.98	(0.66, 1.44)	.9070
4 ACE X Druguse	1.68	(0.92, 3.08)	.0920	**1.76**	**(1.07, 2.89)**	**.0260**
Educational attainment (ref = < High School)						
High school	1.04	(0.64, 1.69)	.8600	1.09	(0.73, 1.63)	.6820
Some college	1.03	(0.62, 1.71)	.9220	0.88	(0.58, 1.33)	.5480
College degree	0.80	(0.46, 1.38)	.4260	**0.64**	**(0.41, 0.99)**	**.0450**
Age (ref = < 20 years)						
20-24	0.91	(0.45, 1.83)	.7940	1.51	(0.81, 2.82)	.1900
25-34	1.46	(0.76, 2.83)	.2580	1.28	(0.69, 2.38)	.4290
≥ 35	**2.19**	**(1.04, 4.59)**	**.0390**	1.38	(0.69, 2.75)	.3640
Race/ethnicity (ref = White)						
Black	0.73	(0.38, 1.41)	.3500	**0.43**	**(0.22, 0.84)**	**.0130**
Am Indian	0.72	(0.50, 1.04)	.0780	**0.62**	**(0.46, 0.83)**	**.0010**
Other	0.86	(0.55, 1.33)	.4900	0.99	(0.69, 1.42)	.9970
Medicaid Status (ref = No Medicaid)						
Medicaid	**2.15**	**(1.45, 3.18)**	**.0001**	0.87	(0.63, 1.20)	.4060
BMI (ref = 18.5-24.9)						
< 18.5	**2.26**	**(1.13, 4.51)**	**.021**	**1.85**	**(1.02, 3.36)**	**.0420**
25.0-29.9	0.75	(0.53, 1.08)	.126	0.77	(0.59, 1.02)	.0700
≥ 30	**0.62**	**(0.42, 0.92)**	**.019**	**0.58**	**(0.43, 0.79)**	**.0010**

Table 7 (continued).

Gestational weight gain (ref = > 35 pounds)						
< 25	**0.38**	**(0.26, 0.54)**	**.0001**	**0.65**	**(0.49, 0.86)**	**.0020**
25-35	**0.22**	**(0.15, 0.34)**	**.0001**	**0.50**	**(0.38, 0.66)**	**.0000**

Bolded values are statistically significant.

Druguse = prenatal illicit drug use; NoDrug = no prenatal illicit drug use.

Abbreviations: CI, confidence interval; LBW, low birth weight; SGA, small for gestational age; ACE, adverse childhood experiences; BMI, body mass index.

N = 78,153 (weighted).

Chapter 5: Discussion

There is an extensive body of research supporting relationships between ACEs and adverse health outcomes throughout the life course, but limited research exploring the relationships between a woman's ACEs and adverse birth outcomes. The purpose of this cross-sectional, secondary data analysis was to build on previous, limited research in order to provide further insight into the relationships between maternal ACEs and the adverse birth outcomes of LBW and SGA.

The study, with a weighted sample of 78,153 respondents from PRAMS who had recently given birth, met the three intended research aims of (1) examining the association between maternal ACEs and delivering an infant with LBW; (2) examining the association between maternal ACEs and delivering an infant with SGA; (3) evaluating if the association between maternal ACEs and LBW or SGA is moderated by prenatal smoking or prenatal illicit drug use. This chapter provides a synthesis of the study findings, discussion of strengths and weaknesses of the study, and concludes with implications for clinical practice and further research.

Aims 1 and 2

Previous research examining the association between maternal ACEs and the adverse birth outcome of LBW are limited. Initial studies suggest that exposure to ACEs is associated with an increased risk of delivering a LBW infant.[48,49,281] In contrast, this study found no significant association between maternal ACEs and LBW. No significant findings were found between 1, 2 or 3 ACEs or 4 or more ACEs and LBW. A study by Smith et al.,[5] reported significant results between ACEs and LBW utilizing a community sample as opposed to the current study that used data obtained by PRAMS through a stratified random sample of

respondents by state. A community sample likely differs from a random sample in ways that may impact study outcomes.

Mersky & Lee,[48] found a significant association between maternal ACEs and LBW using a community sample of primarily low income individuals (98% at or below 200% of the FPL). Poverty is a risk factor for ACEs and a sample of impoverished women will likely lead to a proportionally higher incidence of ACEs as compared to the current study with a sample of women where income variability is more distributed.[105] In addition, poverty itself is a risk factor for negative birth outcomes making it difficult to sort out effects on birth outcomes attributable just to ACEs.

