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Original Contribution

Air Pollution Exposure During Pregnancy and Fetal Markers of Metabolic Function

The MIREC Study

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Previous evidence suggests that exposure to outdoor air pollution during pregnancy could alter fetal metabolic function, which could increase the risk of obesity in childhood. However, to our knowledge, no epidemiologic study has investigated the association between prenatal exposure to air pollution and indicators of fetal metabolic function. We investigated the association between maternal exposure to nitrogen dioxide and fine particulate matter (aerodynamic diameter ≤2.5 μm) and umbilical cord blood leptin and adiponectin levels with mixed-effects linear regression models among 1,257 mother-infant pairs from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, conducted in Canada (2008–2011). We observed that an interquartile-range increase in average exposure to fine particulate matter (3.2 μg/m^3) during pregnancy was associated with an 11% (95% confidence interval: 4, 17) increase in adiponectin levels. We also observed 13% (95% confidence interval: 6, 20) higher adiponectin levels per interquartile-range increase in average exposure to nitrogen dioxide (13.6 parts per billion) during pregnancy. Significant associations were seen between air pollution markers and cord blood leptin levels in models that adjusted for birth weight *z* score but not in models that did not adjust for birth weight *z* score. The roles of prenatal exposure to air pollution and fetal metabolic function in the potential development of childhood obesity should be further explored.

adiponectin; air pollution; birth cohort; umbilical cord blood; leptin; maternal exposure; pregnancy

Abbreviations: BMI, body mass index; CI, confidence interval; IQR, interquartile range; LUR, land use regression; MIREC, Maternal-Infant Research on Environmental Chemicals; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm.

The prevalence of childhood obesity has increased dramatically in the past 30 years, having more than doubled in children and quadrupled in adolescents in the United States (1). This trend has emerged as a major public health concern because obesity is associated with lifelong health consequences, such as the development of type 2 diabetes mellitus and cardiovascular disease (2). One mechanism proposed for the increase in childhood obesity is that exposure to environmental factors such as outdoor air pollution might alter metabolic function, predisposing affected children to the development of obesity (2, 3). Metabolic function can be evaluated by measuring blood levels of leptin and adiponectin, 2 adipocyte-secreted hormones commonly termed adipokines that are important in energy, glucose, and lipids homeostasis (4, 5). Elevated adipokine levels in cord blood are considered potential predictors of the early development of obesity (6–9) and have been associated with higher birth weight (10) and being born large for gestational age (11).

Investigators have examined the relationship of cord blood leptin and adiponectin levels with childhood obesity-related

outcomes. Among 80 Mexican-American children in the CHAMACOS birth cohort, leptin levels were positively related to body mass index (BMI) throughout the childhood period (9). Although the relationship between cord blood adiponectin and childhood BMI is less clear, higher adiponectin levels at birth seem to be related to increases in central adiposity and elevated lipid levels during infancy (7, 9). Recently, higher levels of arsenic, lead, cadmium, and phthalate metabolites measured in blood or urine were associated with elevated leptin levels in umbilical cord blood (12–14). However, to our knowledge, the association between prenatal exposure to air pollution and cord blood adipokine levels has not yet been investigated.

Associations between prenatal exposure to air pollution and adverse birth outcomes have been previously reported (15–18). In addition, previous evidence suggests that exposure to ambient air pollution during pregnancy could increase the risk of obesity in childhood (19), although evidence remains sparse. For example, in previous laboratory studies, investigators have shown that prenatal or early-life exposure to air pollution is associated with weight gain, increases in fat mass, and increases in measures of adiposity in offspring mice (20, 21). This might occur when in utero exposure to air pollution inappropriately activates receptors of genes important to adipocyte differentiation and regulation of metabolic efficiency (2, 20). A better understanding of the association between prenatal environmental exposures and metabolic function at birth could provide further insight into the mechanism linking such exposures to childhood obesity.

The aim of the present study was to investigate the associations between maternal exposure to ambient air pollution and umbilical cord blood levels of leptin and adiponectin among the cohort of mother-infant pairs enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. We used measurements of nitrogen dioxide and particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$).

METHODS

Study population

The MIREC Study has been described in detail previously (22). Briefly, a total of 2,001 women were recruited from 10 sites across Canada (Vancouver, Edmonton, Winnipeg, Toronto, Hamilton, Sudbury, Kingston, Ottawa, Montreal, and Halifax). Women were eligible for inclusion in the study if they were in the first trimester of pregnancy (<14 weeks of gestation), 18 years of age or older, able to communicate in French or English, and planning to deliver at a local participating hospital. Women were excluded from the study if they had any serious medical complications or if there were known fetal or chromosomal anomalies in the current pregnancy (22). Ethics approval for the present study was received from Health Canada and each participating study site.

