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Prenatal oxidative stress and rapid infant weight gain

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Abstract

BACKGROUND AND OBJECTIVES: Infant weight patterns predict subsequent weight outcomes. Rapid infant weight gain, defined as a >0.67 increase in weight-for-age z -score (WAZ) between two time points in infancy, increases obesity risk. Higher oxidative stress, an imbalance between antioxidants and reactive oxygen species, has been associated with low birthweight and paradoxically also with later obesity. We hypothesized that prenatal oxidative stress may also be associated with rapid infant weight gain, an early weight pattern associated with future obesity.

METHODS: Within the NYU Children's Health and Environment Study prospective pregnancy cohort, we analyzed associations between prenatal lipid, protein, and DNA urinary oxidative stress biomarkers and infant weight data. Primary outcome was rapid infant weight gain (>0.67 increase in WAZ) between birth and later infancy at the 8 or 12 month visit. Secondary outcomes included:

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AUTHOR CONTRIBUTIONS

CD-L conceptualized and designed the study, analyzed data, reviewed the analyses, drafted the initial manuscript, and reviewed and revised the manuscript. LT and AG conceptualized and designed the study, supervised acquisition of data, reviewed the analyses, and reviewed and revised the manuscript. KK contributed substantially to the design of the study, supervised acquisition of the data, reviewed the analyses, and reviewed and revised the manuscript. RSG, RO, and AG substantially contributed to interpretation of data, and reviewed and revised the manuscript for important intellectual content. YA, ML, and LS contributed substantially to data collection and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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very rapid weight gain (>1.34 increase in WAZ), low (<2500 g) or high (>4000 g) birthweight, and low (<-1 WAZ) or high (>1 WAZ) 12 month weight.

RESULTS: Pregnant participants consented to the postnatal study ($n = 541$); 425 participants had weight data both at birth and in later infancy. In an adjusted binary model, prenatal 8-iso-PGF 2α , a lipid oxidative stress biomarker, was associated with rapid infant weight gain (aOR 1.44; 95% CI: 1.16, 1.78, $p = 0.001$). In a multinomial model using 0.67 change in WAZ as a reference group, 8-iso-PGF 2α was associated with rapid infant weight gain (defined as >0.67 but <1.34 WAZ; aOR 1.57, 95% CI: 1.19, 2.05, $p = 0.001$) and very rapid infant weight gain (defined as >1.34 WAZ; aOR 1.33; 95% CI: 1.02, 1.72, $p < 0.05$) Secondary analyses detected associations between 8-iso-PGF 2α and low birthweight outcomes.

CONCLUSIONS: We found an association between 8-iso-PGF 2α , a lipid prenatal oxidative stress biomarker, and rapid infant weight gain, expanding our understanding of the developmental origins of obesity and cardiometabolic disease.

INTRODUCTION

Infant weight and growth patterns predict obesity risk across the life course [1]. Rapid infant weight gain is defined as a greater than a 0.67 increase in weight-for-age z-score between two time points in infancy [2]. This growth pattern is common among infants born with low birthweight, and has an overall cited prevalence of up to 30% of all infants from birth to 2 years regardless of birthweight status [3, 4]. Scientists have found that rapid infant weight gain, most notably in the first year of life, increases odds of later obesity by two-to-threefold as well as lifetime cardiometabolic risk [2, 5, 6]. Evidence shows that psychosocial stressors and toxic environmental exposures during pregnancy increase odds of rapid infant weight gain [7], reinforcing the sensitivity of the prenatal period to cardiometabolic programming across the life course. Understanding whether prenatal biomarkers associated with later obesity are also associated with rapid infant weight gain would contribute to scientific efforts to elucidate the developmental biology of early obesity risk.

Oxidative stress occurs when levels of damaging free radicals exceed the balance of protective antioxidants [8]. Excess prenatal oxidative stress has been associated with small for gestational age and low birthweight outcomes [9, 10]. Paradoxically, later in life, oxidative stress is tightly associated with future obesity; scientists refer to adult obesity as “a state of chronic oxidative stress” [11]. Given that oxidative stress is associated with low weight at the beginning of life but with obesity later in life, it may have relationships with early growth patterns known to increase obesity risk. Researchers modeling weight trajectories in childhood have already shown that increased oxidative stress is associated with a “low-high” weight trajectory across multiple years of childhood [12]. Whether prenatal oxidative stress is also associated with rapid infant weight gain, a “low-high” pattern in infancy known to be associated with later obesity, remains underexplored.

