Free Radical Biology and Medicine 143 (2019) 95–100

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Associations between socioeconomic status, psychosocial stress, and urinary levels of 8-iso-prostaglandin-$F_{2\alpha}$ during pregnancy in Puerto Rico

Stephanie M. Eick[a], John D. Meeker[b], Phil Brown[c], Andrea Swartzendruber[a], Rafael Rios-McConnell[d], Ye Shen[a], Ginger L. Milne[e], Carmen Vélez Vega[d], Zaira Rosario[d], Akram Alshawabkeh[f], José F. Cordero[a], Kelly K. Ferguson[b,g,*]

[a] Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, 101 Buck Road, Athens, GA, 30329, United States
[b] Department of Environmental Health Sciences, University of Michigan School of Public Health, 1415 Washington Hts, Ann Arbor, MI, 48109, United States
[c] Social Science Environmental Health Research Institute, Northeastern University, 318 INV 360 Huntington Ave. Boston, MA, 02115, United States
[d] University of Puerto Rico Graduate School of Public Health, UPR Medical Sciences Campus, Paseo Dr. Jose Celso Barbosa, PO Box 365067, San Juan, PR, 00936-5067, United States
[e] Division of Clinical Pharmacology, Vanderbilt University Medical Center, 562 Preston Research Bldg, 2200 Pierce Avenue, Nashville, TN, 37232-6602, United States
[f] College of Engineering, Northeastern University, 501 ST 360 Huntington Ave. Boston MA, 02115-500, United States
[g] Epidemiology Branch, National Institute of Environmental Health Sciences, 111 TW Alexander Drive, Research Triangle Park, NC, 27709, United States

ARTICLE INFO

Keywords:
Psychosocial stress
Oxidative stress
Pregnancy
Social determinants
Isoprostanes

ABSTRACT

Background: Lower socioeconomic status (SES) and psychosocial stress during pregnancy have been associated with adverse birth outcomes. While hypothalamic-pituitary-axis activation is thought to be the primary driver, oxidative stress may also be involved mechanistically. We used data from the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) cohort (N = 476) to examine associations between self-reported psychosocial stress measures, SES indicators, and urinary oxidative stress biomarker concentrations, hypothesizing that women with lower SES and increased psychosocial stress would have elevated oxidative stress biomarkers.

Methods: Maternal age, education, marital status, insurance status, alcohol use and smoking status were obtained via self-reported questionnaires and were used as indicators of SES. Perceived stress, depression, negative life experiences, neighborhood perceptions, and social support were self-reported in questionnaires administered during pregnancy. Responses were grouped into tertiles for analysis, where the highest tertile corresponded to highest level of psychosocial stress. Urinary concentrations of 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) and its primary metabolite were measured at three study visits (median 18, 24, 28 weeks gestation) and averaged to reflect oxidative stress across pregnancy. Linear models were used to examine associations between SES indicators, tertiles of psychosocial stress and oxidative stress biomarkers.

Results: Average levels of 8-iso-$PGF_{2\alpha}$ and the 8-iso-$PGF_{2\alpha}$ metabolite were higher among pregnant women who were younger, who had public compared to private insurance, and who were unemployed compared to employed. However, no associations were observed between psychosocial stress measures and biomarker concentrations in adjusted analyses.

Conclusions: Psychosocial stress during pregnancy, as indicated by self-reported questionnaire measures, was not associated with biomarkers of oxidative stress in the PROTECT study. However, results suggest that these biomarkers are elevated among women of lower SES, which is typically associated with stress. Notably, compared to other populations, self-reported psychosocial stress measures were lower in PROTECT compared to other populations.

1. Introduction

Decreasing socioeconomic status (SES) and increasing psychosocial stress have been associated with adverse pregnancy outcomes [1]. One potential pathway linking these factors to adverse birth outcomes may be elevated oxidative stress. Thus, understanding the origins of

* Corresponding author. Epidemiology Branch, National Institute of Environmental Health Sciences, 111 TW Alexander Drive, Research Triangle Park, NC, 27709, United States.
E-mail address: kelly.ferguson2@nih.gov (K.K. Ferguson).

https://doi.org/10.1016/j.freeradbiomed.2019.07.032
Received 29 May 2019; Received in revised form 17 June 2019; Accepted 28 July 2019
Available online 29 July 2019
0891-5849/ Published by Elsevier Inc.

oxidative stress during pregnancy may lead to improved intervention strategies for preventing poor pregnancy endpoints, such as preterm birth [2].