Women consented to participate and provided biospecimens during scheduled visits to the study clinics during each trimester of pregnancy. Eighteen women withdrew and asked that all their data be destroyed. Of the 1,983 subjects remaining in the study, 1,363 had infants with a cord blood sample and consented to having biospecimens stored in the MIREC Biobank. An additional 106 subjects were excluded, for the following reasons: multiple birth, preterm delivery, cord blood sample unsuitable for analysis, missing data for any of the exposures, or unknown infant sex. The final sample size for the present analysis was 1,257.

Exposure assessment

Information about each participant's residential location (the first 3 characters of the 6-digit postal code) was collected using questionnaires completed in the first and third trimesters. We obtained the population-weighted latitude and longitude coordinates for each participant's 3-digit postal code during the first- and third-trimester visits using Postal Code Conversion File Plus software, version 5K (Statistics Canada, Ottawa, Ontario, Canada) (23). These locations were used to estimate the geographic location of each residence during pregnancy. There were 458 different geographic units among participants' 3-digit postal codes, with an average size of 10.8 km^2 (range, 0.6–32.4 km^2). Prenatal exposure to $PM_{2.5}$ was assigned to women's residential histories based on monthly surfaces of a North American land use regression (LUR) model that incorporated observations from fixed-site monitoring stations and satellite-derived estimates of $PM_{2.5}$ (24, 25). A Bayesian maximum entropy interpolation method (26) was used to create a spatiotemporal prediction model of the space-time residuals from the LUR model that were added to the LUR prediction estimates. The normalized cross-validated R^2 value for the $PM_{2.5}$ LUR model was 0.53 for Canada (25).

In addition, we used data from an updated national LUR model, including satellite nitrogen dioxide estimates and geographic predictors (27) to obtain information on maternal residential exposure to nitrogen dioxide. To capture fine-scale variation in vehicle emissions, kernel density functions describing densities of roadways were incorporated into the LUR model predictions. This model explained 73% of the variation in nitrogen dioxide measurements for 2006, with a root mean square error of 2.9 parts per billion. We used fixed-site monitoring stations to temporally scale nitrogen dioxide estimates to capture trimester-specific estimates (27–29). Exposure was assigned based on the monthly surfaces in which a participant spent most of her pregnancy. These models allowed us to estimate exposure for each study subject across each trimester of pregnancy while accounting for residential mobility during pregnancy. Whole-pregnancy exposure estimates for nitrogen dioxide and $PM_{2.5}$ were obtained by averaging trimester-specific estimates.

Fetal markers of metabolic function

As part of the MIREC Study, stored umbilical cord blood samples were analyzed to measure levels of leptin and adiponectin using Meso Scale Discovery immunoassay kits (Meso Scale Diagnostics, Rockville, Maryland) at Mount Sinai Laboratory (Toronto, Ontario, Canada). Repeated analysis was performed on all samples with a coefficient of variation greater than 15% (12). The inter- and intraassay coefficients of variation, respectively, were 11.8% and 9.3% for leptin

and 8% and 9% for adiponectin. All samples were above the assay's limits of detection.

Covariates

Covariates were identified as potential confounders based on a priori knowledge of their relationships with the exposures and outcomes (12, 14–16). Covariates were assessed during study clinic visits throughout pregnancy or at delivery, and included maternal age at delivery (≤24, 25–29, 30–34, or ≥35 years), prepregnancy BMI (weight (kg)/height $(m)^2$), using categories set by the World Health Organization (30), gestational weight gain according to the Institute of Medicine's recommendations (inadequate, adequate, or excessive) (31), parity (nulliparous or parous), maternal educational level (high school diploma or less, trade school or some college, undergraduate university degree, or graduate university degree), annual household income (in Canadian dollars; ≤30,000, 30,001–50,000, 50,001–100,000, or >100,000), ethnicity (white or nonwhite), maternal smoking (never smoked or quit before pregnancy, quit smoking when pregnancy was confirmed, or current smoker), infant sex, and birth weight z score (which was used as a surrogate of fetal fat mass) (12–14). Previous literature has shown associations between outdoor air pollution and low birth weight (15), and size at birth has been shown to be positively associated with cord blood leptin levels (8). Thus, birth weight z score could be in the causal pathway between outdoor air pollution and cord blood leptin levels. For this reason, the main analyses were conducted with and without adjustment for birth weight z score.

Statistical analyses

We first evaluated whether there were differences in leptin and adiponectin levels by infant sex using a t test of significance with a P value of 0.05. Mixed-effects linear regression models were used to evaluate the associations between average prenatal exposure to ambient air pollutants and natural log-transformed leptin and adiponectin concentrations. The natural log transformation was used to normalize the distributions of adipokine levels (11, 14, 32). Mixed-effects models with random intercepts across the 10 communities and across 3-digit postal codes were used to account for potential clustering of the outcome on a small-scale spatial level. Air pollution exposures ($PM_{2.5}$ and nitrogen dioxide) were evaluated in separate models as well as in a joint model. Results are presented as the percentage change (accompanied by the 95% confidence interval) in plasma leptin and adiponectin concentrations per interquartile-range (IQR) increase in average exposure to $PM_{2.5}$ and nitrogen dioxide. We also modeled $PM_{2.5}$ and nitrogen dioxide as categorical variables (quartiles) to assess potential nonlinearity of exposure-outcome relationships with adipokine levels (32). Natural cubic splines with 3 degrees of freedom were also used to further characterize the functional form of the relationship between ambient air pollutants and adipokine concentrations.

