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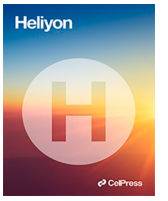

Research article

# Association between F2-isoprostanes and self-reported stressors in pregnant americans of African and European ancestry

Deborah K. Rose [a], Loren Bentley [b], Arnab Maity [c,d], Rachel L. Maguire [b,c], Antonio Planchart [b,c], Ivan Spasojevic [e,f], Andy J. Liu [a,*], John Thorp Jr. [g], Cathrine Hoyo [b,c,**]

[a] Department of Neurology, Duke University School of Medicine, Durham, NC, USA
[b] Department of Biological Sciences, North Carolina State University, Raleigh, NC, USA
[c] Center for Human Health and the Environment, North Carolina State University, Raleigh, NC, USA
[d] Department of Statistics, North Carolina State University, Raleigh, NC, USA
[e] Department of Medicine, Duke University School of Medicine, Durham, NC, USA
[f] Duke Cancer Institute, PK/PD Core Laboratory, Durham, NC, USA
[g] Gillings School of Public Health, University of North Carolina, Chapel Hill, NC, USA

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ABSTRACT

*Background:* Poor birth outcomes such as preterm birth/delivery disproportionately affect African Americans compared to White individuals. Reasons for this disparity are likely multifactorial, and include prenatal psychosocial stressors, and attendant increased lipid peroxidation; however, empirical data linking psychosocial stressors during pregnancy to oxidative status are limited.
*Methods:* We used established scales to measure five psychosocial stressors. Maternal adverse childhood experiences, financial stress, social support, anxiety, and depression were measured among 50 African American and White pregnant women enrolled in the Stress and Health in Pregnancy cohort. Liquid chromatography-tandem mass spectrometry was used to measure biomarkers of oxidative stress (four urinary F2-isoprostane isomers), to estimate oxidative status. Linear regression models were used to evaluate associations between psychosocial stressors, prenatal oxidative status and preterm birth.
*Results:* After adjusting for maternal obesity, gestational diabetes, and cigarette smoking, African American women with higher oxidative status were more likely to report higher maternal adverse childhood experience scores ($\beta = 0.16$, se $= 1.07$, p-value $= 0.024$) and depression scores ($\beta = 0.05$, se $= 0.02$, $p = 0.014$). Higher oxidative status was also associated with lower gestational age at birth ($\beta = -0.13$, se $= 0.06$, $p = 0.04$) in this population. These associations were not apparent in Whites. However, none of the cross-product terms for race/ethnicity and social stressors reached statistical significance ($p > 0.05$).
*Conclusion:* While the small sample size limits inference, our novel data suggest that psychosocial stressors may contribute significantly to oxidative stress during pregnancy, and preterm birth or delivery African Americans. If replicated in larger studies, these findings would support oxidative stress reduction using established dietary or pharmacological approaches present a potential avenue to mitigate adverse effects of psychosocial stressors on birth outcomes.

* Corresponding author. Department of Neurology Department of Pathology Duke University School of Medicine Durham, NC, 27710, USA.
** Corresponding author. Department of Biological Sciences, and, Co-Director, Integrative health Science Facilities Core, Center for Human Health and the Environment, North Carolina State University, Raleigh, NC, 27695, USA.
*E-mail addresses:* andy.liu@duke.edu (A.J. Liu), choyo@ncsu.edu (C. Hoyo).

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## 1. Background

Preterm birth, defined as delivery at less than 37 weeks of gestation, is associated with poor health outcomes in childhood, including neurodevelopmental disorders, respiratory injury, and metabolic disorders [1]. Preterm birth is also an established risk factor for cardiovascular and neurological diseases in adulthood [2,3]. The excess morbidity, mortality, and economic burden associated with preterm births disproportionately affect African Americans, whose prevalence of preterm birth is also higher than other racial and ethnic groups [4,5]. Data from animal models and humans support a role for periconceptional and prenatal stressors in promoting long-lasting changes affecting rapidly differentiating cells, which may elicit adaptive modifications in organs such as the brain [6]. Identifying biomarkers that are hypothesized to link these stressors to preterm birth, such as oxidative stress, is important to guide preventive strategies for a wide range of childhood and adult outcomes.

Established risk factors for disparities in preterm birth and delivery include stress exposures. Indeed, psychosocial stressors such as depression, anxiety, and adverse childhood experiences (ACEs) are linked to preterm birth [7–9] and disproportionately affect minoritized racial and ethnic groups [10]. For example, periconceptional chronic stress (such as racial discrimination and socioeconomic disadvantage) may explain some of the racial disparities seen in preterm birth and delivery [11]. Psychosocial stressors such as depression and perceived stress disproportionately affect African American individuals and are linked to poorer health outcomes in adults [12–14]. Thus, identifying biomarkers of processes that link these prenatal stressors to preterm birth is critical to designing targeted interventions.

