Ambient air pollution during pregnancy and cardiometabolic biomarkers in cord blood

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Background/Objectives: Prenatal air pollution exposure has been associated with adverse childhood cardiometabolic outcomes. It is unknown whether evidence of metabolic disruption associated with air pollution is identifiable at birth. We examined exposure to prenatal ambient air pollution and cord blood cardiometabolic biomarkers among 812 mother-infant pairs in the Healthy Start study.

Methods: Using inverse-distance-weighted interpolation of ambient concentrations obtained from stationary monitors, we estimated daily particulate matter ≤2.5 micrometers ($PM_{2.5}$) and ozone (O_3) concentrations at participant residences. Daily estimates were averaged by trimester, full-pregnancy, and the 7 and 30 days prior to delivery. Associations of air pollution with the following cord blood biomarkers were estimated via multivariable linear regression: glucose, insulin, glucose/insulin ratio (GIR), leptin, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, free fatty acids, and triglycerides.

Results: In this Denver-based cohort, $PM_{2.5}$ concentrations were lower than in many US urban areas, but O_3 concentrations regularly exceeded federal air quality standards. Higher O_3 concentrations during pregnancy were consistently associated with higher insulin and lower GIR in cord blood. For example, an interquartile range increase in full pregnancy O_3 (6.3 parts per billion [ppb]) was associated with 0.13 log-µIU/ml (95% confidence interval [CI] = 0.04, 0.22) higher cord blood insulin, after adjusting for $PM_{2.5}$ and other confounders. We found positive, but generally nonsignificant, associations between $PM_{2.5}$ and leptin and isolated associations between pollutants during certain exposure periods and lipids.

Conclusions: In this cohort with moderately high O_3 exposure, prenatal concentrations of O_3 were positively associated with cord blood insulin. Future studies should examine the implications for offspring long-term health.

Keywords: Air pollution; Lipids; Metabolism; Neonate; Prenatal exposure

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Introduction

In the United States, the prevalence of cardiometabolic diseases in childhood, including obesity,[1] type 2 diabetes,[2] and other cardiovascular disease risk factors,[3,4] has risen markedly in recent decades. While dietary factors and increasingly sedentary lifestyle have played a major role in the rising prevalence of childhood obesity, exposure to higher levels of air pollution early in life has also been posited as a potential explanatory factor.[5,6]

The prenatal period may represent a critical time for environmental chemical exposures to impact health later in life.[7,8] For example, maternal exposure to ambient air pollution during pregnancy has been associated with offspring obesity and adverse cardiometabolic outcomes during childhood and beyond, in both animal[9,10] and human studies.[6,11–14]

Despite these suggestive findings, understanding of the potential pathophysiological mechanisms of these observed associations between prenatal air pollution and childhood cardiometabolic outcomes remains limited. *In utero* exposure to air pollutants may adversely affect offspring's metabolic function

What this study adds

Ambient air pollution exposure during gestation has been associated with adverse childhood cardiometabolic outcomes, although it is unknown whether markers of exposure-related altered cardiometabolic profile are identifiable at birth. In the present study, ozone during several periods of pregnancy was consistently associated with higher insulin and lower glucose/insulin ratio in cord blood. Our work highlights the potential for *in utero* exposure to air pollution to impact markers of neonate cardiometabolic status at birth.

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and promote the development of childhood obesity.[15,16] Further, disturbances in leptin and other adipokines in cord blood have been associated with cardiometabolic disease markers in infancy and childhood,[17–21] although there are sparse data describing this relationship with other cardiometabolic biomarkers.[22] Alterations in cord blood cardiometabolic profiles may indicate both short-term, and potentially long-term, consequences of *in utero* air pollution exposure for offspring metabolic health.

A small number of epidemiologic studies have investigated air pollution-related changes in biomarkers of cardiometabolic function at birth in umbilical cord blood.[23–26] Both Alderete et al[23] and Lavigne et al[24] found associations between maternal air pollution exposure and higher levels of cord blood leptin and adiponectin, two adipocyte-secreted hormones associated with adiposity at birth and in childhood.[18,27] Notably, Lavigne et al[24] observed a significant association between maternal air pollution exposure and cord blood leptin only after adjustment for birthweight z-score, suggesting that for any given birth weight, the relative size of the fat compartment may be altered by exposure. Further, in a cross-sectional study of 150 mother-infant pairs, maternal exposures to particulate matter of aerodynamic diameter <1 μm (PM_1), 2.5 μm ($PM_{2.5}$), and 10 μm (PM_{10}) were associated with lipid biomarkers in cord blood, including triglycerides and cholesterol.[26] Finally, Madhloum et al[25] reported that higher maternal $PM_{2.5}$ and PM_{10} exposures during pregnancy were associated with higher cord blood insulin. However, no study has examined multiple markers of cardiometabolic function concomitantly, nor have previous studies examined the role of ozone (O_3), recently linked to diabetes risk in adults.[28]