Evaluation of confounding in the multivariable models was done using a backward deletion approach (33); this was accomplished by adjusting for all potential confounders and then removing the least significant confounding variables one by one as long as the total proportional change in the air pollutant estimate compared with the fully adjusted model was less than 10%. Covariates that were not confounders but increased the precision of the estimates were kept in the final model (33). Sensitivity analyses were conducted by excluding women with gestational diabetes ($n = 32$) and women with impaired glucose tolerance ($n = 44$) and by conducting distinct analyses for each trimester-specific exposure variable. Gestational diabetes and impaired glucose tolerance were defined in accordance with guidelines from the Canadian Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada as described in a previous publication (34).

Table 1. Characteristics of a Sample of Participants ($n = 1,257$) in the Maternal-Infant Research on Environmental Chemicals Study, Canada, 2008–2011

Characteristic	No.	%	Mean (SD)
Maternal age, years			33.1 (5.0)
Prepregnancy body mass index[a]			24.9 (5.4)
Gestational weight gain			
Inadequate	212	18.3	
Adequate	342	29.5	
Excessive	605	52.2	
Missing	98		
Nulliparous	726	57.8	
Educational level			
High school diploma or less	104	8.3	
Trade school or some college	361	28.7	
Undergraduate university degree	478	38.0	
Graduate university degree	312	24.8	
Missing	2		
Household income, Canadian dollars			
≤30,000	91	7.2	
30,001–50,000	117	9.3	
50,001–100,000	514	40.9	
>100,000	487	38.7	
Missing	48		
White	1,087	86.5	
Maternal smoking			
Never smoked or quit before pregnancy	1,113	88.5	
Quit smoking when pregnancy confirmed	79	6.3	
Current smoker	65	5.2	
Male infant sex	672	53.5	
Birth weight, g			3,533.7 (453.0)
Cord blood leptin, ng/mL			19.9 (25.5)
Cord blood adiponectin, μg/mL			18.2 (12.1)

[a] Body mass index was calculated as weight (kg)/height $(m)^2$.

Table 2. Associations Between Percentage Change in Umbilical Cord Blood Leptin and Adiponectin Levels[a] and Exposure to $PM_{2.5}$ and NO_2 During Pregnancy by Quartile and Interquartile-Range Increase, With Adjustment for Birth Weight *z* Score, Maternal-Infant Research on Environmental Chemicals Study, Canada, 2008–2011

Pollutant and Quartile of Concentration	Leptin		Adiponectin	
	% Change	95% CI	% Change	95% CI
$PM_{2.5}$, μg/m^3				
Quartile 1 (3.3–6.0)	0	Referent	0	Referent
Quartile 2 (6.0–8.3)	26	10, 42	19	8, 30
Quartile 3 (8.3–9.2)	14	−2, 31	13	2, 24
Quartile 4 (9.2–11.6)	22	6, 38	19	9, 30
IQR (3.2)	11	1, 21	11	4, 17
NO_2, ppb				
Quartile 1 (3.7–7.1)	0	Referent	0	Referent
Quartile 2 (7.1–13.7)	−5	−22, 11	12	1, 23
Quartile 3 (13.7–20.7)	5	−12, 23	14	2, 26
Quartile 4 (20.7–41.4)	11	−6, 28	22	11, 34
IQR (13.6)	12	2, 23	13	6, 20
Multipollutant model				
IQR (3.2) increase in $PM_{2.5}$	0	−13, 13	8	0, 17
IQR (13.6) increase in NO_2	12	1, 25	9	1, 17

Abbreviations: CI, confidence interval; IQR, interquartile range; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; ppb, parts per billion.
[a] Adjusted for maternal age, parity, prepregnancy body mass index, birth weight *z* score, and infant sex.

We also evaluated effect modification of infant sex by including a term for interaction between infant sex and each exposure. In addition, analyses were stratified by infant sex because in utero exposure to environmental contaminants might be associated with cord blood adipokine levels in a sex-dependent manner (12). All models for leptin and adiponectin

Table 3. Associations Between Percentage Change in Umbilical Cord Blood Leptin and Adiponectin Levels[a] and Exposure to $PM_{2.5}$ and NO_2 During Pregnancy by Quartile and Interquartile-Range Increase, Without Adjustment for Birth Weight *z* Score, Maternal-Infant Research on Environmental Chemicals Study, Canada, 2008–2011