Certain health behaviors frequently associated with lower SES may contribute to higher oxidative stress levels. For example, relative to higher SES individuals, smoking, alcohol use, and unhealthy diets are more common among those with lower SES [3,4]. These behaviors are known to increase oxidative stress [5,6]. Additionally, individuals of lower SES may be disproportionately exposed to environmental contaminants, such as air pollution and phthalates [7], which have been associated with increased concentrations of oxidative stress biomarkers [8,9].

Individuals who are socioeconomically disadvantaged may also experience higher levels of psychosocial stress, in part due to experiencing a greater number of daily hassles, anxiety, and poorer living conditions [1]. Studies in non-pregnant populations have shown that individuals with higher levels of psychosocial stress, such as those who experience stressful life events and symptoms of depression and anxiety, have elevated oxidative stress biomarkers compared to their less stressed counterparts [10–12]. Few studies, however, have been conducted among pregnant women [13,14] where it may be particularly important. Furthermore, these studies have been limited by a small number of scales used to measure psychosocial stress [11,14]. Thus, we sought to examine the relationships between SES, 5 measures of psychosocial stress, and oxidative stress biomarkers in a cohort of pregnant women residing in Puerto Rico. We hypothesized that increased psychosocial stress and indicators of SES disadvantage would be associated with elevated oxidative stress levels.

2. Methods

2.1. Study population

Pregnant women included in this analysis delivered between August 2012 and April 2017 and are a subset of women enrolled to date in the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) cohort. Recruitment methods have been previously described in detail [15,16]. Inclusion criteria for PROTECT were as follows: maternal age between 18 and 40 years, residence in the Northern Karst aquifer region, and no known obstetric and medical complications (e.g., diabetes). Women who used *in vitro* fertilization to become pregnant and who used oral contraceptives for 3 months prior to conception were excluded. Participants completed up to 3 study visits, targeted at approximately 20 ± 2, 24 ± 2, and 28 ± 2 weeks gestation, and demographic information is obtained via questionnaire at the first visit. Spot urine samples were obtained at each study visit. All women provided written informed consent prior to participating and the Institutional Review Board at all participating locations (University of Georgia, University of Michigan, Northeastern University, University of Puerto Rico) approved this study.

We included the following categorical covariates as indicators of SES or as sociodemographic characteristics in our analyses: maternal age in years (18-24, 25-29, 30-34, ≥35), marital status (single, married, living together and unmarried), maternal education (< high school, high school degree or equivalent, some college or technical school, ≥college degree), employment status (unemployed, employed), insurance status (public, private, uninsured), alcohol use (never, before pregnancy, current at visit 1) and smoking status (never, before pregnancy, current at visit 1).

2.2. Psychosocial stress

Five questionnaire measures of psychosocial stress were administered to participants in PROTECT. The Life Experience Survey [17] and two questions assessing perceptions of neighborhood safety and quality [18] were administered at the second visit as indicators of negative life experiences and neighborhood perceptions, respectively. The 10-item Perceived Stress Scale [19], 20-item Center for Epidemiologic Studies-Depression scale (CES-D) [20], and 7-item ENRICHD Social Support Instrument [21] were administered at the third visit.

Responses to individual questions on each scale were summed to create continuous measures of stress. If the response to any individual question on the scale was missing, the overall scale was coded as missing for that individual. Continuous measures for each scale were grouped into tertiles (i.e., low, medium, high stress) for analyses, where the highest tertile corresponded to high stress for all scales, except the ENRICHD Social Support Instrument where the lowest tertile indicated low social support (i.e., high stress). Additional information regarding classification of psychosocial stress measures is provided elsewhere [22].

Table 1
Distribution of demographic characteristics in the PROTECT study population (N = 476).

	N (%)
Maternal Age, years	
18-24	189 (39.7)
25-29	148 (31.1)
30-34	85 (17.9)
≥35	54 (11.3)
Maternal Education	
< High school	35 (7.35)
High school or equivalent	72 (15.1)
Some college or technical school	171 (35.9)
≥College degree	198 (41.6)
Employment Status	
Employed	295 (62.0)
Unemployed	181 (38.0)
Marital Status	
Single	91 (19.1)
Married	256 (53.8)
Living together	129 (27.1)
Alcohol Use	
Never	210 (44.1)
Before pregnancy	241 (50.6)
Current	25 (5.25)
Smoking	
Never	392 (82.4)
Before pregnancy	65 (13.7)
Current	19 (4.00)
Insurance Status	
Private	293 (61.6)
Public	177 (37.2)
Uninsured	6 (1.26)

Note: percentages may not sum to 100 due to rounding. The number of imputed values for each variable were as follows: maternal age = 0, maternal education = 4, employment status = 5, marital status = 2, alcohol use = 6, smoking = 2, insurance status = 17.

