Title
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Journal
Paediatric and perinatal epidemiology, 32(4)

ISSN
0269-5022

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Publication Date
2018-07-01

DOI
10.1111/ppe.12465

Peer reviewed

HHS Public Access

Author manuscript

Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Paediatr Perinat Epidemiol. 2018 July ; 32(4): 318–326. doi:10.1111/ppe.12465.

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, hypothesizing that psychological stress is associated with higher concentrations of oxidative stress biomarkers during pregnancy.

Methods—Psychosocial status and stressful life events (SLEs) were self-reported. 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) 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

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vs. good). Linear models estimated associations between these parameters and urinary 8-iso-$PGF_{2\alpha}$ concentrations after adjusting for covariates.

Results—The geometric mean of 8-iso-$PGF_{2\alpha}$ 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-$PGF_{2\alpha}$ in crude 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-$PGF_{2\alpha}$ in crude analyses. Associations were attenuated, but remained suggestive, after covariate adjustment.

Conclusions—Our data suggest that 8-iso-$PGF_{2\alpha}$ 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-$PGF_{2\alpha}$ levels are associated with adverse birth outcomes, oxidative stress could be a mediator in these relationships.

Introduction

Psychological stress during pregnancy has been associated with pregnancy loss, preterm birth, fetal 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 outcome may be oxidative stress. Oxidative stress as measured through the biomarker 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) is elevated in a variety of diseases as well as pregnancy related complications.[9] Increased levels of 8-iso-$PGF_{2\alpha}$ in pregnancy have been observed among mothers who later experienced preterm birth and preeclampsia.[10, 11] Studies in animal models show 8-iso-$PGF_{2\alpha}$, 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-$PGF_{2\alpha}$. To do so, we used data from The Infant Development and the Environment Study (TIDES), a large, multi-center pregnancy cohort study. We hypothesized that levels of oxidative stress would be elevated among women with poor psychosocial status and in women who experienced stressful life events during pregnancy.

Methods

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, University of Rochester Medical Center, University of Minnesota, and University of Washington/Seattle Children's Hospital) 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, lifestyle, psychosocial factors, health, and reproductive history. The institutional review board approved the study at each participating institution. Each participant provided written informed consent.

Psychosocial status

The second visit questionnaire included the Goldenberg scale, designed to assess psychosocial status during pregnancy, which is composed of 27 items on 5 subscales: anxiety, depression, self-esteem, mastery, and subjective stress.[16] The anxiety subscale included 8 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 (e.g., higher scores on the anxiety subscale are associated with lower anxiety, and higher scores on the self-esteem scale is associated with increased self-esteem). We hypothesized that an increase in each of the subscale scores would be associated with a decrease in urinary 8-iso-$PGF_{2\alpha}$ concentrations.

We also used an established method of creating an overall measure of well-being which we then dichotomized.[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 25^{th} percentile of the overall measure; "good" psychosocial status included women whose values were greater than the 25^{th} percentile.[17] Missingness on any individual question resulted in a missing value for overall psychosocial status. We hypothesized that women with "good" psychosocial status have lower levels of 8-iso-$PGF_{2\alpha}$ compared to women with "poor" psychosocial status.

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 analyzed 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 categorized as having experienced "no" SLEs and women reporting one or more SLEs during pregnancy were categorized as having experienced "any" SLEs. We hypothesized that experiencing SLEs during pregnancy would be associated with higher levels of our biomarker of oxidative stress.

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-$PGF_{2\alpha}$, and prostaglandin-$F_{2\alpha}$ ($PGF_{2\alpha}$) using established protocols. For analysis, [$^2H_4$]-8-iso-$PGF_{2\alpha}$ and [$^2H_4$]-$PGF_{2\alpha}$ (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-$PGF_{2\alpha}$ and $PGF_{2\alpha}$ 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-$PGF_{2\alpha}$ metabolite, which has been hypothesized to be a more sensitive biomarker than 8-iso-$PGF_{2\alpha}$ in urine.[21] However, results were similar to those for 8-iso-$PGF_{2\alpha}$ 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-$PGF_{2\alpha}$ derived from chemical vs. enzymatic lipid peroxidation pathways. To do so, we utilized the ratio of 8-iso-$PGF_{2\alpha}$ to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) 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-$PGF_{2\alpha}$ were analyzed separately to determine if stress was increasing 8-iso-$PGF_{2\alpha}$ 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]

Statistical Methods

Frequencies and counts were used to describe demographic characteristics of our study population. Distributions of urinary 8-iso-$PGF_{2\alpha}$ concentrations were examined using geometric means, geometric standard deviations, and selected percentiles.