Pollutant and Quartile of Concentration	Leptin		Adiponectin	
	% Change	95% CI	% Change	95% CI
$PM_{2.5}$, μg/m^3				
Quartile 1 (3.3–6.0)	0	Referent	0	Referent
Quartile 2 (6.0–8.3)	18	1, 36	17	6, 28
Quartile 3 (8.3–9.2)	5	−12, 23	11	0.2, 22
Quartile 4 (9.2–11.6)	10	−7, 28	17	6, 28
IQR (3.2)	3	−8, 14	9	2, 16
NO_2, ppb				
Quartile 1 (3.7–7.1)	0	Referent	0	Referent
Quartile 2 (7.1–13.7)	−11	−28, 7	10	−1, 22
Quartile 3 (13.7–20.7)	0	−19, 18	12	1, 24
Quartile 4 (20.7–41.4)	−4	−23, 14	18	6, 30
IQR (13.6)	3	−9, 15	13	6, 20
Multipollutant model				
IQR (3.2) increase in $PM_{2.5}$	−3	−17, 10	7	−2, 15
IQR (13.6) increase in NO_2	5	−9, 18	8	−1, 17

Abbreviations: CI, confidence interval; IQR, interquartile range; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; ppb, parts per billion.
[a] Adjusted for maternal age, parity, prepregnancy body mass index, and infant sex.