The US Environmental Protection Agency (US EPA) sets the National Ambient Air Quality Standards (NAAQS) for $PM_{2.5}$ (12 μg/m³ annual average) and O_3 (0.070 parts per million annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years), due to the known harmful effects of these pollutants on human health.[29] $PM_{2.5}$ levels in the Denver-metropolitan area are relatively low compared to the levels in some of the other previously studied urban locations, including the United States, Iran, and Belgium.[23,25,26] However, O_3 levels in Denver have been above the NAAQS standard since 2008.[30] In this study, we investigated the relationships between exposure to ambient $PM_{2.5}$ and O_3 during pregnancy and cardiometabolic biomarkers in umbilical cord blood in a birth cohort based in Denver, Colorado. Specifically, we examined associations between period-specific average concentrations of air pollution at the maternal residence and cord blood glucose, insulin, leptin, non-high-density lipoprotein (non-HDL) cholesterol, HDL cholesterol, triglycerides, and free fatty acids (FFAs). We hypothesized that higher exposure to ambient air pollutants during pregnancy would be associated with higher levels of cord blood cardiometabolic biomarkers.

Methods

Study sample

Participants included in this analysis were enrolled in the Healthy Start study, an ongoing, prebirth cohort study of ethnically diverse mother-infant pairs. Between 2009 and 2014, pregnant women ≥16 years old who had not yet reached 24 weeks of gestation were recruited from the obstetrics clinics at the University of Colorado Hospital in Aurora, Colorado. Additional inclusion criteria were singleton pregnancy, no previous stillbirth or birth <25 weeks, and no preexisting chronic diseases, including diabetes, cancer, asthma managed with steroids, or serious psychiatric illness. Participants were invited to attend three in-person visits: in early pregnancy (median 17 weeks gestation), in mid-pregnancy (median 27 weeks gestation), and at delivery (median 1 day after birth). All participants provided written informed consent, and all study protocols were approved by the Colorado Multiple Institutional Review Board.

Of the 1,410 women enrolled in the Healthy Start study, participants were excluded from this analysis if they withdrew from the study prior to delivery (n = 11), experienced fetal demise (n = 17), did not have cord blood analyzed for cardiometabolic biomarkers (n = 527), and/or did not reside in the Denver-metropolitan area or had no O_3 and/or $PM_{2.5}$ monitors within 50 km of the residence with sufficient nonmissing data, as described below (n = 43). This led to a sample of 812 eligible mother-infant pairs (Supplementary Figure 1; http://links.lww.com/EE/A181).

Assessment of exposures

Participants self-reported their residential address at enrollment. Average $PM_{2.5}$ and 8-hour maximum O_3 levels during the study period (2009–2014) were estimated using data collected at stationary monitors located within 50 km from each participant's address via the US EPA Air Quality System. The methods used to estimate air pollution exposure for the Healthy Start cohort have been published previously[31] and are briefly described below.

Average ambient $PM_{2.5}$ and average 8-hour maximum O_3 concentrations outside the maternal residences were estimated for the following periods during pregnancy: first, second, and third trimesters, full pregnancy, and the 30 and 7 days prior to delivery. There were 10 stationary monitors that measured 24-hour average $PM_{2.5}$ and 19 stationary monitors that reported hourly O_3 during the study period that were within 50 km of at least one participant's residence. The frequency of reporting varied by monitor for $PM_{2.5}$, ranging from daily to every 6 days, with most reports occurring every 3 days. All O_3 monitors reported hourly values. We used all monitors within 50 km of the participant's residence at enrollment and for which ≥75% of the expected concentrations were available to estimate period-specific averages for each participant. Inverse-distance-weighting (1/distance²) was used to calculate the average exposure during the specified period for each participant.[32]

Assessment of outcomes

Umbilical cord blood was collected at delivery, and samples were analyzed by the University of Colorado Clinical and Translational Sciences Institute Core Laboratories. Serum leptin (ng/ml) was measured by ELISA (Alpco, Salem, NH). Insulin (μIU/ml) was measured using radioimmunoassay according to manufacturer's instructions (EMD Millipore Corporation, Billerica, MA). Glucose (mg/dl), total cholesterol (mg/dl), HDL (mg/dl), triglycerides (mg/dl), and free fatty acids (μIU/ml) were measured using an AU400e Chemistry Analyzer (Olympus America, Center Valley, PA). We calculated non-HDL cholesterol by subtracting HDL cholesterol from total cholesterol in cord blood. Glucose/insulin ratio (GIR) was used as an indirect measure of insulin sensitivity.[33,34]

Other variables

Maternal age, race, ethnicity, education, and parity were self-reported at the time of study enrollment. Smoking status and exposure to secondhand smoke were self-reported at all three study visits during pregnancy. Maternal prepregnancy body mass index (BMI, kg/m²) was calculated using height measured by research staff at the first visit and prepregnancy weight, which was obtained through medical record abstraction (87.9%) or when unavailable through self-report (12.1%) at the first visit. Gestational diabetes (GDM) status was determined by a positive oral glucose tolerance test and/or a diagnosis in the medical record. Mode of delivery, season of birth, and infant sex were collected from medical records. Median income in the Census tract of the mother's residence was obtained by linkage of the geocoded address reported at enrollment to 2012–2016 American Community Survey data and used an indicator of neighborhood-level socioeconomic status.