2.3. Oxidative stress biomarker assessment

The Eicosanoid Core Laboratory at Vanderbilt University Medical Center (Nashville, TN) analyzed free 8-isoprostane-prostaglandin-$F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) as a biomarker of oxidative stress using stable isotype dilution gas chromatography-negative ion chemical ionization-mass spectrometry in 476 participants (N = 272 samples at visit 1, N = 345 samples at visit 2, N = 221 samples at visit 3) [23]. The major 8-iso-$PGF_{2\alpha}$ metabolite, 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostanes, was also measured, as is thought to be a superior biomarker of oxidative stress than 8-iso-$PGF_{2\alpha}$ in urine [24]. We additionally measured

Table 2
Associations between specific gravity corrected urinary oxidative stress concentrations (ng/mL) and selected demographic characteristics (N = 476).

	8-iso-prostaglandin-$F_{2\alpha}$		8-iso-prostaglandin-$F_{2\alpha}$ metabolite	
	% Difference (95% CI)	p	% Difference (95% CI)	p
Maternal Age, years				
18-24	17.8 (8.31, 28.2)	< 0.01	22.5 (12.0, 33.9)	< 0.01
25-29	Ref	Ref	Ref	Ref
30-34	−1.10 (−10.9, 9.78)	0.84	−1.99 (−12.3, 9.50)	0.72
≥35	−7.62 (−18.2, 4.37)	0.20	0.88 (−11.4, 14.9)	0.89
Maternal Education				
< High school	14.6 (−0.73, 32.3)	0.06	21.1 (4.29, 40.7)	0.01
High school or equivalent	19.3 (7.11, 32.9)	< 0.01	28.1 (14.5, 43.4)	< 0.01
Some college or technical school	13.8 (4.90, 23.4)	< 0.01	18.7 (8.98, 29.3)	< 0.01
≥College degree	Ref	Ref	Ref	Ref
Employment Status				
Unemployed	9.19 (1.40, 17.6)	0.02	14.3 (5.71, 23.7)	< 0.01
Employed	Ref	Ref	Ref	Ref
Marital Status				
Single	6.01 (−3.64, 16.6)	0.23	11.1 (0.49, 22.8)	0.04
Married	Ref	Ref	Ref	Ref
Living together	9.86 (0.89, 19.6)	0.03	18.7 (8.61, 29.8)	< 0.01
Alcohol Use				
Never	Ref	Ref	Ref	Ref
Before pregnancy	−2.43 (−9.42, 5.10)	0.52	−2.36 (−9.77, 5.66)	0.55
Current	−5.90 (−20.8, 11.8)	0.49	−2.59 (−18.8, 16.8)	0.78
Smoking				
Never	Ref	Ref	Ref	Ref
Before pregnancy	8.62 (−2.36, 20.8)	0.13	5.07 (6.11, 17.6)	0.39
Current	12.6 (−6.30, 35.4)	0.21	2.67 (−15.7, 25.1)	0.79
Insurance Status				
Private	Ref	Ref	Ref	Ref
Public	14.2 (6.01, 23.0)	< 0.01	18.1 (9.23, 27.8)	< 0.01
Uninsured	30.0 (−6.62, 80.9)	0.12	36.6 (−2.31, 91.0)	0.07

Note: associations are unadjusted. The number of imputed values for each variable were as follows: maternal age = 0, maternal education = 4, employment status = 5, marital status = 2, alcohol use = 6, smoking = 2, insurance status = 17.
Abbreviations: CI, confidence interval; Ref, reference.

prostaglandin-$F_{2\alpha}$ ($PGF_{2\alpha}$) which can be used to distinguish whether 8-iso-$PGF_{2\alpha}$ derive from chemical or enzymatic pathways [25]. As a sensitivity analysis, we quantified the proportion of 8-iso-$PGF_{2\alpha}$ derived from chemical and enzymatic fractions using the ratio of $PGF_{2\alpha}$ to 8-iso-$PGF_{2\alpha}$, as calculated by a custom interface for the R package "Constrained Linear Mixed Effects (CLME)", and examined associations with these endpoints [25]. For all biomarkers measured, values below the limit of detection (LOD; 0.101 ng/mL) were replaced by LOD/the square root of 2.

