

Association between prenatal psychological stress and oxidative stress during pregnancy

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Abstract

Background: Prenatal psychological stress during pregnancy has been associated with adverse reproductive outcomes. A growing animal literature supports an association between psychological stress and oxidative stress. We assessed this relationship in pregnant women, hypothesising that psychological stress is associated with higher concentrations of oxidative stress biomarkers during pregnancy.

Methods: Psychosocial status and stressful life events (SLE) were self-reported. 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF_{2 α}) was measured as a biomarker of oxidative stress in urine samples at median 32 weeks' gestation. We examined SLEs individually (ever vs never) and in summary (any vs none) and psychosocial status as measured by individual subscales and in summary (poor vs good). Linear models estimated associations between these parameters and urinary 8-iso-PGF_{2 α} concentrations after adjusting for covariates.

Results: The geometric mean of 8-iso-PGF_{2 α} was significantly higher among pregnant women who were non-White, smokers, had less than a college education, higher pre-pregnancy BMI and were unmarried. Having ever had a death in the family ($n = 39$) during pregnancy was associated with a 22.9% increase in 8-iso-PGF_{2 α} in unadjusted models (95% confidence interval [CI] 1.50, 48.8). Poor psychosocial status was associated with a 13.1% (95% CI 2.43, 25.0) greater mean 8-iso-PGF_{2 α} in unadjusted analyses. Associations were attenuated, but remained suggestive, after covariate adjustment.

Conclusions: These data suggest that 8-iso-PGF_{2 α} is elevated in pregnant women with who are at a sociodemographic disadvantage and who have higher psychological stress in pregnancy. Previous studies have observed that 8-iso-PGF_{2 α} levels are associated with adverse birth outcomes, oxidative stress could be a mediator in these relationships.

KEYWORDS

oxidative stress, pregnancy, socio-economic status, stress

1 | INTRODUCTION

Psychological stress during pregnancy has been associated with pregnancy loss, preterm birth, foetal growth restriction, and low birthweight.¹⁻³ Despite these well-established associations, the underlying mechanisms are unclear.⁴ One leading hypothesis is that prenatal psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, which in turn leads to increased synthesis and secretion of cortisol.⁵ An increase in cortisol levels can prematurely activate corticotropin-releasing hormone (CRH), potentially resulting in a greater risk for preterm birth.⁶ This mechanism has been established in animal models, but evidence is lacking in humans.⁷ While this could be due to the limited ability of biomarkers to detect HPA activation, the ambiguity in this evidence may suggest that other mechanisms are at play.⁸

Another possible mechanism underlying associations between stress and poor pregnancy outcomes may be oxidative stress. Oxidative stress as measured through the biomarker 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF_{2 α}) is elevated in a variety of diseases as well as pregnancy related complications.⁹ Increased levels of 8-iso-PGF_{2 α} in pregnancy have been observed among mothers who later experienced preterm birth and preeclampsia.^{10,11} Studies in animal models show that 8-iso-PGF_{2 α} is elevated subsequent to stressful situations.¹² Several studies in humans show that psychological stress is associated with increased oxidative stress biomarkers;^{13,14} however, to our knowledge, this has not been examined in pregnant women.

The objective of the current analysis was to investigate the association between two measures of psychosocial stress and oxidative stress, as indicated by the lipid peroxidation marker urinary 8-iso-PGF_{2 α} using data from The Infant Development and the Environment Study (TIDES), a large, multi-centre pregnancy cohort study. The hypothesis was that levels of oxidative stress would be elevated among women with poor psychosocial status and in women who experienced stressful life events during pregnancy.

2 | METHODS

2.1 | Study population

The TIDES cohort study has been described in detail elsewhere.¹⁵ Briefly, women were recruited from four university-based prenatal clinics: University of California, San Francisco, CA; University of Rochester Medical Center, NY; University of Minnesota, MN; and University of Washington-Seattle Children's Hospital, WA from 2010-2012. Women were eligible if they were less than 13 weeks pregnant, age 18 or older, planned to deliver in a study hospital, and their pregnancy was not medically threatened. In each trimester (median 10.8, 20.6, and 32.7 weeks gestation, respectively), participants completed a questionnaire on demographics, life style, psychosocial factors, health, and reproductive history. The institutional review board approved the study at each participating institution. Each participant provided written informed consent.