Initial studies exploring ACEs and SGA are very limited and not clear with one suggesting an association between maternal ACEs and infants born SGA,[48,281] and one study finding no significant association.[6] This study found no significant association between 1, 2 or 3 ACEs or 4 or more ACEs and SGA infants. A study by Smith et al.,[55] found a significant association between maternal ACEs and SGA in a community sample. No association between ACEs and SGA was reported in a study by Miller et al.,[282] with a community sample of pregnant women receiving obstetric care and having either a history of a mental health condition or current mental health symptoms at the time of the study. It is unclear how a mental health history/symptoms impact SGA in comparison to a random sample.

Aim 3

Consistent with previous research, findings from the current study demonstrate that the risky health behaviors of prenatal cigarette smoking and illicit drug use during pregnancy impact the birth outcomes of LBW and SGA.[67–69,80,83] Exposure to ACEs increases risk for engagement in risky health behaviors, which in turn are associated with increased risk of adverse birth

outcomes.[62,67,86,87,161] It was expected that for respondents who smoke or use illicit drugs during pregnancy, the odds of having a LBW or SGA infant would increase as the number of ACEs increased. While significant findings were limited, respondents with 1, 2 or 3 ACEs who smoked during pregnancy had over twice the odds of having a LBW infant, and respondents with 4 or more ACEs had a little under twice the odds of having a LBW infant compared to respondents with no ACEs who did not smoke even after controlling for relevant control variables. In terms of SGA, after controlling for relevant control variables, respondents who smoked during pregnancy with a history of 4 or more ACEs had twice the odds of having a SGA infant as compared to respondents who did not smoke during pregnancy and had no history of ACEs.

In terms of illicit drug use, significant results were limited but important in that respondents with 4 or more ACEs who used illicit drugs during pregnancy had 1.76 times the odds of having a SGA infant as compared to respondents with no ACEs who did not use illicit drugs. In this study, drug use included one category with several different types of drugs (heroin, methadone, amphetamines, cocaine, marijuana, tranquilizers, hallucinogens, LSD, Adderall/stimulants, sniffing/huffing gas or glue). It is important to note that the most often reported drug used by respondents was Marijuana (4.11%), followed by methamphetamine (1.14%), Adderall/stimulants (0.60%) and methadone (0.52%). Respondent use of the remaining types of drugs were all under 0.35%. Different drugs differ in their types and strengths of associations with negative birth outcomes including LBW, PTB, SGA, miscarriage, stillbirth and neonatal abstinence syndrome (NAS).[79,82,283–285] Future studies need to parse out associations between specific drugs, ACEs and adverse birth outcomes.

Sample

Phase 8 of PRAMS was the first phase to ask ACE questions in the survey and only North Dakota and South Dakota reached the response threshold of 50%. North Dakota and South Dakota differ from other states in certain characteristics reflected in the sample that are important to note when interpreting the study findings. The respondent reported racial/ethnic composition of the sample included 10.58% American Indian, 75.83% White, 5.66% Hispanic, 4.48% Black and 9.11% other. The sample consisted of over 10% American Indian which is well above the national average of 1.3%.[286] Other racial/ethnic categories diverged from national averages as well including Black (national average 13.6%; study average 4.48%) and Hispanic (national average 18.9%; study average 5.66%).[286]

Prevalence

In the current study, the prevalence of LBW and SGA were both below the annual national averages of about 8% and 11% respectively.[58,260] Out of the weighted sample of 78,153 infants, 3,618 or 4.63% were born LBW, and 6,541 infants, or 8.37%, were born SGA. One possible explanation is that respondents who had an adverse birth outcome may have been less able to respond to the survey, particularly if they were stressed, anxious, depressed, tending to a baby in the NICU, or grieving the loss of an infant. Another possible explanation is that the percentage of Black respondents (4.48%) was well below the national average of 13.6%. Rates of delivering LBW and SGA infants are significantly higher for Black women than other races/ethnicities including American Indian, White and Hispanic women.[56,287]

Strengths and Limitations

This study adds to the body of knowledge about maternal ACEs and their impact on adverse birth outcomes. As the first known study to use multi-state population data to

evaluate relationships between maternal ACEs and the birth outcomes of LBW and SGA, this study provides a unique perspective. Another strength of the study is its proportionally high percentage of American Indian respondents in the study sample (10.58%). American Indian populations are traditionally understudied groups that according to a recent study may experience ACEs at higher rates than other races/ethnicities.[288] American Indians typically experience LBW at a rate higher than that of the national average (8%), yet in this study about 6.19% of American Indian infants were LBW.[52] Perhaps American Indian respondents had certain factors that may have contributed protective effects. Potential factors may include adequate social support and/or resilience.

