ABSTRACT

Title of Thesis:	ADVERSE CHILDHOOD EXPERIENCES AND PRETERM BIRTH: A SYSTEMATIC REVIEW
	Morgan Wiggan, Masters of Public Health, 2019
Thesis Directed By:	Luisa Franzini, Professor and Chair, Health Policy and Management

Adverse Childhood Experiences (ACEs) elevate one's risk for poor health outcomes later in life such as psychiatric disorders, anxiety, obesity, and poor fetal health (Poulton et al., 2002; Anda et al., 2007; Jimenez et al., 2017). While the association between ACEs and negative health outcomes is well established in the literature, only ten studies examine the effect of ACEs on one's risk for preterm birth (Benedict et al., 1999; Bublitz et al., 2014; Cammack et al., 2019; Christiaens et al., 2015; Jacobs 1998; Gillespie et al., 2017; Grimstad et al. 1998; Leeners et al. 2010; Margerison-Zilko et al., 2016; Noll et al. 2007). The rate of preterm birth in the United States has steadily risen since 2015, reaching about 10% in 2018 (CDC, 2018). This systematic review seeks to critically assess and synthesize these ten studies and identify proposed mediators and identify gaps in the literature for future research.

ADVERSE CHILDHOOD EXPERIENCES AND PRETERM BIRTH: A SYSTEMATIC
REVIEW

by

Morgan Lynn Wiggan

Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Masters of Public Health
2019

Advisory Committee:
 Professor Luisa Franzini, Chair
 Edmond Shenassa
 Lori Simon-Rusinowitz

Acknowledgements

Throughout the writing of this thesis I have received a great deal of support from many people, including colleagues, peers, and family. I would like to thank my academic advisor, Luisa Franzini, for her continued academic and personal support and encouragement throughout my degree and thesis writing process. I'd also like to thank committee member, Edmond Shenassa, for his countless hours of mentorship. Thank you to Nedelina Tchangalova, the University of Maryland Public Health Research librarian, who was essential in helping me develop my search criteria and strategy. Additionally, I would like to thank Lori Simon-Rusinowitz, for her dedication of time to my thesis committee.

I'd like to thank my family members including my parents, grandparents, and husband for all their emotional support and sacrifice that has helped me complete this thesis and degree. Thank you to all my peers and friends who have lent their support during this rigorous process.

-

Table of Contents

Chapter 1: Background

<u>Introduction</u>

Exposure to trauma during childhood is associated with elevated risk of adverse health outcomes such as cardiovascular disease, mental illness, diabetes, and poor pregnancy outcomes in adulthood (Shonkoff, 2012). Childhood trauma exposure is especially deleterious to the healthy function of individuals' physiologic stress response (Herzog et al., 2018).Though several studies have examined the negative health outcomes associated with these Adverse Childhood Experiences (ACEs) (e.g., Poulton et al., 2002, Anda et al., 2007, Jimenez et al., 2017, Talbot et al., 2009), only ten studies have investigated the association between exposure to ACEs and preterm birth in adult women. One epidemiological review examined the association between a history of maternal childhood sexual abuse and preterm birth but did not consider other forms of abuse or early adverse experiences in the exposure (Wosu et al., 2015).

My thesis examines the association between exposure to ACEs and the risk of giving preterm birth. This systematic review contributes to the literature on best clinical practices and prevention strategies for women with a history of ACEs. I will also identify gaps in the research that can be used for future public health research to advance the literature around this timely topic of preterm birth. This is the only systematic review that examines the relationship between history ACEs and preterm labor.

My thesis seeks to answer whether a maternal history of ACEs is associated with an elevated risk of preterm birth. This question will be explored through the examination of studies that have researched this hypothesized association. This systematic review hypothesizes that

exposure to ACEs elevates one's risk for giving birth to a preterm infant, considering the negative effects early trauma exposure has on the body.

Aims

The first aim is to critically assess the literature examining the relationship between ACEs and preterm delivery I will perform a systematic literature search in PubMed, CINAHL, Academic Search Ultimate, PsychINFO, Sciencedirect, and Web of Science to identify relevant articles. I will then use the Newcastle-Ottawa Quality Assessment Scale adapted for case control, cohort, and cross sectional studies to assess the quality of the individual studies in this review.

The second aim is to synthesize published studies examining the association between ACEs and preterm birth. I will create a narrative review of the currently published literature for researchers and policymakers to easily access the research performed and published to date

The third aim is to identify proposed mediators and moderators between the exposure and outcome to begin to understand the causal pathway. Mediators and moderators allow researchers to communicate causal pathways and effective policy recommendations to policymakers. The identification of these could help make real change towards health equity.

The fourth aim is to identify gaps in current research My research will highlight and recommend next steps for future study of the topic.

ACEs

Adverse Childhood Experiences are traumatic experiences that individuals experience in childhood. They can include physical abuse, emotional abuse, sexual abuse, neglect, exposure to mental illness, incarceration, domestic abuse, and criminal activity (Felitti et al., 1998). Vincent Felitti, a Kaiser Permanente physician working in an obesity weight loss clinic in the mid-1980's, observed that many patients successfully losing weight were the individuals most

2

likely to drop out of the program. Through a review of patient records he later observed that many of these individuals had unresolved problems stemming from trauma in their childhood (Felitti et al., 1998). Through a collaboration with the Centers for Disease Control from 1995-1997 he conducted a study of the early childhood experiences and health of over 17,000 adults. In the sample, 21% reported physical abuse and 28% reported sexual abuse. Almost 40% of the sample reported two or more ACEs and 12.5% reported 4 or more ACEs. Felitti and colleagues found an association between exposure to childhood abuse and adversity and some of the leading causes of death (Felitti et al., 1998). These findings heightened awareness of the risk that Adverse Childhood Experiences contribute to individuals' health trajectories. Subsequently, numerous studies across a wide range of fields have found associations between ACEs and unfavorable health outcomes in adulthood including elevated risk for depression, anxiety, cardiovascular disease, diabetes, poor dental health, behavioral issues, fetal death, and adverse pregnancy outcomes (Poulton et al., 2002, Dube et al., 2003, Chapman et al., 2004). I will review the literature on ACEs and their association with preterm birth, mediated by the dysregulation of the HPA axis which is just one consequence of the "long arm of childhood".

