COVER LETTER

I worked under the guidance of Dr. Emily Stinnett Miller to write “Perinatal Transmission of Trauma: The Association Between Adverse Childhood Experiences and Adverse Pregnancy Outcomes”. Adverse childhood effects (ACEs) have been implicated in the causal pathway of various morbidities, ie. cardiovascular disease. Vulnerable populations, such as racial minorities, already have a greater health burden than their less vulnerable counterparts and suffer significantly from ACEs. Preterm birth is poorly understood though it is known that gestational environment impacts the development of the fetus. Our retrospective study looks at ACEs in delivering mothers and their birth outcomes. Based on current knowledge of ACEs, gestational environment, and disparities in healthcare, we hypothesize that negative birth outcomes can be predicted from maternal ACE score. This research will expand our knowledge of health effects caused by ACEs as well as the importance of gestational environment. We expect stakeholders to include maternal and child health experts and clinicians, housing experts, mental health specialists, and others working with ACEs.

Through my APEx I worked at ICAAP on a housing initiative for children under 6 years old, where I learned that data on this demographic is very inadequate. I have always had a passion for this group, and the Maternal and Child Health class helped me direct my passion towards the life course theory of health. Because the life course theory implicates youth trauma/adverse effects in lifetime health, it became important for me to work towards equitable data collection and interventions to promote the health of children. Ultimately, I hope to promote the health of vulnerable populations as a physician. Preliminary studies on ACEs and their direct causal effects will inform future

integration of ACEs in the healthcare system.

Competency	**Detail How The Competency Was Synthesized In Your Project (may be through project activity, written product, and/or presentation**
Interpret results of data analysis for public health research, policy or practice	We are analyzing data on maternal ACEs and birth outcomes. Causality will not be determined but this will add to existing data on birth outcomes and hopefully help push for more supportive services for children and women.
Communicate audience-appropriate public health content, both in writing and through oral presentation	Abstract presented at Society for Maternal-Fetal Medicine Jan 21, 2021
Evaluate current knowledge of causes of disease to guide epidemiologic practice.	ACEs and life-course theory are topical areas of research on intergenerational health. I did a literature review of reproductive health and ACEs, finding few studies with conflicting results on preterm birth, gestational diabetes mellitus, and other APOs. Our study adds to these findings.
Critique the validity of epidemiologic data, findings, and publications by applying knowledge of epidemiologic principles and methods	Race is now understood as a proxy for SES and ACEs and we must work towards ending racial stigma. Using race as a variable is now known to be incomplete and studies that use race as an explanation of findings are not fully describing their phenomena. While we capture this demographic information in our paper, we do not use race as an explanation.
Apply demographic, epidemiologic and anthropologic methods to assess health disparities at local and global levels.	ACEs and SES are inter-related. Our paper adds to existing literature on effects of ACEs on reproductive health. While ACEs may not be completely generalizable globally, we are starting to understand that certain ACEs have specific health effects. Where ACEs do exist globally (ie food and home insecurity), we may be able to focus on their specific health effects.

Perinatal Transmission of Trauma: The Association Between Adverse Childhood Experiences and Adverse Pregnancy Outcomes

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Abstract
Introduction: Adverse childhood experiences (ACEs) have been consistently associated with chronic health conditions later in life. The relationship between ACEs in girls and adverse pregnancy outcomes is less well understood. We hypothesize that individuals with more ACEs will have a higher frequency of preterm birth (PTB). Our objective was to examine the association between ACEs and PTB. Methods: This retrospective cohort study included individuals who enrolled in the Collaborative Care Model for Perinatal Depression Support Services (COMPASS) between 1/2017 and 9/2020 and who delivered ≥ 24 weeks gestation. Upon enrollment in COMPASS, individuals complete self-reported psychosocial assessments including the ACE screen. Sociodemographic characteristics and perinatal outcomes were abstracted from the electronic health record. The number of ACEs was evaluated both dichotomized (high ACE score defined as ACE > 3) and continuously in bivariate and multivariate analyses. Results: During the study period, 1074 individuals met inclusion criteria; 242 (23%) reported a high ACE score (Table 1). Individuals with a high ACE score had a 2.3-fold increased odds of PTB (95% CI: 1.6-3.3). For each additional point on the ACE screen, the odds of preterm birth increased by 13% (95% CI: 4-23%). After controlling for medical co-morbidities and other social determinants of health, the association between a high ACE score and PTB persisted (aOR 2.0, 95% CI 1.3-3.1; Table 2). Conclusions: ACEs are associated with an increased risk of PTB. This observed relationship may be mediated by the dysregulated hypothalamic-pituitary-adrenal (HPA) axis and immune activity that have been observed in those with early life adversity. Future research should investigate interventions to mitigate these associations to reduce inter-generational cycles of disadvantage.

