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Associations between social, biologic, and behavioral factors and biomarkers of oxidative stress during pregnancy: Findings from four ECHO cohorts

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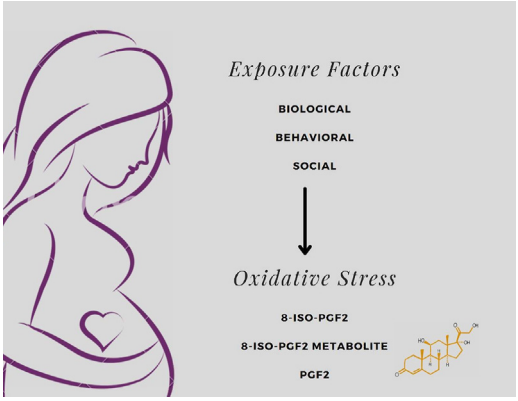
HIGHLIGHTS

- Oxidative stress biomarkers were elevated among pregnant people with higher socio-economic disadvantage.
- Associations were strongest for the chemical fraction of 8-iso-$PGF_{2\alpha}$.
- Oxidative stress may link socioeconomic status to adverse pregnancy outcomes.

GRAPHICAL ABSTRACT



Abbreviations: 8-isoPGF2α, Isoprostane-prostaglandin F2α; CI, Confidence interval; CIOB, Chemicals in Our Bodies; HPA, Hypothalamic-pituitary-adrenal; ICC, Intraclass correlation coefficient; IKIDS, Illinois Kids Development Study; LOD, Limit of detection; PGF2α, Prostaglandin F2α; SD, Standard deviation; SES, Socioeconomic status; SpG, Specific gravity; PROTECT, Puerto Rico Testsite for Exploring Contamination Threats; TIDES, The Infant Development and Environment Study.

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ABSTRACT

Background: Lower socioeconomic status (SES) and elevated psychosocial stress are known contributors to adverse pregnancy outcomes; however, biological mechanisms linking these factors to adverse pregnancy outcomes are not well-characterized. Oxidative stress may be an important, yet understudied mechanistic pathway. We used a pooled study design to examine biological, behavioral, and social factors as predictors of prenatal oxidative stress biomarkers.
Methods: Leveraging four pregnancy cohorts from the Environmental influences on Child Health Outcomes (ECHO) Program spanning multiple geographic regions across the United States (U.S.) ($N = 2082$), we measured biomarkers of oxidative stress in urine samples at up to three time points during pregnancy, including 8-isoprostane-prostaglandin $F_{2\alpha}$ (8-isoPGF$_{2\alpha}$), its major metabolite, 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostane, and prostaglandin $F_{2\alpha}$ (PGF$_{2\alpha}$). Maternal age, pre-pregnancy body mass index, marital/partnered status, parity, and smoking status were included as biological and behavioral factors while race/ethnicity, maternal education, and stressful life events were considered social factors. We examined associations between each individual biological, behavioral, and social factor with oxidative stress biomarkers using multivariable-adjusted linear mixed models.
Results: Numerous biological, behavioral, and social factors were associated with elevated levels of 8-isoPGF$_{2\alpha}$, its major metabolite, and PGF$_{2\alpha}$. Pregnant people who were current smokers relative to non-smokers or had less than a high school education relative to a college degree had 11.04% (95% confidence interval [CI] = −1.97%, 25.77%) and 9.13% (95% CI = -1.02%, 20.32%) higher levels of 8-isoPGF$_{2\alpha}$, respectively.
Conclusions: Oxidative stress biomarkers are elevated among pregnant people with higher socioeconomic disadvantage and may represent one pathway linking biological, behavioral, and social factors to adverse pregnancy and child health outcomes, which should be explored in future work.

1. Introduction

Lower socioeconomic status (SES) and higher levels of psychosocial stressors are well-known contributors to adverse pregnancy outcomes (Lima et al., 2018; Dunlop et al., 2021). Across the United States (U.S.) and globally, large disparities in the rates of adverse birth outcomes, including preterm birth and lower birth weight, persist across economic classes and racial and ethnic groups (Martin et al., 2021; Braveman et al., 2015). Structural inequalities and other social factors often underlie these observed health disparities (Dunlop et al., 2021), as factors such as differences in education, the built environment, or experiences of racism may increase the exposure and susceptibility of an individual to adverse outcomes (Cutter et al., 2003). Additionally, the same populations who face structural inequalities are often disproportionately exposed to the highest level of environmental hazards, which may also increase the risk of adverse pregnancy outcomes (Morello-Frosch and Shenassa, 2006; Eick et al., 2021a; Ferguson et al., 2019a; Barrett and Padula, 2019; Padula et al., 2020a; Padula et al., 2020b).