Prenatal oxidative stress can be detected in the urine with biomarkers, which are lipid, protein, and DNA molecules that respond to increased stress and are modified by reactive oxygen species in vivo [13, 14]. Lipid biomarkers, generated by the oxidation of polyunsaturated fatty acids, measure lipid peroxidation and adipose inflammation common

in obesity [11]. The lipid biomarker 8-iso-prostaglandin F_{2α} (8-iso-PGF_{2α}) has been established as the “gold standard” biomarker of oxidative stress, and is the subject of over 200 publications [12, 14, 15]. Protein biomarkers, generated by the oxidation of protein side chains, are prominent in type 2 diabetes pathology and gestational diabetes, and they signal inactivation of proteins that protect from atherosclerosis [16, 17]. DNA biomarkers, generated by oxidation of DNA bases like guanosine, indicate cellular damage in highly progressed disease, and has been implicated in cancerous and genetic outcomes [14]. Less is known about whether the developmental origins of rapid infant weight gain involve oxidative damage to lipid, protein, or DNA molecules [13, 18].

To close these gaps in understanding, we assessed associations between prenatal oxidative stress in pregnant participants and rapid infant weight gain in their infants in the New York University Children’s Health and Environment Study (NYU CHES), a longitudinal birth cohort with racial, ethnic, and socioeconomic diversity in New York City [19]. Leveraging lipid, protein, and DNA oxidative stress measured in prenatal urine samples, we hypothesized that higher levels of the lipid biomarker 8-iso-PGF_{2α} would be associated with rapid infant weight gain.

METHODS

Study population

NYU CHES is a prospective pregnancy cohort examining the impact of environmental exposures on children’s health and development [19]. Between March 2016 and April 2019, NYU CHES recruited 2000 participants who were 18 years and older, less than 18 weeks pregnant, and planned to deliver at one of 3 NYU-affiliated hospitals: NYU Langone Hospital—Manhattan, serving a higher income population; NYU Langone—Brooklyn, serving a primarily immigrant community; and Bellevue Hospital, a public hospital serving populations with economic disadvantage. Participants were excluded if their pregnancy was medically threatened. All participants provided written informed consent, and the Institutional Review Board of the NYU Grossman School of Medicine approved this study.

Of those recruited, 1120 participants provided urine samples at prenatal study visits. The study randomly selected 680 participants to measure oxidative stress biomarkers in their urine (Supplementary Fig. 1). Of the 680 participants selected, 674 had live births, and 541 consented to the postnatal phase of the study. To calculate rapid infant weight gain, we needed one infant weight data point at birth ($n = 541$) and a second weight data point at either the 8 month ($n = 352$) or at 12 month ($n = 318$) visit. Our analytic sample included 425 mother-infant pairs with the requisite weight data, comprising 78% of the 541 infants who consented to the postnatal study. This sample would have adequate power as per effect sizes detected in prior studies of oxidative stress biomarkers and weight outcomes [12, 20, 21]. We confirmed that participants included in this analysis were comparable with all NYU CHES participants: similar racial sampling (~50% Hispanic, ~30% White), rate of public insurance (~50%), marital status (~10% single), and maternal age (mean of 31 years old) [19]. Using bivariate analyses of sociodemographics, we also confirmed that those followed in the postnatal study reflected those in the prenatal study.

Independent variable: prenatal oxidative stress biomarkers

Pregnant participants provided spot urine samples during prenatal visits in early (<18 weeks), mid (18–25 weeks), and late (>25 weeks) pregnancy. Mean gestational ages at urine collection were 10.8 (standard deviation [SD] = 3.4), 20.8 (SD = 2.2), and 29.3 (SD = 3.6) weeks. Each sample was aliquoted into polyethylene containers and stored in –80 °C refrigerators. Physiological fluctuations can cause variation in biomarker measurement within and between participants, so we analyzed intraclass correlation coefficients to describe how strongly the three values across pregnancy resembled one other. Given that the intraclass correlation coefficients of our biomarkers were of moderate size (0.43–0.66), we averaged the values from three urine samples across pregnancy to define oxidative stress levels with more precision than using a single urine sample [22].

By using high performance liquid chromatography coupled with tandem mass spectrometry, our team measured lipid, protein, and DNA biomarkers in urine samples at the Wadsworth Laboratory at the New York State Department of Health. Lipid biomarkers included *F₂-isoprostanes*, formed from the peroxidation of arachidonic acid (a specific polyunsaturated fatty acid) and *Malondialdehyde [MDA]*, an abundant aldehyde formed from the peroxidation of polyunsaturated fatty acids generally [14]. Four bioactive *F₂-isoprostanes* were measured (*8-iso-prostaglandin F_{2α} [8-iso-PGF_{2α}]*, *11β-prostaglandin F_{2α} [11-PGF_{2α}]*, *15(R)-prostaglandin F_{2α} [15-PGF_{2α}]*, *8-iso,15(R)-prostaglandin F_{2α} [8,15-PGF_{2α}]*). Of these, 8-iso-PGF_{2α} is noteworthy for its stability, specificity, and reproducibility in response to pro-oxidant stimulation [23]. The protein biomarker, *o,o'-dityrosine [diY]*, represents oxidated amino acids (tyrosine) and the DNA biomarker *8-hydroxy-2'-deoxyguanosine [8-OHdG]* is an oxidated purine nucleoside (guanosine) [14].