2.2 | Psychosocial status

The second visit questionnaire included the Goldenberg scale, designed to assess psychosocial status during pregnancy, which is composed of 27 items on five subscales: anxiety, depression, self-esteem, mastery and subjective stress.¹⁶ The anxiety subscale included eight questions, whereas the depression, self-esteem, mastery, and subjective stress included 7, 6, 4, and 2 questions, respectively. Each response was ranked on a 5-point Likert scale ranging from "strongly agree" or "almost always" (score of 5) to "strongly disagree" or "never" (a score of 1). Some questions were reverse-coded so that higher scores were always associated with greater well-being.¹⁶ We calculated subscale scores within each psychosocial status subscale.¹⁶ If one answer from the respective subscale was missing then the subscale score was coded as missing. There were 45, 36, 31, 31, and 27 women who were missing information on one or more questions on the anxiety, self-esteem, depression, mastery, and subjective stress subscales, respectively. An increase in subscale summary score indicates a more positive outcome in that domain (eg, higher scores on the anxiety subscale are associated with lower anxiety, and higher scores on the self-esteem scale are associated with increased self-esteem). We hypothesised that an increase in each of the subscale scores would be associated with a decrease in urinary 8-iso-PGF_{2 α} concentrations.

We also used an established method of creating an overall measure of well-being which we then dichotomised.¹⁷ This was done by summing the individual items, and dividing women into two groups. "Poor" psychosocial status included women whose summary value was less than or equal to the 25th percentile of the overall measure; "good" psychosocial status included women whose values were greater than the 25th percentile.¹⁷ Missingness on any individual question resulted in a missing value for overall psychosocial status. We hypothesised that women with "good" psychosocial status have lower levels of 8-iso-PGF_{2 α} compared to women with "poor" psychosocial status.

2.3 | Stressful life events

Trimester specific stressful life events (SLEs) were assessed through a series of trimester-specific items included in the third visit questionnaire. Questions about SLEs were adapted from validated questionnaires.^{18,19} Women were asked if they had experienced job loss, serious family illness or injury, death of a close family member, relationship difficulties with their partner, serious legal or financial issues, or any other major life event during each trimester of the current pregnancy.

We analysed SLEs in two ways. First, we examined *individual* SLEs by occurrence ever vs never during pregnancy. Second, we determined the presence or absence of *any* SLEs during pregnancy by summing prevalence scores across the six items to create a dichotomous variable. Women reporting no SLEs during pregnancy were categorised as having experienced "no" SLEs and women reporting one or more SLEs during pregnancy were categorised as having



experienced “any” SLEs. We hypothesised that experiencing SLEs during pregnancy would be associated with higher levels of our biomarker of oxidative stress.

2.4 | Oxidative stress biomarker measurement

Urine samples were collected and processed at the third study visit using methods previously described.¹⁵ Urine samples were collected in phthalate-free cups via spot urine sample without fasting during the third study visit. Urine specific gravity (SpG) was measured within 30 minutes of urine collection using a handheld refractometer. Samples were stored at -80°C prior to shipment and analysis. The Eicosanoid Core Laboratory at Vanderbilt University Medical Center (Nashville, TN) quantitated urinary 8-iso-PGF_{2 α} and prostaglandin-F_{2 α} (PGF_{2 α}) using established protocols. For analysis, [²H₄]-8-iso-PGF_{2 α} and [²H₄]-PGF_{2 α} (Cayman Chemical, Ann Arbor, MI) are added as internal standards to 0.2 mL of urine in 5 mL of water. The sample pH is adjusted to pH 3 and loaded onto a C-18 Sep-Pak cartridge that has been prewashed with 5 mL methanol and 5 mL 0.01N HCl. Samples are subsequently eluted with 10 mL ethyl acetate:heptane (50:50, v/v), and dried under nitrogen. The concentrations of 8-iso-PGF_{2 α} and PGF_{2 α} in urine were calculated from the ratio of intensities of the ions m/z 569 to m/z 573.²⁰ We additionally measured an 8-iso-PGF_{2 α} metabolite, which has been hypothesised to be a more sensitive biomarker than 8-iso-PGF_{2 α} in urine.²¹ However, results were similar to those for 8-iso-PGF_{2 α} and thus are not presented here. Values below the limit of detection (LOD; 0.101 ng/mL) were assigned the value of the LOD/square root of 2.