Urinary specific gravity (SpG) was measured using a digital hand-held refractometer to indicate urine dilution. All urinary oxidative stress biomarker concentrations were corrected for SpG using the equation $Ox_c = Ox\ [(1.019\text{-}1)/(SpG\text{-}1)]$, where 1.019 is the median SpG in the PROTECT population, Ox is the measured oxidative stress concentration, and Ox_c is the SpG-corrected measure. We then took the geometric mean of the available SpG-corrected oxidative stress concentrations across visits to reflect pregnancy averages. All averages were natural log transformed for normality in statistical models.

2.4. Statistical analysis

Descriptive statistics were used to summarize participant socio-demographic characteristics. Linear regression models were used to calculate crude estimates and 95% confidence intervals (CI) for the associations between SES indicators, psychosocial stress and each oxidative stress biomarker pregnancy average. Adjusted estimates were also obtained from linear regression models in which psychosocial stress was the exposure. QQ-plots were examined for each model to check linear regression assumptions, including linearity, normality, and homoscedasticity. Beta estimates were converted to percent difference in oxidative stress biomarker concentration in association with SES indicators and psychosocial stress. Tests for linear trend across tertiles were conducted using the Cochrane Armitage test [26]. SES indicators retained in adjusted models changed point estimates by ≥ 10%.

Missing data for psychosocial stress measures and covariates (< 10% for each imputed variable) was imputed using multiple imputation via chained equations (MICE), which was implemented using the 'mice' package in R. Oxidative stress biomarker concentrations were not included as predictors in the imputation procedure. All analyses were conducted in R Version 3.5.0 and SAS 9.4 (Cary, NC).

3. Results

This analytic sample included 476 women who had at least one urine sample analyzed for oxidative stress biomarkers. Most women were between 18 and 24 years of age (39.7%), were married (53.8%), had a college degree or higher (41.6%), and were non-smokers (82.4%; Table 1). The geometric mean of 8-iso-$PGF_{2\alpha}$ and the 8-iso-$PGF_{2\alpha}$ metabolite was 1.84 (geometric standard deviation [SD] = 1.66) and 0.88 (geometric SD = 1.72), respectively.

In bivariate analyses, indicators of lower SES were associated with elevated pregnancy averages of both oxidative stress biomarkers (Table 2). For example, compared to women who were employed, women who were unemployed had 9.19% (95% CI = 1.40-17.6) and

Table 3
Associations between specific gravity corrected urinary 8-iso-prostaglandin-$F_{2\alpha}$ concentrations (ng/mL) and psychosocial stress measures (N = 476).

	Crude		Adjusted[1]	
	% Difference (95% CI)	p	% Difference (95% CI)	p
ENRICHD Social Support Instrument				
High	Ref	Ref	Ref	Ref
Medium	2.41 (−6.83, 12.6)	0.62	−2.44 (−13.1, 9.48)	0.68
Low	4.26 (−5.03, 14.5)	0.38	−1.77 (−11.7, 9.32)	0.74
p trend	0.37		0.75	
Perceived Stress Scale				
Low	Ref	Ref	Ref	Ref
Medium	−3.17 (−11.5, 5.98)	0.48	−5.65 (−13.7, 3.15)	0.20
High	2.09 (−7.05, 12.1)	0.67	−2.11 (−10.8, 7.41)	0.65
p trend	0.71		0.61	
CES-D				
Low	Ref	Ref	Ref	Ref
Medium	−1.18 (−9.66, 8.10)	0.80	−1.62 (−9.95, 7.48)	0.72
High	6.70 (−3.09, 17.5)	0.19	2.89 (−6.50, 13.2)	0.56
p trend	0.21		0.60	
Life Experience Survey				
Low	Ref	Ref	Ref	Ref
Medium	6.85 (−2.39, 17.0)	0.15	5.13 (−3.82, 14.9)	0.27
High	9.59 (0.24, 19.8)	0.04	7.74 (−1.36, 17.7)	0.10
p trend	0.04		0.09	
Neighborhood Perceptions				
Low	Ref	Ref	Ref	Ref
Medium	−1.38 (−9.73, 7.74)	0.76	0.16 (−8.15, 9.23)	0.97
High	0.84 (−9.89, 12.8)	0.88	−1.35 (−11.8, 10.3)	0.81
p trend	0.99		0.86	