Despite high rates of adverse pregnancy outcomes and their high social cost, the biologic pathways linking social and behavioral factors to adverse birth outcomes are not well-characterized. While the hypothalamic-pituitary-adrenal (HPA) axis is hypothesized to be a key contributor (Ng, 2000), oxidative stress may represent an alternative (or complementary) unifying mechanism. 8-isoprostane-prostaglandin $F_{2\alpha}$ (8-isoPGF$_{2\alpha}$), a measure of lipid peroxidation, is widely considered to be the 'gold standard' biomarker of oxidative stress (Kadiiska et al., 2017; Roberts and Morrow, 2000). 8-isoPGF$_{2\alpha}$ is elevated in response to numerous environmental chemical and non-chemical stressors that may be reflective of a socioeconomic disadvantage, such as low educational attainment and smoking status (Cathey et al., 2021; Eick et al., 2018; Janczura et al., 2020; Ferguson et al., 2015a; van der Plas et al., 2019). Prior studies also suggest that certain biological factors, such as obesity, predispose individuals to elevated levels of 8-isoPGF$_{2\alpha}$ (Marseglia et al., 2014). Further, prenatal levels of 8-isoPGF$_{2\alpha}$ are increased among those who go on to experience adverse birth outcomes and pregnancy-related complications (Eick et al., 2020a; Ferguson et al., 2015b; Ferguson et al., 2017). However, most prior studies have been limited by relatively small sample sizes, restricted geographic locations, and racially homogenous study populations, which do not reflect the diversity of the U.S. Thus, better understanding determinants of oxidative stress during pregnancy may help clinicians and public health practitioners better target interventions aimed at improving pregnancy outcomes.

In the current analysis, we used harmonized data from four pregnancy cohorts participating in the National Institutes of Health (NIH) Environmental influences on Child Health Outcomes (ECHO) Program (National Institutes of Health, n.d.). Our combined study population includes a demographically diverse group of predominately Latina and White pregnant people with repeated measures of oxidative stress across gestation. We measured 8-isoPGF$_{2\alpha}$, as well as its major metabolite, as biomarkers of oxidative stress. The 8-isoPGF$_{2\alpha}$ metabolite was included because it may be a superior biomarker than its parent compound when measured in urine (Dorjgochoo et al., 2012). We additionally included a third oxidative stress marker, prostaglandin-$F_{2\alpha}$ (PGF$_{2\alpha}$), as it is enzymatically derived and reflective of inflammation pathways. When measured in combination with 8-isoPGF$_{2\alpha}$, PGF$_{2\alpha}$ may allow us to disentangle the proportion of 8-isoPGF$_{2\alpha}$ that is derived from enzymatic and non-enzymatic lipid peroxidation pathways (van't Erve et al., 2015). We hypothesized that certain biological and behavioral factors (e.g., increasing maternal age, being overweight or obese, increasing parity, or being a current smoker) would lead to increased levels of these biomarkers. We similarly hypothesized that oxidative stress biomarkers would be elevated among those who experience structural inequalities or social factors reflecting lower SES (e.g., persons of color, lower educational attainment, and experiences of stressful life events). Our study is the largest to date that examines behavioral, biological, and social factors in relation to prenatal oxidative stress.

2. Methods

2.1. Study population

Our study population included four cohorts participating in the NIH ECHO Program: Chemicals in Our Bodies (CIOB—San Francisco, California), Illinois Kids Development Study (IKIDS-Champaign-Urbana, Illinois), Puerto Rico Testsite for Exploring Contamination Threats (PROTECT), and The Infant Development and Environment Study (TIDES- Rochester, New York; San Francisco, California; Seattle, Washington; and Minneapolis, Minnesota). Our final sample size included 2082 participants: 229 from CIOB, 230 from IKIDS, 866 from PROTECT, and 757 from TIDES (**Fig. S1**). Together, these cohorts represent a geographically and demographically diverse study population. These cohorts were invited to participate in this combined analysis because they had measures of urinary levels of 8-isoPGF$_{2\alpha}$, the major 8-isoPGF$_{2\alpha}$ metabolite, and PGF$_{2\alpha}$ in a subset of participants at the time of analysis. Detailed information on recruitment

and data collection methods for each cohort is provided elsewhere (Eick et al., 2021b; Ferguson et al., 2019b; Swan et al., 2015). Briefly, for all studies, participants were recruited during pregnancy and were eligible for inclusion if they were not pregnant with multiples and were at least 18 years of age. Each of these cohorts' protocols was reviewed and approved by their local institutional review boards, and all cohort participants provided written, informed consent.

2.2. Biological and behavioral factors

Biological and behavioral factors included maternal age, pre-pregnancy body mass index (BMI; kg/m^2), parity, and smoking status. This information was obtained by self-reported interview questionnaire administered during pregnancy or from the medical record.

2.3. Social factors

We included maternal race/ethnicity, educational attainment, marital status, and self-reported experiences of stressful life events (SLEs) as social factors. While belonging to a certain racial or ethnic group should not predispose one to elevated levels of oxidative stress, people of color often experience higher levels of racism and structural discrimination relative to White individuals (Lee et al., 2019). Information on perceived racism was not available in our analytic sample, and we have included self-identified race/ethnicity as a proxy for experiences of racial discrimination.

All cohorts asked about the occurrence of five SLEs within the last year (CIOB) or during pregnancy (IKIDS, PROTECT, TIDES) using a self-reported interview questionnaire (Eick et al., 2018; Eick et al., 2021b; Eick et al., 2020b). Across all cohorts, stressful life events included: participant or participant's partner lost their job, a close family member was ill or hospitalized, participant or participant's partner experienced legal or financial trouble, participant experienced relationship problems with their partner, or someone close to the participant died. We created a binary measure of SLEs where pregnant people reporting no SLEs were categorized as "none" and those reporting at least one SLE were categorized as having experienced "any."