Introduction

Adverse childhood experiences (ACEs), traumatic events that occur in childhood, have been consistently associated with chronic health conditions later in life with a dose-response relationship.[1,2] Unfortunately, ACEs are common, with 62% of Americans reporting at least one, 25% at least three, and 16% at least four ACEs.[3,4] Moreover, ACEs are disproportionally prevalent among those with facing social adversity, including structural racism and poverty.[5] As ACEs are determinants of life opportunities such as education and employment, primary prevention of ACEs and mitigation of their effects are essential components of an equity-focused public health strategy.

Still not fully understood is the relationship between maternal ACEs on adverse pregnancy outcomes (APOs) such as preterm birth, small for gestational age births, and stillbirth. One prior study attempted to evaluate the relationship between ACEs and preterm birth, however its small sample size precluded examination of the complex interplay between social determinants of health.[6] Another study evaluated the association between ACEs and stillbirth, however its sample was exclusively adolescents and thus may not be generalizable.[7] A recently published study found an association between ACE score and miscarriage among primarily low-income non-white women.[8] A handful of studies examined the presence of ACEs and gestational diabetes mellitus, each with differing results potentially explained by various confounders.[9,10,11] These studies explore various APOs among vulnerable populations of women and increase awareness of the life-course effects of ACEs on reproductive health (Table 1).

Biologic plausibility exists between ACEs and APOs. ACEs are known to affect the development of the neuroendocrine and immune systems with long-term impact on these regulatory processes; these disruptions, in turn, have been associated with APOs.[12,13] In addition to these biologic pathways, social determinants, including education and income, likely mediate these relationships.[14] Regardless of mechanism, evaluating and quantifying the association between maternal ACEs and APOs represent important steps toward optimizing obstetric care to mitigate the inter-generational transmission of trauma. Our objective was to examine the association between ACEs and APOs, including gestational diabetes, hypertensive disorders of pregnancy, preterm birth, and small for gestational age births. We hypothesized that having more ACEs is associated with an increased prevalence of APOs.

Methods

This retrospective cohort study included all pregnant and postpartum individuals who enrolled in the Collaborative Care Model for Perinatal Depression Support Services (COMPASS) between its inception on January 23, 2017 and March 1, 2021, and who delivered after 20 weeks gestational age and prior to March 1, 2021. COMPASS is a perinatal mental health system embedded within all five of the Northwestern Medicine obstetrics clinics. Obstetric patients are eligible for enrollment if they have either a history of a mental health condition or have current mental health symptoms. COMPASS provides mental health services guided by the collaborative care model principles[15] during pregnancy and up to one year postpartum.

Upon enrollment in COMPASS, individuals were asked to complete self-reported psychosocial assessments including the ACE screen (Appendix 1). Those who never completed their ACE screen were excluded from these analyses. Sociodemographic characteristics including maternal age, insurance, self-reported race and ethnicity, marital status, medical history including tobacco use, medical conditions, and body mass index at delivery, obstetric history including parity, and perinatal outcomes including gestational diabetes, hypertensive disorders of pregnancy, preterm birth, and small for gestational age births were abstracted from the electronic health record (EHR). Gestational diabetes was diagnosed by either a glucose challenge test of > 200 or a glucose challenge test.

