

Fine particulate matter exposure and lipid levels among children in Mexico city

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Background: Studies have identified associations between air pollution and lipid levels in adults, suggesting a mechanism by which air pollution contributes to cardiovascular disease. However, little is known about the association between early life air pollution exposure and lipid levels in children.

Methods: Participants included 465 mother–child pairs from a prospective birth cohort in Mexico City. Daily particulate matter <2.5 µm in diameter (PM_{2.5}) predictions were estimated using a satellite-based exposure model and averaged over trimesters, the entire pregnancy, and the first year of life. We assessed associations with several lipid measures at 4–6 years of age, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Linear regression models were used to estimate change in lipid levels with each interquartile range increase in PM_{2.5}. We additionally assessed if associations between PM_{2.5} and lipid levels varied across lipid quantiles using quantile regression. Models were adjusted for maternal education, body mass index, and age, child's age at study visit, prenatal environmental tobacco smoke, and season of conception.

Results: PM_{2.5} exposure during the third trimester was associated with increases in childhood total cholesterol, LDL-C, and non-HDL-C, and decreases in HDL-C and triglycerides. There was additionally an increasing trend in the effect estimate across higher quantiles of total cholesterol, LDL-C, and non-HDL-C during the third trimester and entire pregnancy period. There were no consistent associations for first year of life exposures.

Conclusion: In this longitudinal birth cohort in Mexico City, associations between prenatal PM_{2.5} and childhood lipid (total cholesterol, LDL-C, non-HDL-C) levels were greater for children at higher lipid quantiles.

Introduction

An extensive body of literature exists on the associations between particulate matter <2.5 µm in diameter (PM_{2.5}) and increases in cardiovascular (CVD) morbidity and mortality.^{1,2}

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The main hypothesized mechanistic pathways linking air pollution and progression of atherosclerosis are through increases in systemic inflammation, oxidative stress, and susceptibility to lipid oxidation.^{2,3} Assessing associations with risk factors, or markers, of atherosclerosis may help gain insight into the PM induced CVD health effects, and help us to better understand these complex mechanistic pathways. Low-density lipoprotein cholesterol (LDL-C) is one such risk factor for progression of atherosclerosis.⁴ Recent studies have identified associations between air pollution and lipid levels in adult populations^{5–10}; however, little is known about the association between early life air pollution exposure and lipid levels in children.

Although once considered strictly an adult disease, cardiometabolic disease and its consequences may have its origins in very early life. David Barker first coined the term “fetal origins of disease” from his findings of the importance of the intrauterine environment.¹¹ His findings on low birthweight and increased cardiometabolic risk later in life laid the groundwork

What this study adds

We evaluated the association between pre- and postnatal particulate matter <2.5 µm in diameter (PM_{2.5}) exposure and lipid levels (total cholesterol [TC], Low-density lipoprotein cholesterol [LDL-C], non-HDL-C, high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]) in a cohort of children living in Mexico City. The findings from our study showed associations between prenatal, specifically third trimester, PM_{2.5} exposure and increased LDL-C, non-HDL-C, and total cholesterol levels in the child. We additionally observed an increasing trend across quantiles of the outcome distribution, with stronger associations seen for higher LDL-C levels. This is the first epidemiologic study to specifically address this research question in a younger study population—future studies are warranted to confirm these findings.

for developing the concept of critical windows of susceptibility—life stages when an individual is more susceptible to an environmental factor. Exposures during these time periods may predict early life preclinical cardiometabolic disease better than exposures at other time periods. Such windows may be reflected by dysregulated lipid profiles from toxic exposures, and may lead to later life health effects. The concept is analogous to the predictive value of low birth weight on later life cardiometabolic disease.^{12,13}

There is growing evidence that childhood lipid levels track into adulthood¹⁴ and are associated with cardiometabolic disease later in life.¹⁵ Taken together, these findings suggest that early life alterations in lipid levels may contribute to later life cardiometabolic disease. Early life represents an understudied, yet potentially important, window of susceptibility for development of CVD. Studying associations between early life environmental exposures, such as PM_{2.5}, and lipid levels in children may aid in primary prevention measures and help to gain insight into the early origins of cardiometabolic disease.