The outcome measure, SpG-corrected 8-iso-$PGF_{2\alpha}$, was right skewed and natural log transformed for all analyses. Linear regression models were used to determine crude and adjusted estimates and 95% confidence intervals (CI) for the association between urinary 8-iso-$PGF_{2\alpha}$ 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-$PGF_{2\alpha}$.

Maternal age, recalled prepregnancy body mass index (BMI, kg/m^2), gestational age at urine collection, study center, maternal race/ethnicity, maternal education, household income, marital status, infant sex, alcohol use during the third visit, smoking during the third visit, and prenatal vitamin use during the third visit were examined as potential covariates. Covariates that changed point estimates by >10% were kept 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-$PGF_{2\alpha}$, as described above. The enzymatic fraction of 8-iso-$PGF_{2\alpha}$ 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-$PGF_{2\alpha}$ as compared to the chemical fraction. Second, we explored effect measure modification by maternal race/ethnicity, infant sex, and study site. Last, we examined associations between SLEs and 8-iso-$PGF_{2\alpha}$ 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 (Cary, NC). P-values <0.05 were considered statistically significant.

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 (Table 1).

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-$PGF_{2\alpha}$ (99.7%). Distributions of raw and SpG corrected 8-iso-$PGF_{2\alpha}$ values are presented in Table S1. In bivariate analyses, the geometric mean of urinary SpG corrected 8-iso-$PGF_{2\alpha}$ 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 center. For the overall summary measures, “any” SLE was not associated with urinary 8-iso-$PGF_{2\alpha}$ in crude 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-$PGF_{2\alpha}$ in crude models (% difference in 8-iso-$PGF_{2\alpha}$ with ever vs. never family death 22.9 (95% CI 1.50, 48.8)). This association was still positive, although nonsignificant, in adjusted models (Figure 1; Table S2).

For the overall psychosocial status score, urinary 8-iso-$PGF_{2\alpha}$ was 13.1% higher among mothers with “poor” compared to “good” psychosocial status in crude 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-$PGF_{2\alpha}$ in crude 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-$PGF_{2\alpha}$. Concentrations by demographic characteristics and in association with SLEs 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-$PGF_{2\alpha}$, and differences were consistently more pronounced across groups with the chemical as compared with the enzymatic fraction. The chemical fraction of 8-iso-$PGF_{2\alpha}$ was 23.4% higher among women classified as “poor” vs. “good” psychosocial status in our crude analysis only (95% CI 7.29, 41.9) (Table S5).

We observed few differences in associations in stratified analyses. By study center, the association between psychosocial status and 8-iso-$PGF_{2\alpha}$ was greatest in magnitude at the University of Minnesota, where 8-iso-$PGF_{2\alpha}$ was 21.2% higher among women with “poor” psychosocial status (95% CI 0.51, 4.37) (Table S6). The interaction between center and psychosocial was marginally significant ($p<0.10$). No significant interactions were observed

by infant sex or maternal race/ethnicity (not shown). Among women classified as having "good" psychosocial status, those experiencing "any" SLEs showed decreased levels of 8-iso-$PGF_{2\alpha}$ (% difference −13.3, 95% CI −22.1, −3.55). Among women classified as having "poor" psychosocial status, experiencing "any" SLEs was not associated with 8-iso-$PGF_{2\alpha}$ (% difference −1.17, 95% CI −15.3, 4.0). The interaction between psychosocial status and SLEs was not statistically significant (Table S7).

Comment

We examined the association between prenatal psychological stress and oxidative stress among pregnant women. We hypothesized that an increase in psychological stress would be associated with higher levels of oxidative stress, as indicated by urinary 8-iso-$PGF_{2\alpha}$. Our findings suggest that at least some parameterizations 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.