Our laboratory participated in multiple external quality assurance evaluations and procedures, including the Centers for Disease Control's Biomonitoring Quality Assurance Support Program [24]. The limits of detection (LOD) of our biomarker measurements met acceptable values also described in the literature [14]. We applied standard approaches to address samples with biomarker measurements below LOD, by imputing the LOD value of that oxidative stress biomarker divided by the square root of 2 [25]. The percent below LOD for each of the biomarkers included: 8-iso-PGF_{2α} - 22.8%, 11-PGF_{2α} - 27.7%, 15-PGF_{2α} - 19.6%, 8,15-PGF_{2α} - 6.9%, MDA - 0%, diY - 0%, 8-OHdG - 0%. Per established methods, urinary levels were adjusted for creatinine using the following equation: $1000 * (\text{urinary level of biomarker} / \text{molar weight of biomarker}) * (\text{molar weight of creatinine} / \text{urinary levels of creatinine})$ [26, 27]. Oxidative stress biomarker concentrations were skewed, so our primary analyses were log transformed for improved model fit as done in prior studies [12]. To improve interpretability, we also calculated effect estimates per standard deviation increase in biomarker concentration.

Infant weights

Prenatal oxidative stress biomarkers from pregnant participants were linked to the weight data of the infants they birthed. Information on birthweight and infant sex was obtained from the electronic health record. Weight at the 8 month visit was collected using a

questionnaire where parents were asked to recall the weight from the preceding child well visit. Parents were first asked, “What was the date of your baby’s most recent well-child visit or checkup?” followed by, “What was his/her weight at that visit?” Weight at the 12 month visit was obtained by study team members at an in-person study visit. A trained examiner measured the child’s weight to the nearest 10 g using a calibrated infant scale. The mean of 3 weight measurements was used for the 12 month weight.

Rapid infant weight gain

Sex- and gestational age-specific z-scores for birthweight were calculated from the International Fetal and Newborn Growth Consortium for the 21st Century standard [28]. Sex-specific z-scores were calculated using World Health Organization growth charts and by the child’s precise age in months at the visit [29]. At both the 8 and 12 month visit, we measured change in weight-for-age z-score from birth. Our dichotomous primary outcome was rapid infant weight gain, defined as greater than 0.67 unit increase in weight-for-age z-score, which has been replicated in multiple studies to be associated with later obesity [2, 5, 30]. We also conducted analyses with very rapid infant weight gain – defined as >1.34 unit increase in weight-for-age z-score – which confers a particularly high risk of overweight and obesity [31].

Infant weight outcomes

Our secondary outcomes included birthweight and infant weight at 12 months. We defined low birthweight as less than 2500 g per World Health Organization standards [32] and high birthweight using the macrosomia definition of greater than 4000 g [33]. At the 12 month study visit, we defined high weight as greater than one z-score (>1 SD above the population mean), and low weight as less than negative one z-score (<1 SD below the population mean) [34].

Other characteristics

Sociodemographic factors like race/ethnicity, marital status, maternal age at enrollment, parity, and insurance type were collected by prenatal questionnaires and from electronic health records. Pre-pregnancy weight and height from electronic health records were used to calculate pre- pregnancy body mass index (BMI).

Statistical analysis

We used descriptive statistics to summarize baseline characteristics, prenatal oxidative stress biomarkers, and weight outcomes. Using independent sample unadjusted *t*-tests, we described baseline characteristics and oxidative stress biomarkers by rapid infant weight gain status. Binary adjusted logistic regressions were used to examine whether lipid, protein, and DNA oxidative stress biomarkers were associated with rapid infant weight gain. We selected confounders a priori associated with our predictor and outcome, referencing prior work on early child obesity and oxidative stress [12]. Models were adjusted for maternal pre-pregnancy BMI, maternal race/ethnicity, insurance status (public vs. private), marital status (single vs. married or living as married), maternal age at enrollment, parity (nulliparous yes vs. no), child sex, and child age at visit. As per prior work on oxidative

stress and early child weights, gestational age at birth was considered likely to be on the causal pathway and not included as a covariate [12]. We adjusted for multiple comparisons accounting for lipid, protein, and DNA biomarkers by using a conservative Bonferroni correction and a p -value cutoff of 0.017 [35]. We also conducted two additional sensitivity analyses, one restricting our sample to only include weights collected at the 12 month study visit ($n = 318$) and another to only include infants with normal birthweight ($n = 356$).