2.4. Oxidative stress biomarkers

Urine samples were collected at three time points in PROTECT (mean 18.2, 23.6, and 26.9 weeks gestation), two time points in both CIOB (mean 20.2 and 31.0 weeks gestation) and IKIDS (mean 16.2 and 23.3 weeks gestation), and once in TIDES (mean 32.7 weeks gestation), and were frozen at −80 °C prior to analysis. For all cohorts, the Eicosanoid Core Laboratory at Vanderbilt University Medical Center analyzed urinary levels of 8-isoPGF$_{2\alpha}$, 2,3-dinor-5,6-dihydro-15-F$_{2t}$-isoprostane (8-isoPGF$_{2\alpha}$ metabolite), and PGF$_{2\alpha}$. Biomarker analysis of the PROTECT and TIDES urine samples was conducted using stable isotype dilution gas chromatography-negative ion chemical ionization mass spectrometry; this method has been described in detail elsewhere (Milne et al., 2007). Briefly, this method requires a C18 Sep-Pak column for solid-phase extraction, a thin-layer chromatography purification, and chemical derivation. During analyses, samples are thawed, and 0.25 ml urine is diluted in 10 ml pH 3 water and acidified to pH 3 using 1 N HCl prior to extraction. Analysis for urine samples obtained from CIOB and IKIDS participants was done using liquid chromatography–mass spectrometry. The Eicosanoid Core Laboratory measures quality control (QC) samples with each batch, and urine is aliquoted in large batches to ensure that the same QCs are used for every batch for at least a year. Levels of F_2-Isoprostanes are also measured in these samples to track variation over time.

As an exploratory sensitivity analysis, we additionally quantified the proportions of 8-isoPGF$_{2\alpha}$ derived from each of the respective pathways using the ratio of 8-isoPGF$_{2\alpha}$ to PGF$_{2\alpha}$ (van't Erve et al., 2015). The chemical fraction captures non-enzymatic lipid peroxidation as a result of oxidative stress while the enzymatic fraction is generated from prostaglandin-endoperoxide synthases and is more reflective of inflammation. The chemical and enzymatic fractions were calculated using a custom interface for the R package "Constrained Linear Mixed Effects (CLME)" (van't Erve et al., 2015).

To account for urinary dilution, all biomarker concentrations were corrected for specific gravity (SpG) using the equation $Ox_c = Ox[(SpG_{Median}\text{-}1)/SpG\text{-}1]$, where SpG_{Median} is the SpG population median for each cohort, Ox is the measured oxidative stress biomarker concentration, and Ox_c is the SpG-corrected measure. The constant SpG_{median} was 1.019 for PROTECT, 1.012 for CIOB, 1.015 for IKIDS, and 1.014 for TIDES. All SpG-corrected biomarker concentrations were right-skewed and natural log-transformed for analyses. Oxidative stress biomarker concentrations below the limit of detection (LOD) were imputed using $LOD/\sqrt{2}$.

2.5. Statistical analysis

We examined the distribution of oxidative biomarker concentrations across biological, behavioral, and social factors using geometric means and geometric standard deviations (SD). We additionally utilized generalized additive mixed models with a random intercept for participant ID and a smoothing term for gestational age at sample collection to graphically depict levels of measured oxidative stress biomarkers across gestation. Intraclass correlation coefficients (ICC) were calculated to examine variability in biomarker concentrations across repeated measures. ICC values range from 0 to 1, where ICC values closest to 1 indicate perfect reliability and values closer to 0 indicate greater variability. ICC values between 0.4 and 0.75 indicate good reliability (Rosner, 2011). Because oxidative stress biomarkers were only available at one time point in TIDES, this cohort was excluded from ICC calculations.

For our repeated measures analysis, we used linear mixed models to examine associations between each individual biological, behavioral, and social factor and biomarker concentrations. Oxidative stress biomarkers were treated as separate outcomes. Models included a fixed effect categorical indicator for study cohort, a smoothed term for gestational age at sample collection, and a random intercept for participant ID. Covariates included in models were chosen via a directed acyclic graph (DAG) that was informed via a literature review (**Fig. S2**). Models evaluating maternal education, marital status, maternal age, or pre-pregnancy BMI as primary exposures were only adjusted for cohort and gestational age at sample collection. In models where parity was the exposure of interest, we additionally adjusted for maternal age. When race/ethnicity and smoking status were the exposures, we additionally controlled for education and marital status as indicators of SES. When the SLE indicator was the exposure, we included maternal age, marital status, education, and race/ethnicity. A complete case analysis was used for all multivariable models. The final sample size for all models is presented in **Table S1**.