Dr. Vincent Felitti developed an ACEs screening tool for generating an ACEs score. The Family Health History Questionnaire has a version for males and for females and consists of 68 questions that examine childhood trauma experiences such as emotional, physical, sexual, abuse and neglect. An ACEs score is a cumulative score of the total number of ACEs experiences in each category on the Questionnaire (CDC, 2018). Increasingly, the ACEs "Quiz" has been utilized by clinicians to determine risk factors that may impact adult health. ACEs have a graded dose response relationship with poor health outcomes. As the cumulative ACE score increases, risk for adverse health outcomes is elevated. Additionally many health issues related

to ACEs are comorbid (Merrick et al., 2017, Nurius et al., 2012).

ACEs, mediated through the disruption of the Hypothalamic Pituitary Adrenal (HPA) axis stress response, are linked with long term changes in the structure and function of brain with long term neurobehavioral consequences (Anda et al., 2006, Herzog et al., 2018). Changes to the HPA axis stress response can lead to a decreased ability to regulate stress hormones in the body later in life (Maniam et., 2014). The HPA axis mediates the major processes of the body's stress response system. When activated, the HPA axis releases corticotropin releasing factor (CRF) which stimulates the adrenal release of cortisol. Cortisol suppresses further release of CRF by binding to glucocorticoid receptors in the hypothalamus and pituitary glands. This negative feedback loop reestablishes homeostasis to regulate the stress response.
The negative feedback loop controls the levels of stress hormones in the HPA axis, so that levels return to what is normal. Cortisol terminates the stress response once certain levels of stress hormones are reached in order to maintain the predetermined limits for the body. The dysregulation of the HPA axis involves its hyperactivity and when cortisol levels remain heightened even after the stressor has been removed. Consistently high cortisol levels mean that the body is in allostasis has harmful physiological consequences (Carpenter et al., 2011). The dysfunction of the HPA axis happens as a function of life experiences that can be particularly harmful when they occur in childhood.

The ACEs Pyramid illustrates the connections between ACEs and early death as illustrated in the image below. The impact of ACEs leads to maladaptive changes in the brain that can cause cognitive impairment such as behavioral health which can trigger the adoption of

risky behaviors that elevate one's risk for disease and social problems which can then increase one's risk for early death. ACEs are associated with elevated risk for substance abuse, chronic pulmonary disease, depression, ischemic heart disease, liver disease financial stress, obesity, diabetes, financial stress, poor work performance, unintended pregnancy, and sexually transmitted diseases, among a list of other social, behavioral, and physiological health problems (CDC, 2016).

Preterm Birth

Definition

Preterm birth is defined as birth prior to 37 weeks gestation and has implications for adverse health outcomes throughout the life course (Burris et al., 2011). The three types of preterm birth include 1) spontaneous labor with intact membranes 2) preterm premature rupture of membranes 3) labor induction or caesarean delivery for maternal or fetal indications (Goldenberg et al., 2008) The date of the mother's last menstrual cycle is commonly used to measure gestational age of a baby (Behrman et al., 2007). Preterm birth is a prevalent syndrome caused by multiple factors such as infection or inflammation, vascular disease, and uterine overdistension. Risk factors for preterm birth include substance abuse, illicit drug use, domestic abuse, stress, exposure to harmful environmental pollutants, smoking, ethnicity (specifically being black), high blood pressure, being underweight or obese before pregnancy, insufficient prenatal care, vaginal infections, and diabetes among a list of many other factors (National Institute of Health, 2018).

Preterm birth is associated with numerous negative health outcomes for the infant in childhood and continuing through adulthood including psychiatric disorders, academic problems,

Cerebral Palsy and increased risk of mortality across the lifespan (Lilliecreutz et al., 2016).

Infants born prematurely have elevated risks for respiratory illness, cerebral palsy,

developmental disabilities, and other adverse health outcomes and more than 60% of neonatal

deaths are associated with preterm birth (Frey et al., 2016). Such poor health outcomes

disproportionately impact minorities and people living in poverty. Worldwide 15 million preterm

births occur annually (Frey et al., 2016). Preterm birth is the leading cause of death for children

under 5 years of age (World Health Organization, 2018). The numerous environmental and

genetic factors that contribute to preterm birth makes it difficult for researchers to determine

appropriate targets of analysis when studying preterm birth. Increased specificity in the literature

that closely studies these factors is essential for the development of efficient and effective

prevention strategies.

Historic Trends

Two of the most prevalent adverse birth outcomes, low birthweight and preterm birth

have increased after many years of decline. The preterm birth rate in the United States declined

steadily from 2007 to 2014 but began to rise in 2015 (Centers of Disease Control, 2018). In 2015

the late preterm birth rate in the United States rose 2%, from 9.63% to 9.84% in 2016 (Tanne,

2017), while early preterm birth rates stayed the same (Centers of Disease Control, 2018). The

increase has been attributed to a steep increase in medical intervention in the labor process for

hospital births (Goldenberg et al., 2008).

Health Disparities and Adverse Birth Outcomes

There are well established racial and socioeconomic disparities in adverse birth

outcomes including preterm delivery. About 9% of Non-Hispanic white infants are born

prematurely as compared to 14% of Non-Hispanic black infants (Centers for Disease Control,

2018). Even as preterm birth steadily declined between 2006 and 2014, racial disparities

persisted (Engelhardt et al., 2018). From 2014 to 2017 preterm birth in the United States has

steadily risen and about 10% of babies born in the United States are born too early (Centers for

Disease Control, 2018). Risk factors for preterm delivery include, low socioeconomic status,

previous preterm delivery, substance abuse, black race, and limited access to prenatal care

(Engelhardt et al., 2018). Prevention of prematurity is a public health priority in many high

income countries, including the United States. Prevention efforts can only be informed by

research that identifies harmful exposures and the link between them and preterm birth. Stress

is one proposed mediator for the association between ACEs and premature birth.