There are several limitations to this study. As a retrospective, cross-sectional study, outcomes and exposures were simultaneously assessed, which limits ability to evaluate for a temporal cause/effect relationship with maternal ACEs and birth outcomes.

Another limitation is that data addressing ACEs in PRAMS was restricted to participants from only two states (North Dakota and South Dakota) that differ in racial/ethnic make-up from the United States as a whole. While multi-state data is extensive and useful, it may limit generalizability of findings to all pregnant women in the United States.

Lastly, PRAMS data are collected through retrospective, self-report which may lead to recall or reporting biases. Adverse childhood experiences are often associated with shame, guilt and embarrassment and participants may be unwilling to share their experiences. In addition, ACEs occur in the first 18 years of life, and time may alter an individual's memory or perception of an experience.

Implications

Clinical Practice

Trauma Informed Care.

A history of ACEs is common for expectant mothers with about 70% of pregnant women reporting at least one ACE.[289] Adverse childhood experiences are often traumatic events and a clinical approach to improve health outcomes for ACE-exposed pregnant women is to integrate trauma-informed care (TIC) into maternity practice.[290,291] Trauma-informed care is an organizational approach that has at its core the importance of recognizing trauma, understanding the role of trauma in a person's life, and responding appropriately to the effects of trauma.[291] The National Center for Trauma Informed Care (NCTIC) has developed a framework for providing TIC that directs health care providers to ask "What has happened to you?" instead of "What is wrong with you?" and is made up of the "3 Es" of conceptualizing trauma: Trauma results from an **e**vent (or events) that is **e**xperienced, by an individual and has lasting negative **e**ffects on the individual's physical, mental, social or spiritual well-being. The TIC framework includes 4 essential practice Rs: the care provider **r**ealizes the impact of trauma and directions for recovery, **r**ecognizes signs and symptoms of trauma, **r**esponds through procedures and practices based on understanding of trauma, and actively seeks to **r**esist **r**e-traumatization.[291] Adoption of TIC into clinical practice promotes safety, transparency, trustworthiness, peer support, collaboration, choice and empowerment and can potentially improve patient engagement, treatment adherence and patient health outcomes for women with exposure to ACEs.[291]

Screening for ACEs in Practice.

Screening pregnant women for ACEs may provide important opportunities for health care providers to intervene in ways that prevent or mitigate associated prenatal and post-partum risks, and that promote long-term health for women and their children.[292] Health care providers are well poised to incorporate ACE screening into regular prenatal visits and yet, many choose not to screen for reasons including: concerns that screening will require extra time, concerns that the topic will upset the women, or due to a lack of confidence in one's ability to facilitate the sensitive subject matter.[292] Several studies have found that a majority of women reported a willingness to engage in ACE screening.[292,293] Research has demonstrated that most women are not only comfortable completing ACE questionnaires, but also think that clinicians should be asking about ACEs at prenatal visits.[292] In post-intervention focus groups, clinicians reported minimal time needed to screen for ACEs, an improved confidence to discuss ACEs over time, and a perception that ACE conversations promoted integrated care and trusting relationships between provider and patient.[292,293]

Although widespread screening for ACEs in health care settings seems acceptable and feasible, it may be premature.[294] Routine ACE screening should be contingent upon the following: a solid scientific understanding of what to screen for, an understanding of what interventions are effective for those exposed to ACEs, and resources within the community to meet the needs of those identified by ACE screenings. [294]

There is a sizable body of literature addressing effective interventions for individuals with ACE exposures yet more research is needed. Most ACE questionnaires identify a cumulative ACE score, and yet individual ACEs differ and may require a wide range of varying interventions and treatments. Interventions that have been successful in supporting individuals with ACE exposure include individual therapy, family therapy and parenting education. In a

recent systematic review of interventions to support people with ACE exposure, cognitive behavioral therapy was found in 7 studies to significantly improve mental health outcomes.[295] Other interventions including, psychoeducation, parent training, cross-sector support, and educational interventions, all modestly improved outcomes in individual studies but were less conclusive overall.[295] In addition to identifying successful interventions, there needs to be adequate resources available to enact the interventions at the community level.

While routine ACE screening during perinatal care should continue to be considered and explored, perhaps, with our current understanding of ACEs, the most beneficial clinical interventions would be those that address the potential proximal adverse outcomes or correlates of ACEs in pregnant and postpartum women. ACEs are associated with increased negative mental health outcomes and risky health behaviors during pregnancy. Clinicians should screen for depression as well as prenatal anxiety, PTSD, and suicide ideation and ensure that women are appropriately referred. Clinicians should ask about prenatal smoking and drug use and provide support and referrals. ACEs are common among pregnant women and clinical intervention to address proximal negative health outcomes may serve to decrease more distal negative outcomes including adverse birth outcomes.

