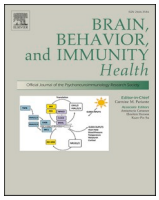
Brain, Behavior, & Immunity - Health 38 (2024) 100775

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



The association between prenatal oxidative stress levels measured by isoprostanes and offspring neurodevelopmental outcomes at 36 months

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ARTICLE INFO

Keywords:
Autism spectrum disorder
Oxidative stress
Isoprostanes
Prenatal
Cohort
Epidemiology
Neurodevelopment
Quantile regression

ABSTRACT

Oxidative stress during pregnancy has been a mechanistic pathway implicated in autism development, yet few studies have examined this association directly. Here, we examined the association of prenatal levels of 8-iso-PGF2α, a widely used measure of oxidative stress, and several neurodevelopmental outcomes related to autism in children. Participants included 169 mother-child pairs from the Early Autism Risk Longitudinal Investigation (EARLI), which enrolled mothers who had an autistic child from a previous pregnancy and followed them through a subsequent pregnancy and until that child reached age 3 years. Maternal urine samples were collected during the second trimester of pregnancy and were later measured for levels of isoprostanes. Child neurodevelopmental assessments included the Mullen Scales of Early Learning (MSEL), the Social Responsiveness Scale (SRS), and the Vineland Adaptive Behavior Scale (VABS), and were conducted around 36 months of age. Primary analyses examined associations between interquartile range (IQR) increases in 8-iso-PGF2α levels, and total composite scores from each assessment using quantile regression. In adjusted analyses, we did not observe statistically significant associations, though estimates suggested modestly lower cognitive scores (β for MSEL = −3.68, 95% CI: -10.09, 2.70), and minor increases in autism-related trait scores (β for SRS T score = 1.68, 95% CI: -0.24, 3.60) with increasing 8-iso-PGF2α. These suggestive associations between decreased cognitive scores and increased autism-related traits with increasing prenatal oxidative stress point to the need for continued investigation in larger samples of the role of oxidative stress as a mechanistic pathway in autism and related neurodevelopmental outcomes.

1. Introduction

Autism spectrum disorder (hereafter referred to as "autism" (Bottema-Beutel et al., 2021; Dwyer et al., 2022)) is a diagnosis defined according to social communication differences and presence of repetitive behaviors, and has impacts on cognition, adaptive functioning, and social interactions (American Psychiatric Association, 2013; Lord et al., 2020). Research demonstrates that both environmental and genetic factors play a role in autism etiology and supports origins of autism in the perinatal period (Lyall et al., 2017; Masini et al., 2020). Research to date has found evidence that both external (e.g., environmental toxicants) and internal (e.g., preterm birth) environmental factors during pregnancy are associated with increased likelihood of autism. Oxidative stress in pregnancy is one mechanism hypothesized to underlie associations between environmental factors and autism as well as other neurodevelopmental outcomes. However, few studies have directly examined biomarkers of oxidative stress in association with neurodevelopmental outcomes related to autism.

Oxidative stress occurs when the body's levels of reactive oxygen species (ROS) exceed its antioxidant capacity (Birben et al., 2012).

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https://doi.org/10.1016/j.bbih.2024.100775
Received 9 April 2024; Accepted 16 April 2024
Available online 24 April 2024

Exogenous factors such as environmental exposure to heavy metals (Modabbernia et al., 2017; Pizzino et al., 2017), pollutants (Pizzino et al., 2017), and pesticides (Maleki et al., 2023), as well as social factors like socioeconomic status (Eick et al., 2019), have all been linked to higher levels of oxidative stress. During pregnancy, the fetus develops in an environment with a low antioxidant capacity that is highly sensitive to ROS (Thompson and Al-Hasan, 2012). There are several pathways by which oxidative stress can cause cellular damage, including lipid peroxidation, protein oxidation, and DNA damage, among others (Pizzino et al., 2017). Isoprostanes are commonly used as a reliable measure of lipid oxidative stress (Ferguson et al., 2017; Miller et al., 2014; Niki, 2008), with 8-iso-PGF2α as the most widely used measure (van't Erve et al., 2015) capturing chemical and non-enzymatic lipid peroxidation (Ferguson et al., 2015).