Maternal stress is among the most important factors that contribute to premature birth.

Maternal stressors such as intimate partner violence (IPV), natural disasters, and perceived

daily stress elevate the risk for adverse birth outcomes such as preterm delivery in animal and

human studies (Nesari et al., 2018). Literature on the link between stress and preterm birth has

largely focused on stress experienced at any point prior to pregnancy or exclusively during

pregnancy, which are both associated with negative birth outcomes such as low birthweight,

infant mortality, and the topic of this thesis, preterm birth independent of socioeconomic status

(Lilliecreutz et al., 2016, Nesari et al., 2018). The exclusive focus on stress at any time in life

prior to pregnancy or only during pregnancy does not account for the specific role of that

childhood trauma plays in elevated risk for preterm birth. By taking a more expansive view of

the specific timing and disruptive impact of childhood stress in the body by studying ACEs and

their impact on preterm labor, earlier and more efficient prevention and interventions can be

implemented for women that may be at risk for giving birth to a preterm infant.

Theoretical Perspective

Life Course Development Theory

The theoretical framework for this thesis is the Life Course Development theory. Life course theory is a public health approach that takes time and place into account when analyzing health outcomes by considering protective and risk factors in determining the health trajectory of an individual. This perspective recognizes the unique role that each life stage plays in health outcomes. Specifically, that early life stages are times when biological processes are being developed which can have permanent adaptations that can be negative or positive based on the types of social and environmental exposures that occur in childhood (Halfon et al., 2014). This perspective is the lens through which it may be useful to examine the effect of ACEs on the risk for preterm birth. Studies utilizing the life course perspective first examined how adverse conditions in childhood, characterized by high stress early in development, can lead to an upregulated stress response system in adulthood (Shonkoff, 2016). While poor conditions early in life can elevate the risk for adverse health outcomes later in life, a strong foundation of positive conditions in early life can alternatively create a strong foundation for positive health outcomes. This perspective supports the association between ACEs and preterm birth. The biological pathway that could explain this association is related to the Life Course Perspective because the maladaptive changes that occur in the HPA axis are caused by early childhood stress and impact adverse health outcomes later in life such as risk of preterm birth.

Chapter 2: Methods

<u>Eligibility Criteria</u>

Studies must

1) Identify Adverse Childhood Experiences (including physical neglect, emotional neglect, physical abuse, emotional abuse, domestic violence, sexual abuse, or emotional abuse, removal from home by government) occurring before the age of 18 as the exposure and preterm birth prior to 37 weeks as the outcome.

2) be published before January 2019.

3) Be written originally in English.

4) Include multivariate analyses

5) Be any type of observational study (cohort, case-control, and cross sectional)

6) This research is excluding studies that include paternal ACEs as the exposure.

7) This research is excluding studies that focus on stress during pregnancy.

8) This research is excluding studies that examine adolescent pregnancy outcomes.

Though not all studies included in this review utilize the term "ACEs" or use the specific ACEs survey developed by Felitti, (Felitti et al., 1998) many studies examine early childhood trauma, stress and abuse.

<u>Information Sources</u>

Databases

I conducted a systematic search of the exposure and outcome in headings and articles in PubMed, CINAHL, Academic Search Ultimate, PsychINFO, Sciencedirect, and Web of Science electronic databases for English language publications testing associations between ACEs and preterm delivery with no limits on the earliest study until January 2019. Keywords

included preterm birth, premature birth, preterm delivery, ACEs, Adverse Childhood Experiences, Childhood trauma, Early adversity, Childhood hardship, Childhood abuse, Early trauma, Adverse Birth Outcomes, Childhood Stress, Adverse Pregnancy Outcomes, and Childhood Maltreatment. Key terms to create an effective search strategy were generated using the Patient, Intervention, Comparison, Outcome (PICO) tool for systematic reviews. I also mined the bibliographies of search result studies to identify additional relevant articles for the review.

Search

Through a systematic search of studies examining the association between the exposure of adverse childhood experiences among women and the outcome of preterm birth outcomes I will examine the results of the ten identified studies and synthesize the information. My specific search strategy was to use the following search string in all databases mentioned above.

(mother or maternal or women) AND ("Adverse Childhood Experiences" OR "ACEs" OR "childhood maltreatment" OR "early trauma" OR "early adversity" OR "childhood abuse" OR "childhood neglect" OR "childhood adverse life events" OR "childhood trauma" OR "childhood stress" OR "childhood hardship" OR ("sexually abused" AND childhood)) AND ("adverse birth outcomes" OR "preterm delivery" OR "preterm birth" OR "premature birth" OR "adverse pregnancy outcomes" OR "neonatal outcome")

Study Selection

This search strategy yielded 351 records retrieved. After duplicates were removed, articles were screened for relevance and eligibility, twelve articles were identified. One article was further excluded because it is not available electronically or in print at this time due to an

embargo by the publisher. Studies found in the bibliographies of selected articles that qualify with my inclusion and exclusion criteria were also selected to be included in the review.

Data Collection Process

Study Characteristics

Following the study search and selection, I extracted data from the studies using an excel sheet where I listed study design, date of publication inclusion criteria, outcome measure, results, research questions, summary, confounders, potential mediators, and limitations of the studies. This excel sheet served as a visualization of the most important findings and characteristics of each study. Following the data extraction process I used the excel sheet tool review the extracted evidence. I then created a summary of the study characteristics as well as a narrative overview of the included studies found in the discussion and summary of evidence section of the thesis.