In addition, we used a novel approach to examine the proportion of 8-iso-PGF_{2 α} derived from chemical vs enzymatic lipid peroxidation pathways. To do so, we utilised the ratio of 8-iso-PGF_{2 α} to prostaglandin F_{2 α} (PGF_{2 α}) as described by van ‘t Erve et al.²² and as calculated by a custom interface for the R package “Constrained Linear Mixed Effects (CLME)”.²² Associations between psychological stress measures and chemical and enzymatically derived 8-iso-PGF_{2 α} were analysed separately to determine if stress was increasing 8-iso-PGF_{2 α} through one pathway more than the other in this exploratory analysis.

For all urinary oxidative stress markers, we adjusted for urine dilution with SpG. Oxidative stress biomarker concentrations were corrected for SpG using the formula: $Ox_c = Ox[(1.014-1)/(SpG-1)]$, where 1.014 is the median SpG in the TIDES population, Ox is the oxidative stress biomarker concentration as measured, and Ox_c is the SpG corrected oxidative stress measure.²³

2.5 | Statistical methods

Frequencies and counts were used to describe demographic characteristics of our study population. Distributions of urinary 8-iso-PGF_{2 α} concentrations were examined using geometric means, geometric standard deviations, and selected percentiles. The outcome measure, SpG-corrected 8-iso-PGF_{2 α} , was right skewed and natural log transformed for all analyses. Linear regression models were fit to

determine unadjusted and adjusted estimates and 95% confidence intervals (CI) for the association between urinary 8-iso-PGF_{2 α} and individual and summary psychological stress measures. Psychosocial status subscale measures were examined continuously and psychosocial status (“good” vs “poor”) was examined as a binary exposure. Individual and summary SLEs were examined categorically (“ever” vs “never”; “any” vs “none”). Standard regression assumptions were checked by examining QQ-plots for each model. For ease of interpretation, we converted beta estimates to percent change in 8-iso-PGF_{2 α} .

Maternal age, recalled prepregnancy body mass index (BMI, kg/m²), gestational age at urine collection, maternal race/ethnicity, maternal education, household income, marital status, infant sex, alcohol use during the third visit, smoking during the third visit, prenatal vitamin use during the third visit, and study centre, were examined as potential covariates. Covariates that changed point estimates by at least 10% were retained in the model.

We conducted several sensitivity analyses for models of “any” vs “none” SLEs and “good” vs “poor” psychosocial status. First, we examined associations between the chemical and enzymatic fractions of 8-iso-PGF_{2 α} , as described above. The enzymatic fraction of 8-iso-PGF_{2 α} is thought to be more closely linked to inflammation, which would change more rapidly because of acute stressors like those examined here.²² Therefore, our hypothesis was that the associations with stress measures would be greater with the enzymatic fraction of 8-iso-PGF_{2 α} as compared to the chemical fraction. Second, we explored effect measure modification by maternal race/ethnicity, infant sex, and study site. Third, we examined associations between SLEs and 8-iso-PGF_{2 α} within strata of “good” and “poor” psychosocial status with the hypothesis that women with higher levels of psychological distress would have greater elevations in oxidative stress in response to external stressors like SLEs.²⁴

Statistical analyses were conducted using RStudio Version 1.0.143 and SAS 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

Women were included in our analysis if they had provided urine samples and SLE data at the third visit (n = 761). Of these, there were 718 (94.3%) participants who responded to questions on psychosocial status. Most of the study population was non-Hispanic White (65.4%), was married or living with a partner (83.2%), and roughly half had a household income of \$75 000 or greater (47.0%) (Table 1). Few women reported alcohol use (7.78%) or smoking (4.73%) during the third trimester. 297 (39.0%) women reported “any” SLE and 182 (23.9%) women were considered as having “poor” psychosocial status. Among women experiencing SLEs, 144 women reported one, 53 reported two, 46 women reported three and 54 women reported three or more SLEs. In bivariate analyses, women reporting “any” SLE or having “poor” psychosocial status were younger, had a higher BMI, and were more likely to be non-White, have a lower level of

education, have a lower household income, and be unmarried than referent groups.

Nearly every pregnant woman had detectable urinary 8-iso-PGF_{2α} (99.7%). Distributions of raw and SpG corrected 8-iso-PGF_{2α} values are presented in Table S1. In bivariate analyses, the geometric mean of urinary SpG corrected 8-iso-PGF_{2α} was significantly higher among those who were non-White, unmarried, smokers, had less than a college education, had a yearly household income of <\$25 000, or were classified as “poor” psychosocial status compared to referent categories (Table 2).