While several prior studies have reported elevated levels of oxidative stress in individuals already diagnosed with autism (James et al., 2004, 2006; Bjørklund et al., 2020; Liu et al., 2022), and animal models support roles of specific biomarkers of oxidative stress in autism development (De Felice et al., 2016), we are aware of only two human studies to date that have examined oxidative stress biomarker associations with autism in the prenatal time period, as is needed to inform etiologic questions (Carey et al., 2022; Rommel et al., 2020). In our prior work using data from an autism family-based cohort, we examined oxidative stress through DNA damage, protein oxidation, and antioxidant balance pathways in association with autism and related traits, and did not observe an association between 8-oxo-deoxy-guanine (8-OHdG; capturing OS due to DNA damage), and 3-nitrotyrosine (capturing protein oxidation) and SRS scores, but did find minor increases in SRS scores with an increasing ratio of GSH:GSSG (capturing antioxidant balance) (Carey et al., 2022). Rommel et al. (2020) identified a modest increase between an interquartile increase in third trimester 8-iso--PGF2α levels, a biomarker of oxidative stress in the lipid peroxidation pathway, and SRS scores. However, this association was only observed in mothers with higher levels of educational attainment. In the past several years, there has been a growing body of literature supporting increasing levels of 8-iso-PGF2α are associated with: 1) preterm birth (Eick et al., 2020; Rosen et al., 2019), which is strongly associated with autism, and 2) other neurodevelopmental or psychiatric outcomes such as emotional and behavioral problems in young children (Pham et al., 2023; Steullet et al., 2017). Thus, additional examination of the relationship between oxidative stress biomarkers and neurodevelopmental outcomes related to autism are warranted, particularly to clarify prior suggestive associations with 8-iso-PGF2α.

The objective of this study was to expand our prior work and address existing gaps in the association between prenatal oxidative stress and child neurodevelopmental outcomes related to autism. Specifically, we focused on relationships between prenatal 8-iso-PGF2α levels and a set of neurodevelopmental scores relating to cognition, autism-related traits, and adaptive behaviors. We hypothesized that higher levels of prenatal oxidative stress, according to measured isoprostane levels (a biomarker of the lipid peroxidation pathway) – specifically 8-iso-PGF2α, would be associated with poorer neurodevelopmental scores on a set of continuous neurodevelopmental measures related to autism and a higher likelihood of autism diagnosis.

2. Material and methods

2.1. Study population

Participants for this study were drawn from the Early Autism Risk Longitudinal Investigation (EARLI), a multi-site cohort study conducted in the US between 2009 and 2012 (Newschaffer et al., 2012). EARLI enrolled mothers of autistic children (n = 256) and followed them during a subsequent pregnancy, birth, and until the younger sibling was 36 months old. As such, the infants with an older sibling with autism more often are diagnosed with autism but also are more likely experience cognitive or developmental delays (Hansen et al., 2019; Miller et al., 2019; Ozonoff et al., 2011). To be eligible to participate in EARLI, mothers had to: 1) be < 29 weeks gestation at enrollment; 2) be ≥ 18 years of age; 3) reside within 2 hours of a study site; and 4) be able to communicate in English or Spanish. Participation included the collection of biological samples, completion of interviews and questionnaires, and neurodevelopmental assessments of the followed sibling until 36 months of age. Full details on EARLI are reported elsewhere (Newschaffer et al., 2012).

From the overall EARLI sample we excluded all non-singleton births (8 pairs, n = 16 excluded). Moreover, to be included in the present analyses, child participants must have had at least one neurodevelopmental outcome measure of interest (further described below; n = 65 excluded) and a maternal urine sample collected around the second trimester of pregnancy for measurement of oxidative stress biomarkers (n = 22 excluded). Based on this criteria, 169 mother-child pairs were included in analyses (Figure A1). The sample size varied across the different outcomes examined to maximize sample size and use of available data (n = 145–159). Information on covariates was assessed from maternal interviews conducted about the first 20 weeks of pregnancy. The IRBs at all four data collection sites approved the EARLI study, and the Drexel University IRB approved the current study.

