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The association between prenatal F_2-isoprostanes and child wheeze/asthma, and modification by maternal race

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Abstract

Background: Childhood wheeze, asthma, and allergic rhinitis are common and likely have prenatal origins. Oxidative stress is associated with respiratory disease, but the association of oxidative stress during the prenatal period with development of respiratory and atopic disease

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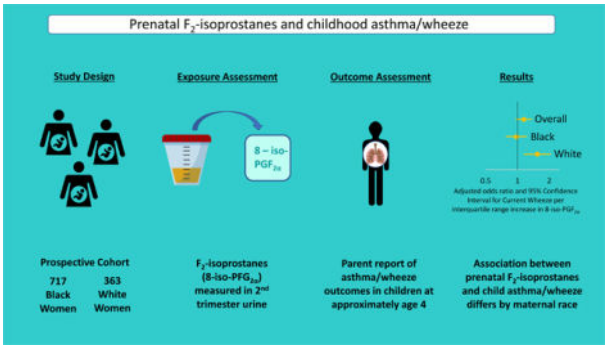
in childhood, particularly beyond the infancy period, is unknown. This study aims to investigate associations between prenatal oxidative stress, measured by maternal urinary F_2-isoprostanes, and child respiratory outcomes, including effect modification by maternal race.

Methods: We prospectively studied Black (n=717) and White (n=363) mother-child dyads. We measured F_2-isoprostanes in 2nd-trimester urine (ng/mg-creatinine). At approximately age 4, we obtained parent report of provider-diagnosed asthma (ever), current wheeze, current asthma (diagnosis, symptoms and/or medication), and current allergic rhinitis (current defined as previous 12 months). We used multivariable logistic regression to estimate adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) per interquartile range (IQR) increase in F_2-isoprostane concentration, controlling for confounders. We examined modification by maternal race using interaction terms.

Results: The prevalence of provider-diagnosed asthma and current wheeze, asthma and allergic rhinitis was 14%, 19%, 15%, and 24%, respectively. Median (IQR) F_2-isoprostane levels were 2.1 (1.6, 2.9) ng/mg-creatinine. Associations between prenatal F_2-isoprostanes and provider-diagnosed asthma, current wheeze, and current asthma were modified by maternal race. Results were strongest for current wheeze (aOR [95%CI]: 1.55 [1.16, 2.06] for White; 0.98 [0.78, 1.22] for Black; p-interaction=0.01). We observed no association between F_2-isoprostanes and allergic rhinitis.

Conclusion: Prenatal urinary F_2-isoprostanes may be a marker associated with childhood wheeze/asthma in certain populations. Research is needed to understand underlying mechanisms and racial differences.

Graphical Abstract



Keywords

oxidative stress; isoprostane; prenatal; asthma; wheezing; allergic rhinitis; pediatric

Introduction

Atopic diseases, such as asthma and allergic rhinitis, are common chronic diseases of childhood. Asthma and wheeze, in particular, disproportionately affect low-income, non-Hispanic Black children with respect to both prevalence and severity[1]. These respiratory illnesses are influenced by a combination of societal, environmental and genetic factors and likely have prenatal or early life origins[2,3]. Oxidative stress, characterized as an imbalance

between reactive oxygen species and antioxidant defenses, may be a potential mechanistic contributor to the development of wheeze/asthma[4–6]. While oxidative stress typically increases during normal pregnancy, the developing fetus and neonate may experience detrimental developmental effects if pregnancy complications or environmental exposures exacerbate oxidative stress beyond tolerable levels[7]. Observational studies have consistently reported protective associations between maternal antioxidant levels and/or intake and early childhood asthma and wheeze[8]. Neonatal oxidative stress is linked to adverse respiratory outcomes among preterm births,[9,10] and strategies to reduce oxidative stress in preterm infants (e.g., low oxygen resuscitation) result in lower incidence of adverse outcomes such as bronchopulmonary dysplasia[11,12]. However, the association between validated markers of prenatal oxidative stress and childhood asthma/wheeze, as well as characterization of associations that may differ across racial/ethnic groups, are important areas of investigation.