While differences in levels of psychosocial stress are known to contribute to disparities in oxidative stress and attendant systemic inflammation [15], which have been hypothesized to contribute to disparities in adverse birth outcomes including preterm birth, empirical data linking prenatal stressors to increased oxidative stress are limited. To fill this gap, we sought to determine whether maternal prenatal stressors increase oxidative stress and if associations were similar in African Americans and Whites. Specifically, we measured lipid peroxidation using four urinary F2-isoprostanes [iPF(2α)-III, 2,3-dinor-iPF(2 α)-III, iPF(2 α)-VI, and 8,12-iso-iPF (2α)-VI)] and their mass spectrometry channels. These urinary F2-isoprostanes are established biomarkers of oxidative stress [16–18]. The psychosocial stressors examined in this study vary by race, according to the literature, as does the outcome of gestational age at birth. If some of these differences are in part due to variability in the oxidative stress response, it thus becomes important to identify the psychosocial stressors that account for these differences by race. Our overarching hypothesis is that differences in lived experiences contribute substantially to race-based differences in documented observed birth outcomes. We sought to determine if these were reasonable biomarkers of oxidative stress linking prenatal psychosocial stress to adverse birth outcomes including gestational age at delivery and lower birth weight of offspring in African Americans.

## 2. Materials and methods

### 2.1. Study participants

Placental and urine specimens were obtained from the demographically diverse Stress and Health In Pregnancy (SHIP) study (2017–2020). Informed consent was obtained from all participants. This cohort of pregnant women is comprised of 48 % African Americans, 13 % non-Hispanic Whites, and 32 % Hispanics, and 6 % other. Accrual procedures for this cohort were previously detailed [19]. Briefly, SHIP is a birth cohort of offspring and their mothers, and comprises a rich specimen repository with carefully annotated clinical and epidemiologic data. The target population was pregnant women attending the WakeMed prenatal clinic in Raleigh, North Carolina, between late 2017 and mid-2020. Eligibility criteria were age 18 years or older, pregnant with gestation age less than 30 weeks, ability to read and write in English or Spanish, intent to maintain residence in the WakeMed catchment area until delivery, and intent to deliver and maintain custody of the offspring. Among these, we excluded women who experienced fetal demise and who planned to donate their cord blood and/or placenta for uses other than the present study, infection with human immunodeficiency virus (HIV), or hepatitis B or C. Of the n = 753 women who met these inclusion and exclusion criteria and were approached, 336 (44.6 %) consented and were enrolled in the study. Among the 336 participants who met these criteria and enrolled in the study, we excluded those who could not be followed, specifically those who 1) declined further participation, 2) experienced fetal demise, or 3) were otherwise withdrawn from the study before delivery (n = 41). We further limited to African American and White individuals with complete data and samples for an effective sample size of n = 130. The present analyses are limited to the first Non-Hispanic African American (n = 25) and White (n = 25) women matched on pre-pregnancy BMI category, maternal age at delivery (within 5 years), and gestational age at urine sample collection (within 4 weeks). These n = 50 women were comparable with respect to age and smoking status from those who were not included ($p > 0.1$).

### 2.2. Data and specimen collection

Psychosocial stressors that include depression severity, perceived stress, financial stress, perceived discrimination, social stressors, and Adverse Childhood Experiences (ACEs) were evaluated using validated scales. Covariate data includes ethnicity/race, maternal body mass index (BMI), cigarette smoking during pregnancy, maternal age, maternal educational level, and gestational age at the time of urine collection and were collected using a combination of medical records abstraction and questionnaires. Urine specimens were collected from all consenting pregnant women. Medical records were used to obtain pregnancy variables and parturition variables including birth outcomes. Questionnaires were used for exposures that occurred before or during pregnancy such as ACEs and pre-

pregnancy obesity.