Full models for both scales were adjusted for maternal race/ethnicity, education, maternal age, prepregnancy body mass index, and marital status, as well as infant sex and study centre. For the overall summary measures, “any” SLE was not associated with urinary 8-iso-PGF_{2α} in unadjusted or adjusted models (Table 3). For models of individual SLEs, the only significant finding was a positive association between experiencing a family death ($n = 39$) and an increase in urinary 8-iso-PGF_{2α} in unadjusted models difference in 8-iso-PGF_{2α} with ever vs never family death 22.9%, 95% CI 1.50, 48.8). This association was still positive, although less precise, in adjusted models (Figure 1; Table S2).

For the overall psychosocial status score, urinary 8-iso-PGF_{2α} was 13.1% higher among mothers with “poor” compared to “good” psychosocial status in unadjusted analysis (95% CI 2.43, 25.0). This relationship became attenuated to non-significance, but was still positive, after adjusting for confounders (Table 3). For psychosocial status subscales, higher scores on anxiety (difference -1.07%, 95% CI -1.99, 0.15), depression difference -1.31%, 95% CI -2.23, -0.38), and mastery difference -1.75%, 95% CI -3.02, 0.46) subscales, all indicative of better psychosocial status, were associated with decreased levels of urinary 8-iso-PGF_{2α} in unadjusted models, with smaller and less precise effect estimates in adjusted models (Figure 2; Table S3).

In sensitivity analyses, we examined distributions and associations for the enzymatic and chemical fractions of 8-iso-PGF_{2α}. Concentrations by demographic characteristics and association with SLE and psychosocial stress are presented in the supplement (Tables S4 and S5, respectively). Associations with demographic characteristics were similar to those observed with 8-iso-PGF_{2α}, and differences were consistently more pronounced across groups with the chemical as compared with the enzymatic fraction. The chemical fraction of 8-iso-PGF_{2α} was 23.4% (95% CI 7.29, 41.9) higher among women classified as “poor” vs “good” psychosocial status in our unadjusted analysis only (Table S5).

We observed few differences in associations in stratified analyses. By study centre, the association between psychosocial status and 8-iso-PGF_{2α} was greatest in magnitude at the University of Minnesota, where 8-iso-PGF_{2α} was 21.2% (95% CI 0.51, 4.37) higher among women with “poor” psychosocial status (Table S6). The interaction between centre and psychosocial was marginally significant ($P < .10$). No significant interactions were observed by infant gender or maternal race/ethnicity (not shown). Among women classified as having “good” psychosocial status, those experiencing “any” SLE

showed decreased levels of 8-iso-PGF_{2α} difference -13.3%, 95% CI -22.1, -3.55). Among women classified as having “poor” psychosocial status, experiencing “any” SLE was not associated with 8-iso-PGF_{2α} (difference -1.17%, 95% CI -15.3, 4.0). The interaction between psychosocial status and SLEs was not statistically significant (Table S7).

4 | COMMENT

4.1 | Principal findings

The association between prenatal psychological stress and oxidative stress was examined among pregnant women. The hypothesis was that an increase in psychological stress would be associated with higher levels of oxidative stress, as indicated by urinary 8-iso-PGF_{2α}. These findings suggest that at least some parameterisations of stress, such as depression and anxiety, as well as extremely stressful life events, such as family death, are associated with increases in oxidative stress in pregnant women.

4.2 | Interpretation

The psychosocial status measure was composed of five individual summary scores: depression, anxiety, self-esteem, mastery, and subjective stress.¹⁶ In unadjusted models, these data were associated with higher scores on the anxiety and depression subscales (indicative of lower anxiety and lower depression) were associated with lower levels of 8-iso-PGF_{2α}, which is consistent with the hypothesis. Previous human data have demonstrated that oxidative stress levels are elevated among individuals experiencing depression²⁵ and anxiety,²⁶ which is supported by these unadjusted findings. These measures, as compared to SLEs, may be a better reflection of current coping and mental health because they are capturing how an individual feels rather than quantifying an objective stressor like job loss. These findings suggest that 8-iso-PGF_{2α} levels may be more tightly associated with certain measures of perceived status rather than more objective measures of adverse experiences. This idea is consistent with prior data showing that among women with low levels of chronic stress, greater perceived stress and anticipatory threats were associated with lower levels of oxidative stress.¹³ It is also consistent with this study's finding that family death was associated with an increase in 8-iso-PGF_{2α}. Family death is arguably a stronger stressor than other SLEs examined here, indicating that the magnitude of the stressor may be important for changes in oxidative stress. While these associations were not statistically significant after adjustment for confounders, this may be due to over-adjustment by including measures of socio-economic status in our full models.