Gestational age at delivery was calculated from the estimated due date, derived using ACOG standards.[16] Infants were classified as small for gestational age if their birth weight was below the 10th percentile of normative birthweights for singletons.[17]

The number of ACEs was evaluated as a categorical variable with a high ACE score defined as greater than three by Felitti in his seminal ACEs study.[1] Secondary analyses evaluated ACE as a continuous variable.

Bivariate analyses were conducted using Student's t-tests or Mann Whitney U tests for continuous variables or chi squared or Fisher's exact tests for categorical variables, as appropriate. Given the complex inter-relatedness of social determinants of health, a directed acyclic graph (Figure 1) was generated to represent potential causal networks and determine covariate adjustment. While race and ethnicity have been associated with both ACEs and adverse pregnancy outcomes,[8,18] their role as a surrogate for structural racism and discrimination is antecedent to ACEs and thus does not fit as a confounder.

For APOs with significant associations with ACE score in bivariate analyses, mediation analyses were performed to inform the underlying pathways of the association.[19,20] The percentage of the total effect that was mediated was calculated by dividing the beta coefficient of the indirect pathway by the summation of the beta coefficients of the indirect and direct pathways. As indirect effects are often non-parametric, standard errors and confidence intervals for each mediator were estimated via bootstrapping with 5000 replications and bias correction. STATA v15.0 was used for analyses. This study was approved by Northwestern's IRB prior to its initiation.

Results

During the study period, 2016 individuals were referred to COMPASS for mental health care and met eligibility criteria; 742 (37%) were excluded as they did not complete their ACE screen. ACE scores for the remaining participants are shown in Figure 2. Of the 1274 pregnant or postpartum individuals included, 290 (23%) reported a high ACE score of greater than 3.

Sociodemographic and clinical characteristics of the sample, stratified by high ACE score, are shown in Table 2. Patients with high ACE scores were more likely to be

younger at time of delivery, more likely to be on public insurance, use tobacco, have a chronic medical condition, and have a higher body mass index (BMI) or be obese at delivery. Patients with high ACE scores were less likely to be married. Self-identified race and ethnicity also differed by ACE exposure, with people identifying as White or Asian less likely to have a high ACE score whereas those who identified as Black or Latinx were more likely to have a high ACE score.

Associations between high ACE score and adverse pregnancy outcomes are described in Table 3. Individuals with high ACE score had a 1.58-fold increased odds of hypertensive disorders of pregnancy and a 2.16-fold increase odds of preterm birth. No differences were observed in gestational diabetes, preterm birth before 34 weeks, or small for gestational age births, though it should be noted that the point estimates for each of these outcomes was higher in those with high ACE scores. When analyzed as a continuous variable, each additional point on the ACE screen was associated with a 10% increased odds of hypertensive disorders of pregnancy (OR 1.10, 95% CI 1.03-1.18) and a 15% increase odds of preterm birth (OR 1.15, 95% CI 1.08-1.23).

Mediation analyses were conducted for the outcomes of hypertensive disorders of pregnancy and preterm birth. For hypertensive disorders of pregnancy, tobacco use (5.3%), chronic medical problems (11.5%), and obesity (17.4%) each partially mediated the observed association with high ACE scores. For preterm birth, having public insurance (17.4%) and chronic medical problems (6.7%) each partially mediated the observed association with high ACE scores. There was no other statistically significant mediation present.

Discussion

In this study, we found an increase in ACE score to be correlated with an increase in hypertensive disorders of pregnancy and PTB. Our findings suggest a dose-response relationship between ACEs and each of these adverse pregnancy outcomes. Other studies have shown a dose-response relationship between ACEs and various health conditions.[1] Results from our study are consistent with results of a 2019 study of low-income women receiving federal support in Wisconsin, in which each additional ACE increased the odds of preterm birth by 8%.[21]

In Felitti's seminal study on ACEs, seven categories of negative experiences occurring in childhood were correlated to negative differences in health outcomes later in life.[1] Since then, many studies have expanded the understanding of health outcomes caused by ACEs, finding both a dose-response relationship as well as a difference between categorical high versus low ACE score.[22] Though some studies define high ACE score as greater than 4 ACEs, the majority of studies define high ACE score as greater than 3 ACEs. We followed convention and chose our dichotomized high ACE score as greater than 3 ACEs. Low ACEs score is less than 3.