Our psychosocial status measure was composed of 5 individual summary scores: depression, anxiety, self-esteem, mastery, and subjective stress.[16] In our crude models, we found that higher scores on the on the anxiety and depression subscales (indicative of lower anxiety and lower depression) were associated with lower levels of 8-iso-$PGF_{2\alpha}$, which is consistent with our hypothesis. Previous human data have demonstrated that oxidative stress levels are elevated among individuals experiencing depression[25] and anxiety,[26] which is supported by our crude 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. Thus, our findings suggest that that 8-iso-$PGF_{2\alpha}$ 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] Furthermore, it is consistent with our finding that family death was associated with an increase in 8-iso-$PGF_{2\alpha}$. 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, it is possible that we were over-adjusting by including socio-economic status adjustments in our full models.

We wanted to further explore oxidative stress in this context by using a novel approach to examine enzymatic as compared to chemical fractions of 8-iso-$PGF_{2\alpha}$.[22] Previously, 8-iso-$PGF_{2\alpha}$ was thought to reflect non-enzymatic lipid peroxidation only, i.e., oxidative stress consequent to excess free radical production. However, animal studies indicate that the 8-iso-$PGF_{2\alpha}$ also captures upregulation of some 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-$PGF_{2\alpha}$ through an enzymatic rather than a chemical pathway. We observed a 23% higher chemical fraction of 8-iso-$PGF_{2\alpha}$ in participants with "poor" psychosocial status, but no differences for the enzymatic portion.

This results gives us confidence in concluding that the association between psychosocial status and 8-iso-$PGF_{2\alpha}$ is truly reflective of increased oxidative stress and not inflammation, despite the fact that this was contrary to our hypothesis. However, the associations observed with the chemical fraction could also indicate that there is residual confounding, e.g., unaccounted differences in environmental chemical stressors.

We did not detect any associations between SLEs experienced during pregnancy and urinary 8-iso-$PGF_{2\alpha}$ concentrations, except for the crude association between family death and an increase in 8-iso-$PGF_{2\alpha}$. 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-$PGF_{2\alpha}$ levels were significantly elevated among non-pregnant women experiencing SLEs.[28] Our inconsistent findings may be due to differences in sample sizes and characteristics of the study populations. Our sample included a much larger sample size than the prior study and focused only on pregnant women.

Strengths and limitations

Our assessment of stress was limited in that we examined parameters from two scales, and 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] Notably we would expect misclassification and recall bias to be lowest for family death, where we observed the strongest associations with 8-iso-$PGF_{2\alpha}$. Additionally, psychosocial status was assessed at the second visit, and may have changed by the third visit when 8-iso-$PGF_{2\alpha}$ was measured, which may have led to non-differential misclassification of our exposure. Third, we examined many associations, 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] we do not believe these results occurred by chance. Finally, like all observational studies, we were unable to establish causality.

Despite these limitations, our study has many strengths. Our outcome measure 8-iso-$PGF_{2\alpha}$ 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.[10, 31] 8-iso-$PGF_{2\alpha}$ 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-$PGF_{2\alpha}$ concentration measured in spot urine vs. 24-hour urine is similar on the population level.[34] After SLEs, a prolonged change in the signaling 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-$PGF_{2\alpha}$ in the urine of individuals with

SLE. In addition, our sensitivity analysis using the 8-iso-$PGF_{2\alpha}$ / $PGF_{2\alpha}$ ratio shows that our associations are with the oxidative stress fraction of the biomarker and are independent of inflammation. We were also able to examine multiple stress measures in our analysis, allowing us to examine how oxidative stress is associated with different indices of stress. Finally, our study included women from four study centers, increasing the generalizability of our findings to pregnant women in the US.