Statistical analysis

Spearman correlation coefficients were calculated for each pair of cardiometabolic markers. Insulin, GIR, leptin, and triglycerides in cord blood had right-skewed distributions and were natural log-transformed prior to analysis to better approximate normality and minimize the influence of outliers.

Multivariable linear regression models were used to investigate the relationships between prenatal $PM_{2.5}$ and O_3 and cardiometabolic biomarkers in cord blood. Associations were expressed as beta-coefficients and 95% confidence intervals (CIs) per interquartile range (IQR) increase in air pollutant exposure. Potential confounders were identified via directed acyclic graphs based on published literature, and included maternal age at delivery (years), prepregnancy BMI (kg/m²), race/ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black, all others), maternal smoking during pregnancy (any, none), exposure to secondhand smoke during pregnancy (>1 hour per week at any point during pregnancy), median annual income in the census tract (per $1,000), maternal education completed (<12th grade, high school degree or General Education Development [GED], some college or Associate's degree, four years of college, graduate degree), mode of delivery (cesarean, vaginal), previous pregnancy (any, none), season of birth (winter, spring, summer, fall), and the corresponding copollutant during the specified pregnancy period ($PM_{2.5}$ or O_3). Infant sex (male, female) was included as a precision covariate of the outcome. Birth weight and gestational age at birth were considered potential causal intermediates and accordingly were not included in the models. Because there is some evidence that fetal metabolic response to maternal environmental chemical exposures may differ by sex,[35] potential effect modification by infant sex was assessed by including product interaction terms between each air pollutant exposure and infant sex in fully adjusted models. We hypothesized that the corresponding pollutant ($PM_{2.5}$ or O_3) confounded the relationships between the other pollutant and the cardiometabolic biomarkers; therefore, we included both pollutants in all primary models. However, in a sensitivity analysis, we investigated the results of single pollutant models. To evaluate the potential for nonlinear relationships between the air pollutants and the cardiometabolic markers, adjusted generalized additive models with penalized regression splines were run. The fit of models with the linear air pollutant exposure term was compared to that of models with the spline-transformed exposure using Akaike Information Criterion (AIC). We additionally assessed associations with quartiles of the exposure. Finally, because the levels of cardiometabolic biomarkers of infants born to mothers with GDM may differ,[36] we conducted a sensitivity analysis excluding 34 participants with gestational diabetes.

We conducted all analyses in SAS (Version 9.4; The SAS Institute, Cary, NC) and R (Version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

The mean ± SD of maternal age at delivery was 28±6 years, and the mean prepregnancy BMI was 26±7kg/m². There were 34 participants (4%) with GDM. The sample was racially and ethnically diverse (Hispanic, 25%; non-Hispanic White, 53%; non-Hispanic Black, 16%; and all others, 7%). Approximately 9% of participants smoked during pregnancy, and 23% of participants were exposed to secondhand smoke (>1 hour per week at any point during pregnancy) (Table 1). There were 432 (53%) male infants. Characteristics of participants in this subsample were comparable to those of the excluded participants and to the full potentially eligible cohort (Supplemental Table 1; http://links.lww.com/EE/A181).

The median full pregnancy average $PM_{2.5}$ exposure was 7.5 µg/m³, the 5th percentile was 6.6 µg/m³, and the 95th percentile was 8.4 µg/m³. Similar median and range values were observed

Table 1.

Characteristics of 812 eligible mother-infant pairs in the Healthy Start Study

Characteristic	Mean ± SD, median (25th–75th percentiles), or N (%)
Covariates	
Maternal age at delivery (years)	27.5±6.2
Prepregnancy body mass index (kg/m²)	25.9±6.5
Race/ethnicity	
Hispanic	201 (25)
Non-Hispanic White	428 (53)
Non-Hispanic Black	127 (16)
All others	56 (7)
Maternal smoking during pregnancy (any)	77 (9)
Exposure to secondhand smoke during pregnancy	186 (23)
Median annual income in the census tract ($)	63,500±26,500
Maternal education completed	
Less than 12th grade	122 (15)
High school degree or GED/high school equivalency diploma	163 (20)
Some college or associate's degree	178 (22)
Four years of college (BA, BS)	174 (21)
Graduate degree (Master's, PhD)	175 (22)
Mode of delivery = cesarean	172 (21)
Previous pregnancy	510 (63)
Gestational diabetes[a]	34 (4)
Season of birth	
Winter	173 (21)
Spring	199 (25)
Summer	250 (31)
Fall	190 (23)
Infant sex = male	432 (53)
Exposures	
Average $PM_{2.5}$ (µ/m³)[a]	
Trimester 1	7.5 (6.9–8.2)
Trimester 2	7.4 (6.8–8.1)
Trimester 3	7.3 (6.8–8.1)
Full pregnancy	7.5 (7.0–7.9)
Prior 30 days to delivery	7.2 (6.4–8.3)
Prior 7 days to delivery	6.7 (5.6–8.2)
Average 8-hour maximum O_3 (ppb)	
Trimester 1	41.8 (33.0–53.0)
Trimester 2	42.6 (33.9–52.4)
Trimester 3	46.6 (35.5–54.0)
Full pregnancy	43.9 (40.7–47.0)
Prior 30 days to delivery	48.0 (34.2–55.9)
Prior 7 days to delivery	47.0 (35.5–55.6)