2.2. Exposure ascertainment

Urine samples were collected from mothers at a single time point in pregnancy and stored at −20 °C. Samples collected around the second trimester of pregnancy were used for analysis here (median: 21.9 weeks, IQR 19.1–25.9 weeks; Table A1), consistent with prior literature measuring prenatal oxidative stress (Cathey et al., 2021; van′ t Erve et al., 2019). 8-iso-PGF2α, a biomarker of oxidative stress-induced lipid peroxidation (Lawson et al., 1999), was measured using high performance liquid chromatography mass spectrometry (TSQ Altis) (Milne et al., 2015). Increasing levels of 8-iso-PGF2α represent higher levels of oxidative stress. Urine is considered a more stable matrix for measuring 8-iso-PGF2α compared to blood (Holder et al., 2020), and has been used as a preferred matrix in many studies (Eick et al., 2024; Ferguson et al., 2015; Rommel et al., 2020).

2.3. Child outcomes

Continuous neurodevelopmental outcome measures and diagnostic assessments were conducted when the child was around 36 months of age. Primary outcome measures here included the Mullen Scales of Early Learning (MSEL) Early Learning Composite Score (Mullen, 1995), the Social Responsiveness Scale (SRS) T Scores (Constantino et al., 2003; Constantino and Gruber, 2012), and the Vineland Adaptive Behavior Scales Adaptive Behavior Composite scores (Sparrow and Cicchetti, 1989). These assessments were chosen because of their relativity to the autism phenotype (American Psychiatric Association, 2013; Lord et al., 2020), their variability in measuring different aspects of autism, and for consistency with prior work (Carey et al., 2022; Rommel et al., 2020; Vecchione et al., 2022; Zhong et al., 2022).

In secondary analyses, we created dichotomous cut-off scores based on these continuous neurodevelopmental outcome scores, defined according to the distribution in our sample and representing scores at least a 1/2 SD above (SRS) or 1 SD below (MSEL, VABS) the population mean: SRS (T > 55), MSEL (ELC<85), and Vineland (<85). We were not able to use standard cut-offs, e.g. <70 for MSEL as is consistent with the definition for intellectual disability, or SRS >65 for autism, given our study score distribution and sample size limitations.

Additionally, we examined associations of 8-iso-PGF2α with a categorical measure of autism diagnosis. Using criteria put forth in prior publications, expert clinical evaluation according to the Autism Diagnostic Observation Schedule (Lord et al., 1989), and scores on the MSEL, were used to classify children into one of three categories: autism

spectrum disorder (ASD), non-typical development but not ASD (non-TD), and typically developing (TD). Briefly, those in the non-TD group did not meet criteria for ASD but had either 1) cognitive development scores >1.5 standard deviations (SDs) below the mean for 2+ subscales of the MSEL or 2) scores >2 SDs below the mean on 1+ subscales of the MSEL, and/or 3) scores ≤3 points below the ASD cutoff for ADOS. Those classified as TD did not meet the criteria for the ASD or non-TD categories. Further details on the groupings can be found in prior work (Ozonoff et al., 2014).

2.3.1. Social Responsiveness Scale (SRS)

The SRS is a 65-item informant-report questionnaire that captures a child's behaviors in reciprocal social interactions and provides a quantitative score of traits related to the autistic phenotype. Individual items are summed to yield a total raw score, which can be converted to a sex-normed T score to facilitate clinical interpretation (mean 50, SD 10). Higher scores are indicative of more autism-related behaviors (Constantino et al., 2003). The SRS has been validated against gold-standard autism diagnostic assessments, with strong results (Constantino and Gruber, 2012). In primary analyses, we used total SRS T-scores; raw scores are shown in supplemental analyses for comparison to previous work (Carey et al., 2022).

2.3.2. Mullen Scales of Early Learning (MSEL)

The MSEL is a developmental assessment used to measure early life (ages birth to 68 months) cognitive and language skills and is strongly correlated with intellectual quotient (IQ) scores (Bishop et al., 2011). The MSEL includes five domains assessing fine and gross motor skills, receptive and expressive language, and visual reception that yield a single composite score (the early learning composite, ELC, mean of 100, standard deviation 15). Lower scores are indicative of poorer intellectual functioning (Bishop et al., 2011).