Conclusions

In summary, we have found that women with indications of poor psychosocial status and occurrence of some stressful life events during pregnancy had elevated levels of urinary 8-iso-$PGF_{2\alpha}$, an indicator of oxidative stress, in crude 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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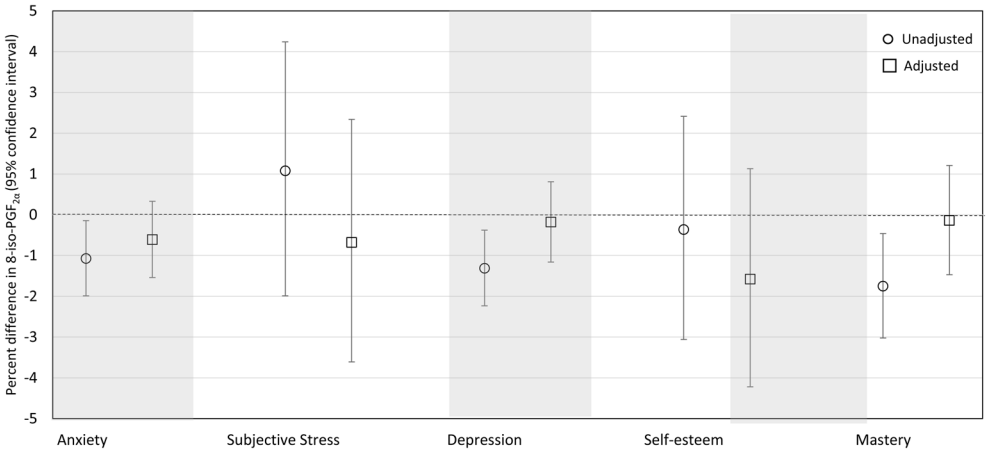

Figure 1.

Crude and adjusted[a] associations (95% confidence intervals) between ever vs. never stressful life events in pregnancy and urinary 8-iso-$PGF_{2\alpha}$[b] concentrations.

[a]Models adjusted for maternal race/ethnicity, education, maternal age, prepregnancy body mass index, and marital status, as well as infant sex and study center.

[b]8-iso-$PGF_{2\alpha}$ concentrations corrected for urinary specific gravity.

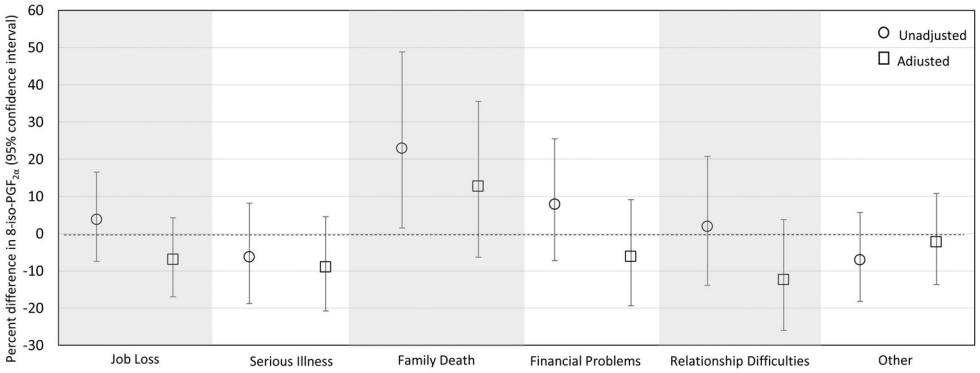

Figure 2.

Crude and adjusted[a] associations (95% confidence intervals) between individual and summary psychosocial status measures and urinary 8-iso-$PGF_{2\alpha}$[b] concentrations. Increase in each measure represents greater psychosocial well-being.

[a]Models adjusted for maternal race/ethnicity, education, maternal age, prepregnancy body mass index, and marital status, as well as infant sex and study center.

[b]8-iso-$PGF_{2\alpha}$ concentrations corrected for urinary specific gravity.

Table 1

Demographic characteristics and selected health behaviors of the study population by stressful life events[a] and psychosocial status[b] categories during pregnancy.

	Total	Stressful Life Events			Psychosocial Status		
	(n=761)	None (n=646)	Any (n=297)		Good (n=536)	Poor (n=182)	
Continuous variables	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p**	**Mean (SD)**	**Mean (SD)**	**p**
Maternal age (years)	31.7 (5.49)	32.4 (5.16)	30.6 (5.80)	**<0.01**	32.0 (5.32)	31.1 (5.56)	**0.05**
Pre-pregnancy BMI (kg/m^2)	26.2 (6.22)	25.6 (5.91)	27.2 (6.56)	**<0.01**	25.6 (5.90)	27.5 (6.32)	**<0.01**
Gestational age at urine collection (weeks)	32.7 (3.03)	32.9 (3.10)	32.4 (2.90)	**0.02**	32.8 (3.11)	32.2 (2.64)	**0.03**
Categorical variables	N (%)	%	%		%	%	
Study Center				**<0.01**			**<0.01**
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				**<0.01**			0.20
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				**<0.01**			**<0.01**
< 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				**<0.01**			**<0.01**
<$15,000–$25,00 per year	177 (23.3)	41.2	58.8		60.6	39.4	
$25,001–$75,000 per year	199 (26.1)	58.8	41.2		75.5	24.5	
>$75,000 per year	358 (47.0)	71.5	28.5		80.4	19.6	
Married or living together				**<0.01**			**<0.01**