### 2.3. Psychosocial stress exposure and covariate data

At enrollment, gestational age of 28–32 weeks of the index child, consenting pregnant women completed questionnaires regarding their health at enrollment (median gestational age of 28–32 weeks): last menstrual period, pre-pregnancy weight and height from where Body Mass index (BMI) was calculated, lifestyle behaviors: cigarette smoking and dietary habits, and sociodemographic characteristics. The questionnaire also included scales used to obtain information on social factors such as ACEs, Anxiety, Social Support, Financial Stress and Depression. ACEs [20] were self-reported and measured using the 10-item ACE measure developed by Felitti et al. [21] that assesses childhood physical, emotional, and sexual abuse, and emotional and physical neglect. Scores are summed to create a total ACE score. Financial stress was measured at enrollment (median gestational age 28 weeks) using the 6-item Financial Stress Index [22,23]. The scale queries the frequency of financial stressors in the three months preceding the interview (e.g., difficulty paying bills, fears of losing home/job). Items are Likert scaled from 0 (never) to 4 (always) and summed (range: 0 to 24) with higher scores indicating more financial stress. We measured social support using the Duke- UNC Functional Social Support Questionnaire [24], –an eight-item Likert-scaled instrument that was used to measure the strength of maternal social support network (Broadhead et al., 1988) with scores summed up into a score.

PROMIS 7A Anxiety [25] was used to measure anxiety from a 7-item scale that queried pregnant women on fears, anxious misery, hyperarousal and somatic symptoms of hyperarousal, also summed up into a single score.

[2721]Depression was measured using the 10 item-scale Center for Epidemiological Studies-Depression Scale [26,27], that was also summed up into a score for each individual. For all scales except social support, higher scores are indicative of higher experiences of stress.

Covariate data that include maternal height, pre-pregnancy weight, date of birth, and parity were obtained from the questionnaire and verified with information from medical records. After delivery, child sex, delivery date, gestational age at birth, weight and length plus maternal gestational diabetes and delivery route were obtained from medical records. Maternal BMI was calculated as kilograms per square meter ($kg/m^2$) using height and pre-pregnancy weight. Maternal age was calculated using maternal date of birth and date of delivery.

### 2.4. Oxidative stress -measurement of F2-isoprostanes

We used spot urine samples obtained during pregnancy to estimate oxidative stress, i.e., systemic overabundance of reactive oxygen species (ROS). F2-isoprostanes, formed by free-radical–mediated peroxidation of arachidonic acid, are accepted biomarkers for estimating oxidative status in animals and humans [16]. Urine concentrations of F2-isoprostanes were adjusted for urinary creatinine (CR) to account for individual differences in urine diluteness, which varies depending on liquid ingestion and kidney function [28].

Four F2-isoprostane isomers—iPF(2α)-III, 2,3-dinor-iPF(2 α)-III, iPF(2 α)-VI, and 8,12-iso-iPF(2α)-VI—were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) on a Shimadzu 20A series LC and Applied Biosystems API 4000 QTrap MS/MS instrument as previously described, and optimized for the present study [16,29]. Creatinine levels were used to normalize urine samples for F2-isoprostane analysis. Namely, for very dilute urine, i.e. CR $<$ 1 mg/mL, 200 μL urine was used to ensure assay sensitivity; for CR between 1 and 3 mg/mL, 100 μL urine was used; and, to prevent signal suppression in cases where CR $>$ 3 mg/mL, 50 μL urine was used. An Agilent Eclipse Plus 50 $\times$ 4.6 mm, 1.8 μm column was used for separation.

Sample volumes were increased to 300 μL with deionized water, to which 20 μL of 1 M HCl, 20 μL of 100 ng/mL internal standard mix [iPF(2α)-III-d4, 8,12-iso-iPF(2α)-VI-d11, iPF(2α)-VI-d4], and 1 mL of methyltert-butylether were added and vigorously mixed in FastPrep (Thermo) for 3 $\times$ 45 s at speed 4. After centrifugation, 800 μL of the ether layer was evaporated under a nitrogen stream, and the resulting samples were reconstituted in 50 μL methanol and 70 μL mobile phase A (see below), after which 50 μL were injected into the LC/MS/MS system. Two C18 columns (Agilent Eclipse Plus, 150 $\times$ 4.6 mm and 50 $\times$ 4.6 mm, 1.8 μm) were used in series, with 0.1 % acetic acid as mobile phase A and methanol as mobile phase B; samples were fractionated using a 40–75 % B gradient over 26 min at room temperature. The mass spectrometer was operated in negative mode with the following MS/MS transitions ($m/z$): 353/193 [iPF(2α)-III], 357/197 [iPF(2α)-III-d4], 325/237 [2,3-dinor-iPF(2α)-III], 353/115 [iPF(2α)-VI and 8,12-iso-iPF(2α)-VI], 364/115 [iPF(2α)-VI-d11], and 357/115 [8,12-iso-iPF(2α)-VI-d4]. Lower limits of quantification ($>$80 % accuracy) were 0.06, 0.63, 0.63, and 0.31 ng/mL for iPF(2α)-III, 2,3-dinor-iPF(2α)-III, iPF(2α)-VI, and 8,12-iso-iPF(2α)-VI, respectively.