We conducted numerous sensitivity analyses to determine if any associations could be attributed to underlying differences (i.e., heterogeneity) across cohorts. We first examined associations stratified by cohort to compare cohort-specific associations. Second, we conducted an analysis excluding participants from the PROTECT cohort given that PROTECT contributed the largest number of participants and experiences of certain social factors in Puerto Rico may not be representative of experiences in the mainland U.S. Third, we restricted our analysis to only include the latest oxidative stress measurement for each cohort. Next, we compared our primary model that used a fixed effect for cohort to a model that used a random effect for cohort. When both approaches give similar estimates, it indicates that heterogeneity across cohorts is minimal (Basagaña et al., 2018). Lastly, because specific gravity may also be influenced by other covariates (e.g., age, race/ethnicity, BMI), we separately standardized SpG concentration using an established covariate-adjustment approach (Kuiper et al., 2021; O'Brien et al., 2016). Using this approach, we applied the equation $Ox_c = Ox[(SpG_{predict}\text{-}1)/SpG\text{-}1]$, where $SpG_{predict}$ corresponds to the predicted specific gravity concentration based on a prediction model

of specific gravity (Kuiper et al., 2021; O'Brien et al., 2016). We included the covariate standardized SpG corrected biomarkers as outcomes in our linear mixed models and compared effect estimates to those obtained in our primary analysis, which corrected oxidative stress biomarkers using the sample mean of SpG.

All statistical analyses were conducted on complete cases using R version 4.0.1.

3. Results

The majority of participants included in this analysis were married (65%), had a normal pre-pregnancy BMI (51%), and had a college (40%) or graduate (30%) degree (Table 1). Approximately half of our study population were Latina; 5% were Black; 5% were Asian or Pacific Islander; 2% were multi-racial; and nearly 40% were White. The high percentage of Latinas was attributed to the inclusion of the PROTECT cohort, as nearly all PROTECT participants self-identified as Latina (**Table S2**). In the overall analytic sample, 34% experienced at least one stressful life event. The prevalence of stressful life events varied widely across cohorts, with 62% of CIOB participants experiencing stressful life events compared with only 22% of IKIDS participants (**Table S2**).

The distribution of oxidative stress biomarkers is presented in Table 2. All biomarkers were detected in nearly 100% of participants (**Table S3**).

Table 1
Distribution of biological, behavioral, and social factors in the overall study population (N = 2082).

	N (%)
Biological and behavioral factors	
Maternal age (years)	
18–24	458 (22%)
25–29	531 (26%)
30–34	616 (30%)
≥35	429 (21%)
Missing	48 (2.3%)
Pre-pregnancy BMI (kg/m^2)	
Underweight	88 (4%)
Normal	1069 (51%)
Overweight	466 (22%)
Obese	394 (19%)
Missing	65 (3.1%)
Parity	
0	900 (43%)
1+	991 (48%)
Missing	191 (9.2%)
Current smoker	
No	1929 (93%)
Yes	76 (4%)
Missing	77 (3.7%)
Social factors	
Maternal race/ethnicity	
White	781 (38%)
Black	114 (5%)
Asian/Pacific Islander	108 (5%)
Latina	999 (48%)
Other/multi-racial	49 (2%)
Missing	31 (1.5%)
Maternal education	
<High school	145 (7%)
High school or some college	459 (22%)
College degree	832 (40%)
Graduate degree	628 (30%)
Missing	18 (0.9%)
Marital status	
Married	1347 (65%)
Living together	396 (19%)
Single	325 (16%)
Missing	14 (0.7%)
Stressful life events	
None	1251 (60%)
Any	701 (34%)
Missing	130 (6.2%)

BMI, body mass index.

Table 2
Distribution of urinary levels of oxidative stress biomarkers corrected with specific gravity (ng/mL).

	N	Geometric mean (Geometric SD)	Percentile 5	25	50	75	95
Measured							
8-iso-PGF$_{2\alpha}$							
Overall	3255	1.34 (2.01)	0.43	0.90	1.43	2.12	3.59
Average	2082	1.23 (1.94)	0.41	0.82	1.29	1.91	3.29
8-iso-PGF$_{2\alpha}$ metabolite							
Overall	3251	0.90 (3.1)	0.07	0.60	0.91	1.42	5.4
Average	2081	0.83 (2.64)	0.2	0.55	0.83	1.28	3.88
PGF$_{2\alpha}$							
Overall	3255	2.31 (2.44)	0.51	1.56	2.55	3.98	7.35
Average	2082	2.25 (2.12)	0.59	1.51	2.39	3.61	6.71
Derived							
8-iso-PGF$_{2\alpha}$ chemical							
Overall	3255	0.91 (2.47)	0.19	0.56	1.01	1.66	3.17
Average	2082	0.8 (2.41)	0.17	0.5	0.87	1.48	2.86
8-iso-PGF$_{2\alpha}$ enzymatic							
Overall	3255	0.13 (9.55)	0	0.09	0.32	0.56	1.09
Average	2082	0.14 (6.49)	0	0.06	0.27	0.49	0.96

Overall distributions are calculated using all subject-specific values. Average values are calculated using biomarker concentrations averaged across all available time points for each participant. 8-iso-PGF2α, 8-isoprostane-prostaglandin F2α; PGF2α, prostaglandin F2α; SD, standard deviation.