Previous studies have used linear models to assess associations between air pollution exposure and continuous outcome measures, such as LDL-C. This particular analytical technique assesses the change in the mean of, for instance, the LDL-C distribution with each unit increase in air pollution exposure. While the change in the overall distribution of outcome measures is important, another critical question is whether air pollution exposure impacts different levels of the outcome distribution. Quantile regression is one alternative analytical approach that allows the assessment of the impacts of exposures on continuous outcome levels at different quantiles of the outcome. We applied this method to assess associations with early life air pollution for children at the low (i.e., 10th percentile) and high (i.e., 90th percentile) end of the lipid outcome distribution.

The objective of this study was to assess associations between early life PM_{2.5} exposure and childhood cholesterol and triglyceride levels and to investigate if associations between PM_{2.5} and lipid levels varied across lipid quantiles.

Methods

Study population

We used data from the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) longitudinal birth cohort in Mexico. Briefly, pregnant women were recruited between 2007 and 2011 at 12–24 weeks' gestation through the Mexican Social Security System (IMSS). In order to be included in the study, pregnant women needed to be 18 years or older and plan to live in Mexico City. Additionally, women were eligible if they were <20 weeks gestation, had completed primary education, had no medical history of heart or kidney disease, and did not consume alcohol daily. In total, 948 women enrolled in the second trimester and delivered a live child who was then followed longitudinally. For this analysis, we used data from the age 4- to 6-year visit, the first at which a blood draw on the child was performed to allow lipid measurement. A total of 613 children were seen at this visit, of which 465 mother-child pairs had complete exposure, outcome, and covariate information available. Protocols were approved by the institutional review boards at the Icahn School of Medicine at Mount Sinai, Harvard School of Public Health, and Mexican National Institute of Public Health. All women provided informed consent.

Measurement of child lipids

Blood samples were collected from each child at the 4- to 6-year study visit. Children at this visit were not asked to fast due to their young age. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured

using enzymatic methods (Roche Diagnostics, Indianapolis, IN). Low-density lipoprotein cholesterol was calculated using the Friedewald formula, $[(total\ cholesterol) - (HDL-C) - (triglycerides/5)]$. Studies have shown that childhood non-HDL cholesterol (non-HDL-C) levels persist over time into adulthood and are predictive of adult dyslipidemia.¹⁶ Therefore, we additionally included non-HDL-C as an outcome measure by subtracting HDL-C from total cholesterol.

Air pollution exposure assessment and data linking

Residential exposure to PM_{2.5} was estimated using a satellite-based exposure model recently developed by our team.¹⁷ Briefly, Moderate Resolution Imaging Spectroradiometer (MODIS) satellite-derived Aerosol Optical Depth (AOD) measurements were obtained and calibrated with ground monitored data, meteorological data, and land use regression variables (such as roadway density, temperature, relative humidity, planetary boundary layer, and daily precipitation) with output at a daily temporal and 1 km spatial resolution. The model additionally used mixed effect models with temporal and spatial predictors and day-specific random effects to account for temporal variation in the PM_{2.5}-AOD relationship. Model performance was evaluated using monitor-level leave one out cross-validation with an R² of 0.74. Further details on this model, including methods and performance, can be found elsewhere.¹⁷

The nearest 1km exposure grid was linked to each participant based on their residential address during pregnancy. Gestational age was used to link the air pollution exposures on time. Gestational age at birth was estimated based on last menstrual period, as reported by the mother. Average levels of PM_{2.5} were calculated for each trimester of pregnancy (first trimester: 1–13 weeks, second trimester: 14–27 weeks, third trimester: 28 weeks–delivery) and across the entire pregnancy period. We additionally investigated associations with first year of life PM_{2.5} exposure in order to assess the impact of early postnatal exposures.