In addition to absolute quantification of the four F2-isoprotane isomers using available calibration standards, we also integrated all peaks found on each MS/MS transition (i.e., integration of the entire mass transition “channel”), with assumption that additional abundant peaks on the same channel likely originate from other isoprostane isomers yet to be identified and may represent additional important biomarkers of oxidative stress in preterm birth.

### 2.5. Statistical analyses

We describe the characteristics of the study population, overall and separately for African Americans and Whites, using means and standard deviations for continuous variables and relative frequencies for each category for categorical variables. Maternal age at delivery, pre-pregnancy BMI, education level and smoking were assessed for potential confounders in all our analyses, and only maternal education level and cigarette smoking changed the effect size by more than 10 %, and were therefore included in all models. For the overall analysis (n = 50), we also included race as a confounder and a cross-product term. We fitted linear regression models to

investigate associations between prenatal psychosocial stressors and F2-isoprostanes. Separate regression models were fit for the overall and race-specific analyses. We investigated residual normal Q-Q plots and Cook's distance for each fitted model to detect any possible outliers and influential points. The same analysis strategy was used to examine associations between F2-isoprostanes and birth outcomes. Regression coefficients, standard error, and the p-value obtained from t-tests are reported for each fitted model.

The overall power analysis was completed based on a combined sample size of n = 50, assuming the response SD is 0.84 (from the data for log(isoprostane channel 6,12)), and a model R2 of 0.3.

For race specific power analysis.

1) Black: sample size n = 25, response SD is 0.90. We have about 48 % power to detect an effect size of 0.3.
2) White: sample size n = 25, response SD is 0.78. We have about 59 % power to detect an effect size of 0.3.

## 3. Results

*Study participants.* At the time of urine collection, African American and White pregnant women were similar in maternal age, obesity status, maternal educational levels, mode of delivery, and gestational age at delivery (Table 1). However, 24 % of African American women were nulliparous at enrollment, compared to 32 % of White women, and were three times less likely to be cigarette smokers. Birthweight was lower in infants born to African American women, although birth length and gestational age at delivery were comparable to those of infants born to White women. Average depression, social support, anxiety, and financial stress scores on the psychosocial questionnaires were significantly higher in African American women, whereas ACEscores were higher in White women (Table 1).

*Associations between prenatal psychosocial stressors and F2-isoprostanes.* Urinary F2-isoprostane levels varied widely among all participants and within each racial group. African American women had with a median 2.91 ng/L (interquartile range 2.08 ng/L) for the isoprostane 8 (i8) channel, median 24.67 ng/L (interquartile range (IQR), 18.05 ng/L) for the isoprostane 2,3 channel, and median 5.23 ng/L (IQR 6.06 ng/L) for the isoprostane 6,12. White women had comparable concentrations of isoprostane 8 channel (median 2.65 ng/L (IQR 1.68)) and isoprostane 6,12 channel (median 5.23 ng/L (IQR 3.66 ng/L), slightly lower concentrations of isoprostane 2,3 channel (median 20.22 ng/L (IQR 13.91 ng/L)) (Table 2). These differences in F2 isoprostane concentrations, by ethnicity/race did not reach statistical significance. The correlations among the F2-isoprostane isomers and psychosocial stressors ranged from 0.31 to 0.74 (Supplemental Table 1).

In regression models, we detected associations between the five psychosocial stressors examined and the three creatinine-adjusted F2-isoprostane channels (Table 2). These models were adjusted for cigarette smoking during pregnancy, education level, and race/ethnicity. Pregnant women reporting high levels of ACE had significantly higher i8 channel F2-isoprostane ($\beta = 0.12$, SE = 0.06, $p = 0.033$) and 2,3 channel F2-isoprostane levels ($\beta = 0.11$, SE = 0.04, $p = 0.014$). Women reporting higher levels of depression had borderline higher levels of these F2-isoprostane isomers ($\beta = 0.05$, SE = 0.02, $p = 0.095$ and $\beta = 0.02$, SE = 0.04, $p = 0.064$ for the i8 channel and 2,3 channels, respectively). These associations were most apparent in African American women (Table 3). In contrast, women reporting higher levels of financial stress had lower levels of 6,12 channel F2-isoprostanes ($\beta = -0.05$, SE = 0.02, $p = 0.007$) and this borderline significant association was comparable in African American women ($\beta = -0.06$, SE = 0.03, $p = 0.079$) and Whites