F_2-isoprostanes, of which the 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) isomer is the most widely studied, arise from free radical-catalyzed oxidation of arachidonic acid and are widely recognized as reliable oxidative stress biomarkers because of their chemical stability and relative abundance in biological specimens[13,14]. F_2-isoprostanes have been associated with anthropometric outcomes in children[15] and adverse health outcomes in adult populations,[16,17] however, little is known regarding whether prenatal maternal isoprostane concentrations are associated with child respiratory outcomes such as asthma. Further, isoprostanes have not been well studied in diverse populations where effect modification by population characteristics has been shown to be important.[17,18] The association between isoprostanes and health outcomes may be modified by race,[19,20] but studies of these racial differences are few and results are inconsistent[21–24]. As a result, in this study we investigate the relationship between prenatal oxidative stress, measured as maternal urinary F_2-isoprostanes, and childhood asthma, wheeze and allergic rhinitis in a large, prospective, racially-diverse cohort of mothers and children. We hypothesize that maternal F_2-isoprostanes, indicative of underlying oxidative stress, are associated with adverse respiratory outcomes in children. We further hypothesize that these associations will vary by race/ethnicity.

Material and methods

Study Design

We studied 1080 mother-child dyads enrolled in the Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) study[25,26]. CANDLE staff enrolled women ages 16 – 40 with singleton, medically low-risk pregnancies during the second trimester (16–28 gestational weeks) between December 2006 and June 2011. All women spoke English and were residents of Shelby County (Memphis), TN. Medically low-risk pregnancies were defined as those without certain chronic medical conditions or pregnancy complications at enrollment (e.g., chronic hypertension requiring medication, oligohydramnios, insulin-dependent (type-1) diabetes), although women with asthma were allowed. Follow-up clinic visits occurred at one year of age, then annually up to age three and at approximately 4.5 years. The current analysis includes dyads in which women provided a second trimester urine sample for F_2-isoprostane measurement, the child had a

gestational age ≥ 32 weeks and completed a follow-up visit at approximately 4 to 6 years of age. In order to explore effect modification by maternal race, we further limited our analysis to Black and White dyads as other race groups were too few to study. Of 1503 women enrolled in CANDLE during pregnancy, 1435 had births at gestational age ≥32 weeks and remained active in the study. Of these, 1110 had a child who completed a 4.5 year study visit (child age range 3.7–6.5 years; median [interquartile range]: 4.2 [4.1, 4.5]). F_2-isoprostane measurements were obtained for 1097 of these women, of whom, 1080 identified as Black or White. Women provided written informed consent for themselves and their children. The study was approved by Institutional Review Boards of Vanderbilt University and the University of Tennessee Health Science Center.

F_2-isoprostanes Assessment

The primary oxidative stress measure included a mix of F_2-isoprostanes with 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) as the predominant isomer[13]. Women provided spot urine samples during the second trimester baseline clinic visit; F_2-isoprostanes were measured during the second trimester (median [interquartile range] 23 [21, 26]) as mid-pregnancy is a period of maturation and differentiation of the immune and pulmonary systems.[27,28] Aliquots were stored at −80C in our study repository prior to shipment to institutional Eicosanoid Core Laboratory where F_2-isoprostane analyses were completed. We determined F_2-isoprostanes levels using gas chromatography-mass spectrometry, according to established methods[13,29]. Measurements were corrected for urinary creatinine (ng/mg creatinine).