	Total	Stressful Life Events			Psychosocial Status		
	(n=761)	None (n=646)	Any (n=297)		Good (n=536)	Poor (n=182)	
Continuous variables	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p**	**Mean (SD)**	**Mean (SD)**	**p**
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	0.12	75.3	24.7	0.21
No	72 (9.5)	50.0	50.0		66.7	33.3	
Alcohol use during 3rd trimester				0.39			0.95
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				0.10			**<0.01**
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 sex				0.89			0.28
Boy	361 (47.4)	60.7	39.3		77.3	22.7	
Girl	389 (51.1)	61.4	38.6		72.1	27.9	

Abbreviations: SD, standard deviation.

[a]Stressful life events categorized as none (no stressful life event during pregnancy) vs. any (one or more stressful life events during pregnancy).

[b]Psychosocial status categorized as good (sum of individual scores>25th percentile) vs. poor (sum of individual scores ≤ 25th percentile).

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

Table 2

Geometric means (geometric standard deviations) of specific gravity corrected urinary 8-iso-$PGF_{2\alpha}$ concentrations (ng/mL) by demographic characteristics and selected health behaviors during pregnancy.

	Geometric Mean (Geometric SD)	p
Study center		
Rochester, NY	1.20 (1.84)	Reference
San Francisco, CA	0.78 (1.72)	**<0.01**
Minneapolis, MN	0.92 (1.83)	**<0.01**
Seattle, WA	0.93 (1.67)	**<0.01**
Race/ethnicity		
Non-Hispanic white	0.89 (1.78)	Reference
Other	1.09 (1.85)	**<0.01**
Education		
≥ college graduate	0.85 (1.73)	Reference
< college graduate	1.27 (1.88)	**<0.01**
Household income		
<$15,000–$25,00 per year	1.21 (1.80)	Reference
$25001–$75,000	0.97 (1.87)	**<0.01**
>$75,000 per year	0.82 (1.72)	**<0.01**
Married or living together		
Yes	0.90 (1.78)	Reference
No	1.24 (1.87)	**<0.01**
Prenatal vitamin use during 3rd visit		
Yes	0.93 (1.81)	Reference
No	1.03 (1.80)	0.18
Alcohol use during 3rd visit		
No	0.96 (1.83)	Reference
Yes	0.81 (1.62)	**0.04**
Smoking during 3rd visit		
No	0.93 (1.80)	Reference
Yes	1.22 (1.92)	**<0.01**
Infant sex		
Boy	1.01 (1.81)	Reference
Girl	0.90 (1.81)	**<0.01**
Stressful life events[a]		
None	0.96 (1.77)	Reference
Any	0.94 (1.88)	0.79

	Geometric Mean (Geometric SD)	p
Psychosocial status[b]		
Good	0.91 (1.85)	Reference
Poor	1.03 (1.67)	**0.02**

Abbreviations: SD, standard deviation.

[a]Stressful life events categorized as none (no stressful life event during pregnancy) vs. any (one or more stressful life events during pregnancy).

[b]Psychosocial status categorized as good (sum of individual scores>25th percentile) vs. poor (sum of individual scores ≤ 25th percentile).

Note: P-values calculated from chi square test for categorical variables and linear models for continuous variables; bold indicates statistical significance.

Table 3

Crude and adjusted[a] associations between specific gravity corrected urinary 8-iso-$PGF_{2\alpha}$ concentrations (ng/mL) and stressful life events and psychosocial status.

	Crude		Adjusted	
	N	**% Change (95% CI)**	**N**	**% Change (95% CI)**
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)

Abbreviations: CI: confidence interval.

[a]Models adjusted for maternal race/ethnicity, education, maternal age, prepregnancy body mass index, and marital status, as well as infant sex and study center.

[b]Stressful life events categorized as none (no stressful life event during pregnancy) vs. any (one or more stressful life events during pregnancy).

[c]Psychosocial status categorized as good (sum of individual scores>25th percentile) vs. poor (sum of individual scores ≤ 25th percentile).

Note: Bold indicates statistical significance.