**Table 1**
Distribution of characteristics among 50 study participants.

| Characteristic | All (n = 50) | African American women (n = 25)[a] | White women (n = 25) |
|---|---|---|---|
| Maternal age at delivery (mean, SD) | 28.45, 6.00, 0.91 | 28.35, 6.04 | 28.54, 6.08 |
| Maternal BMI (mean, SD) | 30.75, 10.48, 0.52 | 31.71, 10.68 | 29.79, 10.4 |
| Parity (% nulliparity) | 32.00 %, 0.36 | 24.00 % | 40.00 % |
| Cigarette smoking (% yes) | 24.49 %, 0.09 | 12.50 % | 36.00 % |
| Maternal educational level (% graduated from high school) | 82.00 %, 0.46 | 88.00 % | 76.00 % |
| Sex of child (% male) | 54.00 %, 0.57 | 60.00 % | 48.00 % |
| Delivery route (% C-section) | 30.61 %, 1.0 | 29.17 % | 32.00 % |
| Birth weight, grams (mean, SD) | 3269.00, 544.34, 0.49 | 3215.40, 421.45 | 3322.60, 649.12 |
| Child length, inches (mean, SD) | 19.87, 1.34, 0.73 | 19.80, 0.72 | 19.93, 1.76 |
| Gestational age at delivery (mean, SD) | 38.77, 1.55, 0.95 | 38.76, 1.45 | 38.79, 1.67 |
| Adverse childhood experiences (ACEs) scores (mean, sd) | 1.3, 2.05, 0.19 | 0.92, 1.68 | 1.68, 2.34 |
| Financial stress scores (mean, sd) | 8.6, 6.01, 0.05 | 6.96, 4.84 | 10.24, 6.69 |
| Social support score (mean, sd) | 12.9, 5.69, 0.64 | 13.28, 6.24 | 12.52, 5.17 |
| Anxiety score (mean, sd) | 10.96, 5.07, 0.18 | 10.00, 5.09 | 11.92, 4.96 |
| Depression score | 11.9, 8.57, 0.68 | 11.4, 7.27 | 12.4, 9.83 |
| Isoprostane 8 Channel (median, IQR) | 2.82, 1.84, 0.31 | 2.91, 2.08 | 2.65, 1.68 |
| Isoprostane 2,3 Channel (median, IQR) | 23.28, 16.28, 0.26 | 24.67, 18.05 | 20.22, 13.91 |
| Isoprostane 6,12 Channel (median, IQR) | 5.23, 5.25, 0.55 | 5.23, 6.06 | 5.23, 3.66 |

Two-sample *t*-test for Maternal age at delivery, Maternal BMI, Birth weight, Child length, Gestational age.
Fisher's exact test for Parity, Cigarette smoking, Maternal educational level, Sex of child, Delivery route, and all the stress scores.
Due to outliers and asymmetric distributions, we report median, IQR and p-values from a two-sample Wilcoxon rank sum test for Isoprostane 8 channel, Isoprostane 2,3 channel, and Isoprostane 6,12 channel after adjusting for creatinine.
[a] n = 24 for Cigarette smoking, Delivery route.

**Table 2**
Association between 5 stress scales and F2-isoprostanes (All).

| Stress Scales | Isoprostane 8 Channel β (SE), p-value | Isoprostane 2,3 Channel β (SE), p-value | Isoprostane 6,12 Channel β (SE), p-value |
|---|---|---|---|
| ACEs | 0.12 (0.06), p = 0.033 | 0.11 (0.04), p = 0.014 | 0.03 (0.07), p = 0.632 |
| Financial Stress | 0.02 (0.02), p = 0.904 | −0.02 (0.01), p = 0.882 | −0.05 (0.02), p = 0.007 |
| Depression | 0.05 (0.02), p = 0.095 | 0.02 (0.01), p = 0.064 | 0.01 (0.02), p = 0.955 |
| Social Support | −0.03 (0.02), p = 0.135 | −0.02 (0.02), p = 0.196 | −0.06 (0.02), p = 0.027 |
| Anxiety | 0.03 (0.02), p = 0.188 | 0.01 (0.02), p = 0.415 | 0.01 (0.03), p = 0.953 |

N = 50 pregnant women (25 African American and 25 White). Linear regression models were fit to investigate associations between five prenatal psychosocial stressors and three creatinine-adjusted F2-isoprostane channels. These models were adjusted for cigarette smoking during pregnancy, education level, and race/ethnicity. Pregnant women reporting high levels of ACE had significantly higher i8 channel F2-isoprostane (β = 0.12, SE = 0.06, p = 0.033) and 2,3 channel F2-isoprostane levels (β = 0.11, SE = 0.04, p = 0.014). Two-sample t-tests were completed.