Note: the number of imputed values for each variable were as follows: ENRICHD Social Support Instrument = 36, Perceived Stress Scale = 37, CES-D = 45, Life Experience Survey = 35, Neighborhood Perceptions = 17.
Abbreviations: CI, confidence interval; Ref, reference; CES-D, Center for Epidemiologic Studies-Depression.
[1] Models are adjusted for maternal age, maternal education, and marital status.

Table 4
Associations between specific gravity corrected urinary 8-iso-prostaglandin-$F_{2\alpha}$ metabolite concentrations and psychosocial stress measures (N = 476).

	Crude		Adjusted[1]	
	% Difference (95% CI)	p	% Difference (95% CI)	p
ENRICHD Social Support Instrument				
High	Ref	Ref	Ref	Ref
Medium	9.46 (−0.18, 20.0)	0.06	1.68 (−8.84, 13.4)	0.77
Low	12.3 (1.87, 23.7)	0.02	3.31 (−7.23, 15.0)	0.55
p trend	0.01		0.55	
Perceived Stress Scale				
Low	Ref	Ref	Ref	Ref
Medium	3.72 (−5.68, 14.1)	0.45	0.46 (−8.51, 10.3)	0.92
High	7.83 (−2.43, 19.2)	0.14	1.93 (−7.67, 12.5)	0.70
p trend	0.14		0.71	
CES-D				
Low	Ref	Ref	Ref	Ref
Medium	0.36 (−8.62, 10.2)	0.94	−0.14 (−8.81, 9.36)	0.98
High	7.22 (−2.96, 18.5)	0.17	1.87 (−7.74, 12.5)	0.71
p trend	0.18		0.73	
Life Experience Survey				
Low	Ref	Ref	Ref	Ref
Medium	−0.98 (−10.0, 8.99)	0.84	−3.57 (−12.1, 5.82)	0.44
High	2.73 (−6.59, 13.0)	0.58	0.30 (−8.61, 10.8)	0.95
p trend	0.62		0.97	
Neighborhood Perceptions				
Low	Ref	Ref	Ref	Ref
Medium	−0.52 (−9.38, 9.20)	0.91	0.84 (−7.84, 10.3)	0.86
High	4.53 (−7.20, 17.8)	0.47	1.78 (−9.42, 14.4)	0.77
p trend	0.58		0.75	

Note: the number of imputed values for each variable were as follows: ENRICHD Social Support Instrument = 36, Perceived Stress Scale = 37, CES-D = 45, Life Experience Survey = 35, Neighborhood Perceptions = 17.
Abbreviations: CI, confidence interval; Ref, reference; CES-D, Center for Epidemiologic Studies-Depression.
[1] Models are adjusted for maternal age, maternal education, and marital status.

14.3% (95% CI = 5.71-23.7) higher 8-iso-$PGF_{2\alpha}$ and 8-iso-$PGF_{2\alpha}$ metabolite levels, respectively. Women with public insurance also had elevated levels of 8-iso-$PGF_{2\alpha}$ (% difference = 14.2, 95% CI = 6.01-23.0) and 8-iso-$PGF_{2\alpha}$ metabolite (% difference = 18.1, 95% CI = 9.23-27.8) compared to women with private insurance. Additionally, women who had less than a college education and who were between 18 and 24 years of age had elevated levels of both biomarkers compared to those who had a college education and who were between 25 and 29. Associations between SES indicators and $PGF_{2\alpha}$ and the chemical and enzymatic fractions of 8-iso-$PGF_{2\alpha}$ were similar to those observed with 8-iso-$PGF_{2\alpha}$ and the 8-iso-$PGF_{2\alpha}$ metabolite (Table S1).

In crude models of the associations between psychosocial stress and 8-iso-$PGF_{2\alpha}$, women with high compared to low scores on the Life Experience Survey had increased 8-iso-$PGF_{2\alpha}$ (% difference = 9.59, 95% CI = 0.24-19.8; p-trend = 0.04). High compared to low scores on the CES-D were also somewhat associated with elevated 8-iso-$PGF_{2\alpha}$ in crude models (% difference = 6.70, 95% CI = -3.09-17.5). Maternal age, education, and marital status were retained as covariates in final adjusted models. No associations were observed in adjusted models examining associations between psychosocial stress measures and 8-iso-$PGF_{2\alpha}$ (Table 3).