Outcome Assessment

We assessed outcomes (current wheeze, current asthma, current allergic rhinitis and diagnosed asthma) using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire[30] and parent-reported medication and healthcare utilization, as previously described[26]. Outcome definitions were based on the following questions: current wheeze, “Has your child ever had wheezing or whistling in the chest?” and “Has your child had wheezing or whistling in the chest in the last 12 months?”; parent report of provider-diagnosed asthma, “Has a physician or other health care provider ever told your family that your child had asthma or reactive airway disease?”; and allergic rhinitis, “In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?” We defined current asthma as having any two of the following: current wheeze, provider-diagnosed asthma, or report of asthma-specific medication use in previous 12 months. For current asthma, subjects with missing or unknown medication data and only one affirmative response to either current wheeze or diagnosed asthma (n = 17), or who had missing medication and diagnosed asthma data with a negative current wheeze response (n =1), were categorized as non-cases.

Covariates

At enrollment, women self-reported demographic and health information, including maternal age, race, parity, smoking status, highest level of educational attainment, income, and height and weight used to calculate pre-pregnancy body mass index (BMI) defined as (kg/m^2). We standardized and averaged maternal education and income variables to

derive the socioeconomic status (SES) composite score, as described in previously[26]. Following delivery, we reviewed medical records to characterize pregnancy complications (e.g., gestational diabetes, hypertension) and obtained information on infant sex, gestational age at delivery, delivery route and neonatal characteristics (neonatal intensive care unit (NICU) admission, Apgar scores, resuscitation). Breastfeeding history and maternal history of atopy (ever having asthma, allergic rhinitis or atopic dermatitis) were assessed at the age 4.5 follow up visit.

Statistical Analysis

We used multivariable logistic regression to calculate adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) per interquartile range (IQR) increase in F_2-isoprostanes. Primary models were adjusted for maternal age, race, SES composite score, parity, prenatal smoking, pre-pregnancy BMI, maternal history of atopy, infant sex and gestational week at urinary sample collection. Additional covariates were included individually in separate secondary sensitivity analyses (gestational diabetes, gestational hypertension, gestational age at delivery, second trimester plasma folate,[25] cesarean delivery, and breastfeeding duration). Effect modification by maternal race was explored by adding a cross-product interaction term for race and F_2-isoprostanes to primary models. Additionally, we repeated both the primary and secondary sensitivity analyses, stratified by race. We defined statistical significance at $p < 0.05$. We used R version 3.6.3 (the R Foundation, Vienna, Austria) for all analyses.

Results

Sixty-six percent of women identified as Black (n=717) and 34% as White (n=363). Children were approximately 4 years of age at follow up (median [IQR]: 4.2 [4.1, 4.5]). The overall prevalence of current wheeze, current asthma, provider-diagnosed asthma and allergic rhinitis in children was 19%, 15%, 14% and 24%, respectively. On average, Black women were younger than White women (24 vs. 29 years, $p < 0.001$), had higher pre-pregnancy BMI (27 vs 24 kg/m^2, $p < 0.001$), had lower SES composite score ($p < 0.001$), were more likely to be parous (63% vs 55%, $p = 0.011$) and had higher creatinine levels (1.2 vs 0.7 mg/dl, $p < 0.001$) (Table 1). Children of Black women had higher prevalence of current asthma and provider-diagnosed asthma compared to children of White women (17% vs 12% current asthma, $p = 0.02$; 16% vs 9% provider-diagnosed asthma, $p < 0.001$). Prevalence did not differ by race for current wheeze (20% vs 16% for Black and White dyads, respectively, $p = 0.11$) or allergic rhinitis (23% vs 25% for Black and White dyads, respectively, $p = 0.56$) (Supplemental Table 1). Median (IQR) F_2-isoprostane levels were 2.1 (1.6, 2.9) ng/mg-creatinine. These levels did not differ between Black and White women (median (IQR): 2.1 (1.6, 2.9) and 2.1 (1.5, 2.9) ng/mg-creatinine, respectively, $p = 0.34$). In White women, higher F_2-isoprostane levels were associated with younger maternal age ($p < 0.001$), lower SES ($p < 0.001$), higher pre-pregnancy BMI ($p = 0.005$), and prenatal smoking ($p = 0.005$). In Black women, higher F_2-isoprostanes were associated with lower SES ($p = 0.048$), lower creatinine ($p = 0.01$) and NICU admission ($p = 0.002$), but not other factors (Table 1, Supplemental Table 2).