(β = −0.05, SE = 0.02, p = 0.050) (Table 3). Women reporting higher levels of social support had lower levels of F2-isoprostanes (β = −0.06, SE = 0.02, p = 0.027). While maternal anxiety and depression were also associated with individual isomers in both groups, the magnitudes of the associations were lower and did not reach statistical significance (Table 2). Sensitivity analyses that included re-running the unadjusted models without maternal cigarette smoking during pregnancy, education level as they may be in the causal pathway, and fully adjusted models, did not materially alter our findings.

*Associations between F2-isoprostanes and birth outcomes*. In evaluating the link between oxidative stress and birth outcomes, we found that an elevated isoprostane 2,3-channel (β = −0.02, SE = 0.01, p = 0.14), was only borderline associated with lower gestational age at delivery in African American women (β = −0.03, SE = 0.02, p = 0.076) (Table 4) despite being under-powered. Newborns of women with elevated iPF(2 α)-VI also had a shorter gestation at delivery (β = −0.13, SE = 0.06, p = 0.040); remarkably higher levels of this F2-isoprostane was associated with the opposite effect in White women (β = 0.12, SE = 0.05, p = 0.015). No associations were found between the F2-isoprostane isomers and birth weight (Table 1).

## 4. Discussion

Despite a hypothesis linking prenatal psychosocial stressors to adverse outcomes via the induction of systemic oxidative stress, empirical data have been lacking. Our key finding is that although associations between maternal psychosocial stressors and individual F2-isoprostanes did not reach statistical significance, integrated channels— with presumably all similar isoprostane isomers that might as a whole be a good measurement for oxidative stress—were significantly associated with psychosocial stressors, including depressive mood, anxiety, and ACEs and these associations were apparent in African American women only. In contrast, these biomarkers were associated with lower social support only in White women. While elevated oxidative stress is associated with offspring gestational age at birth in African American women, we observed an association of comparable magnitude in the opposite direction in White women, consistent with the recent Behavioral Risk Factor Surveillance System (BRFSS) data [30]. Financial stress, anxiety and depression scores were also higher in African American women. While small sample limits inference, our findings are consistent with the idea that the higher social stress scores in African American women may contribute to differences in oxidative status, which may increase the

**Table 3**
Association between 5 stress scales and F2-isoprostanes (African American and White mothers).

| African American women | | | |
|---|---|---|---|
| Stress Scales | Isoprostane 8 Channel β (SE), p-value | Isoprostane 2,3 Channel β (SE), p-value | Isoprostane 6,12 Channel β (SE), p-value |
| ACEs | 0.18 (0.10), p = 0.082 | 0.16 (0.07), p = 0.024 | 0.11 (0.12), p = 0.351 |
| Financial Stress | 0.06 (0.04), p = 0.875 | −0.01 (0.03), p = 0.699 | −0.06 (0.03), p = 0.079 |
| Depression | 0.05 (0.02), p = 0.042 | 0.05 (0.02), p = 0.014 | 0.02 (0.03), p = 0.465 |
| Social Support | −0.02 (0.03), p = 0.575 | 0.08 (0.02), p = 0.728 | −0.04 (0.04), p = 0.286 |
| Anxiety | 0.08 (0.04), p = 0.041 | 0.04 (0.03), p = 0.134 | 0.03 (0.05), p = 0.489 |
| White women | | | |
| Stress Scales | Isoprostane 8 Channel β (SE), p-value | Isoprostane 2,3 Channel β (SE), p-value | Isoprostane 6,12 Channel β (SE), p-value |
| ACES | 0.05 (0.07), p = 0.414 | 0.08 (0.06), p = 0.202 | 0.03 (0.10), p = 0.972 |
| Financial Stress | −0.07 (0.02), p = 0.971 | 0.02 (0.02), p = 0.900 | −0.05 (0.02), p = 0.050 |
| Depression | −0.05 (0.02), p = 0.978 | 0.04 (0.02), p = 0.774 | −0.08 (0.02), p = 0.740 |
| Social Support | −0.05 (0.02), p = 0.040 | −0.06 (0.02), p = 0.004 | −0.07 (0.03), p = 0.061 |
| Anxiety | −0.08 (0.03), p = 0.738 | −0.09 (0.02), p = 0.690 | −0.03 (0.04), p = 0.517 |

N = 50 pregnant women (25 African American and 25 White. Linear regression models were fit to investigate associations between five prenatal psychosocial stressors and three creatinine-adjusted F2-isoprostane channels in African American and White women. These models were adjusted for cigarette smoking during pregnancy, education level, and race/ethnicity. No p-values were significant for interaction by race (range from 0.06 to 0.94). Two-sample t-tests were completed for these analyses.