[a]Sample sizes differ for the following variables due to missing data: gestational diabetes, n = 774; average $PM_{2.5}$ trimester 1, n = 749; average $PM_{2.5}$ trimester 2, n = 749; average $PM_{2.5}$ trimester 3, n = 787; average $PM_{2.5}$ full pregnancy, n = 806; average $PM_{2.5}$ prior 30 days to delivery, n = 765; and average $PM_{2.5}$ prior 7 days to delivery, n = 771.

for trimester-average $PM_{2.5}$ exposures and the 30- and 7- day exposure windows. The median full pregnancy average 8-hour maximum O_3 concentration was 43.9 parts per billion (ppb), the 5th percentile was 36.6 ppb, and the 95th percentile was 49.9 ppb (Table 1 and Supplemental Table 2; http://links.lww.com/EE/A181).

Glucose, insulin, GIR, and leptin in cord blood were generally weakly correlated with each other, except for a strong inverse correlation between insulin and GIR ($r_s = -0.92$). Most cord blood lipid biomarkers were weakly to moderately correlated with each other, with the strongest correlation observed between triglycerides and non-HDL cholesterol ($r_s = 0.44$) (Table 2).

Higher average 8-hour maximum O_3 during trimesters 2 and 3, full pregnancy, and the prior 7 and 30 days to delivery was associated with higher insulin (Table 3). For example, an IQR increase in prior 30-day O_3 (21.7 ppb) was associated with a 0.21 log-unit (95% CI = 0.07, 0.35) increase in cord blood insulin, after adjusting for covariates. Additionally, higher O_3 during all

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Table 2.

Levels and pairwise spearman correlations of cardiometabolic biomarkers in cord blood among eligible mother-infant pairs in the Healthy Start Study

Cardiometabolic biomarker	Median (25th–75th percentiles)	Glucose (mg/dl)[a]	Insulin (μIU/ml)[a]	Glucose/ insulin ratio[a]	Leptin (ng/ml)[a]	Non-HDL cholesterol (mg/dl)[a]	HDL (mg/dl)[a]	Free fatty acids (μIU/ml)[a]	Triglycerides (mg/dl)[a]
Glucose (mg/dl)[a]	79 (70–90)	1.00	0.19	0.17	0.10	−0.03	−0.07	0.10	0.08
Insulin (μIU/ml)[a]	7 (5–11)		1.00	−0.92	0.27	−0.09	−0.02	−0.23	−0.26
Glucose/insulin ratio[a]	11 (7–15)			1.00	−0.23	0.07	−0.02	0.26	0.28
Leptin (ng/ml)[a]	11 (6–21)				1.00	−0.06	−0.01	0.09	0.02
Non-HDL cholesterol (mg/dl)[a]	33 (26–41)					1.00	0.40	0.13	0.44
HDL (mg/dl)[a]	25 (21–30)						1.00	0.06	−0.13
Free fatty acids (μIU/ml)[a]	260 (178–366)							1.00	0.36
Triglycerides (mg/dl)[a]	39 (29–55)								1.00

[a]Missing data for cord blood: glucose, n = 19; insulin, n = 50; glucose/insulin ratio, n = 52; leptin, n = 144; non-HDL cholesterol, n = 109; HDL, n = 109; free fatty acids, n = 108; and triglycerides, n = 50.

exposure windows, except for trimester 1, was associated with lower GIR. For example, an IQR increase in prior 30-day O_3 (21.7 ppb) was associated with a 0.22 log-unit (95% CI = −0.36, −0.09) decrease in cord blood GIR, after adjusting for covariates. Higher full pregnancy $PM_{2.5}$ was associated with higher leptin, and average $PM_{2.5}$ in each trimester was nonsignificantly positively associated with leptin. We did not observe consistent associations between O_3 and leptin, nor between $PM_{2.5}$ or O_3 and glucose (Table 3). Associations in single pollutant models

were similar to those observed in copollutant adjusted models (Supplemental Table 3; http://links.lww.com/EE/A181).