For oxidative stress biomarkers associated with rapid infant weight gain at the Bonferroni-corrected threshold of significance, we used multinomial logistic regressions to examine whether significant oxidative stress biomarkers were associated with rapid (defined in this model here as an increase in weight-for-age z-score >0.67 but <1.34) and very rapid infant weight gain (defined as an increase in weight-for-age z-score >1.34), using 0.67 change in weight-for-age z-score as a reference group (3 categories). For our secondary outcomes, we used multinomial logistic regressions to examine whether significant oxidative stress biomarkers were associated with birthweight (low/high) extracted from the electronic medical record or weight outcomes (low/high) from the 12 month study weights, using weight within 1 standard deviation as a reference group (3 categories). Finally, we explored effect modification by examining subgroups within key sociodemographic variables: sex (male vs. female), race and ethnicity (membership in a racial or ethnic minority group vs. White), insurance status (public vs. private). We created models with interaction terms between the oxidative stress biomarker and the sociodemographic variable and examined stratified models. We used Stata/SE version 15.1 (Stata Corp, College Station, TX) to perform statistical analyses.

RESULTS

Our final sample included 425 mother-child infant dyads (Table 1). This was a diverse sample as 54.5% of mothers identified as Hispanic, 9.0% as non-Hispanic Asian, and 5.1% as non-Hispanic Black. Over half of families (56.5%) were on public insurance. Mean gestational age was full-term (39.1 weeks, $SD = 1.8$) and mean birthweight was in the healthy range (3.3 kg, $SD = 1.8$). Table 1 shows that in unadjusted analyses, mothers whose infants had rapid infant weight gain differed by race (more likely to identify as Hispanic or Black), public insurance status (more likely to be on public insurance), recruitment site (more likely to be from Bellevue Hospital), gestational age (earlier gestational age), and birthweight (lower birthweight). In a population of mothers with a mean pre-pregnancy BMI in the overweight range (26.5, $SD = 5.9$), infants had a median weight-for-age z-score of 0.5 (69.2nd percentile) at the 12 month visit (Table 2), and 39.2% of infants had rapid infant weight gain at either the 8 month or the 12 month visit.

Prenatal oxidative stress biomarkers and rapid infant weight gain

Table 3 displays descriptive statistics of prenatal oxidative stress biomarkers by rapid infant weight gain. In pregnant participants who had infants with rapid infant weight gain, unadjusted t-tests describe mean levels of 8-iso-PGF 2α that were significantly higher ($0.2 \mu\text{mol mol Cr}^{-1}$, $SD = 0.4$) than in pregnant participants who had infants without rapid infant weight gain ($0.08 \mu\text{mol mol Cr}^{-1}$, $SD = 0.1$). Using increments modeled in prior work with

oxidative stress biomarkers [12], a ln-unit increase in 8-iso-PGF2 α was associated with increased odds of rapid infant weight gain (aOR 1.44; 95% CI: 1.16, 1.78) with a *p*-value of 0.001. Similarly, a standard deviation increase in 8-iso-PGF2 α level was associated with increased odds of rapid infant weight gain (aOR 2.09; 95% CI: 1.18, 3.69) with a *p*-value of 0.01. Results from both models met the Bonferroni-corrected significance threshold. We conducted sensitivity analyses examining associations between each ln-unit increase of 8-iso-PGF2 α and rapid infant weight gain using a sample restricted to 12 month study weights (aOR 1.38; 95% CI: 1.08, 1.75) and a sample restricted to infants with normal birthweights (aOR 1.33; 95% CI: 1.06, 1.69), with similar results. We did not detect associations between other oxidative stress biomarkers and rapid infant weight gain.

Figure 1 displays a multinomial model showing that 8-iso-PGF2 α was associated with 1.57 greater odds of rapid infant weight gain (defined here as >0.67 and <1.34 increase in weight-for-age z-score; 95% CI: 1.19, 2.05) and a 1.33 increased odds of very rapid infant weight gain (defined as >1.34 increase in weight-for-age z-score; 95% CI: 1.02, 1.72), using 0.67 change in weight-for-age z-score as the reference group. We detected similar results when examining standard deviation increases in 8-iso-PGF2 α (Rapid infant weight gain: aOR 2.07; 95% CI: [1.16, 3.68]; Very rapid infant weight gain: aOR 2.07 [1.17, 3.70]).