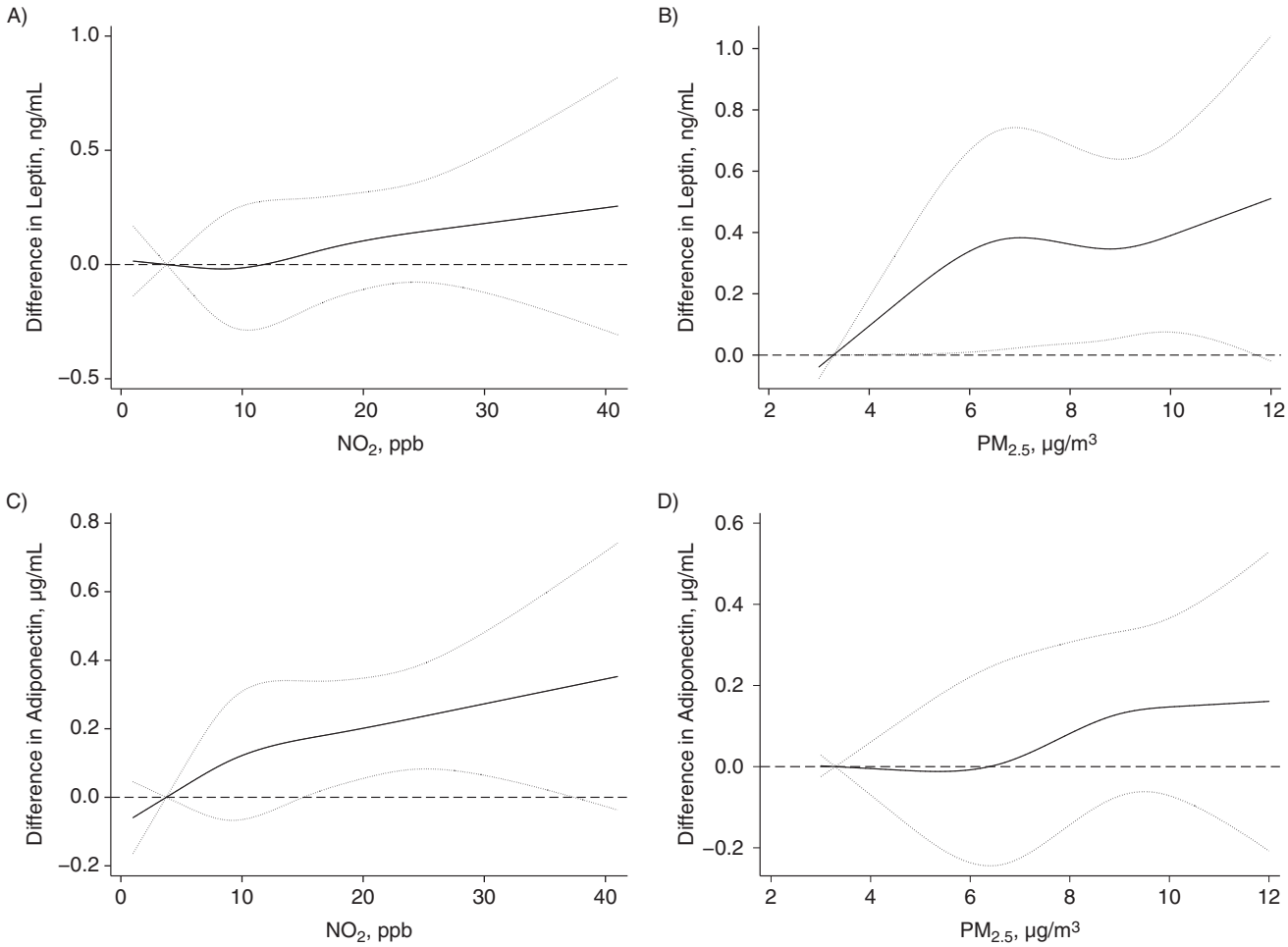

Figure 1. Associations between levels of adipokines and prenatal exposure to pollutants, adjusted for birth weight *z* score, Maternal-Infant Research on Environmental Chemicals Study, Canada, 2008–2011. A) Nitrogen dioxide (NO_2) and umbilical cord blood leptin levels; B) particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) and cord blood leptin levels; C) nitrogen dioxide and cord blood adiponectin levels; D) $PM_{2.5}$ and cord blood adiponectin levels. Associations were adjusted for maternal age, parity, prepregnancy body mass index, birth weight *z* score, and infant sex. Adjustments for birth weight *z* score were fitted using a natural cubic spline with 3 degrees of freedom. Dotted lines, 95% confidence intervals. ppb, parts per billion.

analyses adjusted for maternal age, parity, prepregnancy BMI, and infant sex. We performed the analyses with and without adjustment for birth weight *z* score. Analyses were performed using Stata, version 12.1 (StataCorp LP, College Station, Texas), and R, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study participants were predominantly white and ranged in age from 19 years to 48 years at recruitment. The majority had a university degree and had a household income greater than $50,000 (Table 1). Leptin concentrations ranged from 0.086 ng/mL to 243 ng/mL, and adiponectin concentrations ranged from 0.19 μg/mL to 239 μg/mL. Leptin concentrations were significantly higher among female infants (median, 16.0 ng/mL; IQR, 26.3 ng/mL) than among male infants (median, 8.7 ng/mL; IQR, 3.6 ng/mL). There were no differences in adiponectin concentrations by infant sex. Mean levels of nitrogen dioxide and $PM_{2.5}$ were 14.4 (standard deviation, 7.6) parts per billion and 7.7 (standard deviation, 1.9) μg/m^3, respectively. Nitrogen dioxide and $PM_{2.5}$ were moderately correlated (Pearson correlation coefficient = 0.49).

$PM_{2.5}$ appeared to be positively associated with umbilical cord blood leptin levels in models adjusting for birth weight *z* score (Table 2). For example, we found that an IQR increase (3.2 μg/m^3) in $PM_{2.5}$ was associated with 11% (95% confidence interval (CI): 1, 21) higher leptin levels. We also found 12% (95% CI: 2, 23) higher leptin levels associated with an IQR (13.6 parts per billion) increase in nitrogen dioxide. However, most associations between $PM_{2.5}$ (per IQR increase, 3%, 95% CI: −8, 14) or nitrogen dioxide (per IQR increase, 3%, 95% CI: −9, 15) and umbilical cord blood leptin levels decreased and were not statistically significant in