The overall geometric means were 1.34 for 8-isoPGF$_{2\alpha}$ (geometric SD = 2.01), 0.9 for the 8-isoPGF$_{2\alpha}$ metabolite (geometric SD = 3.1), and 2.31 for PGF$_{2\alpha}$ (geometric SD = 2.44). Among individual cohorts, the geometric mean of 8-isoPGF$_{2\alpha}$ (geometric mean = 1.13) was highest for IKIDS, whereas the geometric mean of the metabolite and PGF$_{2\alpha}$ were highest in CIOB and PROTECT, respectively (geometric mean = 2.14 and 2.84, correspondingly) (**Table S3**). ICC values for 8-isoPGF$_{2\alpha}$ indicated moderate reliability (ICC = 0.55, 95% confidence interval [CI] = 0.51, 0.59), whereas the values for the 8-isoPGF$_{2\alpha}$ metabolite and PGF$_{2\alpha}$ were less stable (ICC = 0.24, 95% CI = 18, 0.29; ICC = 0.14, 95% CI = 0.08, 0.19, respectively). Levels of 8-isoPGF$_{2\alpha}$ and the 8-isoPGF$_{2\alpha}$ metabolite increased slightly during mid-gestation, whereas levels of PGF$_{2\alpha}$ declined across pregnancy (Fig. 1).

In our repeated measures analysis using linear mixed models (Fig. 2; **Table S4**), we observed that 8-isoPGF$_{2\alpha}$ levels were higher among those who were single relative to married (% difference = 21.5, 95% CI = 14.2, 29.3), current smokers relative to non-smokers (% difference = 11.04, 95% CI = -1.97, 25.77), and overweight (% difference = 15.4, 95% CI = 9.41, 21.7) or obese (% difference = 34.54, 95% CI = 26.98, 42.45) relative to a normal weight. Effect estimates were similar when the 8-isoPGF$_{2\alpha}$ metabolite and PGF$_{2\alpha}$ were the outcomes of interest. Compared with White participants, Black participants had 25.44% higher 8-isoPGF$_{2\alpha}$ (95% CI = -0.93, 55.8), whereas those who were Asian or Pacific Islander had 34.7% higher levels of the major 8-isoPGF$_{2\alpha}$ metabolite (95% CI = 11.2, 62.2). When examining the chemical and enzymatic fractions of 8-isoPGF$_{2\alpha}$, associations were consistently strongest for the chemical fraction, whereas associations with the enzymatic fraction were null (**Table S4**). This indicates that increases in 8-isoPGF$_{2\alpha}$ occurring as a result of biological, behavioral, and social factors were through chemical free radical lipid peroxidation, as opposed to enzymatic inflammatory pathways.

In our supplemental analysis, models adjusted for cohort alone similarly showed that levels of 8-isoPGF$_{2\alpha}$ and the 8-isoPGF$_{2\alpha}$ metabolite were elevated among those who were overweight or obese, between 18 and 24 years of age, and unmarried relative to reference groups (**Table S5**). When stratifying by cohort, experiencing stressful life events was associated with a significant increase in 8-isoPGF$_{2\alpha}$ within the PROTECT cohort only (% difference = 6.97, 95% CI = 1.08, 13.2), as has been previously reported (**Table S6**) (Eick et al., 2018; Eick et al., 2019). Effect estimates restricted to CIOB and IKIDS had wide CIs, which reflected the relatively

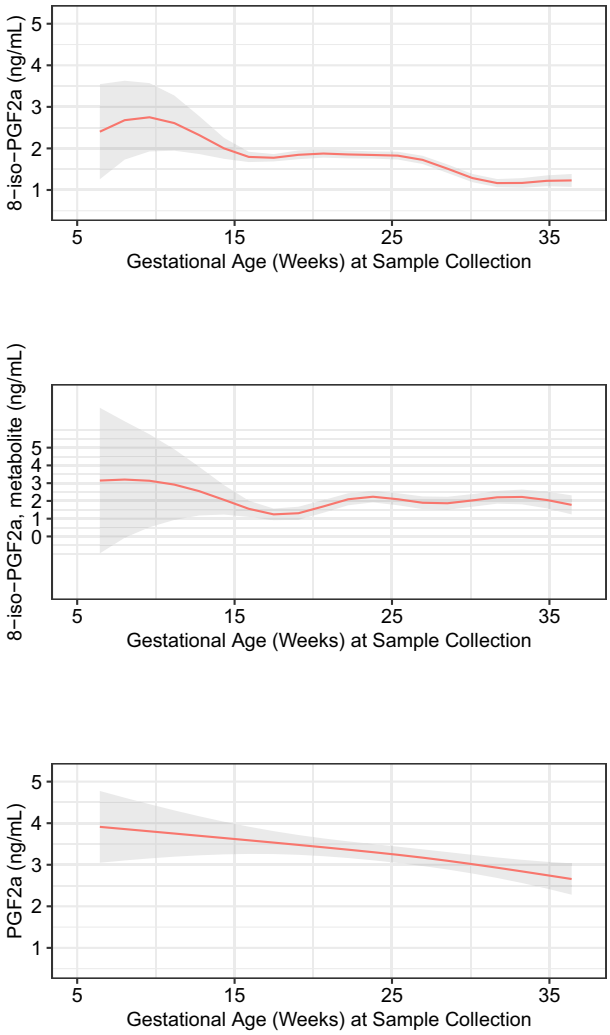

Fig. 1. Predicted values (95% confidence intervals) of specific gravity-corrected urinary oxidative stress biomarker concentrations by gestational age at sample collection obtained from generalized additive mixed models with a random intercept for participant ID.