8-iso-PGF2 α lipid oxidative stress biomarker and weight outcomes

In adjusted models of 8-iso-PGF2 α and infant weight outcomes, each ln-unit increase in 8-iso-PGF2 α was associated with a decrease of 48.3 g in birthweight (95% CI: -95.6, -1.0). Similarly, each standard deviation increase in 8-iso-PGF2 α was associated with a decrease of 53.2 g (95% CI: -106.1, -0.40) in birthweight. Table 4 displays results of our multinomial models examining associations between 8-iso-PGF2 α and secondary infant weight outcomes. Each ln-unit increase in 8-iso-PGF2 α was associated with increased odds of low birthweight (aOR 1.45, 95% CI: 1.04, 2.03), but a standard deviation increase in 8-iso-PGF2 α was not significant in a similar model. We did not find associations between 8-iso-PGF2 α and weight outcomes at 12 months (Table 4).

In our investigation of effect modification by child sex, race/ethnicity, and insurance type, we did not find statistically significant interactions (Supplementary Table 1).

DISCUSSION

In a diverse prospective pregnancy cohort from New York City, we found that increased urinary concentrations of a lipid oxidative stress biomarker in a pregnant participant were associated with increased odds of a greater than 0.67 increase in weight-for-age z-score between birth and later infancy in their infant, which has not been described previously. This study also replicates prior modest associations between oxidative stress and low birthweight outcomes [12, 21]. By detecting a potential longitudinal relationship between prenatal oxidative stress and rapid infant weight gain, we extend prior work showing that oxidative stress biomarkers are associated with low weight at the beginning of life but with obesity later in life. These findings frame future lines of inquiry to delineate the potential roles of lipid-derived oxidative stress in the developmental biology of obesity risk across the life course.

This is one of the first studies to examine rapid infant weight gain alongside lipid, protein, and DNA urinary oxidative stress biomarkers. Our analysis identified associations between 8-iso-PGF2 α and rapid infant weight gain, expanding prior work with comparable effect sizes showing modest associations between 8-iso-PGF2 α and weight outcomes in children and adults [12, 36]. Among the F₂ prostaglandins, 8-iso-PGF2 α is a particularly durable biomarker of oxidative stress and may be more specific than MDA, which reflects lipid peroxidation of polyunsaturated fatty acids more generally. Rapid infant weight gain increases obesity risk but in of itself is not a disease status. Therefore, it may not be associated with the oxidative damage to protein or DNA molecules characteristic of advanced cellular pathology. Future studies should continue to clinically correlate lipid, protein, and DNA biomarkers longitudinally to follow the progression of cardiometabolic processes across the life course.

Low weight early in life and poor cardiometabolic outcomes later in life have been explained using the “thrifty phenotype” hypothesis, which theorizes that early undernutrition may activate metabolic settings that favor later weight gain [37, 38]. A prior study from The Infant Development and the Environment Study also identified 8-iso-PGF2 α as associated with a two-to-three fold increase in the odds of a “low-high” weight trajectory from birth to 3 years of age relative to a normal weight trajectory [12]. We found that 8-iso-PGF2 α had modest associations with both rapid infant weight gain and low birthweight, reinforcing this “low-high” pattern in infancy. Decreased fetal growth may occur due to decreased blood and nutrient flow in pregnancy, increasing free radicals and reactive oxygen species from perfusion injury. Resultant oxidative stress may trigger inflammation in fetal adipose tissue, favoring weight gain later on [11]. Our findings show that this association does not only happen in the setting of “catch-up growth” triggered by low birthweight (<2500 g), as sensitivity analyses with only normal birthweights yielded similar results and overall less than 10% of infants had a low birthweight in this cohort. Future studies should expand upon this work by examining the role of birthweight or fetal size in mediating associations between prenatal oxidative stress levels and infant growth patterns.

The “fetal overnutrition hypothesis” theorizes that exposure to maternal obesity prenatally increases lifetime risk of obesity. For example, developing adipose tissue and vasculature may be particularly susceptible to lipid oxidative stress signaling from excessive maternal adipose tissue during fetal periods of rapid growth [11, 39]. Maternal obesity is also associated with an increased risk of gestational diabetes [33, 40], which confers increased risk of high birthweight, another infant weight outcome associated with future obesity [41]. Scientists have found associations between gestational diabetes and oxidative stress biomarkers, including 8-iso-PGF2 α , but primarily in protein biomarkers [17]. In our sample, while about 18% of pregnant participants had gestational diabetes, only 7% infants had high birthweight while almost 40% met rapid infant weight gain standards. Despite shared associations with oxidative stress, our findings may not reflect a high birthweight pathway but rather they support future work to continue disentangling lipid, protein, and DNA sources of prenatal oxidative stress in the context of maternal obesity.