In primary multivariable models, we observed no association between F_2-isoprostanes and childhood wheeze, asthma, and allergic rhinitis outcomes (Figure 1). Adjustment for additional covariates in secondary models did not substantially change these results (not shown). Interaction models indicated effect modification by race for current wheeze (p-interaction=0.01) and current asthma (p-interaction=0.02), with positive associations observed in White, but not Black dyads [White aOR (95%CI): 1.55 (1.16, 2.06) for current wheeze; 1.35 (0.97, 1.86) for current asthma; Black aOR (95%CI): 0.98 (0.78, 1.22) for current wheeze; 0.82 (0.63, 1.05) for current asthma] (Figure 1). The interaction was of borderline significance for provider-diagnosed asthma (p-interaction=0.05), suggesting a modest inverse association among Black, but not White dyads [White aOR (95%CI): 1.22 (0.83, 1.79); Black aOR (95%CI): 0.77 (0.59, 1.00)]. We did not observe effect modification for current allergic rhinitis (p-interaction=0.29), with confidence interval estimates including the null in both Black and White dyads. In race-stratified analyses with additional adjustment for secondary covariates (e.g., gestational diabetes, gestational hypertension, etc.), results were consistent in analyses for all outcomes (not shown).

Discussion

In this study, we demonstrate the novel finding that maternal prenatal urinary F_2-isoprostanes were associated with childhood wheeze and asthma in White, but not Black mother-child dyads. For dyads in which the mother was White, positive associations were strongest for report of current wheeze in the child. Associations were robust to adjustment for multiple potential confounders. Additionally, while F_2-isoprostane levels did not differ between Black and White women overall, characteristics such as younger age, obesity and smoking that have previously been associated with oxidative stress[31] were associated with F_2-isoprostanes in White, but not Black women, in our study. Maternal prenatal F_2-isoprostanes were not associated with childhood allergic rhinitis.

Urinary F_2-isprostanes are an index of integrated systemic oxidant stress over time[13]. Higher levels during pregnancy have been associated with pregnancy complications[32] as well as lower birth weight and higher early childhood weight and BMI[15]. Urinary F_2-isprostanes have also been shown to be elevated among individuals with asthma,[16] and can reflect a biologic response to asthma triggers, such as allergens or air pollutants.[33] Epidemiologic literature demonstrates that prenatal exposures to pro-oxidant stressors such as tobacco smoke, air pollution, and maternal obesity are associated with asthma and related atopic diseases[3,5]. Likewise, maternal antioxidant intake has been associated with reduced risk of asthma[8].

Additional research is needed to more fully understand the role of oxidative stress in the development of asthma, and whether it is acting directly on lung or immune system development or is a marker of other important exposures or processes that influence asthma development. Multiple pathways are plausible. For example, oxidative stress has been shown to upregulate a T helper 2 (Th2) cellular immune response in vitro[34]. Asthma and related diseases are commonly characterized by a Th2-dominant phenotype,[35] and further, enhancement of maternal Th2 cytokines can promote transmission of asthma risk to offspring in murine models[36]. Further, evidence from the smoking and air pollution

literature suggest that early life oxidative stress may be contributing to the development of chronic respiratory disorders through multiple possible pathways, including programming of the autonomic nervous system and inhibition of fetal detoxification pathways[37].