Covariates

A directed acyclic graph (DAG) (eFigure 1; <http://links.lww.com/EE/A75>) was used to identify the minimally sufficient adjustment set. Covariate information was obtained from baseline questionnaires or field measurements. Covariates include, maternal age at enrollment (continuous), maternal education (less than high school, high school, or greater than high school), environmental tobacco smoke exposure during pregnancy (present or absent in home), pre-pregnancy body mass index (weight in kg/height in m²), child's age at testing, and season of conception. Season of conception was categorized as cold-dry (November–February), warm-dry (March–April), and rainy (May–October). We additionally adjusted for child sex and gestational age in sensitivity analyses.

Statistical analyses

We first estimated associations between trimester-specific, entire pregnancy, and first year of life PM_{2.5} averages and childhood lipid levels using linear regression models. The estimates from these analyses can be interpreted as the difference in lipid level per unit increase in PM_{2.5}. Next, we estimated associations between pre- and postnatal PM_{2.5} and childhood lipid levels using quantile regression at the 10th, 30th, 50th, 70th, and 90th percentiles of each outcome. Instead of modeling the change in outcome level at the mean as linear regression does, quantile regression models the effect estimate at specific quantiles and uses the entire outcome distribution. For example, we can compare associations with PM_{2.5} across the outcome distribution, by

investigating the change in outcome level at the 90th percentile compared with the 10th or 50th.

Analyses were run separately for each outcome measure (total cholesterol, LDL-C, non-HDL-C, HDL-C, and triglycerides). Models were mutually adjusted for the other developmental windows of interest. Trimester-specific associations were mutually adjusted for exposures during the other trimesters and for concentrations during the first year of life.¹⁸ For example, estimates for first trimester PM_{2.5} exposure were mutually adjusted for PM_{2.5} concentrations during the second and third trimesters, as well as first year of life exposures. Average first year of life exposure was additionally adjusted for in entire pregnancy PM_{2.5} models; average entire pregnancy exposure was mutually adjusted for in the first year of life models. Regression coefficients from all models were scaled to the interquartile range (IQR) increases in PM_{2.5} concentrations averaged over the entire pregnancy period (3.8 µg/m³), to allow for comparison in results across all developmental windows. Finally, previous studies have found differences in effects of PM_{2.5} exposure for males and females. Therefore, as a sensitivity analysis, we assessed PM_{2.5}-lipid associations stratified by child sex.

Results

Table 1 shows a description of the 465 mother-child pairs included in our study. Children were on average 4.8 years at the 4- to 6-year follow-up visit. The study population consisted of an even distribution of boys and girls. Mothers were on average 28 years old at enrollment and primarily lower educated and of lower socioeconomic status. About one-third of mothers reported exposure to a smoker in the home during the pregnancy period.

Table 2 includes the distribution of childhood lipid levels and pre- and postnatal PM_{2.5} concentrations. Levels are displayed for the mean and also by percentile of the outcome and exposure distribution (10th, 30th, 50th, 70th, and 90th). Overall, about 11% of the study population had high LDL-C (≥130 mg/dl) and total cholesterol (≥200 mg/dl) levels. The 10th percentile for LDL-C was 70.2 mg/dl, 50th percentile: 94.8 mg/dl, and 90th percentile: 131.0 mg/dl.

The average PM_{2.5} level for study participants averaged across the pregnancy period was 22.5 µg/m³ (range: 16.4–29.2 µg/m³), with an interquartile range of 3.8 (SD: 2.6). Entire pregnancy exposure averages were moderately correlated with each of the trimester-specific averages (correlations of 0.52–0.71) (eTable 1;

<http://links.lww.com/EE/A75>); however, they were only weakly correlated with first year of life averages (0.25). Trimester-specific averages were not strongly correlated with each other (eTable 1; <http://links.lww.com/EE/A75>).