Of the ten studies published prior to January 2019, nine were published between 2004 and 2019. Only one study was conducted outside the United States, in Germany. Two studies were prospective cohort studies, three were case control studies, three were cross sectional studies, and two were prospective observational studies, and two are retrospective cohort studies. The sample size ranged from 28 to 51434. Nine studies focused on preterm birth as the only outcome measure and one included other adverse birth outcome measures such as low birthweight.

Risk of Bias

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Checklist was utilized to create the structure of this review. PRISMA " is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions" (PRISMA, 2015).

The Newcastle-Ottawa Quality Assessment Scale adapted for case control, cohort, and cross sectional studies was used to assess the quality of the individual studies in this review (see Appendices A and B) (Ottawa Hospital Research Institute, 2019). The tool uses a "star system" to rate the quality of studies based on selection, comparability, and outcome measures. Table 1 below summarizes the results of the quality assessment using this tool. Overall, studies included in this review had an average high quality level of selection, comparability, and outcome measures using this assessment tool. Two studies scored low (two or fewer stars) in selection, one study scored low (zero stars) in comparability, and three studies scored low (two or fewer stars) in outcome measures. The remaining studies scored moderately or highly on each scoring scale of the three categories.

There is a low risk of bias across studies included in this review. Risk of bias was mitigated through a rigorous search of the literature. The generation of search terms that were reviewed by a University of Maryland research librarian ensured that different terms used by articles were captured in the search even if they differed from the exact wording of the exposure and outcome in my hypothesis. Despite this strength, it is possible that some potentially relevant search terms were not included in the search string. Additionally, all relevant databases were searched to generate studies to be considered for the review. There is some risk of bias in that this systematic review was developed by one researcher only. A search of the literature by more

than one person could have reduced risk of bias further but due to the nature of a MPH thesis, the review was developed by one researcher only. Overall, the risk of bias across the studies in this review is low.

Chapter 3: Results

Types of Abuse

Through a review of the studies selected, eight of the ten studies found a significant association between at least one domain of child maltreatment and abuse and elevated risk for preterm birth. Five articles investigated the effect of childhood sexual abuse on the risk for preterm birth, while one examined the cumulative effect of both childhood and adulthood sexual abuse. The other four articles studied the impact of multiple domains of child maltreatment and abuse on an individual's risk for preterm birth. Two articles measured participant cortisol levels to examine the potential being a mediator in the relationship between child abuse and preterm birth. One article used foster care system or childhood adoption exposure as a proxy for childhood maltreatment.

Sexual Abuse

Sexual abuse is recognized as an important risk factor for preterm birth (Noll et al., 2007). Of the five studies focused only on childhood sexual abuse, three articles found a significant association between the exposure and preterm birth (Leeners et al., 2010; Margerison-Zilk et al., 2016; Noll et al., 2007). Of the remaining five articles that investigated broader definitions of abuse, instances of sexual abuse were only analyzed independently in one article (Cammack et al., 2019). The three articles with significant findings for an association between childhood sexual abuse and preterm birth give further evidence for sexual abuse as a risk factor for preterm birth and contribute important future opportunities for methodological approaches that can contribute to literature about the topic.

A case control study examining pregnancy complications of survivors of childhood sexual abuse revealed that the survivors had higher rates of overall pregnancy complications as

well as hospitalizations during pregnancy in a sample of women seeking care in a unique

German society that cares for victims of sexual abuse (Leeners et al., 2010). Women with

histories of CSA had 2.54 greater odds of presented premature contractions compared to

women without and 2.58 greaters odds for giving birth to a premature baby. This study is the

only study in the literature that includes premature contractions into its outcome measures.

Premature birth occurs as a result of premature contractions opening the cervix earlier than the

37th week when the baby has reached full term (Centers for Disease Control, 2018). Therefore

premature contractions play an important role in the risk of premature birth and should also be

included as an outcome measure in future studies.

A case control study measuring cortisol levels among childhood sexual abuse victims

and mothers without a history of sexual abuse as well as preterm birth in the sample found that

survivors had 2.58 greater odds of giving birth to a premature infant (Noll et al., 2007). Maternal

prenatal alcohol use was mediated the relationship between childhood sexual abuse and

preterm birth while cortisol levels without a specific stress exposure did not. Though there was

not elevated levels of cortisol in the case group, this may be indicative of the hypothesis that

victims of early trauma can have either upregulated or downregulated cortisol excretion as an

adaption to early exposure to stress (Noll et al., 2007). CSA survivors also reported significantly

higher levels of physical discomfort on a daily basis and higher rates of daily smoking as well as

unemployment. Differences in risk of preterm birth between the case and control groups was not

independently significant, with the inclusion of potential mediator analyses there was a

significant relationship. This conclusion highlights the importance of mediator analyses. Though

traumatic childhood experiences may not directly cause elevated risk for preterm birth by

independently, they may lead to risky behaviors that mediate the relationship and can be placed

on the biological pathway between early abuse and preterm birth in adulthood.

In a prospective case control study of the effect of stressors at different phases in the life course on the risk of preterm birth women experiencing any type of child abuse had increased odds of preterm birth by 50% while women who experienced CSA and sexual abuse in adulthood had 60% increased odds of late preterm birth defined as 35-36 weeks gestation (Margerison-Zilk et al., 2016). The study also independently analyzed the impact of child abuse on white and African American women as separate groups. White women with histories of child abuse had increased odds of preterm birth while African American women did not. Though this study's conclusions are that the abuse in childhood impacts preterm birth rates of the white women in the sample than the African American women, but it may be difficult to isolate stressor effects that white women may experience as compared to African American women (like segregation, racism, discrimination).