For the 8-iso-$PGF_{2\alpha}$ metabolite, point estimates were generally elevated among women in the upper two tertiles of each stress scale compared to reference groups in crude and adjusted models (Table 4). In crude models, medium and high levels of the ENRICHD Social Support Instrument were associated with an 9.46% (95% CI = -0.18-20.0) and 12.3% (95% CI = 1.87-23.7) increase in the 8-iso-$PGF_{2\alpha}$ metabolite relative to women in the lowest tertile (p-trend = 0.01). Women with high compared to low scores on the Perceived Stress Scale also had moderately increased levels of the metabolite (% difference = 7.83, 95% CI = -2.43-19.2; p-trend = 0.14). However, no associations between psychosocial stress measures and the 8-iso-$PGF_{2\alpha}$ metabolite were observed in adjusted models (Table 4). These associations, as well as associations between psychosocial stress measures and 8-iso-$PGF_{2\alpha}$, were similar in unimputed data (data not shown).

No associations between psychosocial stress measures and $PGF_{2\alpha}$ were observed in crude or adjusted models (Table S2). Additionally, our sensitivity analysis revealed no associations between psychosocial stress measures and the chemical and enzymatic fractions of 8-iso-$PGF_{2\alpha}$ (Tables S3–S4).

4. Discussion

We examined associations between indicators of SES as well as self-reported psychosocial stress and oxidative stress biomarkers during pregnancy. Overall, our results suggest that women at a socioeconomic disadvantage have higher levels of oxidative stress, but we did not observe associations between self-reported psychosocial stress and oxidative stress biomarkers.

Our finding that women of lower SES have higher oxidative stress biomarker concentrations is consistent with the literature. For example, another pregnancy cohort found that women who had less than a college degree and were unmarried had elevated 8-iso-$PGF_{2\alpha}$ in the third trimester [14]. Additionally, in a population of pregnant women from

Boston, MA, participants with higher education levels had lower 8-iso-$PGF_{2\alpha}$ compared to women with a high school education only [13].

Other evidence has shown that 8-iso-$PGF_{2\alpha}$ levels are elevated among pregnant and non-pregnant individuals who experience extreme stressful life events and elevated levels of perceived stress [12,14]. Although our results do not support this hypothesis, other studies in non-pregnant populations have shown that psychosocial stress is associated with other oxidative stress biomarkers, specifically 8-hydroxy-2′-deoxyguanosine (8-OH-dG), a measure of oxidative DNA damage. For example, women who experienced anxiety and anger had elevated 8-OH-dG concentrations compared to women with lower scores on these scales [27]. An additional study found that increasing workplace social support was associated with decreasing 8-OH-dG [28].

We did not observe any associations between psychosocial stress measures and oxidative stress biomarkers in adjusted analyses. Some of our previous work has shown that the mean levels of self-reported psychosocial stress questionnaires in PROTECT are lower than mean stress levels observed in other cohorts [22]. For example, in PROTECT, the mean CES-D score was 11 as compared to 24.4 among women in the Boston Puerto Rico Health Study [29] or 21.8 among women recruited from primary care clinics in San Juan, PR [30]. The lower levels of reported stress in our population may be a result of differences in self-report across scales or due to features of the cohort's institutional context. For example, participants in PROTECT receive multiple prenatal care visits as a result of their participation in the study.

An important limitation of our study was that our scales only measured psychosocial stress during pregnancy. We had no measure prior to pregnancy and some literature suggests that it is the accumulation of stress across the life course that is more relevant for adverse health outcomes [31]. Additionally, oxidative stress biomarkers measured in our study are markers of lipid peroxidation only. Future research should examine associations between SES, psychosocial stress, and other biomarkers of oxidative stress, such as metabolites of DNA or RNA oxidation, as SES and psychosocial stress may be influencing oxidative stress through different pathways. Nonetheless, our study has many strengths, as we examined multiple indices of psychosocial stress and SES. We also had repeated measures of oxidative stress biomarkers across pregnancy, which were averaged across study visits and allowed us to obtain a more stable measure of oxidative stress. Lastly, 8-iso-$PGF_{2\alpha}$ and its metabolite are considered to be the best biomarkers of oxidative stress [32] and these biomarkers were quantified using a highly sensitive and specific mass-spectrometry method which is preferred over immunoassay-based methods [33].