A novel approach to examine enzymatic as compared to chemical fractions of 8-iso-PGF_{2α} was used to further explore oxidative stress in this context.²² Previously, 8-iso-PGF_{2α} was thought to reflect non-enzymatic lipid peroxidation only, ie, oxidative stress consequent to excess free radical production. However, animal studies indicate that the 8-iso-PGF_{2α} also captures upregulation of some



TABLE 1 Demographic characteristics and selected health behaviours of the study population by stressful life events^a and psychosocial status^b categories during pregnancy

	Total (n = 761)	Stressful life events		Psychosocial status	
		None (n = 464)	Any (n = 297)	Good (n = 536)	Poor (n = 182)
Continuous variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Maternal age (years)	31.7 (5.49)	32.4 (5.16)	30.6 (5.80)	32.0 (5.32)	31.1 (5.56)
Pre-pregnancy BMI (kg/m ²)	26.2 (6.22)	25.6 (5.91)	27.2 (6.56)	25.6 (5.90)	27.5 (6.32)
Gestational age at urine collection (weeks)	32.7 (3.03)	32.9 (3.10)	32.4 (2.90)	32.8 (3.11)	32.2 (2.64)
Categorical variables	N (%)	%	%	%	%
Study centre					
Rochester, NY	213 (28.0)	47.4	52.6	64.3	35.7
San Francisco, CA	205 (26.4)	65.7	34.3	74.5	25.5
Minneapolis, MN	205 (26.9)	62.9	37.1	80.9	19.1
Seattle, WA	142 (18.7)	71.8	28.2	81.3	18.8
Race/ethnicity					
Non-Hispanic White	492 (65.4)	65.0	35.0	76.4	23.6
Other	260 (34.6)	54.2	45.8	71.6	28.3
Education					
<College graduate	199 (26.1)	45.7	54.3	64.0	36.0
College graduate	555 (72.9)	66.7	33.3	78.1	21.9
Household income (per year)					
<\$15 000-\$25 000	177 (23.3)	41.2	58.8	60.6	39.4
\$25 001-\$75 000	199 (26.1)	58.8	41.2	75.5	24.5
>\$75 000	358 (47.0)	71.5	28.5	80.4	19.6
Married or living together					
Yes	633 (83.2)	65.1	34.9	78.7	21.3
No	126 (16.6)	41.3	58.7	53.5	46.5
Prenatal vitamin use during 3rd trimester					
Yes	655 (86.1)	60.3	39.7	75.3	24.7
No	72 (9.5)	50.0	50.0	66.7	33.3
Alcohol use during 3rd trimester					
No	642 (84.4)	58.4	41.6	74.6	25.4
Yes	60 (7.78)	65.0	35.0	74.1	25.9
Smoking during 3rd trimester					
No	670 (88.0)	59.7	40.3	75.4	24.6
Yes	36 (4.73)	44.4	55.6	51.5	48.5
Infant gender					
Boy	361 (47.4)	60.7	39.3	77.3	22.7
Girl	389 (51.1)	61.4	38.6	72.1	27.9

SD, standard deviation.

^aStressful life events categorised as none (no stressful life event during pregnancy) vs any (one or more stressful life events during pregnancy).

^bPsychosocial status categorised as good (sum of individual scores >25th percentile) vs poor (sum of individual scores ≤25th percentile).