ACEs

Studies included in this systematic review that took a more expansive view of early abuse utilized ACEs criteria, early life stressors, or exposure to the foster care system or childhood adoption as their exposure criteria. Of the seven studies that examined these exposure measures, five found an association or effect of early childhood abuse, trauma, or neglect on the risk of preterm birth. Studies hypothesized smoking, maternal prenatal alcohol use, and other risky behaviors as mediators between ACEs and preterm birth. One study examined the differential effects of ACEs on different types and timing of preterm birth (Cammack et al., 2019). One study used placement in the foster care system or childhood adoption as a proxy for instability, abuse, and/or neglect in childhood (Bublitz et al., 2014). In one case control study of 332 women, exposure to ACEs presented a dose response

relationship with elevated risk for preterm birth (Christiaens et al. 2015). Exposure to two ACEs was found to have a two fold increase in preterm birth and for every additional ACE exposure, when using a cumulative score, the risk for preterm birth increased 18%. When combining an individual's ACEs score with instances of abuse in adulthood, every additional ACE increased one's risk for preterm birth by 34%. This study found that a woman's ACE score was significantly associated with spontaneous preterm birth. Adulthood abuse was also found to be significantly associated with spontaneous preterm birth.

In a retrospective nurses cohort study of 51434 women a significant association was found between forced sexual activity in childhood and preterm birth (Selk et al., 2014). Both alcohol and smoking mediated the relationship between them. Though there was no significant association between the other exposure outcomes examined in the study, like physical abuse and harsh parenting, and preterm birth, important characteristics of women with a history of ACEs were identified. Women with a history of ACEs in the sample were more likely to smoke during pregnancy, earn less income, smoke or drink during pregnancy, and of the 40% of women who reported physical abuse, 40% of them also reported sexual abuse. This study further supports research that shows a strong association between sexual abuse in childhood and preterm birth. In a prospective case control study of 89 African American women, after controlling for stress in adulthood, childhood stress related to interpersonal loss and physical danger was associated with preterm birth in adulthood. Maternal cortisol mediated the relationship (Gillespie et al., 2017). But after controlling for sleep quality and hours awake, cortisol was not longer a mediator in the relationship. This study examined the specific effects of different types of childhood stress, abuse, and instability. Their outcome measures went beyond those of the ACEs questionnaire. Outcome measures for this study included interpersonal loss,

physical danger, humiliation, entrapment, and role disruption through a Stress and Adversity Inventory (STRAIN) Interview. This study found that specific types of stress in childhood may differentially impact elevated risk for preterm birth. A major strength of this study is that stress in adulthood was controlled for, which is unique to all other studies included in this systematic review.

In the only cross sectional study included in this systematic review, the association between maternal exposure to multiple forms of child abuse and preterm as well as very preterm birth was examined in a sample of 4181 women (Cammack et al., 2019). Only sexual abuse was associated with increased odds of very preterm birth of 94%. For the other types of exposures the findings were mostly null. Though important limitations of the study are that the prevalence of vPTB in the sample was very small and or due to random error since the study investigated different types of exposures as well as timings. This study does align with research that has found sexual abuse to have a strong association with preterm birth as well as studies that look at a wide range of abuse categories beyond sexual abuse that have found a stronger association between childhood sexual abuse and preterm birth. The age of the sample was also skewed towards younger people which may contribute to the lack of association in terms of other types of abuse because the disparities between African American and White preterm birth are largely driven by older women.

In a prospective cohort study of 502 women placement in the foster care system or childhood adoption exposure was significantly associated with elevated risk of preterm birth (Bublitz et al., 2014). Women with a history of the exposure had four times the odds of giving birth to a preterm baby than women who were not exposed. This association remained significant even after controlling for known risk factors such as substance use during pregnancy

and psychosocial health. The foster care system or experience of being adopted was used as a proxy for childhood stress, instability, maltreatment, and neglect. This is the only study in the literature that examines the potential association between this exposure and preterm birth. This study also included the mental health status of mothers as an exposure independent of home placement history to determine its impact. Contrary to other studies, this study did not find an association between maternal depression or anxiety and preterm birth. Foster care or adoption placement in childhood is an important factor to include in research about risk for preterm birth. In a prospective cohort study of 2303 women, each additional ACE score decreased the gestational age of the sample's infants by .063 (Smith et al., 2016). Smoking was the strongest mediator of the effect of ACEs on gestational age. Other mediators tested in the study were illicit substance and alcohol use during pregnancy, serotonin reuptake inhibitor during pregnancy. Adverse childhood experiences were associated with some mediators like psychiatric disorders including panic disorder, generalized depressive disorder, and posttraumatic stress disorder, smoking, and fewer years of education.

One study did not find a significant association between ACEs and preterm birth (Jacobs 1998). In a retrospective cohort study with a sample size of 28, no significant association was found between childhood sexual abuse and preterm birth (Jacobs 1998). One limitation of this study that may have affected the conclusion could be the small size.

Mediators

Some studies incorporate mediators into their multivariate analysis models to give more specific conclusions on the association between ACEs and preterm birth. Mediators help to explain the relationship between an exposure and an outcome. They can also illustrate the

pathway leading from maternal ACEs to preterm birth. The inclusion of potential mediators in analytical models is useful in determining how maternal ACEs impact the life course and may lead to poor health outcomes later in life. Important factors analyzed as potential mediators in the studies included in this review include cortisol, alcohol use, smoking, and psychiatric disorders.

Cortisol

Though all studies included in this review discuss the important role that cortisol plays in the relationship between ACEs and preterm birth, only two studies included in the review examined two types of maternal cortisol levels as a potential mediator (Gillespie et al., 2017; Noll et a., 2007). In one prospective observational study, there was a significant indirect effect of role disruption and physical danger related childhood abuse on birth timing through the maternal plasma cortisol mediated pathway however the cumulative effect of childhood stress on birth timing did not reach significance (Gillespie et al., 2017). Without consideration for maternal cortisol levels, there was no significant effect of role disruption or physical danger on birth timing which highlights to important role that cortisol may play in the relationship between childhood stress or maltreatment and preterm birth.