2.3.3. Vineland Adaptive Behavior Scales (VABS)

The VABS was used to assess adaptive behavior. The VABS is a semi-structured interview administered to parent/respondents for children up to 18 years of age, with items addressing daily living skills including four domains (communication, daily living skills, socialization, and motor skills) that are then combined into an overall Adaptive Behavior Composite (ABC) score (mean of 100, standard deviation 15) where a higher score is indicative of better adaptive behavior and functioning (Perry and Factor, 1989).

2.4. Statistical analysis

Bivariate comparisons of basic characteristics of the study population, as well as descriptive statistics of 8-iso-PGF2α levels, were examined overall and by outcome groupings. Crude and adjusted regression models were used to examine associations between 8-iso-PGF2α and each child neurodevelopmental outcome. Covariates considered in adjusted models were selected based on *a priori* knowledge. In addition to a base set of covariates (including maternal age, child sex, and prenatal vitamin use in the first month of pregnancy) we selected additional covariates based on known associations with autism and suspected or known relationship with oxidative stress) and retained covariates that affected estimates by ≥ 10% for at least 2/3 of the continuous neurodevelopmental outcome measures and diagnostic outcomes of interest (Table A2). Final models included pre-pregnancy body mass index (BMI), maternal race and ethnicity (Hispanic, Non-Hispanic White, and other groups, collapsed due to small numbers; included as a proxy for potential disparities related to oxidative stress and autism), and maternal education (High school or less, Some college, Bachelor's degree, and Graduate or professional degree; included as a proxy for socioeconomic status), prenatal smoking (active, passive, none) in addition to the base model covariates (maternal age, child sex, and prenatal vitamin use in the first month of pregnancy). Maternal alcohol intake was the only additional variable examined as a potential confounder, but it did not meet our criteria for inclusion and was not retained in final models.

Primary analyses parameterized 8-iso-PGF2α according to an interquartile (IQR) increase and used Quantile regression, a flexible modeling approach that does not assume normality (see Figure A2 for outcome distributions in the analytic sample) (Koenker and Hallock, 2001), and allows for examination of effects across quantiles of continuous outcomes. Quantiles, or percentiles, represent the proportion of individuals with an outcome value at or below that percentile value, tau (τ), where tau can take on any value $0 < \tau < 1$ (Yu et al., 2003). Regression coefficients are calculated by minimizing the sum of weighted absolute residuals compared to squared residuals (Beyerlein, 2014). Primary results show the relationship between 8-iso-PGF2α levels and neurodevelopmental outcomes at the 50th percentile of scores from the quantile regression analysis. The 50th percentile is equivalent to the median scores for each measure, and most analogous to estimates in traditional linear regression (modeled at the mean). In appendix tables, we provide quantile regression estimates at the 10th, 25th, 75th and 90th percentile of outcomes.

In secondary analyses, we explored associations with binary indicator variables of these continuous outcomes. For the MSEL and VABS, we used a cut-off of one standard deviation below the mean (<85) and for the SRS T score we used a cut-off of >55 (1/2 SD above the mean). We used multivariate logistic regression, adjusted as described above, to examine associations between an IQR increase in 8-iso-PGF2α levels and these categorical outcome measures. We also conducted a logistic regression with clinical diagnostic categories (ASD, non-TD, and TD) determined at the 36-month follow-up and examined the association with an IQR increase in 8-iso-PGF2α levels. All analyses were conducted using SAS 9.4 (SAS Institute, Cary NC).

3. Results

Overall, 169 mother-child pairs were included in our analyses. We did not observe major demographic differences between our analytic sample and the total sample of enrolled EARLI participants (Table A3). Characteristics of the mother-child pairs included in our analytic sample are provided in Table 1. Mothers in our analytic sample had a mean age of 34 years (SD = 4.5) and a mean pre-pregnancy BMI of 27.9 (SD = 7.06). Most of the mothers were non-Hispanic white (54.4%), did not smoke during the prenatal period (76.3%), and initiated prenatal vitamin use during the first month of pregnancy (56.8%). Of the 169 children, 33 (19.5%) had a confirmed diagnosis of autism, a prevalence broadly consistent with sibling recurrence risk estimates (Sandin et al., 2014).