P-values calculated from chi square test for categorical and linear models for continuous variables; totals may not add to 100% due to missing values.

enzymatic pathways, particularly cyclooxygenase activity, which are responsive to inflammation.²² Acutely stressful situations, such as stressful life events, may alter glucocorticoid sensitivity and increase

inflammation.²⁷ This could lead to increased 8-iso-PGF_{2α} through an enzymatic rather than a chemical pathway. Results from this study showed a 23% higher chemical fraction of 8-iso-PGF_{2α} in participants

TABLE 2 Geometric means (geometric standard deviations) of specific gravity corrected urinary 8-iso-PGF_{2α} concentrations (ng/mL) by demographic characteristics and selected health behaviours during pregnancy

	Geometric mean (Geometric SD)	Difference ^a (% 95% CI)
Study centre		
Rochester, NY	1.20 (1.84)	0.00 (Reference)
San Francisco, CA	0.78 (1.72)	-34.9 (-41.7, -27.2)
Minneapolis, MN	0.92 (1.83)	-22.8 (-30.9, -13.8)
Seattle, WA	0.93 (1.67)	-22.1 (-31.1, -12.0)
Race/ethnicity		
Non-Hispanic white	0.89 (1.78)	0.00 (Reference)
Other	1.09 (1.85)	22.2 (11.9, 33.5)
Education		
College graduate	0.85 (1.73)	0.00 (Reference)
<College graduate	1.27 (1.88)	48.3 (35.1, 62.6)
Household income (per year)		
<\$15 000-\$25 000	1.21 (1.80)	0.00 (Reference)
\$25 001-\$75 000	0.97 (1.87)	-19.5 (-28.4, -9.52)
>\$75 000	0.82 (1.72)	-31.8 (-38.6, -24.3)
Married or living together		
Yes	0.90 (1.78)	0.00 (Reference)
No	1.24 (1.87)	37.9 (23.3, 54.1)
Prenatal vitamin use during 3rd visit		
Yes	0.93 (1.81)	0.00 (Reference)
No	1.03 (1.80)	-12.2 (-32.6, 14.3)
Alcohol use during 3rd visit		
No	0.96 (1.83)	0.00 (Reference)
Yes	0.81 (1.62)	-15.1 (-27.4, -0.70)
Smoking during 3rd visit		
No	0.93 (1.80)	0.00 (Reference)
Yes	1.22 (1.92)	31.6 (7.93, 60.4)
Infant sex		
Boy	1.01 (1.81)	0.00 (Reference)
Girl	0.90 (1.81)	-10.8 (-18.1, -2.86)
Stressful life events^b		
None	0.96 (1.77)	0.00 (Reference)
Any	0.94 (1.88)	-1.18 (-9.40, 7.79)
Psychosocial status^c		
Good	0.91 (1.85)	0.00 (Reference)
Poor	1.03 (1.67)	13.1 (2.43, 25.0)

SD, standard deviation; CI, confidence interval.

^aModels are unadjusted.

^bStressful life events categorised as none (no stressful life event during pregnancy) vs any (one or more stressful life events during pregnancy).

^cPsychosocial status categorised as good (sum of individual scores >25th percentile) vs poor (sum of individual scores ≤25th percentile).

TABLE 3 Associations between specific gravity corrected urinary 8-iso-PGF_{2α} concentrations (ng/mL) and stressful life events and psychosocial status

	Difference (% 95% confidence interval)			
	n	Unadjusted	n	Adjusted ^a
Any stressful life event ^b	759	-1.17 (-9.40, 7.79)	700	1.52 (-22.9, 36.4)
Poor psychosocial status ^c	717	13.1 (2.43, 25.0)	676	7.27 (-2.83, 18.42)

^aModels adjusted for maternal race/ethnicity, education, maternal age, prepregnancy body mass index, and marital status, as well as infant sex and study centre.

^bStressful life events categorised as none (no stressful life event during pregnancy) vs any (one or more stressful life events during pregnancy).

^cPsychosocial status categorised as good (sum of individual scores >25th percentile) vs poor (sum of individual scores ≤25th percentile).

with “poor” psychosocial status, but no differences in the enzymatic portion. These results provide confidence in concluding that the association between psychosocial status and 8-iso-PGF_{2α} is truly reflective of increased oxidative stress and not inflammation, despite the fact that this was contrary with the hypothesis. The associations observed with the chemical fraction could also indicate that there is residual confounding, eg, unaccounted differences in environmental chemical stressors.

There were no associations detected between SLEs experienced during pregnancy and urinary 8-iso-PGF_{2α} concentrations, except for the unadjusted association between family death and an increase in 8-iso-PGF_{2α}. This association has been shown previously, where bereaved individuals showed increased levels of oxidative stress following a family death.¹⁴ Additionally one previous study found that 8-iso-PGF_{2α} levels were significantly elevated among non-pregnant women experiencing SLEs.²⁸ The inconsistent findings may be due to differences in sample sizes and characteristics of the study populations. The sample size of the current analysis included a much larger sample size than the prior study and focused only on pregnant women.