5. Conclusions

In conclusion, demographics indicative of a socioeconomic disadvantage were associated with elevated oxidative stress biomarkers in our analyses. However, we did not observe any associations between psychosocial stress and oxidative stress biomarkers. It is possible that women enrolled in PROTECT experience lower levels of psychosocial stress or respond to these questionnaires differently than other cohorts, which could explain our inability to detect associations. Future research should explore other pathways through which psychosocial stress may lead to adverse pregnancy outcomes.

Funding

This work was supported by the National Institute of Environmental Health Sciences (NIEHS) grants P42ES017198 and P50ES026049, the National Institutes of Health (NIH) Office of the Director grants UG3OD023251 and UH3OD023251, and grant U54MD007600 from the National Institute on Minority Health and Health Disparities. This work was also supported in part by the Intramural Research Program of the NIEHS, NIH.

Conflicts of interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.freeradbiomed.2019.07.032.

References

[1] P.D. Wadhwa, S. Entringer, C. Buss, M.C. Lu, The contribution of maternal stress to preterm birth: issues and considerations, Clin. Perinatol. 38 (3) (2011) 351–384.
[2] K.K. Ferguson, T.F. McElrath, Y.H. Chen, R. Loch-Caruso, B. Mukherjee, J.D. Meeker, Repeated measures of urinary oxidative stress biomarkers during pregnancy and preterm birth, Am. J. Obstet. Gynecol. 212 (2) (2015) 208.e201-208.
[3] R. Hiscock, L. Bauld, A. Amos, J.A. Fidler, M. Munafò, Socioeconomic status and smoking: a review, Ann. N. Y. Acad. Sci. 1248 (1) (2012) 107–123.
[4] B.F. Grant, Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey, J. Stud. Alcohol 58 (5) (1997) 464–473.
[5] T.J. van 't Erve, M.B. Kadiiska, S.J. London, R.P. Mason, Classifying oxidative stress by F2-isoprostane levels across human diseases: a meta-analysis, Redox biology 12 (2017) 582–599.
[6] C. Vetrani, G. Costabile, L. Di Marino, A.A. Rivellese, Nutrition and oxidative stress: a systematic review of human studies, Int. J. Food Sci. Nutr. 64 (3) (2013) 312–326.
[7] R.W. Kobrosly, L.E. Parlett, R.W. Stahlhut, E.S. Barrett, S.H. Swan, Socioeconomic factors and phthalate metabolite concentrations among United States women of reproductive age, Environ. Res. 115 (2012) 11–17.
[8] K.K. Ferguson, Y.H. Chen, T.J. VanderWeele, T.F. McElrath, J.D. Meeker, B. Mukherjee, Mediation of the relationship between maternal phthalate exposure and preterm birth by oxidative stress with repeated measurements across pregnancy, Environ. Health Perspect. 125 (3) (2017) 488–494.
[9] S. Kannan, D.P. Misra, J.T. Dvonch, A. Krishnakumar, Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition, Environ. Health Perspect. 114 (11) (2006) 1636–1642.
[10] S. Salim, Oxidative stress and psychological disorders, Curr. Neuropharmacol. 12 (2) (2014) 140–147.
[11] C. Shimanoe, M. Hara, Y. Nishida, et al., Perceived stress, depressive symptoms, and oxidative DNA damage, Psychosom. Med. 80 (1) (2018) 28–33.
[12] K. Aschbacher, A. O'Donovan, O.M. Wolkowitz, F.S. Dhabhar, Y. Su, E. Epel, Good stress, bad stress and oxidative stress: insights from anticipatory cortisol reactivity, Psychoneuroendocrinology 38 (9) (2013) 1698–1708.
[13] K.K. Ferguson, T.F. McElrath, Y.H. Chen, B. Mukherjee, J.D. Meeker, Urinary phthalate metabolites and biomarkers of oxidative stress in pregnant women: a repeated measures analysis, Environ. Health Perspect. 123 (3) (2015) 210–216.
[14] S.M. Eick, E.S. Barrett, T.J. van 't Erve, et al., Association between prenatal psychological stress and oxidative stress during pregnancy, Paediatr. Perinat. Epidemiol. 32 (4) (2018) 318–326.
[15] J.D. Meeker, D.E. Cantonwine, L.O. Rivera-Gonzalez, et al., Distribution, variability, and predictors of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico, Environ. Sci. Technol. 47 (7) (2013) 3439–3447.
[16] K.K. Ferguson, Z. Rosario, T.F. McElrath, et al., Demographic risk factors for adverse birth outcomes in Puerto Rico in the PROTECT cohort, PLoS One 14 (6) (2019) e0217770.
[17] I.G. Sarason, J.H. Johnson, J.M. Siegel, Assessing the impact of life changes: development of the Life Experiences Survey, J. Consult. Clin. Psychol. 46 (5) (1978) 932–946.
[18] Eunice Kennedy Shriver National Institute of Child Health and Human Development, National children's study (NCS), https://www.nichd.nih.gov/research/supported/NCS, (2017) Accessed Septembr 21, 2018.
[19] S. Cohen, T. Kamarck, R. Mermelstein, A global measure of perceived stress, J. Health Soc. Behav. 24 (4) (1983) 385–396.
[20] L.S. Radloff, The CES-D scale, Appl. Psychol. Meas. 1 (3) (1977) 385–401.
[21] P.H. Mitchell, L. Powell, J. Blumenthal, et al., A short social support measure for patients recovering from myocardial infarction: the ENRICHD Social Support Inventory, J. Cardpulm. Rehabil. 23 (6) (2003) 398–403.
[22] S.M. Eick, J.D. Meeker, A. Swartzendruber, et al., Psychosocial Factors during Pregnancy and Preterm Birth in Puerto Rico, (2019) Unpublished.
[23] G.L. Milne, S.C. Sanchez, E.S. Musiek, J.D. Morrow, Quantification of F2-isoprostanes as a biomarker of oxidative stress, Nat. Protoc. 2 (1) (2007) 221–226.
[24] T. Dorjgochoo, Y.T. Gao, W.H. Chow, et al., Major metabolite of F2-isoprostane in urine may be a more sensitive biomarker of oxidative stress than isoprostane itself, Am. J. Clin. Nutr. 96 (2) (2012) 405–414.
[25] T.J. van 't Erve, F.B. Lih, M.B. Kadiiska, L.J. Deterding, T.E. Eling, R.P. Mason, Reinterpreting the best biomarker of oxidative stress: the 8-iso-PGF(2alpha)/PGF (2alpha) ratio distinguishes chemical from enzymatic lipid peroxidation, Free Radic. Biol. Med. 83 (2015) 245–251.
[26] P. Armitage, Tests for linear trends in proportions and frequencies, Biometrics 11 (3) (1955) 375–386.
[27] M. Irie, S. Asami, S. Nagata, M. Ikeda, M. Miyata, H. Kasai, Psychosocial factors as a