Research Recommendations

Since the ACE Study[296] in 1998, there has been an extensive, growing body of research investigating ACEs and their impacts on health across the lifespan. Despite the substantial amount of ACE inquiry, gaps still remain. The majority of studies use an individual's cumulative ACE score as the measure of ACEs. More research is needed to clarify the meaningfulness of the cumulative ACE score. Helpful studies would be those addressing individual ACEs, incorporating severity of an ACE and timing of an ACE (occurred in early childhood vs early

teen years). In addition, further research exploring ACEs beyond the original ACEs on the Kaiser-ACE questionnaire are needed. How are community ACEs, such as witnessing community violence, poverty and others, similar to the more studied ACEs of abuse, neglect and household dysfunction in terms of impact on health outcomes?

Pathways leading from ACEs to adverse health outcomes are complex and not clearly understood. While research has made strides into understanding some intricacies of the puzzle including, the chronic stress response, altered hypothalamic-pituitary axis, epigenetic pathways, and biobehavioral and social pathways there is still much room for scientific exploration.[297]

Adverse childhood experiences impact birth outcomes. In order to better understand these relationships, more studies with larger samples that reflect the overall United States population are needed. It is important that PRAMS participating states be encouraged to ask ACE questions in their surveys and consider any obstacles in data collection that might contribute to below threshold response rates.

Conclusion

Adverse childhood experiences impact the health of mothers and infants during the perinatal period. Prior research has provided evidence that ACEs are associated with the negative birth outcomes of LBW and SGA. Despite limited findings, this study underscores the need for more robust replication research with large population-based samples to continue to examine relationships between ACEs and birth outcomes. Lastly, this study highlights the role that the risky health behaviors of prenatal smoking and illicit drug use play in moderating relationships between ACEs and birth outcomes.

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Appendix A

Phase 8 Pregnancy Risk Assessment Monitoring System Survey Questions

State Developed Questions

NV3. During the time period before you were 18 years of age, how often did the following things happen to you? For each item, check **N** if it never happened, **O** if it happened once, **MO** if it happened more than once, or **DK** if you *don't know*.

How often did your parents or adults in your home ever slap, hit, kick, punch, or beat each other up?

Before age 18, how often did a parent or adult in your home ever hit, beat, kick, or physically hurt you in any way? Do not include spanking

How often did a parent or adult in your home ever swear at you, insult you, put you down?

How often did anyone at least 5 years or older than you or an adult, ever touch you sexually?

How often did anyone at least 5 years or older than you or an adult, try to make you touch sexually?

How often did anyone at least 5 years or older than you or an adult, force you to have sex?

SD75. While you were growing up, during your *first 18 years of life*, did any of the following things happen *often* or *very often*?

No Yes

Did a parent or other adult in the household swear at you, insult you, put you down, or humiliate you **OR** act in a way that made you afraid that you might be physically hurt?

Did a parent or other adult in the household push, grab, slap, or throw something at you **OR** ever hit you so hard that you had marks or were injured?

Did you feel that no one in your family loved you or thought you were important or special **OR** your family didn't look out for each other, feel close to each other, or support each other?

Did you feel that you didn't have enough to eat, had to wear dirty clothes, and had no one to protect you **OR** your parents were too drunk or high to take care of you or take you to the doctor if you needed it?

Was your mother or stepmother pushed, grabbed, slapped, or had something thrown at her **OR sometimes, often or very often** kicked, bitten, hit with a fist, or hit with something hard **OR ever** repeatedly hit at least a few minutes or threatened with a gun or knife?

SD76. While you were growing up, during your *first 18 years of life*, did any of the following things happen?

No Yes

Did your parents get separated or divorced?

Was a household member incarcerated?

Did you live with a household member who was depressed?

Did you live with an alcoholic?

Core Questions

DRUG2
During the *month* before you got pregnant, did you take or use any of the following drugs for any reason? For each item, check **No** if you did not use it or **Yes** if you did.