small sample sizes in these cohorts. Associations between the 8-isoPGF$_{2\alpha}$ metabolite and PGF$_{2\alpha}$ and biological, behavioral, and social factors were similar to those observed for 8-isoPGF$_{2\alpha}$ (data not shown). When restricting to only the latest oxidative stress biomarker measurement, point estimates were similar to our primary analysis (**Table S7**), although confidence intervals were less precise. In a leave-one-out analysis removing the PROTECT cohort, the positive associations between 8-isoPGF$_{2\alpha}$ and lower education (having less than a high school education relative to a high school degree) and younger age (18–24 years of age relative to 25–29) were slightly attenuated (**Table S8**). However, effect estimates were still in the same direction as in our main analysis. The associations between biological, behavioral, and social factors and 8-isoPGF$_{2\alpha}$ were nearly identical when cohort was included as a random effect compared with a fixed effect (**Table S9**). Associations between behavioral, biological, and social factors and covariate-adjusted SpG-corrected oxidative stress biomarker concentrations were similar to those observed when oxidative stress biomarkers were corrected for SpG alone (data not shown).

4. Discussion

In the present analyses, we utilized data from four prospective birth cohorts enrolled in the NIH ECHO Program to examine associations between behavioral, biological, and social factors and prenatal oxidative stress. Our results demonstrate that many of these factors were associated with elevated levels of 8-isoPGF$_{2\alpha}$ and its major metabolite, 2,3-dinor-5,6-dihydro-15-F$_{2t}$-isoprostane. These associations were strongest with the proportion of 8-isoPGF$_{2\alpha}$ generated through chemical lipid peroxidation, indicating that the associations we observed with 8-isoPGF$_{2\alpha}$ may be attributable to oxidative stress rather than inflammation.

Our findings that 8-isoPGF$_{2\alpha}$ levels are sensitive to biological, behavioral, and social factors replicate and extend prior research in this area. Among a group of pregnant people in Boston, 8-isoPGF$_{2\alpha}$ levels were higher among those who self-identified as Black and other/multi-racial relative to White, and among those with a pre-pregnancy BMI ≥ 30 kg/m^2 (Ferguson et al., 2015a). That study also observed inverse associations between educational attainment and 8-isoPGF$_{2\alpha}$ (Ferguson et al., 2015a), which was observed in our study. Among non-pregnant populations, recent meta-analyses have found that 8-isoPGF$_{2\alpha}$ levels are increased among smokers relative to non-smokers and that obesity is associated with permanently increased oxidative stress in adults (van der Plas et al., 2019; Marseglia et al., 2014). In our study, the strongest associations observed were with smoking and obesity, highlighting two potentially modifiable risk factors to lower levels of oxidative stress.

Oxidative stress may be one pathway linking structural inequalities to adverse health outcomes among pregnant people and their offspring. Within the TIDES cohort, we previously showed that increasing levels of 8-isoPGF$_{2\alpha}$ and its metabolite were associated with lower birthweight and increased childhood weight at age 4 (Arogbokun et al., 2021). Numerous studies have further shown that elevated levels of 8-isoPGF$_{2\alpha}$ and its metabolite are associated with increased odds of preterm birth (Eick et al., 2020a; Ferguson et al., 2015b; Rosen et al., 2019; Longini et al., 2007; Peter Stein et al., 2008; Mestan et al., 2012). Some evidence further suggests that 8-isoPGF$_{2\alpha}$ levels are also elevated among those who develop preeclampsia relative to normotensive pregnancies (Ferguson et al., 2017). Higher 8-isoPGF$_{2\alpha}$ and 8-OH-dG, a marker of DNA damage, were also associated with lower scores on a measure of suboptimal health status within a hospital-based study of pregnant people in Ghana (Anto et al., 2020).

A novel aspect of our study was our exploratory analysis that utilized the ratio of 8-isoPGF$_{2\alpha}$ to PGF$_{2\alpha}$ to examine fractions of 8-isoPGF$_{2\alpha}$. This represents an advancement from prior studies that have interpreted 8-isoPGF$_{2\alpha}$ solely as an indicator of oxidative stress (i.e., derived from lipid peroxidation pathways). However, we also acknowledge that the equations described by van 't Erve et al. (Van't Erve et al., 2016), which allowed us to estimate the relative contribution of both enzymatic and chemical lipid peroxidation to the formation of 8-isoPGF$_{2\alpha}$ were developed from animal studies. Preliminary findings in humans suggest that only a small amount of 8-isoPGF$_{2\alpha}$ is produced via enzymatic lipid peroxidation (van't Erve et al., 2018). Nonetheless, recent work indicates that environmental chemical and non-chemical stressors have diverse associations with 8-isoPGF$_{2\alpha}$ fractions. For example, within the TIDES and PROTECT cohorts, phthalate metabolites primarily lead to increases in the chemical fraction of 8-isoPGF$_{2\alpha}$, reflecting increases in 'true' oxidative stress derived from the lipid peroxidation pathway (Cathey et al., 2021; van et al., 2019). We similarly observed that stressful life events were associated with a modest increase in the chemical fraction and a non-significant decrease in the enzymatic fraction (indicative of inflammation) in our study. This suggests that chemical and non-chemical stressors may be more strongly linked to 8-isoPGF$_{2\alpha}$ derived from free radical, non-enzymatic pathways. Taken together, this underscores the importance of differentiating between the 8-isoPGF$_{2\alpha}$ fractions and analyzing associations separately, as the underlying physiologic pathways may be unique.