potential trigger of oxidative DNA damage in human leukocytes, Jpn. J. Cancer Res. : Gann 92 (3) (2001) 367–376.
[28] J. Takaki, Associations of job stress indicators with oxidative biomarkers in Japanese men and women, Int. J. Environ. Res. Public Health 10 (12) (2013) 6662–6671.
[29] L.M. Falcon, I. Todorova, K. Tucker, Social support, life events, and psychological distress among the Puerto Rican population in the Boston area of the United States, Aging Ment. Health 13 (6) (2009) 863–873.
[30] J. Mattei, M. Tamez, C.F. Ríos-Bedoya, R.S. Xiao, K.L. Tucker, J.F. Rodríguez-Orengo, Health conditions and lifestyle risk factors of adults living in Puerto Rico: a cross-sectional study, BMC Public Health 18 (2018).
[31] M.C. Lu, N. Halfon, Racial and ethnic disparities in birth outcomes: a life-course perspective, Matern. Child Health J. 7 (1) (2003) 13–30.
[32] L.J. Roberts, J.D. Morrow, Measurement of F(2)-isoprostanes as an index of oxidative stress in vivo, Free Radic. Biol. Med. 28 (4) (2000) 505–513.
[33] D. Il'yasova, J.D. Morrow, A. Ivanova, L.E. Wagenknecht, Epidemiological marker for oxidant status: comparison of the ELISA and the gas chromatography/mass spectrometry assay for urine 2,3-dinor-5,6-dihydro-15-F2t-isoprostane, Ann. Epidemiol. 14 (10) (2004) 793–797.