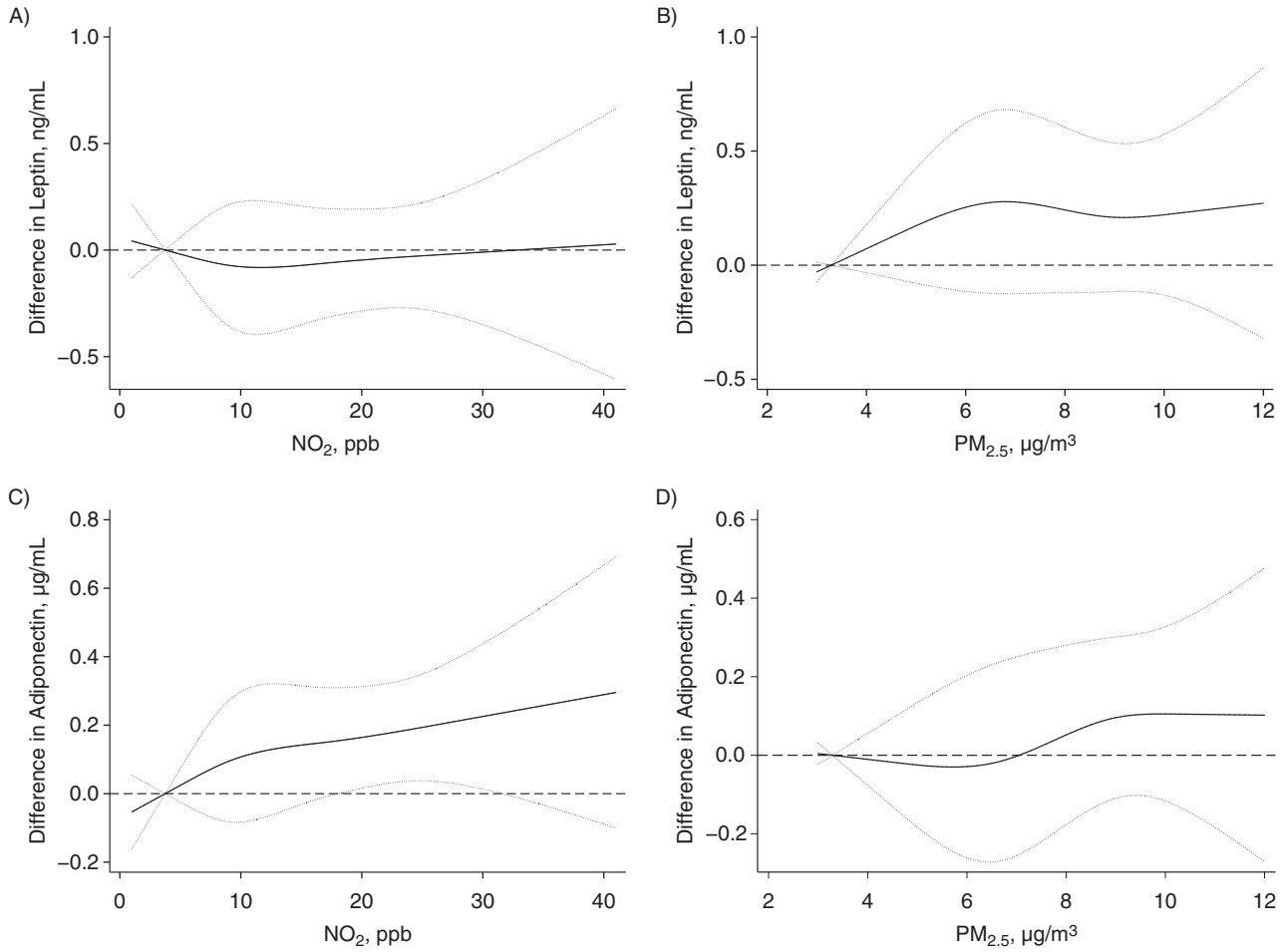

Figure 2. Associations between levels of adipokines and prenatal exposure to pollutants, without adjustment for birthweight *z* score, Maternal-Infant Research on Environmental Chemicals Study, Canada, 2008–2011. A) Nitrogen dioxide (NO_2) and cord blood leptin levels; B) particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) and cord blood leptin levels; C) NO_2 and cord blood adiponectin levels; D) $PM_{2.5}$ and cord blood adiponectin levels. Associations were adjusted for maternal age, parity, prepregnancy body mass index, and infant sex. Dotted lines, 95% confidence intervals. ppb, parts per billion.

models that did not adjust for birth weight *z* score (Table 3). Figures 1 and 2 show the natural cubic spline representations of nitrogen dioxide and $PM_{2.5}$, suggesting that the adjusted associations (with and without adjustment for birth weight *z* score) with leptin and adiponectin levels were approximately linear, except for the association between $PM_{2.5}$ and leptin levels when no adjustment was made for birth weight *z* score.

Some associations were found for adiponectin levels (Table 2). We observed 11% (95% CI: 4, 17) higher adiponectin levels for each IQR increase in $PM_{2.5}$. Statistically significant differences were also observed when comparing the 3 upper quartiles of $PM_{2.5}$ exposure with the lowest (quartile 1) exposure quartile. Higher levels of adiponectin were found for study participants in higher quartiles (quartiles 2–4) compared with the lowest quartile (quartile 1) of nitrogen dioxide exposure and increased monotonically across quartiles. The latter finding is supported by the graphical representations of the natural cubic spline of nitrogen dioxide on adiponectin levels, as shown in Figures 1 and 2. In models not adjusting for birth weight *z* score, associations between $PM_{2.5}$ (per IQR increase, 9%, 95% CI: 2, 16) or nitrogen dioxide (per IQR increase, 13%, 95% CI: 6, 20), and cord blood adiponectin levels decreased slightly but remained statistically significant (Table 3). In addition, multipollutant models (adjusting for $PM_{2.5}$ and nitrogen dioxide) showed that only nitrogen dioxide remained independently and significantly positively associated with levels of leptin and adiponectin when adjusting for birth weight *z* score (Tables 2 and 3).

Figures 3 and 4 show results of the analyses for leptin and adiponectin, respectively, stratified by infant sex and adjusted for birth weight *z* score. No clear patterns can be identified from these figures, although the association between air pollution and adiponectin appeared greater among female infants than among male infants. In addition, results for effect modification by infant sex were not statistically significant for any of the associations (P for interaction > 0.28; results not shown).

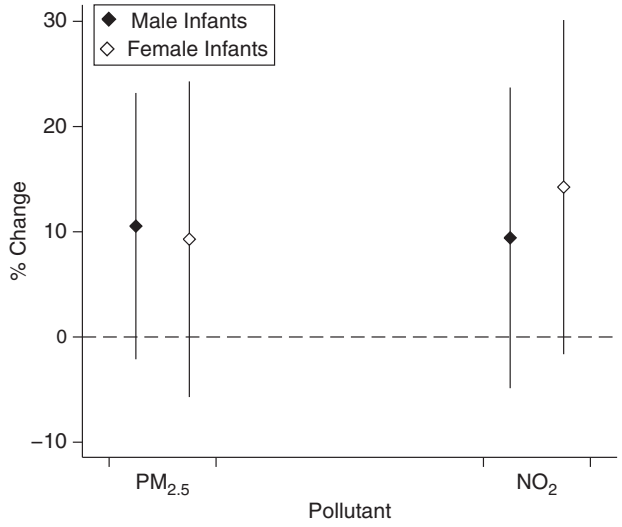

Figure 3. Associations between percentage change in cord blood leptin levels and an interquartile-range increase in exposure to particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) during pregnancy, by infant sex, Maternal-Infant Research on Environmental Chemicals Study, Canada, 2008–2011. Associations were adjusted for maternal age, parity, prepregnancy body mass index, and birth weight *z* score. Bars, 95% confidence interval.