Over-the-counter pain relievers such as aspirin, Tylenol®, Advil®, or Aleve®
Prescription pain relievers such as hydrocodone (Vicodin®), oxycodone (Percocet®), or codeine Adderall®, Ritalin®, or another stimulant
Marijuana or hash

Synthetic marijuana (K2, Spice)

Methadone, naloxone, subutex, or Suboxone®

Heroin (smack, junk, Black Tar, Chiva)

Amphetamines (uppers, speed, crystal meth, crank, ice, agua)

Cocaine (crack, rick, coke, blow, snow, nieve)

Tranquilizers (downers, ludes)

Hallucinogens (LSD/acid, PCP/angel dust, Ecstasy, Molly, mushrooms, bath salts)

Sniffing gasoline, glue, aerosol spray cans, or paint to get high (huffing)

DRUG3

During your most recent pregnancy, did you take or use any of the following drugs for any reason? For each item, check **No** if you did not use it or **Yes** if you did.

Over-the-counter pain relievers such as aspirin, Tylenol®, Advil®, or Aleve®

Prescription pain relievers such as hydrocodone (Vicodin®), oxycodone (Percocet®), or codeine Adderall®, Ritalin® or another stimulant

Marijuana or hash

Synthetic marijuana (K2, Spice)

Methadone, naloxone, subutex, or Suboxone®

Heroin (smack, junk, Black Tar, *Chiva*)

Amphetamines (uppers, speed, crystal meth, crank, ice, *agua*)

Cocaine (crack, rock, coke, blow, snow, *nieve*)

Tranquilizers (downers, ludes)

Hallucinogens (LSD/acid, PCP/angel dust, Ecstasy, Molly, mushrooms, bath salts)

Sniffing gasoline, glue, aerosol spray cans, or paint to get high (huffing)

Prescription antidepressants or selective serotonin reuptake inhibitors (SSRIs) such as Prozac, Zoloft, or Lexapro

Have you smoked any cigarettes in the *past 2 years*? No Yes

In the *last 3 months* of your pregnancy, how many cigarettes did you smoke on an average day? A pack has 20 cigarettes.

41 cigarettes or more 21 to 40 cigarettes 11 to 20 cigarettes

6 to 10 cigarettes

1 to 5 cigarettes Less than 1 cigarette I didn't smoke then

Appendix B

Table 8

Variables with Codes

Construct	Variable Name	Description	PRAMS Source	Level of Measurement	Variable Type
Independent Variables					
ACEs (all in first 18 years of life)					
ACE	YR18_DVRC	Parents separated/divorced	Questionnaire	Nominal	Recoded
ACE	YR18_SUBS	Live with alcoholic	Questionnaire	Nominal	Recoded
ACE	YR18_DPRS	Live with depressed household member	Questionnaire	Nominal	Recoded
ACE	YR18_JAIL	Household member in prison	Questionnaire	Nominal	Recoded
ACE	YR18_SXAB	Sexual abuse	Questionnaire	Nominal	Recoded
ACE	YR18_VBAB	Emotional abuse	Questionnaire	Nominal	Recoded
ACE	YR18_PHAB	Physical abuse	Questionnaire	Nominal	Recoded
ACE	YR18_IGNR	Emotional neglect	Questionnaire	Nominal	Recoded
ACE	YR18_CARE	Physical neglect	Questionnaire	Nominal	Recoded
ACE	YR18_MMAB	Violence to mother/ stepmother	Questionnaire	Nominal	Recoded

Table 8 (continued).

Dependent Variables					
LBW	LBW	Birth weight <2500 grams	Birth certificate	Dichotomous	Recoded
SGA	SGA_10	Birth weight < 10th percentile	Birth certificate	Dichotomous	Direct
Moderation Variables					
Smoking	SMOKING	Cigarette smoking during pregnancy	Questionnaire	Ordinal	Direct
Illicit Drug Use	DRUGUSE	Illicit drug use during pregnancy	Questionnaire	Ordinal	Recoded
Control Variables					
Age	MAT_AGE_ NAPHSIS	>20, 20-24, >24-29, >29-35, >35	Birth certificate	Ordinal	Recoded
Education Level	MAT_ED	<High School, High School, Some College, College Graduate	Birth certificate	Ordinal	Recoded
Race/ Ethnicity	MAT_RACE	Black, White, American Indian	Questionnaire	Ordinal	Direct
Hispanic	HISPANIC	Hispanic	Questionnaire	Dichotomous	Direct
Medicaid Status	MEDIC	Yes or No	Birth certificate	Dichotomous	Direct
Pre-pregnancy BMI	MOM_BMIG_ BC	<18.5, 18,5-24.9, 26-29.9, ≥30	Birth certificate	Ordinal	Direct
Gestational Weight Gain	MOMLBS	<25, 25-35, >35	Birth certificate	Ordinal	Direct

Abbreviations: ACE, adverse childhood experiences; LBW, low birth weight; SGA, small for gestational age; BMI, body mass index