We observed significant exposure-by-infant sex interactions in models for associations between trimester 2 $PM_{2.5}$ and insulin (P = 0.04), and trimester 2 $PM_{2.5}$ and GIR (P = 0.02) (Table 3). Sex-specific analyses indicated different directions of association in male and female infants (Supplemental Tables 5 and 6; http://links.lww.com/EE/A181). There was a nonsignificant, positive association between trimester 2 $PM_{2.5}$ and insulin among males

Table 3.

Associations between average $PM_{2.5}$ and 8-hour maximum O_3 at the residential address during pregnancy and glucose, insulin, glucose/insulin ratio, and leptin in cord blood

Air pollution exposure	n	Glucose (mg/dl) β (95% CI)[a] per IQR	Sex interaction P	n	Log-transformed insulin (log-unit) β (95% CI)[a] per IQR	Sex interaction P	n	Log-transformed glucose/insulin ratio β (95% CI)[a] per IQR	Sex interaction P	n	Log-transformed Leptin (log-unit) β (95% CI)[a] per IQR	Sex interaction P
Trimester 1	731			706			704			614		
Average $PM_{2.5}$ (μg/m³)		−0.91 (−2.64, 0.82)	0.80		0.00 (−0.05, 0.06)	0.54		−0.02 (−0.08, 0.03)	0.58		0.08 (−0.01, 0.18)	0.72
Average 8-hour maximum O_3 (ppb)		2.91 (−1.91, 7.72)	0.56		−0.02 (−0.17, 0.14)	0.11		0.05 (−0.11, 0.20)	0.18		−0.12 (−0.38, 0.14)	0.32
Trimester 2	731			700			698			642		
Average $PM_{2.5}$ (μg/m³)		0.96 (−0.82, 2.74)	0.28		−0.01 (−0.06, 0.04)	0.04		0.03 (−0.03, 0.08)	0.02		0.05 (−0.03, 0.14)	0.42
Average 8-hour maximum O_3 (ppb)		−0.30 (−4.99, 4.40)	0.36		0.15 (0.01, 0.30)	0.32		−0.15 (−0.30, −0.01)	0.25		−0.04 (−0.26, 0.18)	0.47
Trimester 3	768			737			735			662		
Average $PM_{2.5}$ (μg/m³)		0.94 (−0.93, 2.81)	0.64		0.00 (−0.05, 0.06)	0.61		0.00 (−0.06, 0.06)	0.68		0.01 (−0.09, 0.10)	0.29
Average 8-hour maximum O_3 (ppb)		0.04 (−4.62, 4.70)	0.31		0.23 (0.09, 0.37)	0.56		−0.24 (−0.38, −0.10)	0.43		0.08 (−0.16, 0.31)	0.59
Full pregnancy	787			756			754			665		
Average $PM_{2.5}$ (μg/m³)		0.39 (−1.64, 2.42)	0.66		0.02 (−0.04, 0.08)	0.13		−0.02 (−0.08, 0.04)	0.08		0.11 (0.01, 0.21)	0.86
Average 8-hour maximum O_3 (ppb)		0.73 (−2.28, 3.73)	0.96		0.13 (0.04, 0.22)	0.28		−0.13 (−0.22, −0.04)	0.34		0.01 (−0.14, 0.16)	0.94
Prior 30 days to delivery	747			718			716			643		
Average $PM_{2.5}$ (μg/m³)		0.76 (−0.95, 2.48)	0.91		−0.03 (−0.08, 0.03)	0.24		0.03 (−0.02, 0.09)	0.24		−0.01 (−0.10, 0.09)	0.70
Average 8-hour maximum O_3 (ppb)		−0.19 (−4.65, 4.27)	0.17		0.21 (0.07, 0.35)	0.14		−0.22 (−0.36, −0.09)	0.07		0.06 (−0.16, 0.29)	0.83
Prior 7 days to delivery	752			723			721			642		
Average $PM_{2.5}$ (μg/m³)		0.79 (−0.35, 1.93)	0.95		0.02 (−0.01, 0.06)	0.19		−0.01 (−0.05, 0.02)	0.21		0.02 (−0.04, 0.08)	0.90
Average 8-hour maximum O_3 (ppb)		−1.79 (−5.66, 2.08)	0.24		0.12 (0.00, 0.24)	0.15		−0.16 (−0.28, −0.04)	0.08		0.10 (−0.10, 0.30)	0.95

[a]Adjusted for race, maternal age, prepregnancy BMI, smoking status, exposure to secondhand smoke during pregnancy, median income in the census tract, education, mode of delivery, parity, season of birth, infant sex, and the corresponding copollutant during the specified pregnancy period.

and an inverse association among females (Supplemental Table 5; http://links.lww.com/EE/A181). There was a nonsignificant inverse association between trimester 2 $PM_{2.5}$ and GIR observed among males and a positive association among females (β = 0.09 per IQR; 95% CI = 0.02, 0.17) (Supplemental Table 6; http://links.lww.com/EE/A181). We did not observe significant exposure-by-infant sex interactions for glucose, leptin, or lipids (Table 4 and Supplemental Tables 5–8; http://links.lww.com/EE/A181).