The finding that associations were modified by maternal race were consistently observed across the asthma and wheeze outcomes we examined. Racial differences in F_2-isoprostanes production and its relationship with disease are poorly understood. Prior studies have observed lower F_2-isoprostane levels in Black than White individuals[20,31] but we identified few studies in which associations between F_2-isoprostanes and disease outcomes were examined for effect modification by race[19,22–24]. With the exception of one study of F_2-isoprostanes in amniotic fluid,[24] these studies primarily focused on cardiovascular and metabolic outcomes in children and non-pregnant adults, and yielded inconsistent results with respect to modification by race. Similar to our descriptive findings, Il'yasova et al. observed that F_2-isoprostanes increased with BMI among White but not Black adults cross-sectionally[19]. Although race is a social, not biologic, construct and is not a surrogate for genetic ancestry,[38] evidence suggests that consideration of race/ethnicity in investigations of oxidative stress and the subsequent development of disease may be informative in identifying associations that may vary across populations[39]. For example, although F_2-isoprostanes have been considered potential markers or mediators of diseases such as type 2 diabetes, emerging evidence suggests that this relationship may be modified by underlying metabolic factors that may vary by race/ethnicity, such as compensatory mechanisms to higher body mass index[18,39]. Investigators hypothesize that F_2-isoprostanes may reflect intensity of fatty acid oxidation and that *lower* F_2-isoprostane levels may indicate an adverse metabolic profile and increased risk in Blacks but not Whites for certain outcomes[18]. While the relevance of this intriguing hypothesis to our current findings is unclear, it warrants further investigation including mechanistic studies of oxidative stress that address the potential roles of both genetic ancestry and social determinants of health.

Our study has several important strengths. The CANDLE cohort reflects many characteristics of Shelby County, TN, including a majority Black population. Studies of oxidative stress in non-White populations are limited. Our study is novel in both the characterization of oxidative stress during pregnancy among Black women as well as our investigation into how F_2-isoprostanes may be associated with childhood respiratory outcomes. In addition, the outcomes in our study were measured prospectively using a validated questionnaire[30]. Follow-up extended to approximately age 4 years allowing for reliable asthma, wheeze and allergic rhinitis characterization. Finally, our study also included rich covariate data allowing us to adjust for multiple potential confounders.

We also note some limitations. We acknowledge that our measure of oxidative stress, urinary 8-iso-$PGF_{2\alpha}$, is a widely accepted marker of oxidative stress driven by lipid peroxidation. However, additional markers of oxidative stress or protection from oxidative damage may be informative for future studies[32,40]. Despite our rich set of covariates, we acknowledge the potential for residual confounding. Additionally, while our study included robust longitudinal data from pregnancy to approximately 4 years of age, we measured F_2-isoprostanes at a single time point in pregnancy during the second trimester. Additional research characterizing F_2_isoprostanes levels at other time points in pregnancy,

as well as postnatal measures, should be considered in future studies. While this study shows a potential role for maternal oxidative stress in the development of childhood asthma, it does not clearly elucidate the mechanism by which oxidative stress may be acting on asthma development. We further acknowledge that the observed associations between F_2-isoprostanes and childhood asthma/wheeze do not fully encapsulate the complex pathophysiology of childhood asthma. In addition to other potentially important prenatal factors, postnatal exposures such as respiratory infection and tobacco smoke remain important modifiable factors that may influence asthma risk.

Conclusions

In summary, our findings suggest that the association between prenatal urinary F_2-isoprostanes and adverse childhood respiratory outcomes is modified by maternal race. More research characterizing F_2-isoprostanes levels at additional time points in pregnancy, as well as postnatal measures, and in other racially diverse populations, with emphasis on wheeze/asthma phenotypes and lung function in older children, will be important to further elucidate this association. Moreover, consideration of additional oxidative stress biomarkers may provide additional insight into links between prenatal oxidative stress, asthma, and other adverse respiratory outcomes in children, which may differ across groups. As we seek to understand potential prenatal programming mechanisms underlying childhood disease, expansion of research into racial differences related to F_2-isoprostane production and function, and other potential biomarkers, is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest:

Authors report receiving grant support from the National Institutes of Health (M.A.A.; T.G.; F.A.T.; R.J.W.; K.N.C.) and the Urban Child Institute (N.B.) in relation to this work. Other authors have nothing to disclose.