Trimester-specific, entire pregnancy, and first year of life associations between IQR (3.8 µg/m³) increases in PM_{2.5} and changes in lipid levels (TC, LDL-C, non-HDL-C, HDL-C, and TG) are presented in Table 3. In linear models, increased PM_{2.5} exposure during pregnancy was associated with increases in several of the lipid outcomes. In particular, effects were strongest for exposures during the third trimester with increases in total cholesterol (β: 3.02, 95% confidence interval [CI] = 0.26, 6.85), LDL-C (β: 4.49, 95% CI = 2.01, 6.97), and non-HDL-C (β: 3.99, 95% CI = 1.47, 6.52). There were additionally elevated effect estimates for first year of life exposures in relation to LDL-C and non-HDL-C, however the confidence intervals for the estimate included the null. We observed associations between increases in PM_{2.5} and decreases in HDL-C, particularly for exposures during the third trimester. Additionally, there were decreases in triglyceride levels for several of the exposure windows; however, the confidence intervals for these effect estimates include the null (Table 3). Overall, results were similar in crude, individual window models, and when adjusting for other covariates such as gestational age and child sex (eTable 2; <http://links.lww.com/EE/A75>).

Figure 1 shows the associations between IQR increases in PM_{2.5} concentrations during each trimester of pregnancy, the entire pregnancy period, and first year of life for each of the lipid outcome measures (TC, LDL-C, non-HDL-C, HDL-C, and TG) (see eTable 3; <http://links.lww.com/EE/A75>, for numeric results). Results are presented for the 10th, 30th, 50th, 70th, and 90th percentiles of the lipid outcome distributions using quantile regression. In quantile regression analyses, there was an increasing trend across quantiles of the LDL-C, non-HDL-C, and total cholesterol outcome distributions for exposures during the third trimester and across the entire pregnancy period (Figure 1). Increases in LDL-C, non-HDL-C, and total cholesterol levels were primarily seen for children with lipid levels above the median. For example, the β for LDL-C for the 30th percentile was 3.55 (95% CI = 1.02, 6.08); for the 90th percentile, the β was 10.2 (95% CI = 5.62, 14.8)) (Figure 1; eTable 3; <http://links.lww.com/EE/A75>). There were no consistent associations across quantiles of the HDL-C outcome distribution. There appeared to be a decreasing trend in triglyceride levels for exposures during the second trimester and entire pregnancy. Overall, there were no consistent trends for any of the outcomes for first year of life exposures (Figure 1).

Finally, we assessed associations between PM_{2.5} exposure averaged across the entire pregnancy and childhood lipid levels, stratified by child sex. Overall, results did not significantly differ by child sex (eFigure 2; <http://links.lww.com/EE/A75>).

Table 1.
Characteristics of mother-child dyads in the PROGRESS study

Characteristic	N (%) or Mean ± SD
Child's sex	
Female	234 (50)
Male	231 (50)
Child age at lipid measurement (years)	4.8 ± 0.6
Birth weight (kg)	3.1 ± 0.4
Gestational age (weeks)	38.3 ± 1.7
Mother's age at enrollment (years)	27.9 ± 5.6
Maternal body mass index (kg/m ²)	26.3 ± 4.1
Prenatal environmental tobacco smoke exposure	
Yes	165 (35)
No	300 (65)
Maternal education	
<High school	188 (40)
High school	173 (37)
College	104 (22)
Socioeconomic status	
Low	249 (54)
Medium	171 (37)
High	45 (10)

Table 2.
Distribution of childhood lipid levels and pre- and postnatal PM_{2.5} concentrations

Lipid Levels (mg/dl)	Mean ± SD	10th	30th	50th	70th	90th
Total cholesterol	163 ± 27	131	147	161	173	201
LDL cholesterol	97 ± 25	70	84	95	105	131
Non-HDL cholesterol	113 ± 25	85	100	110	123	148
HDL cholesterol	50 ± 9.1	38	44	49	54	62
Triglycerides	82 ± 42	49	61	71	89	124
PM _{2.5} Concentrations (µg/m ³)						
First trimester	23 ± 4.2	18	20	22	25	29
Second trimester	22 ± 4.2	18	19	21	24	28
Third trimester	23 ± 5.1	16	19	22	27	30
Entire Pregnancy	22 ± 2.6	19	21	23	24	26
First year of life	22 ± 2.3	19	21	23	24	25