The mean scores for the child neurodevelopmental outcome measures were as follows: SRS T-score: 47.9 (SD = 11.3), MSEL-ELC: 99.2 (SD = 20.5), and Vineland ABC: 95.7 (SD = 26.6) (Figure A2). The mean concentration of 8-iso-PGF2α was 1.61 ng/ml (SD = 0.74) with a minimum of 0.34 and a maximum of 3.90 (Table A4), a distribution similar to that observed in a prior sample of pregnant individuals drawn from the general population (Rommel et al., 2020). Mean levels of 8-iso--PGF2α were similar between mothers with children who scored above and below cut-off scores on continuous neurodevelopmental assessments (Table A5). Mean levels of 8-iso-PGF2α were also similar across diagnostic categories (ASD, non-TD, and TD; Table A6).

Table 2 shows associations examined between an IQR increase in 8-iso-$PGF2_{\alpha}$ levels and scores on continuous neurodevelopmental outcomes measured at the 50th percentile (the median), using quantile regression. We observed a statistically significant increase in SRS T scores (consistent with increases in autism-related behaviors) with an IQR increase in 8-iso-$PGF2_{\alpha}$ in crude analyses, though this was attenuated in adjusted models, with confidence intervals narrowly crossing over the null (SRS T score adjusted β = 1.68, 95% CI: -0.24, 3.60). There was also a modest, non-significant decrease in MSEL-ELC scores

Table 1
Basic characteristics of the study population.

	Analytic Dataset (n = 169)
	N (%)
Child's sex	
Male	87 (51.48)
Female	82 (48.52)
Household income[a]	
Low	43 (25.44)
Medium	56 (33.14)
High	66 (39.05)
Missing	4 (2.37)
Maternal race and ethnicity	
Non-Hispanic white	92 (54.44)
Hispanic	30 (17.75)
Other[b]	47 (27.81)
Maternal education	
High school or less	21 (12.43)
Some college, Associate or technical/vocational school	50 (29.59)
Bachelor's degree	50 (29.59)
Graduate or Professional degree	47 (27.81)
Missing	1 (0.59)
Prenatal smoking	
Active	8 (4.73)
Passive	2 (1.18)
None	129 (76.33)
Missing	30 (17.75)
Prenatal vitamin in month 1 of pregnancy	
Yes	96 (56.80)
No	72 (42.60)
Missing	1 (0.59)
Autism diagnosis	
Yes	33 (19.53)
No	133 (78.70)
Missing	3 (1.78)
	Mean (SD)
Maternal age, years	33.97 (4.53)
Parity[c]	1.79 (0.90)
Pre-Pregnancy BMI, kg/m^2	27.94 (7.06)
Total alcohol intake, g/day	0.12 (0.56)

Abbreviations: BMI (Body Mass Index).
[a] Low income category defined as <$50,000, medium category as $50,000-$100,000, high as >$100,000.
[b] Includes individuals who identified as "Black, African American," "American Indian/Alaskan Native," "Asian," "Native Hawaiian/Pacific Islander," and "Multiple or Other Race".
[c] Parity value does not include the study child in EARLI; by design, all children in EARLI were 2nd or later birth order.

Table 2
Associations (β estimates and 95% confidence intervals at 50th percentile of outcome measure) between IQR increases in 8-iso-PGF2α and outcome measures.[a]

Measure	Total n	Crude β (95% CI)	Adjusted[b] β (95% CI)
MSEL-ELC	159	−2.0 (−7.69, 3.70)	−3.68 (−10.08, 2.70)
SRS T	145	**2.39 (0.06, 4.72)**[c]	1.68 (−0.24, 3.60)[d]
Vineland ABC	155	−0.74 (−3.82, 2.35)	2.62 (−0.64, 5.88)

Abbreviations: Confidence Interval (CI).
[a] Estimates shown from quantile regression modeled at the 50th percentile of outcome measure.
[b] Adjusted for pre-pregnancy BMI, maternal age, maternal race/ethnicity, child sex, prenatal vitamin use in the first month of pregnancy, smoking, and maternal education.
[c] $p < 0.05$.
[d] Regression models for SRS T scores were adjusted for all variables mentioned in note b excluding child sex.