Abbreviations:

95%CI	95% confidence interval
aOR	adjusted odds ratio
BMI	body mass index

CANDLE	Conditions Affecting Neurocognitive Development in Early Childhood study
IQR	interquartile range
SES	socioeconomic status

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Highlights

- Maternal race modified the association of the 2nd trimester urinary F_2-isoprostanes and child asthma/wheeze
- Association with child wheeze at age 4–6 was significant for White, but not Black, dyads
- Creatinine-adjusted urinary F_2-isoprostanes levels did not differ by maternal race

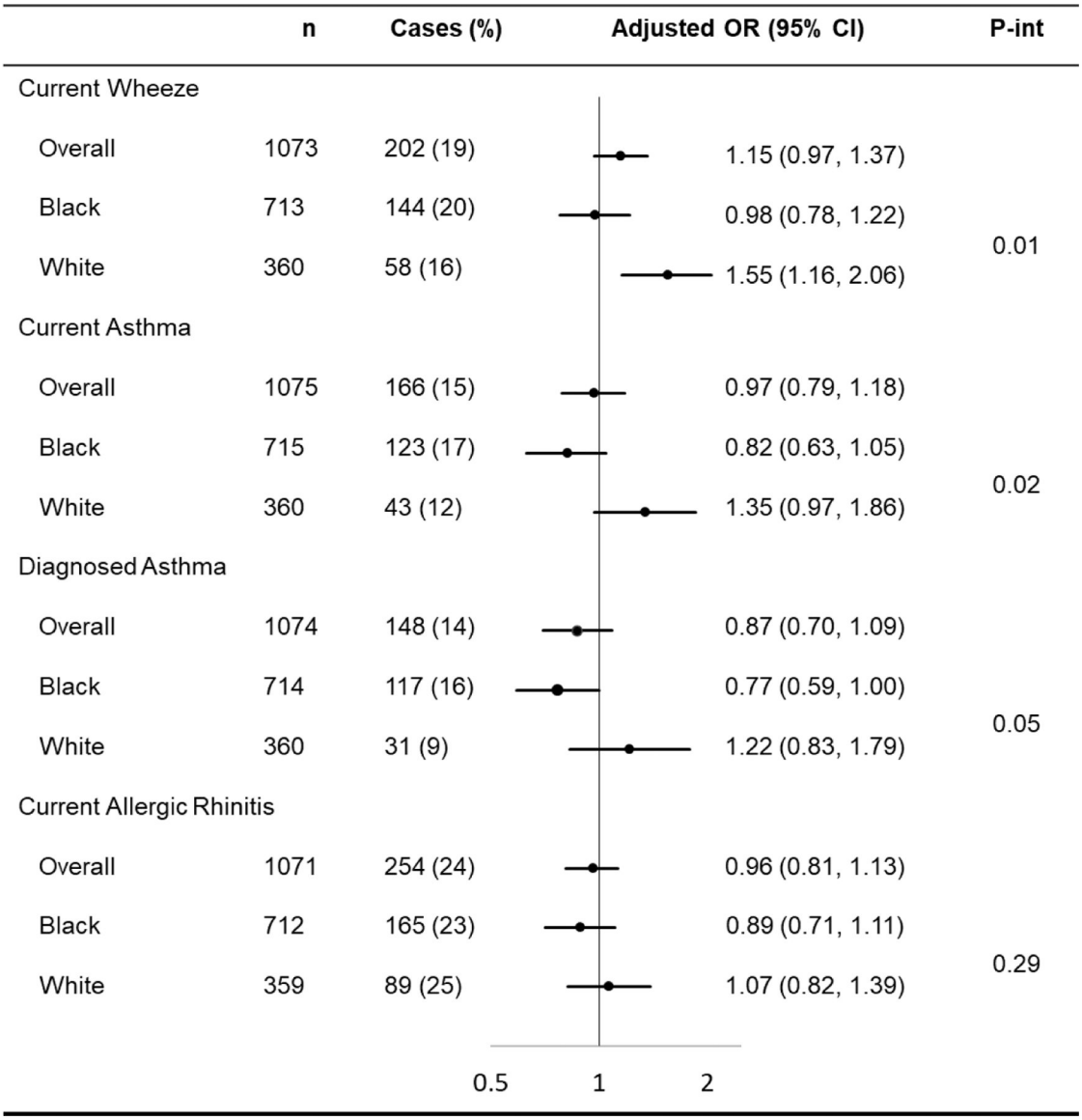

Figure 1.

Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for asthma and allergic rhinitis outcomes per interquartile range (IQR) increase in maternal urinary F_2-isoprostane (ng/mg-creatinine) (IQR: 1.59, 2.87) for the overall model and model with F_2-isoprostane * maternal race interaction term; p-interaction (p-int) corresponds to the p-value for the interaction term.

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Table 1.

Characteristics of CANDLE study population by F_2-isoprostane level, by maternal race

	Urinary F_2-isoprostane (ng/mg-creatinine) quartiles				
	Q1 (0.2, 1.6)	**Q2 (1.6, 2.1)**	**Q3 (2.1, 2.9)**	**Q4 (2.9, 8.1)**	**Total**
Black Dyads	170	183	187	177	717
Maternal age, years	25 (21, 30)	24 (21, 28)	24 (20, 28)	24 (20, 29)	24 (21, 29)
Parity, 1+, n (%)	112 (66)	109 (60)	119 (64)	110 (62)	450 (63)
Maternal atopy, yes, n (%)[a]	73 (44)	76 (42)	83 (44)	72 (41)	304 (43)
Prenatal smoking, yes, n (%)[a]	11 (7)	13 (7)	19 (10)	12 (7)	55 (8)
Body mass index, kg/m^2 [a]	27 (23, 33)	26 (22, 33)	27 (22, 33)	28 (24, 34)	27 (23, 33)
SES composite *	−0.3 (−0.8, 0.3)	−0.3 (−0.9, 0.2)	−0.4 (−1.0, −0.0)	−0.4 (−0.9, 0.0)	−0.3 (−0.9, 0.1)
Gestational age at sample, weeks	24 (21, 26)	23 (21, 26)	23 (20, 25)	23 (20, 26)	23 (21, 26)
Creatinine, mg/dL *	1.3 (1.0, 1.7)	1.3 (0.8, 1.7)	1.2 (0.9, 1.7)	1.1 (0.7, 1.6)	1.2 (0.9, 1.6)
Child sex, male, n (%)	79 (46)	90 (49)	95 (51)	98 (55)	362 (50)
White Dyads	103	85	85	90	363
Maternal age, years *	30 (27, 33)	30 (26, 33)	30 (27, 34)	26 (23, 31)	29 (26, 32)
Parity, 1+, n (%)	58 (56)	52 (61)	50 (59)	41 (46)	201 (55)
Maternal atopy, yes, n (%)[b]	51 (51)	34 (41)	34 (40)	35 (39)	154 (43)
Prenatal smoking, yes, n (%) *	3 (3)	10 (12)	10 (12)	17 (19)	40 (11)
Body mass index, kg/m^2 *	23 (21, 26)	24 (22, 29)	25 (22, 30)	26 (22, 31)	24 (22, 29)
SES composite *	1.1 (0.6, 1.4)	0.8 (0.1, 1.2)	0.9 (0.3, 1.2)	0.7 (−0.2, 1.1)	0.9 (0.1, 1.2)
Gestational age at sample, weeks	22 (20, 25)	23 (21, 26)	23 (20, 26)	22 (20, 25)	23 (20, 25)
Creatinine, mg/dL	0.8 (0.4, 1.2)	0.8 (0.4, 1.1)	0.7 (0.3, 1.2)	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)
Child sex, male, n (%)	46 (45)	43 (51)	43 (51)	41 (46)	173 (48)

[a] missing: maternal atopy n = 6; prenatal smoking n = 1; body mass index n = 3

[b] missing: maternal atopy n = 6

* $p < 0.05$ for comparison across quartiles; CANDLE: Conditions Affecting Neurocognitive Development in Early Childhood study; values for continuous variables are shown as median (interquartile range).