Table 3.
Adjusted^a associations between early life PM_{2.5} exposure and childhood lipid levels

	Total cholesterol	LDL-C	Non-HDL-C	HDL-C	Triglycerides
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
First trimester	2.41 (−0.49, 5.30)	1.71 (−0.89, 4.32)	2.34 (−0.31, 4.99)	0.06 (−0.90, 1.03)	3.14 (−1.36, 7.64)
Second trimester	−1.57 (−4.46, 1.31)	−1.31 (−3.90, 1.28)	−2.12 (−4.76, 0.52)	0.55 (−0.41, 1.51)	−4.04 (−8.52, 0.44)
Third trimester	3.02 (0.26, 5.78)	4.49 (2.01, 6.97)	3.99 (1.47, 6.52)	−0.97 (−1.89, −0.05)	−2.47 (−6.76, 1.83)
Entire pregnancy	3.25 (−0.76, 7.25)	4.11 (0.49, 7.73)	3.36 (−0.32, 7.05)	−0.12 (−1.45, 1.22)	−3.73 (−9.95, 2.49)
First year of life	0.90 (−3.45, 5.25)	2.55 (−1.38, 6.48)	1.62 (−2.39, 5.62)	−0.72 (−2.17, 0.73)	−4.66 (−11.41, 2.10)

Results are reported per IQR (3.8 μg/m³) increases in PM_{2.5}.

^aModels are adjusted for maternal education, maternal age at enrollment, maternal body mass index, child's age at testing, season of conception, and prenatal environmental tobacco smoke exposure. Pregnancy and first year of life models are mutually adjusted for PM_{2.5} averages during the other exposure window; trimester models are mutually adjusted for other trimester, and first year of life PM_{2.5} concentrations.

Discussion

In our prospective birth cohort study, we found associations between late pregnancy PM_{2.5} exposure and increases in LDL-C, non-HDL-C, and total cholesterol in the child. We additionally assessed associations between prenatal PM_{2.5} and quantiles of the lipid outcome distributions. We demonstrated associations between PM_{2.5} and an increasing trend of higher lipids with the strongest results seen for the higher quantiles of the LDL-C, non-HDL-C, and total cholesterol outcome distribution.

To our knowledge, this is the first epidemiologic study to assess associations between early life PM_{2.5} exposure and childhood lipid levels. Our findings of an association with prenatal PM_{2.5} exposure and elevated LDL-C and total cholesterol levels, and decreased HDL-C levels are in accordance with previous studies in adult populations.^{5,9,10} We additionally observed associations between increases in PM_{2.5} exposure and decreases in triglyceride levels, which is consistent with a recent study in adults,¹⁹ but conflicting with a few other previous studies in adult populations.^{6,8} Although no previous study has assessed associations with air pollution and lipid levels in children, a few previous studies have assessed associations between other environmental chemicals and lipid levels in children, with several finding inverse associations between prenatal exposures (such as phthalates and polyfluoroalkyl chemicals) and childhood lipid levels.^{20,21}

We found stronger associations with PM_{2.5} levels for several of our outcomes for levels above the 50th outcome percentile. Using quantile regression, we were able to use the entire outcome distribution, instead of modeling the change from the mean as is commonly done with continuous outcomes. A few previous studies have assessed associations with air pollution exposure and continuous outcomes using quantile regression.⁶ A recent US-based analysis in a cohort of cardiac catheterization patients found associations between long-term PM_{2.5} exposure and increases in LDL concentrations and sizes in adults, with the strongest results observed for those with the highest LDL levels.¹⁰