Recently, the link between ACEs and the next generation has been of concern. It has been shown that maternal ACEs affect the development of children through at least 4 years of age.[23,24,25,26] These studies highlight the myriad ways by which ACEs cause

intergenerational trauma: Parents' Evaluations of Developmental Status (PEDS) concerns, psychological development, and lack of preventive healthcare, among others. Our study narrows the focus from child development to birth outcomes, linking ACEs to PTB.

PTB is known to cause a wide array of health effects ranging in severity. Neurodevelopmental health effects include cerebral palsy and intellectual and developmental delay. Preterm babies are more likely to suffer from asthma, learning disabilities, or even visual impairments. It is important to note that these diseases are not entirely preventable in full-term infants, but they exist in higher frequency among preterm infants. According to the Institute of Medicine, the annual disease burden caused by PTB is in excess of $26 billion in 2005 dollars, at a rate of $51,600 per infant.**Error! Bookmark not defined.**

Survival rates of babies born as early as 22 weeks of gestational age have radically increased thanks to technological advances. Though reducing PTB is still poorly understood, avoiding drug and alcohol consumption during pregnancy can help. Other interventions include adequate prenatal care, and interpregnancy intervals of at least 6 months.[27]

One mechanism by which ACEs affect lifelong health is by raising levels of perceived stress and cortisol.[28] The hypothalamic-pituitary-adrenal (HPA) axis acts with cortisol via a negative feedback loop, in which high levels of cortisol increase pro-inflammatory cytokines and low cortisol levels increase anti-inflammatory cytokines.[29] Chronic stress and high cortisol levels typical of ACEs have been associated with preterm birth.[30] Interestingly, dysregulated HPA axes and immune activity have been observed in those with early life adversity, acting to protect the body against negative health effects. Dysregulation of the HPA axis is due to a reduction of cumulative cortisol levels, possibly via social support, which has been found to reduce inflammation particularly in the third trimester.[31] This may serve to mitigate the negative outcomes that are seen among pregnant women with high ACE scores.

Knowing maternal ACE scores may help to connect the mother to appropriate resources to mitigate health effects for both her and her child, but this score may add shame and stigma to an already stressful time of life. Care must be taken to navigate ACE scores and their implications in clinic.[32]

Limitations

One limitation of this study is that the ACE screen was administered retrospectively, thus may be subject to response bias. Underreporting of negative childhood experiences is more likely than overreporting due to incomplete memories or stigma, therefore affecting our results. Another limitation is that only women with a history of depression were included. Though these women varied by age, race, and medical history, they shared one major characteristic. We feel this does not reduce the power of the study, but suggests a future need for larger scale research.

Future research should investigate interventions that mitigate these associations to reduce inter-generational cycles of disadvantage, such as social support and HPA dysregulation. We chose the conventional risk accumulation approach to ACEs, but it is possible that certain ACEs are likely to cause greater severity; thus, future research might benefit to separate ACEs and study their direct relationship to specific outcomes.[33,34] Future data collection should include ACE score and birth outcomes when available, to aid in the continued study of this topic.

Conclusion

Instead of gaining control of health outcomes during pregnancy, preventing ACEs or mediating ACE health effects earlier in life may serve as preventive measures to positively impact the health of the fetus.