Increased oxidative stress has been associated with multiple potential sources, including psychosocial stress (e.g., socioeconomic disadvantage), toxic environmental exposures (e.g.,

air pollution, toxic metals), and unhealthy lifestyle practices (e.g., dietary patterns lacking antioxidants, cigarette smoke) [15, 42]. Our descriptive characteristics reflect socioeconomic differences by rapid infant weight gain status like race/ethnicity and insurance status. Researchers have previously noted that rapid infant weight gain may account for between 15–70% of obesity disparities between children identifying as White and their peers from racial and ethnic minority groups [43]. Of note, our sample included a high percentage of participants who self-identified as Hispanic, a historically marginalized group with higher rates of obesity [44]. Supplemental analyses showed an interaction trend ($p = 0.12$) between race/ethnicity and the association between 8-iso-PGF2 α and rapid infant weight gain. Future cohort studies should include an in-depth examination of racial and ethnic disparities in rapid infant weight gain in the context of exposures to established sources of oxidative stress like psychosocial and environmental stressors [7, 45–47]. Understanding these disparities could eventually inform prenatal interventions applying a life course framework [48] to target modifiable health practices (e.g., dietary patterns [49], smoking [50]) and leverage community-derived cultural assets to potentially mitigate levels of oxidative stress during vulnerable time periods

We found that 8-iso-PGF2 α was associated with very rapid infant weight gain (>1.34 increase in weight-for-age z-score), but that the effect size was smaller or equivocal to the odds of rapid infant weight gain between >0.67 and <1.34 weight-for-age z-score. Pediatric researchers have already identified numerous feeding practices and styles that increase risk for rapid infant weight gain, particularly in the first year of life [51, 52]. These early feeding practices may have joint effects with potential risk related to prenatal oxidative stress, increasing the magnitude of rapid infant weight gain (e.g., very rapid) and subsequent risk for obesity. Current work assessing the utility of oxidative stress biomarkers for risk stratification are in early developmental stages [13, 18]. Considering their use in early child obesity will rely on future studies to delineate how oxidative stress levels may interact with modifiable infant feeding practices.

These results must be interpreted in context of the study's limitations: the quality of weight data at the 8 month visit and followup loss. The 8 month weight variable relied on parent report of the child's weight from the most recent well child check, which is subject to recall bias. Still, our findings are supported by robust weight data used in this study: birthweight was recorded using the electronic health record, and 12 month visit weights were measured with precision by a trained research team. Seventy-five percent of weights from the 8 month visit also had a 12 month visit in-person weight. Another limitation was followup loss, as this study was conducted in a sample of mother-child dyads with complete available data. While using a subsample increases risk of selection bias, we compared our subsample with the full cohort and found similar baseline characteristics, supporting representation of the full cohort.

CONCLUSION

We detected an association between prenatal 8-iso-PGF2 α – a lipid oxidative stress biomarker—and rapid infant weight gain outcomes. Our findings contribute to a body of work showing how prenatal oxidative stress biomarkers have associations with infant weight