4.3 | Limitations of the data

The assessment of stress was limited in that only parameters from two scales were examined. There are many other domains of stress and methods for measurement that might be relevant in this context. As individuals vary in their perceptions of stress, an explicit measure of perceived stress, rather than reports of mood and well-being, would have been informative. However, this work provides initial examination of this research question using available data. A second limitation is that questionnaires assessing SLEs were performed at the third study visit and asked about events that occurred in each trimester, which could have incurred recall bias, though recall bias for major life events is quite low.^{29,30} Misclassification and recall bias would be expected to be lowest for family death, where the strongest associations with 8-iso-PGF_{2α} were observed. Additionally, psychosocial

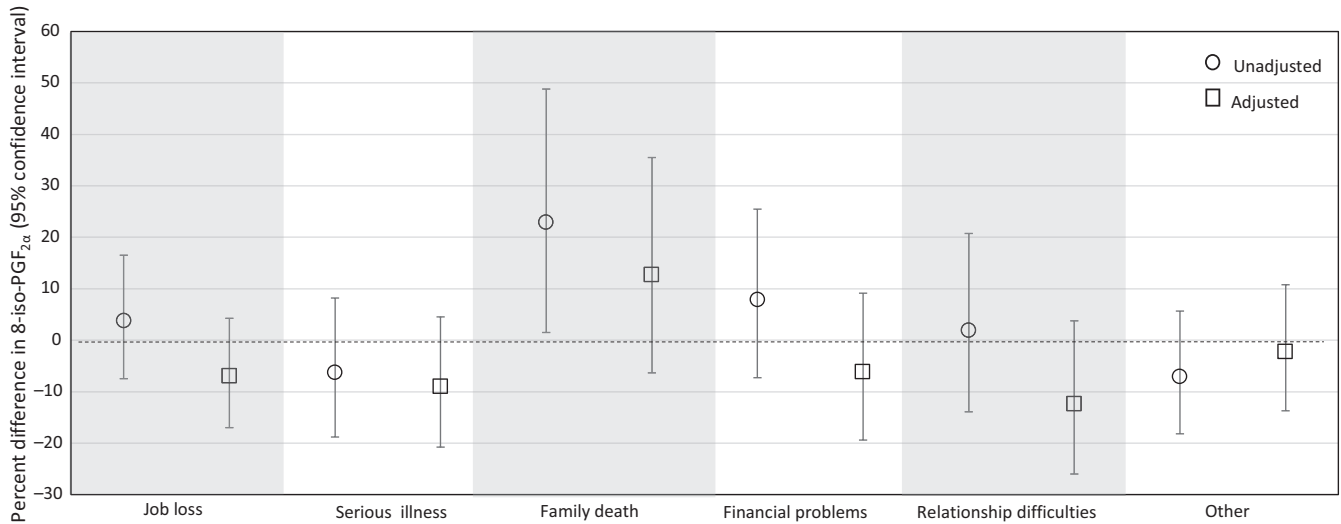


FIGURE 1 Associations (95% confidence intervals) between ever vs never stressful life events in pregnancy and urinary 8-iso-PGF_{2α}^b (corrected for urinary specific gravity) concentrations. Models are adjusted for maternal race/ethnicity, education, maternal age, prepregnancy body mass index and marital status, as well as infant sex and study centre