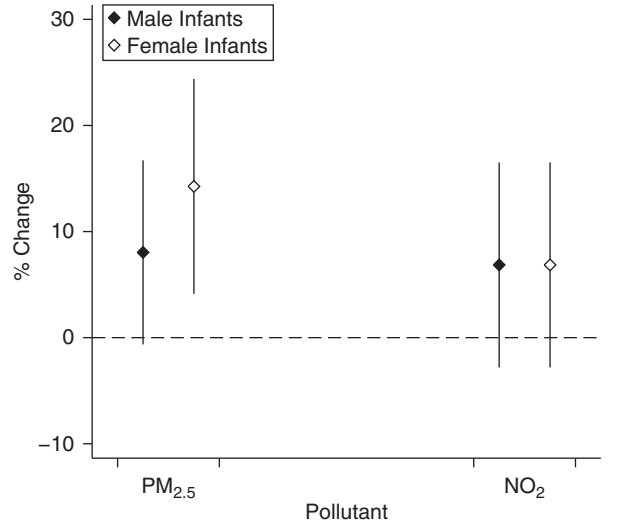

Figure 4. Associations between percentage change in cord blood adiponectin levels and an interquartile-range increase in exposure to particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) during pregnancy, by infant sex, Maternal-Infant Research on Environmental Chemicals Study, Canada, 2008–2011. Associations were adjusted for maternal age, parity, prepregnancy body mass index, and birth weight *z* score. Bars, 95% confidence intervals.

In the sensitivity analyses, similar estimates were observed for all associations when excluding study participants with gestational diabetes and impaired glucose tolerance (results not shown). Additional adjustment for annual household income in the multivariable models provided results similar to the ones obtained in the main analysis, suggesting that this variable, a proxy for socioeconomic status, had little influence on the estimates (Web Table 1, available at http://aje.oxfordjournals.org/). Results for trimester-specific periods of exposure to $PM_{2.5}$ and nitrogen dioxide revealed that estimates were similar to those obtained for pregnancy average exposures (Table 4). In addition, exposures to $PM_{2.5}$ (Pearson correlation coefficients ranged from 0.72 to 0.75) and nitrogen dioxide (Pearson correlation coefficients ranged from 0.59 to 0.90) were highly correlated between trimesters (results not shown).

DISCUSSION

Our study presents novel findings for ambient levels of air pollution and fetal metabolic function using measurements of leptin and adiponectin in cord blood. We found evidence that greater prenatal exposure to outdoor $PM_{2.5}$ and nitrogen dioxide was associated with higher cord blood levels of adiponectin. Greater exposure to air pollution during the whole pregnancy was associated with higher levels of cord blood leptin when adjusting for birth weight *z* score, but no associations were observed when birth weight was not accounted for in the models. We found no evidence of significant effect modification by infant sex, although the associations between air pollution and adiponectin appeared greater in female infants than in male infants.

Prenatal exposure to air pollution is associated with low birth weight (15). Our findings raise questions regarding the role of air pollution in fetal growth, because high leptin levels

Table 4. Associations[a] Between Percentage Change in Cord Blood Leptin and Adiponectin Levels and an Interquartile-Range Increase in $PM_{2.5}$ or Nitrogen Dioxide by Trimester of Pregnancy, Maternal-Infant Research on Environmental Chemicals Study, Canada, 2008–2011

Pollutant and Trimester of Pregnancy	IQR	Leptin		Adiponectin	
		% Change	95% CI	% Change	95% CI
$PM_{2.5}$, μg/m^3					
First trimester	3.4	12	3, 22	13	7, 19
Second trimester	3.4	9	0, 19	7	0, 13
Third trimester	3.3	7	0, 13	8	2, 15
NO_2, ppb					
First trimester	13.1	12	2, 22	10	3, 16
Second trimester	12.1	11	1, 21	9	2, 15
Third trimester	12.3	10	1, 21	10	3, 16

Abbreviations: CI, confidence interval; IQR, interquartile range; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; ppb, parts per billion.