(consistent with a decrease in overall cognitive ability) with an IQR increase in 8-iso-PGF2$_\alpha$ levels, though again the confidence interval included the null (adjusted β = −3.68, 95% CI: -10.08, 2.70). There was also a modest, not statistically significant positive association between 8-iso-PGF2α and Vineland ABC scores in adjusted models (adjusted β = 2.62, 95% CI: -0.64, 5.88), suggesting better adaptive behavior scores with increasing oxidative stress. Examining associations at other quantiles of Vineland ABC scores, we did not observe evidence for stronger associations at other quantiles, nor a clear pattern across quantiles (Table A7). For MSEL-ELC scores, estimates at other quantiles were all in the same direction, indicating lower cognitive scores with increasing oxidative stress, but no results were statistically significant. The estimate at the highest quantile of SRS T scores was larger than for other quantiles, though this association was estimated with little precision (adjusted β at 90th percentile of SRS = 6.78, 95% CI: -3.86, 16.84; Table A7).

In secondary analyses exploring associations with continuous neurodevelopmental outcomes parameterized dichotomously, no statistically significant associations were observed (Table 3). However, results were consistent with the direction of associations suggested with continuous outcomes, and the odds of lower cognitive scores was modestly elevated (OR for MSEL-ELC scores 1 SD or more below the mean with an IQR increase in 8-iso-PGF2α levels = 1.40, 95% CI: 0.73, 2.70). In adjusted secondary analyses examining associations with categorical ASD, non-TD, and TD diagnoses, again we observed no statistically significant associations, though point estimates for odds of both ASD and non-TD were modestly elevated at approximately 1.3 with an IQR increase in 8-iso-PGF2α levels.

4. Discussion

Oxidative stress is a pathway that has been implicated as a potential mechanism underlying associations between autism and many environmental exposures, such as exposure to air pollution, heavy metals, or certain chemicals (Pugsley et al., 2022; Volk et al., 2021). However, limited work has directly examined this mechanistic pathway of maternal oxidative stress and offspring autism in human studies. In this study, we examined prenatal oxidative stress levels in association with a suite of neurodevelopmental outcomes related to autism in young children, capturing cognition, social communication, and adaptive behavior. While we did not observe statistically significant associations in adjusted analyses, our primary and secondary results for both cognitive scores and autism-related behaviors were suggestive of potential associations between higher levels of prenatal oxidative stress and lower cognitive scores and higher autism-related behaviors in children. Given our relatively small sample size, and our use of a familial cohort with increased likelihood of autism, these suggestive findings should be further examined in larger studies and in cohorts from the general population.

This is the first study to our knowledge to assess the relationship between 8-iso-PGF2α during pregnancy and MSEL-ELC scores. Our previous work examined the association between other prenatal biomarkers of oxidative stress, including glutathione (GSH), glutathione disulfide (GSSG), and 8-oxo-deoxy-guanine (8-OHdG), and 3-nitrotyrosine and MSEL-ELC scores, and did not observe associations (Carey et al., 2022). These other biomarkers captured different pathways of oxidative stress, including antioxidant balance (the ratio of GSH:GSSG), DNA oxidation (8-OHdG), and nitrosylation formed under oxidative stress (3-nitrotyrosine), which may contribute to differences across signals observed in these studies. Another study, conducted in a different study population, examined plasma isoprostane levels in the first month of life among prematurely born infants in association with scores of neurodevelopment as measured by the Developmental Assessment of Young Children (DAYC) assessment. They found that a 50 pg/mL increase in isoprostanes was associated with decreases in cognitive scores at 12-months corrected age (Matthews et al., 2016). While some

Table 3
Associations (Odds Ratio and 95% confidence intervals) between IQR increases in 8-iso-PGF2α and dichotomous outcomes threshold scores.