In the second study, salivary cortisol levels were measured at four different times to control for potential variation (Noll et al., 2007). Salivary cortisol was not a mediator or moderator in any association between childhood sexual abuse and preterm birth in this study but higher rates of maternal salivary cortisol was a significant predictor of preterm birth in the non abused comparison group. This may suggest that the pathways to preterm birth may be different for abused versus non abused women. Though plasma and salivary cortisol did not mediate the association between ACEs and preterm birth for abused women, in both studies

there was an association that may have been impacted by other environmental and behavioral factors like smoking and maternal prenatal alcohol use.

Risky Health Behaviors

In one of the studies that examined maternal cortisol levels as a potential mediator, the maternal use of alcohol during pregnancy was also independently analyzed as a mediator (Noll et al., 2007). Prenatal alcohol use mediated the relationship between childhood sexual abuse and preterm birth in the study. Another study used a multiple mediation model which allows for a causal relationship to be mediated by more than one factor. They measured the role that illicit substance use during pregnancy, which included alcohol use, played in the risk of preterm birth (Smith et al., 2016). Substance use was most strongly associated with shorter gestations. Another study examining the role of alcohol use in the association did not find that it mediated the relationship (Selk et al., 2015). Though only three articles examined alcohol in their multivariate analysis, three additional articles found that alcohol use was much more prevalent among abused women than non abused women . This supports the large body of literature explaining elevated risk for victims of childhood abuse for heavy use of alcohol (Appleyard et al., 2011).

Though all studies in the review acknowledged the role of smoking as a major risk factor of preterm birth and collected data on smoking status of study participants, only one study examined maternal smoking status as a potential mediator in the association between ACEs and preterm birth (Smith et al., 2016). Most other studies included smoking as a covariate or suggested that neurological changes that result from early abuse can lead to an elevated risk in unhealthy behaviors such as substance use and smoking. In comparison to the other factors examined as potential mediators such as illicit drug us, psychiatric disorders during pregnancy,

serotonin reuptake inhibitor (SRI), and social support during pregnancy- smoking status had the strongest mediator relationship to the exposure and outcome. Of the .041 week decrease in gestational age for every ACE experienced, smoking accounted for .02 weeks of the total decrease.

Mental Health

One study included in the review examined the role of psychiatric disorders as a mediator in the relationship between ACEs and preterm birth (Smith et al., 2016). In this prospective cohort study psychiatrics disorders both as a group and individually were associated with shorter gestations. While serotonin reuptake inhibitor usage, smoking, education status, and marital status were also mediators identified, psychiatric disorders had the strongest mediating relationship. Psychiatric disorders reduced gestational age .1 weeks. These findings raise the importance of thinking of exposures that may be considered exposures for preterm birth or outcomes of ACEs as potential factors that mediate the relationship between an early exposure such as ACEs and a later life health outcomes like preterm birth.

Methodological Implications

The measure of the outcome preterm birth in the studies varied across the review. Traditionally, studies have premature birth as giving birth prior to 37 weeks gestation (Goldenberg et al., 2008). One study in the review defined spontaneous premature birth as spontaneous preterm labor (i.e. intact membranes, regular contractions, and cervical changes in the absence of labor induction) or preterm premature rupture of membranes and medically indicated as induction of labor before the onset of labor (Margerison-Zilko et al., 2017). Expanding the measure of preterm birth as an outcome to include premature rupture of

membranes as well as medically indicated labor will enable researcher to identify mothers who are experiencing the same effects of ACEs. The measure exposure also varied by study. Creating a standard for a holistic view of trauma to capture the experiences of victims of abuse in childhood would create a consistent method for measure exposure. This could improve the ability of researchers to compare results across studies to examine an association. Additionally, expanding our thinking of different experiences or factors as being proxies for traumatic experiences. The foster care and adoption systems could serve as a potential opportunity for extracting already collected data about children who have experiences in unstable and sometimes traumatic households.

Screening and Intervention for Preterm Birth

Screening and interventions are the two main ways to directly reduce the risk of preterm birth on a population level. Currently only IPV and maternal depression are screened as major risk factors during prenatal care (Committee on Obstetric Practice, 2015). In a recent review of over 2000 interventions, only two interventions targeted at women with high risk for preterm birth: smoking cessation and progesterone therapy were found to be effective (Barros et al., 2010). Though cervical ultrasounds and progesterone treatments for high risk women are used to screen for and prevent preterm birth, the preterm birth rate remains high and these methods must be reimagined and expanded.

Recommendations

Expanded Screening Requirements throughout Life Course

I.   Expanded screening requirements for care throughout the Life Course

Though results vary, eight of the ten studies included in this review support my

hypothesis that a maternal history of ACEs elevates one's risk for preterm birth. This hypothesis

supports incorporating ACEs as an important risk factor for pregnant women. The addition of

this risk factor should be addressed both in prenatal care and during childhood in primary care

as a preventative measure to address the exposure when it's most detrimental to the

development of an individual.

A. Screen for Maternal Adverse Childhood Experiences during Prenatal Care

In addition to IPV and maternal depression screening during prenatal care, women

should also be screened for ACEs. The screening of ACEs could help to identify pregnant

women who could benefit from additional mental health care such as therapy. It is important to

recognize the potential upregulation of stress hormones that can occur as a result of a history of

ACEs which has direct implications for elevated risk for preterm birth.

B. Screen for Adverse Childhood Experiences at Primary Care visits in Childhood

Primary prevention of ACEs much in advance of pregnancy is ideal not only for reducing

the risk of preterm birth but also to improve health outcomes overall considering the long list of

adverse health outcomes that are associated with early childhood trauma. The identification of

ACEs by a pediatrician during childhood could help connect the family to resources such as

counseling, a home visiting program, or parental education. This could also include treatment to

mitigate the effects of violence or trauma exposure in childhood to prevent further exposure and

adverse health outcomes.