**Table 4**
Association between F2-isoprostanes and gestational age at delivery.

| Name of F2-Isoprostane Channel | Regression Coefficient, SE and p-value (All) | Regression Coefficient, SE and p-value (African American) | Regression Coefficient, SE and p-value (White) |
|---|---|---|---|
| mui_8ip_channel_353_193_CRadjusted | −0.17, 0.17, 0.332 | −0.26, 0.21, 0.225 | −0.01. 0.31, 0.971 |
| mui_23d_channel_325_237_CRadjusted | −0.02, 0.01, 0.144 | −0.03, 0.02, 0.076 | 0.001, 0.03, 0.963 |
| mui_VI_12i_channel_353_115_CRadjusted | 0.005, 0.04, 0.891 | −0.13, 0.06, 0.040 | 0.12, 0.05, 0.015 |

observed higher risk of shorter gestational age at birth—an established risk factor for lower birth weight and attendant metabolic impairment in adulthood of the exposed offspring.

We analyzed a set of four F2-isoprostane isomer channels including iPF(2α)-III and three molecules similar in structure to iPF(2α)-III [2,3-dinor-iPF(2 α)-III, iPF(2 α)-VI, and 8,12-iso-iPF(2α)-VI], which may be useful markers of oxidative stress. Although prenatal psychosocial stressors were not associated with these four F2-isoprostanes themselves, they were associated with the corresponding MS/MS channels. Together these data suggest the existence of unidentified but very abundant isoprostanes that could serve as reasonable oxidative biomarkers associating prenatal psychosocial stress with adverse birth outcomes in African Americans, but larger studies that examine these molecules in ethnically and racially diverse populations, are needed. In addition to our small sample size, we were limited by the lack of fetal sex data. Given some of the differences observed between Black and White women in our sample (i.e. social stress and oxidative status), fetal sex may potentially drive some of these differences. Importantly, our race-stratified analysis (Table 3) was an exploratory attempt to determine the extent to which lived experiences, estimated by these social stressors, contribute to observed differences in birth outcomes. We found no evidence of significant differences, as all estimates had overlapping confidence intervals. Effect modification by race should be explored in a future, larger study.

Urinary cortisol is an accepted marker that, when found in high concentrations, is associated with transient and acute stress, but levels vary widely throughout the day [31,32]. F2-isoprostanes, however, are an established and reliable indicator of chronic oxidative stress [33,34] that are associated with a wide range of outcomes including hypertension [35], cardiovascular diseases [36], malignancies [37], and neuropsychiatric conditions such as depression [38]. At the community level, elevated concentrations of four F2-isoprostane isomers (2,3-dinor-iPF2a-III, 8-iso-PGF2a, and in particular 5-iPF2a-VI, and PGE2) analyzed in wastewater during the COVID-19 pandemic were found to be reliable markers of community oxidative stress and anxiety [39]. Others have corroborated the association between specific F2-isoprostane isomers and long-term psychosocial, neurodevelopmental, and metabolic impact, including the association of iPF2α-III, 2,3-dinor-iPF2α-III, iPF2α-VI, and 8,12-iso-iPF2α-VI with select malignancies [40] and obesity [41]; iPF2alpha-III and iPF2alpha-VI with hypercholesterolemia [42]; and 8,12-iso-iPF2α-VI with the cognitive deficits seen in Konzo among Congolese children [43], the neuropathogenesis of Alzheimer's disease and frontotemporal dementia [44], pathogenesis of Down syndrome [45], and relapsing-remitting multiple sclerosis [46].

Plasma levels of F2-isoprostanes have been previously evaluated in pregnant women, revealing validated methods to simultaneously measure seven isomers [-iso-15®-prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), 8-iso-$PGF_{2\alpha}$, 15(R)-$PGF_{2\alpha}$, $iPF_{2\alpha}$-IV, $iPF_{2\alpha}$-VI, 5-$iPF_{2\alpha}$-VI, and (±) 5–8,12-iso-$iPF_{2\alpha}$-VI] [47]. Further, class VI isomers are significant predictors of subsequent development of pre-eclampsia [48]. To our knowledge, we present the first data linking four F2-isoprostane biomarkers of oxidative stress [iPF(2α)-III, 2,3-dinor-iPF(2 α)-III, iPF (2 α)-VI, and 8,12-iso-iPF(2α)-VI] and psychosocial stress in pregnant African American and White women.