Our results should be interpreted in light of study limitations. The different cohorts included in our analytic sample assessed stressful life events using different scales with different timeframes (including year prior to pregnancy versus during the current pregnancy period only), which may have resulted in exposure misclassification. We also had no indicator for severity of stressors or measures of stress in childhood or in the years leading up to the current pregnancy, which may have a stronger effect on 8-

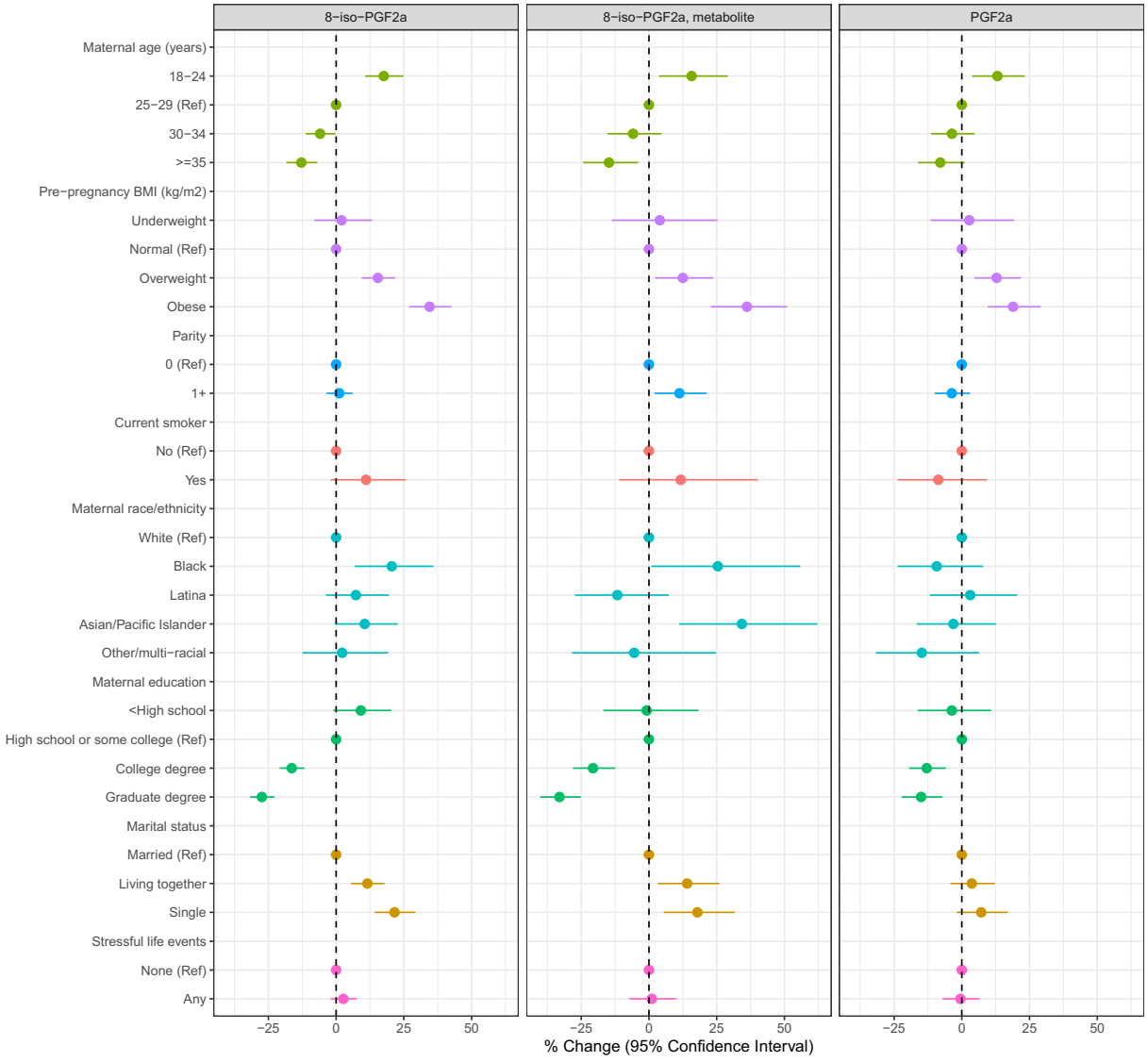

Fig. 2. Repeated measures analyses: percent change (95% confidence interval) in urinary specific gravity–corrected oxidative stress biomarker concentrations (ng/mL) in relation to biological, behavioral, and social factors. Sample sizes for all models are provided in Table S1. All models are adjusted for cohort and include a random intercept for participant ID and smoothed term for gestational age at study visit. Models that include race/ethnicity and current smoker as exposures are additionally adjusted for marital status and education. A model including parity as the exposure is additionally adjusted for maternal age. A model that includes stressful life events as the exposure is additionally adjusted for maternal age, race/ethnicity, education, and marital status. BMI, body mass index.