Trimester 1, 2 and full-pregnancy average 8-hour maximum O_3 were positively associated with non-HDL cholesterol in cord blood, although the 95% CI for trimester 1 included the null. We observed inverse associations of third trimester and full pregnancy average $PM_{2.5}$ with triglycerides in cord blood. Generally, there were nonsignificant, inverse associations between $PM_{2.5}$ and FFA, and nonsignificant, positive associations between O_3 during trimesters 2 and 3 and the prior 30 and 7 days to delivery and FFA. We did not observe consistent patterns of associations between either $PM_{2.5}$ or O_3 and HDL cholesterol (Table 4). Results from single pollutant models were similar (Supplemental Table 4; http://links.lww.com/EE/A181).

In a sensitivity analysis excluding participants with gestational diabetes (n = 34), results did not change appreciably (Supplemental Tables 9 and 10; http://links.lww.com/EE/A181). Evidence for nonlinearity, defined as lower AIC in the model with spline transformation of the exposure, was observed for some associations; therefore, we ran additional models in which cord blood biomarkers were regressed on quartiles of exposure

(Supplemental Tables 11 and 12; http://links.lww.com/EE/A181). We observed a nonsignificant, U-shaped relationship between O_3 in the 7 days prior to delivery and cord blood glucose (Supplemental Table 11; http://links.lww.com/EE/A181). Several quartile models showed nonmonotonic responses between both pollutants and non-HDL cholesterol, HDL cholesterol, FFA, and triglycerides in cord blood, but results were generally nonsignificant (Supplemental Table 12; http://links.lww.com/EE/A181).

Discussion

In this prospective birth cohort study, greater average 8-hour maximum O_3 during trimesters 2, 3, full-pregnancy and the 30 and 7 days prior to delivery was associated with higher levels of cord blood insulin and lower GIR. Additionally, average $PM_{2.5}$ during certain periods of pregnancy was positively associated with cord blood leptin, and O_3 was positively associated with non-HDL cholesterol and inversely associated with triglycerides and FFA. Our findings provide suggestive evidence that prenatal air pollution exposure may be associated with dysregulation of metabolism at birth. Alterations in some metabolic biomarkers in cord blood have been associated with cardiometabolic health outcomes later in infancy and childhood, including weight gain, BMI, and body size and composition.[17–22] Notably, the Denver-metropolitan area represents a unique exposure profile with regard to these two criteria pollutants. While $PM_{2.5}$ levels are below the NAAQS standard, the area has been out of

Table 4.

Associations between average $PM_{2.5}$ and 8-hour maximum O_3 at the residential address during pregnancy and lipid biomarkers in cord blood

Air pollution exposure	n	Non-HDL Cholesterol (mg/dl) β (95% CI)[a] per IQR	Sex interaction P	n	HDL (mg/dl) β (95% CI)[a] per IQR	Sex interaction P	n	Free fatty acids (µIU/ml) β (95% CI)[a] per IQR	Sex interaction P	n	Log-transformed triglycerides (log-unit) β (95% CI)[a] per IQR	Sex interaction P
Trimester 1	647			647			657			703		
Average $PM_{2.5}$ (µg/m³)		0.12 (−1.63, 1.86)	0.41		0.18 (−0.64, 1.00)	0.69		−8.98 (−24.13, 6.16)	0.15		−0.02 (−0.07, 0.03)	0.24
Average 8-hour maximum O_3 (ppb)		3.20 (−1.69, 8.09)	0.91		1.54 (−0.77, 3.85)	0.39		−32.34 (−74.76, 10.07)	0.64		−0.08 (−0.21, 0.06)	0.77
Trimester 2	647			647			644			701		
Average $PM_{2.5}$ (µg/m³)		−0.71 (−2.38, 0.96)	0.70		−0.55 (−1.35, 0.25)	0.12		−2.04 (−16.85, 12.76)	0.28		−0.02 (−0.07, 0.03)	0.29
Average 8-hour maximum O_3 (ppb)		6.19 (1.71, 10.68)	0.32		0.69 (−1.46, 2.84)	0.65		25.44 (−12.70, 63.57)	0.52		0.07 (−0.05, 0.20)	0.45
Trimester 3	684			684			682			737		
Average $PM_{2.5}$ (µg/m³)		−0.91 (−2.60, 0.79)	0.59		0.42 (−0.39, 1.24)	0.74		−12.65 (−28.43, 3.14)	0.97		−0.05 (−0.10, 0.00)	0.47
Average 8-hour maximum O_3 (ppb)		0.24 (−4.10, 4.58)	0.76		0.62 (−1.46, 2.70)	0.20		31.63 (−8.44, 71.70)	0.94		0.08 (−0.04, 0.20)	0.28
Full pregnancy	698			698			700			756		
Average $PM_{2.5}$ (µg/m³)		−0.74 (−2.61, 1.12)	0.55		0.13 (−0.77, 1.03)	0.84		−11.38 (−27.83, 5.07)	0.54		−0.05 (−0.11, 0.00)	0.47
Average 8-hour maximum O_3 (ppb)		2.97 (0.12, 5.81)	0.54		1.54 (0.17, 2.91)	0.77		3.28 (−21.02, 27.58)	0.90		−0.02 (−0.10, 0.06)	0.86
Prior 30 days to delivery	663			663			661			716		
Average $PM_{2.5}$ (µg/m³)		−1.42 (−3.03, 0.18)	0.99		−0.28 (−1.05, 0.49)	0.92		−15.22 (−30.12, −0.33)	0.59		0.00 (−0.04, 0.05)	0.93
Average 8-hour maximum O_3 (ppb)		−0.08 (−4.30, 4.15)	0.80		1.14 (−0.88, 3.16)	0.24		15.83 (−22.58, 54.23)	0.73		0.01 (−0.11, 0.12)	0.39
Prior 7 days to delivery	667			667			666			721		
Average $PM_{2.5}$ (µg/m³)		−0.61 (−1.68, 0.45)	0.39		−0.57 (−1.07, −0.06)	0.88		−2.95 (−12.27, 6.38)	0.24		0.01 (−0.02, 0.04)	0.10
Average 8-hour maximum O_3 (ppb)		−1.33 (−4.99, 2.33)	0.77		0.95 (−0.79, 2.68)	0.16		5.98 (−26.75, 38.70)	0.68		−0.03 (−0.13, 0.07)	0.38