Figure 1: Directed Acyclic Graph for the Association between ACEs and Adverse Pregnancy Outcomes

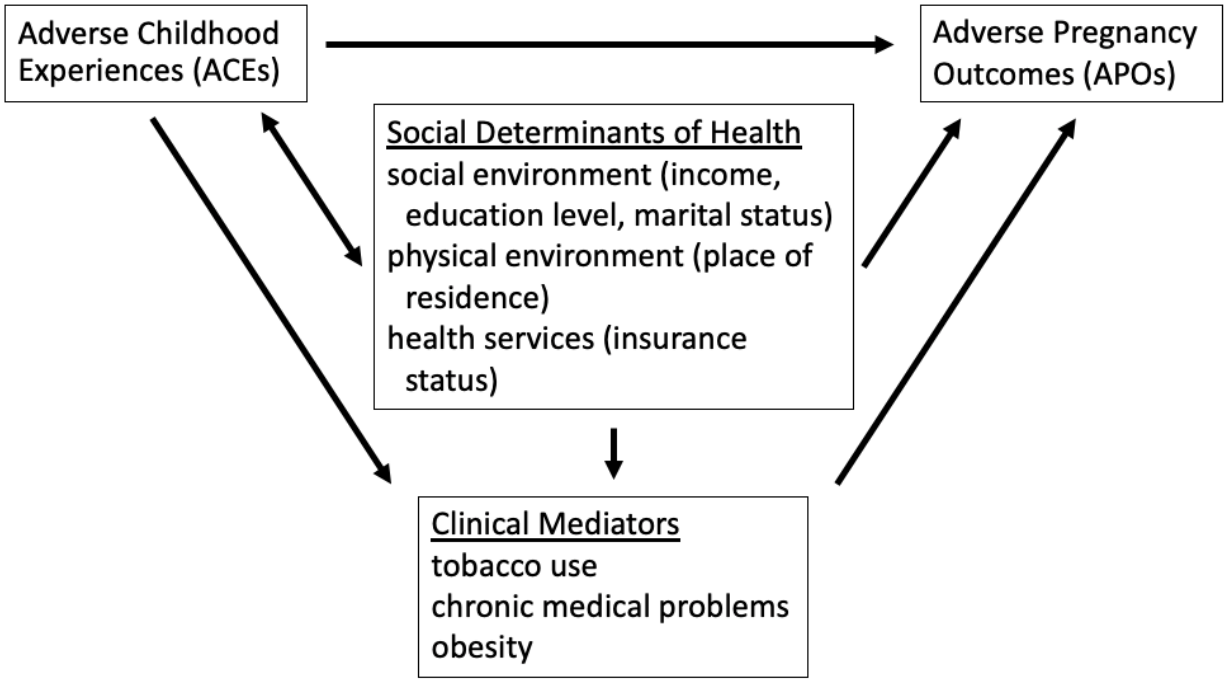

Figure 2: Distribution of ACE Scores

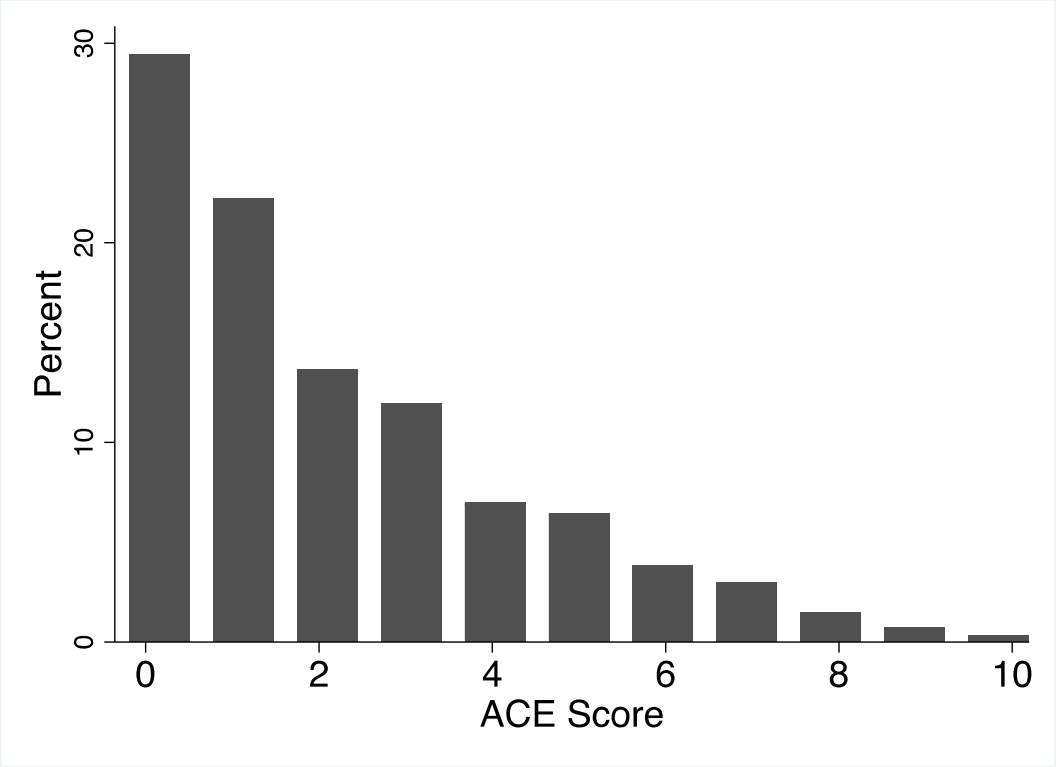

Table 1: Literature Review of Studies on APO and ACEs

Title	Authors	Sample Size	Exposure	Categorization of Exposure	Primary Outcome	Results
The Association Between Adverse Childhood Experiences and Adolescent Pregnancy, Long-Term Psychosocial Consequences, and Fetal Death	Hillis SD, Anda RF, Dube SR, Felitti VJ, Marchbanks PA, Marks JS	9,159	All ACEs	Low ACE: 0-6 High ACE: 7-8	Adolescent pregnancy	High ACE associated with adolescent pregnancy: (OR, 6.0 [CI=4.1, 8.4])
Adverse childhood experiences are associated with spontaneous preterm birth: a case–control study	Christiaens I, Hegadoren K, Olson DM	622	All ACEs	Low ACE: 0-1 High ACE: 2+	Spontaneous preterm birth	High ACE associated with spontaneous preterm birth: (OR, 2.45 [CI=1.37, 4.38])
Adverse Childhood Experiences are Associated with Miscarriage in Adulthood: The GROWH Study	Kerkar S, Shankar A, Boynton-Jarrett R, Harville EW	1,511	All ACEs	Low ACE: 0-3 High ACE: 4+ Childhood: <12 years Adolescence: 12–17 years	Self-reported miscarriage at first pregnancy or at any pregnancy	High ACE associated with miscarriage at first or any pregnancy, in childhood or adolescence. High ACE, child, first: (OR, 1.89 [CI=1.13, 3.16]) High ACE, child, any: (OR, 1.81 [CI=1.23, 2.66]) High ACE, teen, first: (OR, 1.89 [CI=1.16, 3.08]) High ACE, teen, any: (OR, 1.70 [CI=1.16, 2.49])