The main mechanistic pathway linking prenatal air pollution exposure with changes in lipid levels may be through an inflammatory response in the mother and offspring. Studies suggest PM_{2.5} can increase systemic inflammation and interfere with lipid metabolism and oxidation.^{3,22} A recent study in mothers and their newborns found associations with prenatal air pollution exposure and increases in oxidative DNA damage and lipid peroxidation in the newborns, but not the mothers.²³ Further, a recent PROGRESS study assessed associations between prenatal PM_{2.5} exposure and changes in mitochondrial DNA content in cord blood, as a marker of cumulative oxidative stress.²⁴ Findings from this study showed decreases in mitochondrial DNA, particularly for exposures during the third trimester, which is similar to the developmental window we observed in the current study. A potential unifying theory that brings together observations that higher in utero air pollution is associated with child obesity^{25,26} as well as adult cardiovascular disease is that air pollution may operate through both chronic and acute inflammatory pathways.^{27,28} Chronically, air pollution inflammation in utero may

promote obesity in children, with pregnancy exposures representing a critical exposure window. This increase in obesity rates from in utero PM_{2.5} exposure in turn elevates serum lipid levels in children beginning in the preschool years. These increased lipid levels may add to an increased risk for later life cardiovascular disease as the child transitions to adulthood.

A few previous studies have found conflicting results for prenatal vs childhood environmental exposures and childhood lipid levels.²⁰ We were unable to assess the impact of childhood air pollution exposures in the current study as our model has not yet been extended beyond 2014; however, this is of interest in future studies using PROGRESS data. Due to their young age, children in the study were not asked to fast. This may have overestimated the triglyceride levels in the child. However, studies have shown minimal differences in fasting and non-fasting lipid levels,^{29,30} and that non-fasting lipid values may be more reflective of one's actual daily levels and equally predictive of future CVD events.^{31,32} Also, the temporality of recent eating and the timing of the blood draw for lipids is likely random with respect to air pollution in pregnancy, and therefore would have induced nondifferential misclassification into our analysis. Finally, we used one address to link air pollution exposure to participants for the entire pregnancy period and first year of life, and did not assess residential mobility during pregnancy. This may have resulted in exposure misclassification; however, previous studies have found minimal differences in air pollution exposure assignment and resulting effect estimates when using the full address history during pregnancy.^{33,34}

Despite these limitations, our study has several strengths. To our knowledge, this is the first epidemiologic study to assess associations between early life air pollution exposure and childhood lipid levels. Our study additionally makes use of a state-of-the-art air pollution model at a fine temporal and spatial scale. We addressed this research question using data from a prospective birth cohort in Mexico City, an area with considerably high PM_{2.5} levels. Women in our study population had average PM_{2.5} levels during pregnancy of 22.5 μg/m³. For comparison, the World Health Organization PM_{2.5} annual mean standard is 10 μg/m³.³⁵ Previous studies have cautioned against analyzing trimester-specific averages in separate models, as this can induce bias in the resulting estimates.¹⁸ Thus, an additional strength of the current study is that our trimester models were mutually adjusted for the other trimesters of interest. Finally, in addition to linear models, we assessed associations at different percentiles of the outcome distribution using quantile regression.

Conclusions

In conclusion, we found associations between late pregnancy PM_{2.5} exposure and increased LDL-C, non-HDL-C, and total cholesterol levels in the child. We additionally observed an increasing trend across quantiles of the outcome distribution, with stronger associations seen for higher LDL-C levels. Results were inconsistent for first year of life exposures. This study begins to reveal potential associations between early life air