[a]Adjusted for race, maternal age, prepregnancy BMI, smoking status, exposure to secondhand smoke during pregnancy, median income in the census tract, education, mode of delivery, parity, season of birth, infant sex, and the corresponding copollutant during the specified pregnancy period.

attainment for O_3 since 2008.[30] Although the changes observed in the present study are small at the individual level, given the widespread nature of the exposure, on a population-scale these changes may be associated with an increased prevalence of obesity and adverse metabolic outcomes.

We noted consistently positive associations between 8-hour maximum O_3 concentrations during multiple periods of pregnancy with cord blood insulin. One previous study investigated air pollution exposure during pregnancy and cord blood insulin.[25] Among 590 mother-infant pairs enrolled in a cohort study in Belgium, cord blood insulin was positively associated with full pregnancy $PM_{2.5}$ and PM_{10}, but not nitrogen dioxide (NO_2).[25] The study did not examine associations with O_3, nor did they find any significant pollutant-by-sex interactions. While there is a dearth of literature examining this relationship in the perinatal period, chronic exposure to PM_{10} and NO_2 and proximity to a major roadway at the birth address has been associated with insulin resistance in children 10 years old.[37] Importantly, cord blood collection in the Healthy Start study did not discriminate between the umbilical vein (from the mother) and artery (from the fetus) sources, and thus, the origin of insulin in our samples is unknown. However, given that the fetal pancreas produces measurable levels of insulin by mid-gestation, and maternal insulin does not typically cross the placenta (with a few exceptions),[38,39] we can assume that most of the insulin in our cord blood samples collected at delivery is from fetal production. In our study, we used GIR as a measure of insulin sensitivity; alterations in GIR in cord blood have been identified in infants whose mothers were overweight or obese[33] and had impaired glucose tolerance,[40] suggesting it is a useful marker in cord blood of metabolic homeostasis.

Studies from animal models also support an association between prenatal air pollution exposure and impaired metabolic homeostasis later in life.[10,41] Among mice exposed prenatally to diesel exhaust and fed a high-fat diet postnatally, males developed hyperinsulinemia and insulin resistance, and excess weight gain was observed in both sexes.[10,41] We also noted sex-specific effects for some of the $PM_{2.5}$ exposure windows and cord blood insulin. Moreover, our finding of an inverse association between O_3 and GIR is consistent with animal studies of insulin resistance. There are several proposed mechanisms through which particulate matter and ozone may induce insulin resistance, including oxidative stress and inflammation.[42,43]

We found positive associations between trimester-long and full-pregnancy $PM_{2.5}$ and cord blood leptin. However, we did not find consistent associations between $PM_{2.5}$ during any of the shorter exposure windows and cord blood leptin. In infants, cord blood leptin is a known marker for neonatal fat mass,[44] however, the nature of the relationship between cord blood leptin and adiposity across infancy and childhood is complex.[18,21] In a Canadian cohort study, authors reported a positive association between full pregnancy $PM_{2.5}$ and NO_2 and cord blood leptin, when adjusting for birthweight z-score.[24] More recently, results from a California-based birth cohort suggest positive associations between full pregnancy nonfreeway Nitrogen oxide (NOx) exposure and proximity to major roadways and cord blood leptin.[23] Further, an epigenetic study found $PM_{2.5}$ exposure during trimester 2 was associated with lower deoxyribonucleic acid methylation of the leptin gene in the placenta.[45]