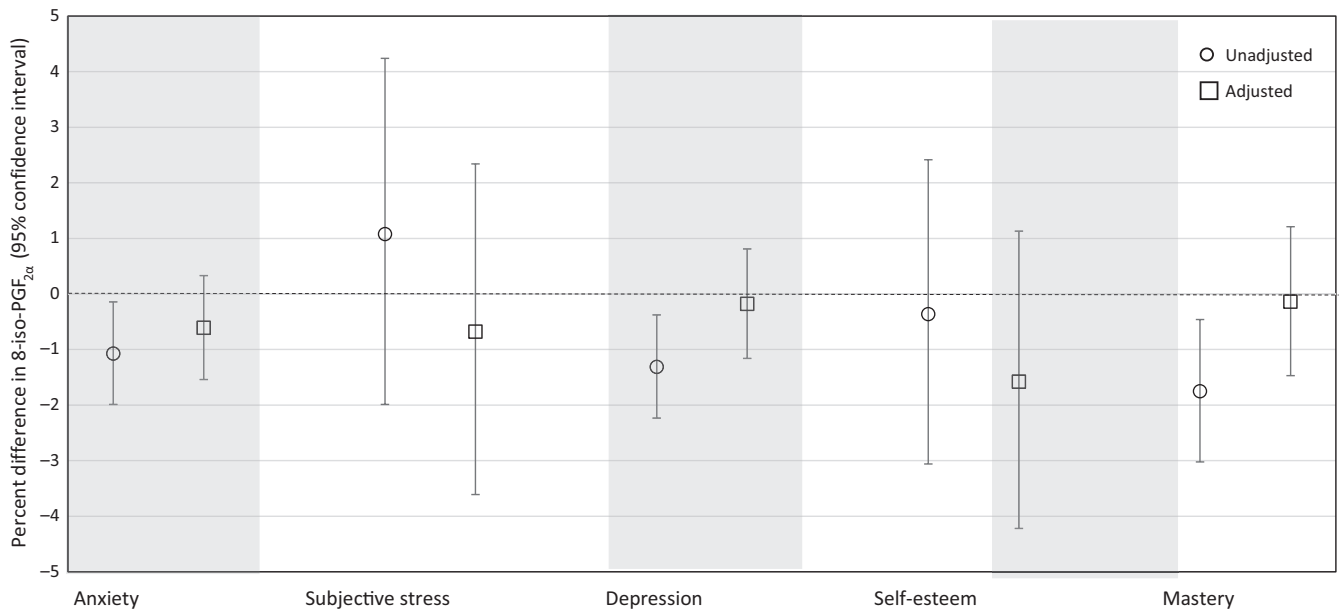


FIGURE 2 Associations (95% confidence intervals) between individual and summary psychosocial status measures and urinary 8-iso-PGF_{2α} concentrations (corrected for urinary specific gravity). Increase in each measure represents greater psychosocial well-being. Models adjusted for maternal race/ethnicity, education, maternal age, prepregnancy body mass index, and marital status, as well as infant sex and study centre

status was assessed at the second visit, and may have changed by the third visit when 8-iso-PGF_{2α} was measured, which may have led to non-differential misclassification of exposure. Third, many associations were examined, thus increasing the likelihood of chance associations. However, since previous associations between family death, anxiety, depression, and oxidative stress have been observed in non-pregnant populations,^{24,25,30} it is unlikely that these results occurred by chance. In addition, TIDES has not yet extracted detailed information on birth outcomes, therefore gestational age was not examined as part of these analyses despite associations between oxidative

stress and gestational age in previous studies.¹¹ As with all observational studies, these results do not provide evidence of causality.

4.4 | Strengths of the study

Despite these limitations, this study has many strengths. The outcome measure 8-iso-PGF_{2α} is one of the best biomarkers of oxidative stress because it is relatively stable, including in human pregnancy, unaffected by dietary lipid intake as some other oxidative stress measures are, and is readily detectable in urine.^{11,31} 8-iso-PGF_{2α} concentration

is not significantly affected by differences in dietary lipid intake of participants.^{32,33} Furthermore, the influence of diurnal fluctuations or fasting status is minimal. 8-iso-PGF_{2α} concentration measured in spot urine vs 24-hour urine is similar on the population level.³⁴ After SLEs, a prolonged change in the signalling network of the body, could lead to significant elevation in the production rate of damaging free radicals.³⁵ This elevated rate of free radical production would lead to prolonged and systemic oxidative stress as indicated by the increased accumulation of the oxidative stress biomarker 8-iso-PGF_{2α} in the urine of individuals with SLE. In addition, the sensitivity analysis using the 8-iso-PGF_{2α} / PGF_{2α} ratio shows that associations are with the oxidative stress fraction of the biomarker and are independent of inflammation. Multiple stress measures were examined in these analysis, allowing for examination between oxidative stress and different indices of stress. Finally, this study included women from four study centres, increasing the generalisability of these findings to pregnant women in the US.

5 | CONCLUSIONS

Poor psychosocial status and occurrence of some stressful life events during pregnancy was associated with elevated levels of urinary 8-iso-PGF_{2α}, an indicator of oxidative stress, in unadjusted analyses. This may be an important underexplored pathway mediating the relationship between psychological stress and later poor pregnancy outcomes. Future research should explore how perceived stress and the intensity of the stressor impact oxidative stress levels during pregnancy.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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