and growth patterns known to increase obesity and cardiometabolic risk. Understanding prenatal oxidative stress may have implications for understanding the developmental origins of cardiometabolic disease and inform strategies for the primary prevention of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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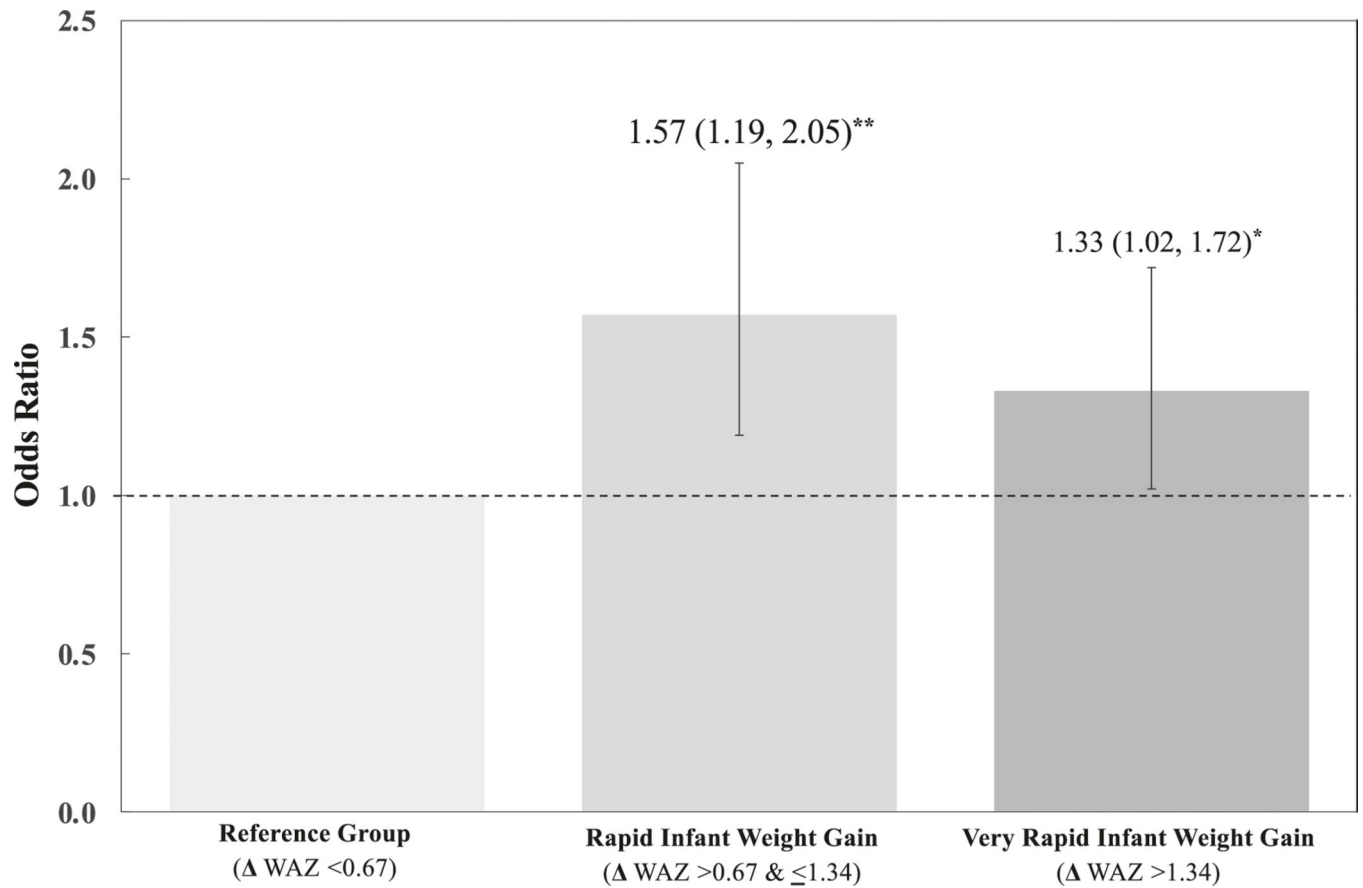


Fig. 1. Multinomial model of 8-iso-PGF2 α and rate of infant weight gain.

Three-category multinomial logistic regressions (aOR [95% CI]) showing an increase in odds ratio per ln-unit increase in 8-iso-PGF2 α for rapid infant weight gain and very rapid infant weight gain using 0.67 change in weight-for-age z-score as the reference group. Adjusted for maternal BMI, race/ethnicity, insurance type, single marital status, maternal age, parity, child sex, child age at visit; * $p < 0.05$; ** $p < 0.01$.

Table 1.

Sample characteristics.

Variable, n (%) or Mean (SD)	Total (N = 425)	Rapid Infant Weight Gain ^a	
		No (n = 258)	Yes (n = 167) ^b
Maternal Characteristics			
Maternal age (years)	31.9 (5.6)	32.2 (5.1)	31.5 (6.2)
Pre-pregnancy BMI ^c	26.5 (5.9)	26.2 (6.0)	27.0 (5.8)
Nulliparous	195 (46.1)	122 (47.3)	93 (55.7)
Gestational Diabetes	76 (17.9)	48 (18.6)	28 (16.8)
Race/Ethnicity^c			
Hispanic	234 (55.1)	122 (47.3)***	112 (67.1)***
White (non-Hispanic)	128 (30.1)	101 (39.2)***	27 (16.2)***
Black (non-Hispanic)	18 (4.2)	6 (2.3)*	12 (7.2)*
Asian (non-Hispanic)	34 (8.0)	21 (8.1)	13 (7.8)
Multirace/Other	11 (2.6)	5 (3.1)	3 (1.8)
Public Insurance	238 (56.0)	129 (50.0)**	109 (65.3)**
Marital Status^c			
Married/Living as Married	382 (89.9)	233 (90.3)	159 (89.2)
Divorced/Separated	5 (1.2)	2 (0.8)	3 (1.8)
Single/Widowed	38 (8.9)	8.9 (23)	15 (9.0)
Recruitment Site			
Bellevue Hospital	117 (27.5)	56 (21.7)***	61 (36.5)***
NYU Manhattan Hospital	183 (43.1)	132 (51.2)***	55 (30.5)***
NYU Brooklyn Hospital	125 (29.4)	70 (27.1)	51 (32.9)
Child Birth Characteristics			
Assigned female sex	210 (49.4)	127 (49.2)	83 (49.7)
Gestational age at birth	39.1 (1.8)	39.6 (1.2)***	38.3 (2.2)***