Methodological challenges in assessing prenatal stressors in multi-ethnic studies and the lack of reliable measurements of oxidative status in humans have contributed to a major knowledge gap in the field. F2-isoprostanes, and multiple prenatal stressors have emerged as reliable indicators of oxidative stress [16], enabling epidemiological studies to seek mechanistic insights into observed relationships between self-reported stress and oxidative status. In pregnant women, excess ROS induced by prenatal stressors contribute to systemic inflammation [35], which is an established risk factor for adverse maternal and fetal outcomes, including preterm delivery, depressive symptoms, and recurrent fetal loss [49]. Mechanistically, the increase in free radicals and oxidative stress leads to increased levels of circulating pro-inflammatory cytokines and chemokines [50]. It is therefore plausible that psychosocial stress can lead to decreased length of gestation at birth although larger studies, designed to also gain these mechanistic insights, are needed to clarify these findings.

Reasons for the differential effects of social stressors on oxidative status, and prenatal oxidative stress on birth outcomes between African American and White mothers are unclear. While point estimates differed by race, no test of interaction was statistically significant at $p = 0.05$ and the magnitude of difference was small. Without additional context, these findings could be interpreted as suggesting biological differences across race which is unlikely to be the explanation for the results. Additionally, while our novel findings linking maternal social stressors to offspring outcomes are intriguing, we cannot exclude the possibility that these differences could be due to chance alone. Nonetheless, ethnic differences in the effects of social stressors on children's phenotypes have been reported by others. For example, higher ACE scores for Hispanic children of immigrant parents did not associate with poorer outcomes in offspring (preterm birth) [51].

Others have suggested that this may be due in part to the universal use of the ACEs questionnaire, which was developed in White populations and may inadequately capture adversities of similar magnitude in other cultural groups. It is also possible that, depending on the stressor, there is an as-yet-unknown threshold below which social stressors may not contribute to poorer outcomes. Such a possibility is consistent with social stress scores being lower in White women than African Americans. These possibilities emphasize the need for larger studies, powered to not only examine three or higher order interactions to evaluate the effects of race/ethnicity and sex on differential oxidative stress status and birth outcomes, if we are to address disparities in health outcomes.

Our finding that psychosocial stressors during pregnancy were associated with increased oxidative stress during gestation, contributing to preterm birth in African Americans only, should be interpreted in the context of the study limitations. We have been under-powered to detect associations between some F2-isoprostane channels and birth outcomes, as well as between five prenatal stressors and oxidative stress; thus, the seeming differences in associations between F2 isoprostanes and birth outcomes, in African Americans and Whites, may be spurious. Thus, our study cannot interpret these results as identifying strong evidence of effect in African American women. Larger studies are required to confirm these findings.

## 5. Conclusion

F2-isoprostanes, established biomarkers for oxidative stress, are significantly associated with self-reported psychosocial stressors such as depressed mood, anxiety, and ACEs in a small sample of African American pregnant women—these associations are not present in a small sample of Whites. While reasons for these ethnic differences are unclear, they are consistent with the hypothesis that ethnic/race-dependent effects of prenatal stress on oxidative status, which may contribute to disparate health outcomes at birth. If confirmed in larger studies, reducing oxidative stress could be a potential avenue to mitigate adverse effects of psychosocial stressors on birth outcomes in ethnic minorities.

## Data availability statement

The data associated with the study has not been deposited into a publicly available repository. Data will be made available on request.

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## Ethics approval

The study was approved by the WakeMed Health Ethics committee and the NC State IRB. The IRB protocol number at WakeMed: IRBNet# 678553-14. NCSU IRB protocol number: 14262.

## Consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and material

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

## Code availability

Not applicable.

## CRediT authorship contribution statement

**Deborah K. Rose:** Writing – review & editing, Writing – original draft, Validation, Resources, Funding acquisition, Conceptualization. **Loren Bentley:** Writing – original draft, Conceptualization. **Arnab Maity:** Visualization, Software, Methodology, Formal analysis, Data curation. **Rachel L. Maguire:** Resources, Project administration, Methodology, Formal analysis, Data curation. **Antonio Planchart:** Writing – review & editing, Supervision. **Ivan Spasojevic:** Writing – review & editing, Methodology, Data curation. **Andy J. Liu:** Writing – review & editing, Supervision. **John Thorp:** Supervision. **Cathrine Hoyo:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Abbreviations

| | |
|---|---|
| ACEs | Adverse childhood experiences |
| CR | Urinary creatinine |
| BMI | Body mass index |
| LC-MS/MS | Liquid chromatography-tandem mass spectrometry |
| ROS | Reactive oxygen species |
| SE | Standard error |
| SHIP | Stress and Health in Pregnancy |

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25578.

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