Adverse childhood experiences and lifetime adverse maternal outcomes (gestational diabetes and hypertensive disorders of pregnancy) in the Hispanic Community Health Study/Study of Latinos	Stanhope KK, Cammack AL, Perreira KM, et al.	2,319	All ACEs	Low ACE: 0-3 High ACE: 4+	Any gestational diabetes mellitus (GDM) or hypertensive disorder of pregnancy (HDP)	High ACE and GDM: (OR, 0.88 [CI=0.57, 1.34]) High ACE and HDP: (OR, 1.03 [CI=0.71, 1.47])
The Role of Childhood Adversity in the Development of Gestational Diabetes	Schoenaker DA, Callaway LK, Mishra, GD	6,317	All ACEs	No ACE: 0 Low ACE: 1-2 Moderate ACE: 3 Severe ACE: 4+	Gestational diabetes (GDM)	ACEs associated with GDM. Low ACE: (RR, 0.98 [CI=0.75, 1.28]) Moderate ACE: (RR, 1.14 [CI=0.73, 1.77]) Severe ACE: (RR, 1.24 [CI=0.68, 2.26])
Abuse in Childhood or Adolescence and Gestational Diabetes: A Retrospective Cohort Study	Mason SM, Tobias DK, Clark CJ, et al.	45,550	Physical abuse sexual abuse*	Physical abuse: none, mild, moderate, severe Sexual abuse: none, touch only, forced sex	Gestational diabetes (GDM)	Physical abuse associated with GDM. Mild: (RR, 1.13 [CI=1.01, 1.27]) Moderate: (RR, 1.16 [CI=1.05, 1.29]) Severe: (RR, 1.50 [CI=1.30, 1.73]) Sexual abuse associated with GDM. Touch only: (RR, 1.11 [CI=1.00, 1.23]) Forced sex: (RR, 1.31 [CI=1.15, 1.49])