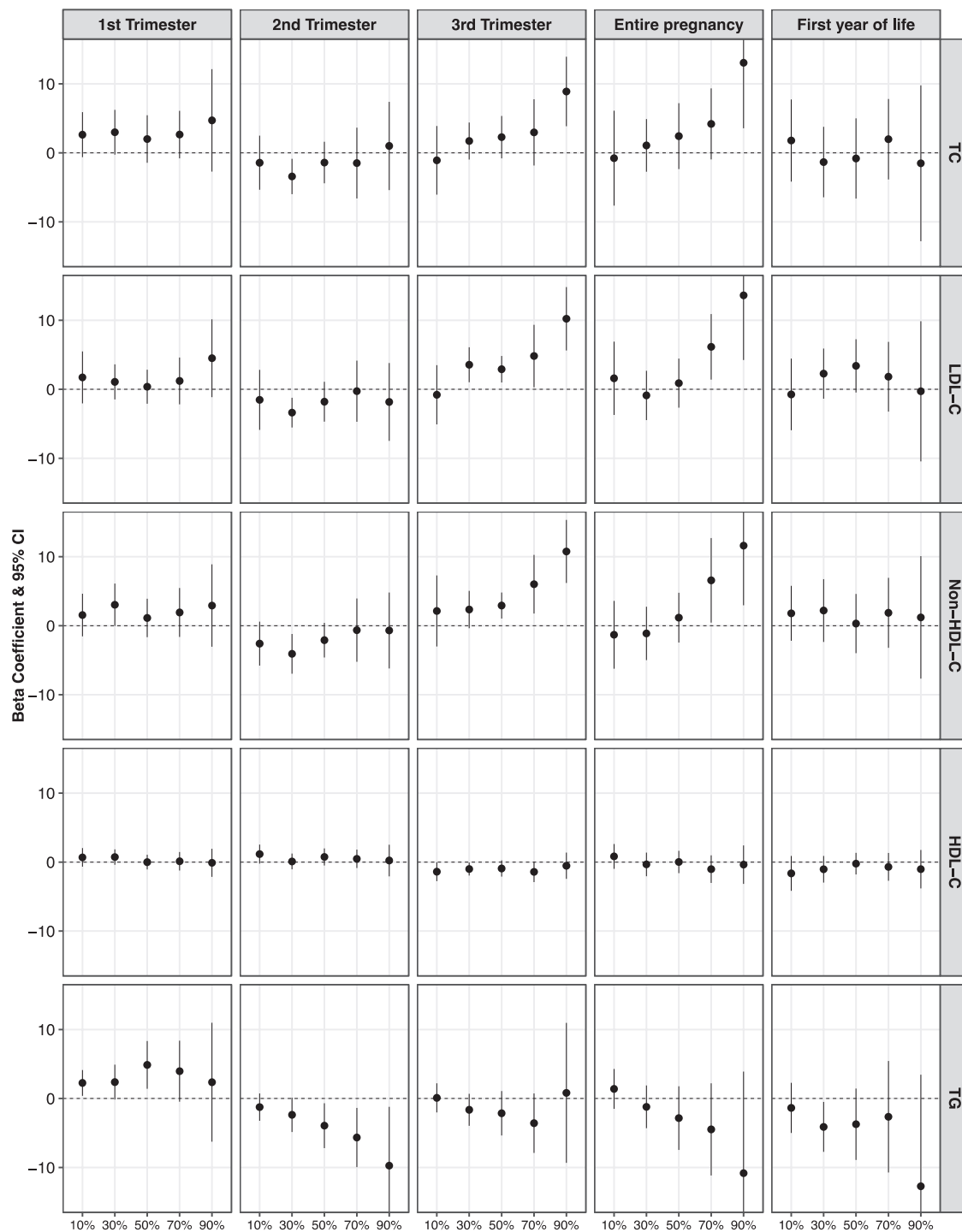


Figure 1. Trimester-specific, entire pregnancy, and first year of life quantile regression estimates (β and 95% CI) for associations between IQR ($3.8 \mu\text{g}/\text{m}^3$) increases in $\text{PM}_{2.5}$ exposure and childhood lipid levels (TC, non-HDL-C, LDL-C, HDL-C, and TG). Results are shown for the 10th, 30th, 50th, 70th, and 90th quantiles. Models are adjusted for maternal education, maternal age at enrollment, maternal BMI, child's age at testing, season of conception, and prenatal environmental tobacco smoke exposure. Trimester-specific effect estimates are mutually adjusted for other trimester and first year of life exposure averages; pregnancy estimates are mutually adjusted for first year of life $\text{PM}_{2.5}$ averages; first year of life estimates are mutually adjusted for average pregnancy exposure.

pollution exposure and early life CVD risk factors. Future studies using PROGRESS data will examine associations between $\text{PM}_{2.5}$ and other CVD risk factors in children and adolescents, including carotid intima-media thickness.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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