isoPGF$_{2\alpha}$ than our stressful life events measure, as prior work suggests that a history of childhood maltreatment or experiencing intimate partner violence is associated with higher levels of 8-isoPGF$_{2\alpha}$ (Kim et al., 2017; Boeck et al., 2019). We did not have a measure of perceived discrimination, and we utilized race/ethnicity as a proxy. A study of over 3700 adults in Maryland showed that self-reported racial discrimination was associated with higher levels of red blood cell oxidative stress, and associations were strongest for Black adults (ages 30–64) (Szanton et al., 2012). Within the context of our particular study, utilizing race/ethnicity as a proxy may not be applicable for Latinas, as the majority of Latina participants were enrolled in the PROTECT cohort and experiences of Latinas living in Puerto Rico are different than those of participants living in the mainland U.S. Additionally, other biological markers of stress and other measures of oxidative stress, including other 8-isoPGF$_{2\alpha}$ metabolites, were not measured in our study population and would be important to consider in future work. Further, while we did utilize the 8-isoPGF$_{2\alpha}$ ratio formula to derive chemical and enzymatic fractions, allowing us to differentiate between oxidative stress and inflammation, it would be worthwhile to explore inflammatory cytokines as well. We did not make any adjustment for multiple comparisons, which may increase the likelihood of chance findings. However, we focused the interpretation of our results on identifying consistent patterns as opposed to specific point estimates (Rothman, 1990). Importantly, adjusting for multiple comparisons is not always necessary in exploratory observational studies, as it may increase the probability of type II error due to low statistical power (Rothman, 1990). Lastly, while we did adjust for known covariates using a DAG, as with all observational studies, we cannot rule out the possibility of residual confounding.

Despite these limitations, our study has many strengths. First, capitalizing on the ECHO Program, we had a large sample size of over 2000 pregnant people spanning multiple geographic regions in the continental U.S. and Puerto Rico. These cohorts had repeated measures of oxidative stress across pregnancy, robust information on covariates, and together provided a study population that was racially and ethnically diverse. The results from our study provide important insights into demographically diverse pregnant populations that are not routinely included in environmental epidemiologic studies. Additionally, our analysis included 8-isoPGF$_{2\alpha}$, which is considered to be the 'gold standard' biomarker of oxidative stress (Kadiiska et al., 2017). 8-isoPGF$_{2\alpha}$ is robust to dietary lipid intake

(Gopaul et al., 2000; Richelle et al., 1999) and on a population level, 8-isoPGF$_{2\alpha}$ levels in a spot urine sample are similar to what is observed in a 24-h fasting sample (Helmersson and Basu, 2001). Our biomarkers were also measured in urine, which is preferred over plasma, as samples are not subject to auto-oxidation during storage (Morrow et al., 1990). Oxidative stress biomarkers were also measured using highly specific mass spectrometry methods, which is preferred over immunoassay (Klawitter et al., 2011).

5. Conclusions

Our study is the largest to date examining behavioral, biological, and social factors in relation to prenatal oxidative stress. We found that these factors were associated with elevated levels of oxidative stress, which highlights one potential pathway linking structural inequalities to adverse pregnancy and maternal health outcomes. Our study adds to the literature characterizing contributors to elevated prenatal oxidative stress.

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Role of the funding source

The sponsor had no role in the study design; the collection, analysis, and interpretation of the data; the writing of the report; or in the decision to submit the article for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Ethical approval

Each of these cohorts' protocols was reviewed and approved by their local institutional review boards, and all cohort participants provided written, informed consent.

Data availability statement

The datasets for this manuscript are not publicly available because, per the NIH-approved ECHO Data Sharing Policy, ECHO-wide data have not yet been made available to the public for review/analysis. Requests to access the datasets should be directed to the ECHO Data Analysis Center, ECHO-DAC@rti.org.

CRediT authorship contribution statement

Stephanie M. Eick was responsible for funding acquisition, data cleaning and analysis, interpretation of results, writing-original draft, revisions and editing.

Sarah Dee Geiger contributed to data analysis, interpretation of results, writing-reviewing and editing.

Akram Alshawabkeh was responsible for funding acquisition, project administration, and writing-reviewing and editing.

Max Aung contributed to data analysis, interpretation of results, writing-reviewing and editing.

Emily Barrett contributed to project administration, and writing-reviewing and editing.

Nicole R. Bush contributed to project administration, and writing-reviewing and editing.

José F. Cordero was responsible for funding acquisition, project administration, and writing-reviewing and editing.

Kelly K. Ferguson contributed to data analysis, interpretation of results, writing-reviewing and editing.

John D. Meeker was responsible for funding acquisition, project administration, and writing-reviewing and editing.

Ginger L. Milne was responsible for the measurement of urinary oxidative stress biomarkers and contributed to writing-reviewing and editing.

Ruby HN Nguyen contributed to project administration, and writing-reviewing and editing.

Amy M. Padula contributed to data analysis, interpretation of results, writing-reviewing and editing.

Sheela Sathyanarayana contributed to project administration, and writing-reviewing and editing.

Barrett M. Welch contributed to data analysis, interpretation of results, writing-reviewing and editing.

Susan L. Schantz was responsible for funding acquisition, project administration, and writing-reviewing and editing.

Tracey J. Woodruff was responsible for funding acquisition, project administration, and writing-reviewing and editing.

Rachel Morello-Frosch contributed to data analysis and interpretation of results and was responsible for funding acquisition, project administration, and writing-reviewing and editing.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.155596.

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