Modfiy Best Practices to focus on Social and Mental Wellness

A. Incorporate Parenting Classes as part of Prenatal Care

There is evidence to support the important role that parenting practices have in shaping

the physical, social, and emotional wellness of children. Evidence based interventions that

support parents in creating a safe and healthy environment for their children have shown that

parent trainings can improve the wellbeing of young children (Child Welfare Information Gateway, 2019). The World Health Organization currently defines health as "a state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity" (World Health Organization, 2019). Prenatal care currently focuses on the physical wellness of the mother and baby, but mental health and social wellbeing directly affect one's state of physiological health (Slade, 2010). If wellbeing is the ultimate goal in any health related activity then researchers and clinicians must not only focus on the physical but also the mental and social. Promoting healthier parenting strategies could prevent ACEs.

B. Incorporate Mental Health Care as part of Prenatal Care

In order to mitigate the upregulating effect that a history of ACEs can have on the body's stress response system and the adverse health outcomes that can then proceed, expecting mothers should be provided with adequate mental health support as part of their prenatal care. There are many different ways to implement mental health care. One example could be providing mental health counseling to pregnant women or to implement prenatal care in a group setting such as in the Centering Pregnancy model. The Centering Pregnancy model has been found to reduce preterm birth racial disparities among otherwise low risk women by conducting group prenatal care. Increased confidence to seek medical care early one, improved relationships between the patient and provider, and the social support fostered through relationship formed among the women that may help them combat stress and develop coping strategies have been identified as potential mechanisms through which the program improves birth outcomes (Picklesimer et al., 2012).

Limitations

This review is not without its limitations. The quality of the studies directly impacts the

overall accuracy of the review. One important limitation is the variability in exposure measures and lack of "gold standard" in the field for quantifying trauma that occurs in childhood. Studies utilized different interview protocol and surveys to measure exposure to ACEs. One study did not use any survey to measure exposure to ACEs but rather used exposure to the foster care system or childhood adoption as a proxy for experience of ACEs (Bublitz et al., 2014). Outcome measures also differed by study. Some studies analyzed gestational age as a continuous variable and were able to more precisely analyze the impact of ACEs on gestational age while others used common categories of very preterm birth and preterm birth.

Conclusion

Eight of the ten studies included in this systematic review of the association between Adverse Childhood Experiences and Preterm Birth found some significant assocations between the exposure and outcome. Across all studies that examined the independent associations of multiple types of abuse or only sexual abuse, the strongest relationship was found between childhood sexual abuse and preterm birth (Leeners et al., 2010; Margerison-Zilk et al., 2016; Noll et al., 2007; Cammack et al., 2019). The results of each study should be analyzed within the context of the variations in exposure and outcomes methodology. Differences in how traumatic childhood experiences or ACEs and preterm birth are measured impacts the comparability of the studies. For this reason, a narrative review such as the one included in this thesis is useful to create an overview of the research to date rather than strictly comparing and contrasting quantitative results of the studies.

This review presents strong evidence that there is an association between ACEs and preterm birth, though results vary across different categories, timings, and combinations of abuse. There is a clear gap in the literature concerning this research question and the high

prevalence and negative impact of preterm birth on population health both in the United States and around the world. Only ten studies examine the association. Beyond this research gap, improvements in the methodology of the studies of future research could help to more clearly determine the strength of the association. Examining gestational age as a continuous variable could help to more precisely examine the impact of ACEs and the creation of a type of tool that is considered the "gold standard" for capturing a history of ACEs and other examples of traumatic childhood experiences could create more consistent measures to improve comparability of study results.

Several improvements in clinical practices could improve the risk that ACEs place on population health with regard to preterm birth. There should be expanded screening practices for ACEs across the Life Course including in childhood as well as in prenatal care. There should also be improved best practices for prenatal care related to wellbeing and mental health. Moving from focusing on the physiological health of a child and a mother to while wellbeing which includes mental health could mitigate some of the effects of early experiences of trauma and stress to combat maladaptive changes in the stress response system that lead to many adverse health outcomes such as preterm birth.

Bibliography

Anda, R. F., Brown, D. W., Felitti, V. J., Bremner, J. D., Dube, S. R., & Giles, W. H. (2007).

Adverse childhood experiences and prescribed psychotropic medications in adults.

American journal of preventive medicine, 32(5), 389-94.

Behrman, R. E., Butler, A. S., & Outcomes, I. of M. (US) C. on U. P. B. and A. H. (2007).

Measurement of Fetal and Infant Maturity. Retrieved from

https://www.ncbi.nlm.nih.gov/books/NBK11382/

BUBLITZ, M. H., RODRIGUEZ, D., GOBIN, A. P., WALDEMORE, M., MAGEE, S., &

STROUD, L. R. (2014). Maternal history of adoption or foster care placement in

childhood: A risk factor for preterm birth. American Journal of Obstetrics and

Gynecology, 211(4), 397.e1-397.e6. https://doi.org/10.1016/j.ajog.2014.04.001

Burris, H. H., Baccarelli, A. A., Wright, R. O., & Wright, R. J. (2015). Epigenetics: linking

social and environmental exposures to preterm birth. Pediatric research, 79(1-2),

136-40.

Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F.

(2004). Adverse childhood experiences and the risk of depressive disorders in

adulthood. Journal of Affective Disorders, 82(2), 217–225.

https://doi.org/10.1016/j.jad.2003.12.013

Centers for Disease Control and Prevention . (2018, February 5). Premature Birth.