[a] Adjusted for maternal age, parity, prepregnancy body mass index, birth weight *z* score, and infant sex.

in cord blood are usually correlated with higher birth weight (6). Our findings suggest positive associations between air pollution markers and cord blood leptin levels when adjusting for birth weight z score. However, no associations were observed when birth weight was removed from the models. In the present study, birth weight z score was used as a surrogate for fetal fat mass (12–14) because the latter is a determinant of cord blood leptin (35). Recent evidence suggests that a lower birth weight z score is associated with a higher proportion of abdominal fetal fat mass (36). Because adjusting for birth weight z score has the limitation that it does not distinguish between fat mass and skeletal growth, future investigations that can adjust solely for fetal fat mass could offer an even further refined ability to disentangle the relationships between air pollution and cord blood leptin levels. In addition, air pollution exposure during pregnancy has been previously associated with decreased fetal growth measures (17, 18). Therefore, prenatal exposure to air pollution could potentially affect skeletal growth and, simultaneously, adipose tissues, suggesting that air pollution could affect fetal growth through 2 different pathways. The biological mechanisms underlying these potential pathways require further clarification.

To our knowledge, no previous epidemiologic studies have investigated the association between exposure to air pollution during pregnancy and cord blood adipokine levels. The scientific literature has evaluated mainly the association between perinatal exposure to air pollution and measures of adiposity, which are known to be positively correlated with adipokine levels (37). One previous laboratory study showed that prenatal exposure to polycyclic aromatic hydrocarbons, a family of air pollutants generated during incomplete combustion, was associated with weight gain and increases in fat mass in offspring mice. This occurred through an alteration of adipose gene expression and DNA methylation in genes important to adipocyte differentiation after exposure to polycyclic aromatic hydrocarbons among pregnant dams (20). In an epidemiologic study conducted in New York, New York, Rundle et al. (19) reported results in line with these findings, showing that children of mothers in the highest category of exposure to polycyclic aromatic hydrocarbons during gestation had an increased risk of being obese at 5 and 7 years of age. In another laboratory analysis, investigators found that early life exposure to $PM_{2.5}$ in mice was associated with increased weight gain due to increases in measures of adiposity (21). We found only 1 epidemiologic study of the association between air pollution and blood leptin levels, and those authors reported a positive association between annual mean ambient black carbon exposure and leptin levels in older adults (32).

In a few studies, investigators have shown that cord blood leptin and adiponectin levels are associated with obesity-related outcomes during childhood (9, 11). In addition, it appears that children with higher cord blood adiponectin levels have a rapid decrease in adiponectin levels during infancy (11). This might be of concern, because lower adiponectin levels have been associated with both metabolic syndrome and type 2 diabetes mellitus (38, 39). In light of these findings, it is essential to better understand prenatal factors that can affect cord blood adipokine levels, which might have adverse long-term health consequences.

In models that adjusted for both $PM_{2.5}$ and nitrogen dioxide, we found that nitrogen dioxide remained independently and significantly positively associated with levels of leptin and adiponectin. It is important to note that the 2 exposure models of air pollution used in this study had very different spatial scales and were only moderately correlated ($r = 0.49$), likely reflecting different aspects of residential exposure to air pollution. Nitrogen dioxide is a strong marker of local traffic-related air pollution, and $PM_{2.5}$ reflects a more heterogeneous mixture of regional pollution. This finding could also be attributed to differences in degree of exposure measurement error or exposure variability. Therefore, the validity of the findings based on the multipollutant model can be questioned, and this area requires further clarification.

The strengths of our study include the use of a study population of pregnant women for whom a broad range of covariate data were available and who were located across Canada, which allowed the exploration of different exposure levels. In addition, cord blood leptin and adiponectin data were available for a relatively large proportion of the initial study population. The use of spatiotemporal models for nitrogen dioxide and $PM_{2.5}$ allowed us to calculate average exposures over the duration of pregnancy with a minimal amount of missing data.

Limitations of our study include potential misclassification of exposure to the air pollutants. Air pollution measures were assigned to the population-weighted geographic coordinates of the 3-digit postal codes in which mothers lived during pregnancy and were not based on the actual residential address. In addition, we did not have information about work locations or time spent at home, which could have improved the accuracy of exposure estimates (40). In our study, these systematic nondifferential exposure assessment errors likely resulted in underestimation of associations. We also relied on self-reported prepregnancy weight and height, which might have resulted in underestimates of BMI. Given the small sample size, this study may have had insufficient statistical power to detect any interactions. The generalizability of our findings might be limited because the subjects in our cohort were mostly white, had higher socioeconomic status, had lower BMI, and were less likely to smoke than members of the general population.

In conclusion, we found that exposure to outdoor air pollution during pregnancy was associated with higher cord blood adiponectin levels. Significant associations were seen between air pollution markers and cord blood leptin levels in models adjusted for birth weight z score but not in models unadjusted for birth weight z score. Our findings add evidence to the growing body of literature examining the association between prenatal environmental exposures and fetal metabolic development. Future studies should clarify the relationships between prenatal exposure to air pollution, adipokine levels at birth, fetal fat mass, and the evolution of weight and metabolic status during childhood.

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