Variable, <i>n</i> (%) or Mean (SD)	Total (<i>N</i> = 425)	
	No (<i>n</i> = 258)	Rapid Infant Weight Gain ^a Yes (<i>n</i> = 167) ^b
Birthweight (grams)	3277.4 (544.2)	3464.7 (437.1)*** 2988.1 (567.4)***
Low birthweight (<2500 g)	36 (8.5)	5 (2.0)*** 31 (18.6)***
High birthweight (≥4000 g)	31 (7.3)	26 (10.2)** 5 (3.0)**
Birthweight weight for age z-score	-0.02 (1.2)	0.38 (0.87)*** -0.66 (1.3)***

BM/body mass index, *SD* standard deviation

^aRapid infant weight gain defined as >0.67 weight for age z-score between birth and weight at either 8 or 12 month visits.

^bIndependent sample *t*-tests:

* *p* < 0.05,

** *p* < 0.01,

*** *p* < 0.001;

^cMissingness for each covariate was as follows: pre-pregnancy BMI (*n* = 1); race/ethnicity (*n* = 1); marital status (*n* = 1);

Table 2.

Weight outcomes by study visit.

Study Visit	n	Age at Visit (months)	50th (25th, 75th)	Weight (kg) 50th (25th, 75th)	Weight-for-Age z-score 50th (25th, 75th)	% Rapid Weight Infant Gain
Birth	425	–		3.3 (3.0, 3.6)	0.1 (–0.6, 0.7)	–
8 Month	352	8.3 (8.1, 8.7)		8.3 (7.4, 9.1)	–0.2 (–0.9, 0.7)	27.4%
12 Month	318	12.7 (12.1, 14.3)		10.3 (9.3, 11.2)	0.5 (–0.08, 1.1)	42.5%

Rapid infant weight gain defined as >0.67 change in weight for age z-score from birth.

Table 3.

Prenatal oxidative stress biomarkers and rapid infant weight gain.

	Adjusted concentrations ($\mu\text{mol Cr}^{-1}$)	Descriptive Statistics (N = 425)		Adjusted Analyses (n = 423) ^a		
		By RIWG Status		aOR (95% CI) ^a	p	
		Mean (SD)	No			Yes
Lipid	8-iso-PGF2 α	0.1 (0.3)	0.08 (0.1) *	0.2 (0.4) *	1.44 (1.16, 1.78) *	0.001
	11 – PGF2 α	0.2 (0.4)	0.1 (0.2)	0.2 (0.5)	1.05 (0.89, 1.24)	0.54
	15 – PGF2 α	0.2 (0.3)	0.2 (0.3)	0.1 (0.2)	0.91 (0.76, 1.10)	0.33
	8,15 – PGF2 α	0.3 (0.6)	0.3 (0.5)	0.3 (0.6)	0.89 (0.71, 1.12)	0.34
MDA	33.4 (76.6)	30.8 (16.7)	38.8 (120.5)	1.16 (0.80, 1.69)	0.42	
Protein	diY	0.8 (0.6)	0.8 (0.4)	0.8 (0.8)	0.99 (0.65, 1.49)	0.95
DNA	8-OHdG	1.6 (4.3)	1.4 (0.6)	1.9 (6.9)	1.25 (0.81, 1.95)	0.31

Rapid infant weight gain (RIWG) defined as >0.67 increase in weight-for-age z-score between birth and 8–12 months;

* $p < 0.01$;

^aIn-transformed for analyses for model fit; Adjusted for maternal BMI, race/ethnicity, insurance type, single marital status, maternal age, parity, child sex, child age at visit.

Table 4.

Multinomial models of 8-iso-PGF2 α and secondary infant weight outcomes.

	Per Ln-unit increase PGF2 α of 8-iso-PGF2 α ^a	Per SD increase of 8-iso-PGF2 α
Birthweight aOR (95% CI)	2500–4000 g REFERENCE	
	Low: <2500 g 1.45 (1.04, 2.03)*	1.34 (0.98, 1.82)
	High: >4000 g 1.03 (0.70, 1.52)	0.73 (0.25, 2.09)
12 Month aOR (95% CI)	Weight between –1 & 1 SD of WAZ REFERENCE	
	Low: < –1 SD of WAZ 0.92 (0.72, 1.17)	0.76 (0.44, 1.30)
	High: >1 SD of WAZ 0.91 (0.61, 1.38)	0.68 (0.20, 2.38)

Three-category multinomial logistic regression models adjusted for maternal BMI, race/ethnicity, insurance type, single marital status, maternal age, parity, child sex, child age at visit;

aOR adjusted odds ratio, WAZ weight-for-age z-score, SD standard deviation;

* $P < 0.05$;

^aIn-transformed for analyses for model fit.