*Any instance of physical abuse and any instance of sexual abuse are each considered 1 ACE

Table 2: Sociodemographic and clinical characteristics, stratified by high adverse childhood experiences score

	ACE Score ≤ 3 n=984 (77%)	ACE Score > 3 n=290 (23%)	p value
Maternal age (years)	33 ± 5	32 ± 6	<0.001
Public insurance	138 (14.6%)	106 (37.7%)	<0.001
Race			<0.001
White	555 (58.8%)	112 (39.9%)	
African-American/Black	146 (15.5%)	104 (37.0%)	
Asian	58 (6.1%)	10 (3.6%)	
Other	84 (8.9%)	30 (10.7%)	
Unknown	101 (10.7%)	25 (8.9%)	
Latinx ethnicity	131 (14.8%)	56 (21.3%)	0.013
Married	692 (73.4%)	131 (46.6%)	<0.001
Ever used tobacco	144 (15.4%)	84 (30.2%)	<0.001
Any chronic medical condition	425 (45.4%)	154 (55.4%)	0.003
Pre-existing diabetes	36 (3.7%)	14 (4.8%)	0.37

Chronic hypertension	58 (5.9%)	21 (7.2%)	0.40
BMI at delivery (kg/m^2)	32 ± 7	33 ± 7	0.002
BMI > 30 kg/m^2 at delivery	458 (51.4%)	164 (61.9%)	0.003
Nulliparous	538 (54.7%)	140 (48.3%)	0.055

Data presented as mean ± standard deviation or n (%)

Table 3: Bivariate analyses for each adverse pregnancy outcome

	ACE Score ≤ 3	ACE Score > 3	OR (95% CI)
Gestational diabetes (n=1170)	60 (6.7%)	20 (7.4%)	1.11 (0.66-1.88)
Hypertensive disorder of pregnancy	126 (12.8%)	58 (20.0%)	1.58 (1.08-2.32)
Preterm birth (n=1271)	120 (12.2%)	67 (23.1%)	2.16 (1.54-3.01)
Preterm birth < 34 weeks	57 (5.8%)	24 (8.3%)	1.46 (0.89-2.40)
Small for gestational age (n=1149)	39 (4.4%)	14 (5.3%)	1.20 (0.64-2.25)

Data presented as n (%)
OR = odds ratio

Appendix 1: ACE screen

ACE Questionnaire

While you were growing up, during your first 18 years of life:

1. Did a parent or other adult in the household often ... 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?	◯ Yes ◯ No
2. Did a parent or other adult in the household often ... Push, grab, slap, or throw something at you? (OR) Ever hit you so hard that you had marks or were injured?	◯ Yes ◯ No
3. Did an adult or person at least 5 years older than you ever ... Touch or fondle you or have you touch their body in a sexual way? (OR) Attempt or actually have oral, anal, or vaginal sex with you?	◯ Yes ◯ No
4. Did you often or very often 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?	◯ Yes ◯ No
5. Did you often or very often 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?	◯ Yes ◯ No
6. Were your parents ever separated or divorced?	◯ Yes ◯ No
7. Was your mother or stepmother: Often or very often pushed, grabbed, slapped, or had something thrown at her? (OR) Sometimes or 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?	◯ Yes ◯ No
8. Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?	◯ Yes ◯ No
9. Was a household member depressed or mentally ill, or did a household member attempt suicide?	◯ Yes ◯ No
10. Did a household member go to prison?	◯ Yes ◯ No
Number of YES Answers:	_____

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