Christiaens, I., Hegadoren, K., & Olson, D. M. (2015). Adverse childhood experiences are associated with spontaneous preterm birth: a case-control study. BMC Medicine, 13, 124. https://doi.org/10.1186/s12916-015-0353-0

Engelhardt, K. A., Hisle-Gorman, E., Gorman, G. H., & Dobson, N. R. (2018). Lower Preterm Birth Rates but Persistent Racial Disparities in an Open-Access Health Care System. Military Medicine, 183(9–10), e570–e575. https://doi.org/10.1093/milmed/usy012

Frey, H. A., & Klebanoff, M. A. (2016). The epidemiology, etiology, and costs of preterm birth. Seminars in Fetal and Neonatal Medicine, 21(4), 68–73.

Gillespie, S. L., Christian, L. M., Alston, A. D., & Salsberry, P. J. (2017). Childhood stress and birth timing among African American women: Cortisol as biological mediator. Psychoneuroendocrinology, 84, 32–41. https://doi.org/10.1016/j.psyneuen.2017.06.009

Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. The Lancet, 371(9606), 75–84. https://doi.org/10.1016/S0140-6736(08)60074-4

Halfon, N., Larson, K., Lu, M., Tullis, E., & Russ, S. (2014). Lifecourse Health Development: Past, Present and Future. Maternal and Child Health Journal, 18(2), 344–365. https://doi.org/10.1007/s10995-013-1346-2

Herzog, J. I., & Schmahl, C. (2018). Adverse Childhood Experiences and the Consequences on Neurobiological, Psychosocial, and Somatic Conditions Across the Lifespan. Frontiers in psychiatry, 9, 420. doi:10.3389/fpsyt.2018.00420

Jimenez, M. E., Wade, R., Lin, Y., Morrow, L. M., & Reichman, N. E. (2016). Adverse Experiences in Early Childhood and Kindergarten Outcomes. Pediatrics, 137(2), e20151839.

Leeners, B., Stiller, R., Block, E., Görres, G., & Rath, W. (2010). Pregnancy complications in women with childhood sexual abuse experiences. Journal of Psychosomatic Research, 69(5), 503–510. https://doi.org/10.1016/j.jpsychores.2010.04.017

Lilliecreutz, C., Larén, J., Sydsjö, G., & Josefsson, A. (2016). Effect of maternal stress during pregnancy on the risk for preterm birth. BMC pregnancy and childbirth, 16, 5. doi:10.1186/s12884-015-0775-x

Maniam, J., Antoniadis, C., & Morris, M. J. (2014). Early-Life Stress, HPA Axis Adaptation, and Mechanisms Contributing to Later Health Outcomes. Frontiers in endocrinology, 5,

73. doi:10.3389/fendo.2014.00073

Margerison-Zilko, C. E., Strutz, K. L., Li, Y., & Holzman, C. (2017). Stressors Across the

Life-Course and Preterm Delivery: Evidence From a Pregnancy Cohort. Maternal and

child health journal, 21(3), 648–658. doi:10.1007/s10995-016-2151-5

Merrick, M. T., Ports, K. A., Ford, D. C., Afifi, T. O., Gershoff, E. T., & Grogan-Kaylor, A.

(2017). Unpacking the impact of adverse childhood experiences on adult mental

health. Child Abuse & Neglect, 69, 10–19. https://doi.org/10.1016/j.chiabu.2017.03.016

Nesari, M., Olson, J. K., Vandermeer, B., Slater, L., & Olson, D. M. (2018). Does a maternal

history of abuse before pregnancy affect pregnancy outcomes? A systematic review with meta-

analysis. BMC pregnancy and childbirth, 18(1), 404.

doi:10.1186/s12884-018-2030-8

Nurius, P. S., Logan-Greene, P., & Green, S. (2012). ACEs within a Social Disadvantage

Framework: Distinguishing Unique, Cumulative, and Moderated Contributions to Adult

Mental Health. Journal of Prevention & Intervention in the Community, 40(4), 278–290.

https://doi.org/10.1080/10852352.2012.707443

Ottawa Hospital Research Institute. (n.d.). Retrieved April 29, 2019, from

http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Poulton, R., Caspi, A., Milne, B. J., Thomson, W. M., Taylor, A., Sears, M. R., & Moffitt, T. E. (2002). Association between children's experience of socioeconomic disadvantage and adult health: a life-course study. Lancet (London, England), 360(9346), 1640-5.

PRISMA. (n.d.). Retrieved April 29, 2019, from http://www.prisma-statement.org/

Selk, S. C., Rich-Edwards, J. W., Koenen, K., & Kubzansky, L. D. (2016). An observational study of type, timing, and severity of childhood maltreatment and preterm birth. J Epidemiol Community Health, 70(6), 589–595. https://doi.org/10.1136/jech-2015-206304

Shonkoff, J. P., Garner, A. S., The Committee on Psychosocial Aspects of Child and Family Health, C. on E. C., Siegel, B. S., Dobbins, M. I., Earls, M. F., ... Wood, D. L. (2012).

The Lifelong Effects of Early Childhood Adversity and Toxic Stress. Pediatrics, 129(1), e232–e246. https://doi.org/10.1542/peds.2011-2663

Talbot, N. L., Chapman, B., Conwell, Y., McCollumn, K., Franus, N., Cotescu, S., & Duberstein, P. R. (2009). Childhood sexual abuse is associated with physical illness burden and functioning in psychiatric patients 50 years of age and older. Psychosomatic medicine, 71(4), 417-22.

Tanne, J. H. (2017). Preterm and low weight births rise again in the US. BMJ, 358, j3311.

https://doi.org/10.1136/bmj.j3311

What are the risk factors for preterm labor and birth? (n.d.). Retrieved April 29, 2019, from

http://www.nichd.nih.gov/ website:

http://www.nichd.nih.gov/health/topics/preterm/conditioninfo/who_risk

World Health Organization. (2018, February 19). Preterm Birth.

Wosu, A. C., Gelaye, B., & Williams, M. A. (2015). Maternal history of childhood sexual

abuse and preterm birth: an epidemiologic review. BMC pregnancy and childbirth, 15,

174. doi:10.1186/s12884-015-0606-0