We did not observe associations between exposure to $PM_{2.5}$ and O_3 during pregnancy and glucose in cord blood. To our knowledge, no previous study has examined this relationship in the perinatal period. During gestation, placental transport of maternal glucose serves as the primary source of fuel for the fetus,[46] and it is therefore difficult to compare our findings with existing literature investigating this relationship in childhood. Nonetheless, in one prior study, among overweight and obese African American and Hispanic children in Los Angeles, CA, $PM_{2.5}$, NO_2, and nonfreeway NOx, but not O_3, exposure was associated with higher fasting glucose.[47]

Our findings on lipid biomarkers showed little consistency across lipids or across periods of pregnancy. We observed positive associations between O_3 and non-HDL cholesterol in cord blood during some periods of pregnancy and inverse associations between trimester-long $PM_{2.5}$ exposure and triglycerides. Although we observed limited evidence of associations between $PM_{2.5}$ (inverse) and O_3 (positive) during some periods of pregnancy and cord blood FFA, patterns were inconsistent and generally nonsignificant. In a cross-sectional analysis of Iranian mother-infant pairs, higher exposure to PM_1, $PM_{2.5}$, and PM_{10} was associated with higher total cholesterol levels and triglycerides, but not HDL, in cord blood.[26] It is notable that our study had a much smaller range of variability in average full pregnancy $PM_{2.5}$ (IQR, 0.9 μg/m³) compared to that of the Heydari et al[26] study (IQR, 33.2 μg/m³). A recent investigation in a Mexico city-based birth cohort found that exposure to $PM_{2.5}$ during trimester 3 of pregnancy was associated with higher levels of low-density lipoprotein (LDL), non-HDL, and total cholesterol levels in childhood (mean 4.8 years), suggesting that these alterations may also be identifiable in childhood.[48] Authors also found that prenatal exposure to late-pregnancy $PM_{2.5}$ was associated with lower triglyceride levels in children.[48] While we observed only isolated associations between prenatal air pollution exposure and lipid biomarkers in cord blood, the abovementioned studies suggest that prenatal air pollution exposure remains an important potentially modifiable early-life exposure with evidence of enduring disruptions to cardiovascular risk later in life.[49]

There are several strengths of this study. We used data from a prospective, prebirth cohort study, which allowed for the longitudinal assessment of the relationship between *in utero* air pollution exposure and cardiometabolic biomarker outcomes at delivery. The study population was racially and ethnically diverse, with well-characterized covariate data. We found novel associations between period-specific exposures to $PM_{2.5}$ and O_3 during pregnancy and some cardiometabolic biomarkers in cord blood.

Our study also has some limitations. Residential address information was only collected at enrollment. Because we did not have information on residential mobility during the study period, there is the possibility for misclassification of air pollution exposure. A previous study in New York showed limited residential mobility during pregnancy.[50] While it is unknown if these findings are generalizable to women living in Colorado, it provides evidence that the degree of exposure misclassification due to local moves may be minimal. Further, we were not able to account for differences in human behavior that may affect personal air pollution exposure, including time spent indoors and in nonresidential settings. We also did not account for potential differences in exposure levels due to small-scale spatial variability, such as proximity to roadways or other concentrated sources of air pollution. The measurement error in air pollution due to the relatively sparse monitoring network is likely nondifferential with respect to the cord blood metabolic markers, and thus, may have resulted in an underestimation of associations.[51] While we included several relevant covariates in our models, there is still the possibility for residual confounding due to unmeasured factors related to air pollution, including green space and traffic noise, or due to the use of imperfect proxies of socioeconomic status. There is the possibility of residual confounding due to the use of self-reported smoking data, as it may have resulted in an underestimation of smoking status, in our study. We performed a large number of statistical analyses and did not adjust for multiple testing, because our emphasis was on the magnitude and precision of the associations rather than their statistical significance. It is possible that some of the findings are statistically significant due to chance. However, the main findings of our study were consistent across several exposure time periods, and thus, are less likely to be spurious results. Independent replication of these results in another cohort would strengthen the interpretation.

Conclusions

In conclusion, we found higher average 8-hour maximum O_3 concentrations associated with higher cord blood insulin and lower GIR. We also found limited evidence of associations of ambient air pollution with lipids and the adipocyte-derived hormone leptin. These findings highlight the potential for air pollution exposure during pregnancy to disrupt the metabolic and lipid homeostasis of the offspring in the perinatal period. These findings were noted in an urban area with a unique air pollution profile, with levels of $PM_{2.5}$ below the NAAQS standard, but O_3 regularly out of attainment. Future studies from Healthy Start and other birth cohorts should examine whether air pollution-associated changes in biomarkers persist into childhood, and therefore whether maternal exposure to air pollutants during pregnancy may contribute to insulin resistance and other adverse child cardiometabolic outcomes.

Conflicts of interest statement

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