Threshold scores on SRS (T > 55), MSEL (ELC<85), and Vineland (<85)[a]				
	n	N above cut-off[b]	Crude OR (95% CI)	Adjusted[c]
MSEL-ELC	159	39	1.13 (0.64, 1.97)	1.40 (0.73, 2.70)
SRS T score	145	24	1.20 (0.60, 2.40)	1.10 (0.50, 2.46)[d]
Vineland ABC	155	43	0.84 (0.48, 1.47)	0.75 (0.38, 1.45)

Categorical diagnosis (ASD, non-TD, and TD)[a]					
ASD vs TD (n = 31, 79)		Non-TD vs TD (n = 50, 79)		ASD/non-TD vs TD (n = 81, 79)	
CrudeOR (95% CI)	Adjusted[c]OR (95% CI)	Crude OR (95% CI)	Adjusted[c]OR (95% CI)	CrudeOR (95% CI)	Adjusted[c]OR (95% CI)
0.99 (0.52, 1.88)	1.03 (0.45, 2.37)	1.27 (0.74, 2.18)	1.36 (0.73, 2.54)	1.16 (0.71, 1.88)	1.31 (0.75, 2.28)

[a] Estimates shown from logistic regression.
[b] Modeling the odds of a score below 85 (1 SD below the mean) for MSEL and Vineland and above 55 (1/2 SD above mean) for SRS T score.
[c] Adjusted for pre-pregnancy BMI, maternal age, maternal race/ethnicity, child sex, prenatal vitamin use in the first month of pregnancy, smoking, and maternal education.
[d] Regression models for SRS T scores were adjusted for all variables mentioned in note b excluding child sex.

inconsistencies across studies exist, results suggest that higher perinatal oxidative stress as measured by isoprostanes may negatively relate to offspring cognitive development. However, there is a need for future work in this area.

Our results were suggestive of modest increases in autism-related behaviors, as measured by SRS T scores, with an IQR increase in levels of 8-iso-PGF2α, in primary, and to a lesser extent, secondary analyses. While not statistically significant, the direction and magnitude of our estimates are broadly consistent with those of Rommel et al. (2020) who found a 2.58% increase in SRS T-scores (95% CI: 0.08–5.16) measured in children at age 4–5 years for an IQR increase in 8-iso-PGF2α levels measured in the third trimester of pregnancy with that child. Our results could be impacted by our small sample size. Further, Rommel and colleagues conducted an effect modification analysis and found that the association between 8-iso-PGF2α and SRS T-scores was only present among more educated mothers (Rommel et al., 2020). Our study did not have the power to examine effect modification by education, but the participants in EARLI were also highly educated – 88.5% had some college education or more. Our prior work also did not find statistically significant associations with other oxidative stress biomarkers, though a modest increase in SRS total raw scores with GSH:GSSG ratio was suggested (Carey et al., 2022). Thus, while our work here adds to growing evidence for isoprostanes and other oxidative stress biomarkers in autism-related behaviors, further larger studies are needed to confirm findings and build upon the evidence base.

We also observed minor associations between 8-iso-PGF2α levels in pregnancy and child adaptive behaviors measured by the VABS, though these were counter to hypotheses, with an increase in 8-iso-PGF2α levels suggesting better adaptive functioning. In contrast, another recent study found evidence (Cañizo Vázquez et al., 2022) for poorer adaptive scores and cognitive ability, measured by the VABS and Bayley III, with higher levels of 8-iso-PGF2α. However, this work was conducted among a small sample of infants requiring cardiac surgery, with isoprostane levels measured 24-h post-surgery and adaptive and cognitive scores grouped together in analyses unadjusted for potential confounders. Thus, insufficient data exists on the role of oxidative stress in adaptive functioning.

Oxidative stress may impact neurodevelopmental outcomes via direct impacts on the developing brain, as suggested in animals models demonstrating decreased neural connections with higher levels of isoprostanes, or via indirect mechanisms. Specifically, oxidative stress also influences inflammation, which has been shown to influence neurodevelopmental processes (Kwon et al., 2022), and a broad literature links maternal immune activation and inflammation to autism (McLellan et al., 2022). Additionally, a number of recent studies have examined associations between higher levels of oxidative stress, measured by 8-iso-PGF2α, and increased odds of preterm birth (Eick et al., 2020; Rosen et al., 2019); thus influences on neurodevelopment may be mediated via associations between autism and preterm birth. While oxidative stress is itself a broad mechanistic pathway, there are multiple types of oxidative stress mechanisms, including DNA damage, lipid peroxidation, and protein oxidation. Prior work has suggested a link between low maternal lipid levels and autism in offspring (Park et al., 2021). As lipids are crucial for neurodevelopment (Crawford, 1993), identifying biomarkers that can specifically measure lipid oxidation, like isoprostanes, is important for elucidating the direct impacts of oxidative stress on the developing brain. While our prior work did not suggest links with these other more specific oxidative stress targets, and the associations here may suggest a role of lipid-specific oxidative stress, future work is needed to interrogate more specific pathways.

While our study had several strengths, including use of measured prenatal levels of a reliable, widely-used oxidative stress biomarker, and the ability to examine associations with several child neurodevelopmental outcomes, including continuous measures that capture trait distributions (Sagiv et al., 2015), certain limitations should be noted. First, levels of oxidative stress, measured by levels of 8-iso--PGF2α, were measured at a single time point in the second or third trimester of pregnancy. Elevated oxidative stress levels in these trimesters is thought to be an underlying mechanism for many fetal and pregnancy related complications (Samir et al., 2018). While our biosamples were selected to assess oxidative stress levels in a time frame both relevant as a potential critical window for autism etiology, as well as a period in which several environmental factors have been shown to increase likelihood of autism and neurodevelopmental disorders (including air pollution, (Lin et al., 2021; Volk et al., 2011), future studies should assess oxidative stress at other time points. Second, emerging evidence suggests that the relationship between environmental exposures and levels of 8-iso-PGF2α differ based on the pathway through which is generated (Cathey et al., 2021; van′ t Erve et al., 2019). In this analysis, we did not have the data to explore the pathway through which 8-iso-PGF2α was generated. Third, our small sample size did not allow for analyses examining the potential for effect modification by other factors such as maternal education and child sex that have been implicated as modifiers in prior work (Eick et al., 2024; Rommel et al., 2020), and did not allow for us to use clinically relevant thresholds in secondary analyses with dichotomous cutoff scores. Fourth, associations were estimated with less precision than larger studies. Fifth, there are myriad environmental exposures associated with oxidative stress that were not captured in our data and thus not modeled. If these unmeasured factors affect both oxidative stress and neurodevelopmental outcomes our estimates would be impacted by residual confounding. Finally, this study was conducted in a familial cohort with increased likelihood of autism, and thus findings may not be generalizable to those without family history of autism. Additional research with more diverse and larger samples is warranted.

5. Conclusions

In this cohort with increased likelihood of autism, we observed some suggestive associations between increasing oxidative stress levels during pregnancy and poorer cognition as well as a greater degree of autism-related behaviors in children. Our work points to the need for continued investigation in maternal prenatal levels of 8-iso-PGF2α as a mechanistic pathway in autism and related neurodevelopmental outcomes, in larger, more diverse samples.

Funding

This research was supported by the Eunice Shriver Kennedy National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH) (R21HD096356). The EARLI Study was funded by the National Institute of Environmental Health Sciences, the National Institute of Mental Health, the National Institute of Child Health and Human Development, and the National Institute of Neurologic Disease and Stroke (R01 ES016443; R24 ES030893), with additional funding from Autism Speaks (AS 5938).

CRediT authorship contribution statement

Meghan E. Carey: Methodology, Validation, Writing – original draft, Writing – review & editing. **Apollo Kivumbi:** Writing – original draft, Writing – review & editing. **Juliette Rando:** Data curation, Formal analysis, Software, Visualization, Writing – review & editing. **A. Clementina Mesaros:** Investigation, Resources, Writing – review & editing. **Stepan Melnyk:** Investigation, Writing – review & editing. **S. Jill James:** Conceptualization, Investigation, Writing – review & editing. **Lisa A. Croen:** Conceptualization, Investigation, Writing – review & editing. **Heather Volk:** Conceptualization, Writing – review & editing. **Kristen Lyall:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

Acknowledgements

The authors would like to thank Jimmy Xu for his assistance in sample handling and measurement as well as the original Principal Investigators for the EARLI study: Craig Newschaffer, Daniele Fallin, Irva Hertz-Piccioto, and Lisa Croen.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100775.

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