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Original Investigation Prenatal and Early Life Exposures to Ambient Air Pollution and Development

Sandie Ha, PhD[1], **Edwina Yeung, PhD**[2], **Erin Bell, PhD**[3,4], **Tabassum Insaf, PhD**[4,5], **Akhgar Ghassabian, MD**[6], **Griffith Bell, PhD**[2,7], **Neil Muscatiello, MS**[5], and **Pauline Mendola, PhD**[2]

[1]Department of Public Health, School of Social Sciences, Humanities and Arts, University of California, Merced, CA

[2]Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD

[3]Department of Environmental Health Sciences, School of Public Health, University at Albany, NY

[4]Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, NY

[5]Center for Environmental Health, New York State Department of Health, Albany, NY

[6]Departments of Pediatrics, Population Health, and Environmental Medicine, New York University School of Medicine

[7]Ariadne Labs, Brigham and Women's Hospital, Harvard T.H. Chan School of Public Health, Boston, MA

Abstract

Background: Residential proximity to major roadways, and prenatal exposures to particulate matter <2.5μm ($PM_{2.5}$) and ozone (O_3) are linked to poor fetal outcomes but their relationship with childhood development is unclear.

Objectives: We investigated whether proximity to major roadways, or prenatal and early-life exposures to $PM_{2.5}$ and O_3 increase the risk of early developmental delays.

Study Design: Prospective cohort

Settings: New York State excluding New York City

Participants: 4,809 singletons and 1,016 twins born between 2008 and 2010.

Exposures: Proximity to major roadway was calculated using road network data from the NY Department of Transportation. Concentrations of $PM_{2.5}$ and O_3 estimated by the Environmental

Corresponding author: Sandie Ha, PhD, MPH, Assistant Professor, Department of Public Health, College of Social Sciences, Humanities and Arts, 5200 N Lake Road, SSM 356B, Merced, CA 95343, sha55@ucmerced.edu, Phone: 209-228-3615.

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Protection Agency Downscaler models were spatiotemporally linked to each child's prenatal and early-life addresses incorporating residential history, and locations of maternal work and day-care.

Outcomes: Parents reported their children's development at ages 8, 12, 18, 24, 30 and 36 months in five domains using the Ages and Stages Questionnaire. Generalized mixed models estimated the relative risk (RR) and 95% CI for failing any developmental domain per 10 units increase in $PM_{2.5}$ and O_3, and for those living <1000m away from a major roadway compared to those living further. Models adjusted for potential confounders.

Results: Compared to those >1000m away from a major roadway, those resided 50–100m [RR: 2.12 (1.00–4.52)] and 100–500m [RR: 2.07 (1.02–4.22)] away had twice the risk of failing the communication domain. Prenatal exposures to both $PM_{2.5}$ and ozone during various pregnancy windows had weak but significant associations with failing any developmental domain with effects ranging from 1.6%-2.7% for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and 0.7%-1.7% for a 10ppb increase in ozone. Average daily postnatal ozone exposure was positively associated with failing the overall screening by 8 months [3.3% (1.1%-5.5%)], 24 months [17.7% (10.4%-25.5%)], and 30 months [7.6%, (1.3%-14.3%)]. Findings were mixed for postnatal $PM_{2.5}$ exposures.

Conclusions: In this prospective cohort study, proximity to major roadway and prenatal/early-life exposures to $PM_{2.5}$ and O_3 were associated with developmental delays. While awaiting larger studies with personal air pollution assessment, efforts to minimize air pollution exposures during critical developmental windows may be warranted.

Keywords

child development; neurodevelopment; air pollution; traffic; major roadway

INTRODUCTION

Most structural features of the central nervous system (CNS) are formed by the eighth week of gestation but they continue to grow and develop throughout pregnancy and after birth. Early development is critical and reflects a child's physical, psychological and cognitive functioning. A growing body of evidence has converged in accordance with the developmental origins of health and disease framework, suggesting that environmental exposures during periods of developmental plasticity (i.e., *in utero* and early life) may have life-long effects.[1] While recognizing that neurodevelopment can be driven by genetics, recent research shifts attention towards an emphasis on the early environment.[2,3] Early environmental exposures including maternal infection, maternal alcohol consumption, and smoking during pregnancy are well-established risk factors for neurodevelopmental complications[4–6] but more ubiquitous environmental exposures, including ambient air pollution, have received less attention.

Common air pollutants, such as particulate matter with diameter <2.5 microns ($PM_{2.5}$) and ozone have been linked to mortality and morbidity across the life span.[7,8] Prenatal exposures to these pollutants have also been associated with adverse fetal development, including outcomes of stillbirth, intrauterine growth restriction, preterm birth, and low birthweight.[9,10] Given that much of the neurodevelopmental processes occur *in utero* and early life, it follows that air pollution exposures during these sensitive windows may affect

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neurodevelopment, leading to developmental delays. However, studies are limited and inconsistent with some showing positive associations between air pollution and childhood development while some showing negative or null associations.[11,12] In addition, many studies often lack residential history, which can potentially cause misclassification of exposure. As neurodevelopment continues after birth, postnatal exposures may play an important role but studies on this association are also sparse.

In addition to specific air pollutants, traffic-related air pollution, frequently measured as residential proximity to major roadways, has received attention as an exposure of interest in relation to health. While non-specific, this provides a measure of complex mixtures of pollutants related to traffic. In addition, studies suggest that traffic related air pollution is the primary driver or intraurban variation in pollutant levels, suggesting that proximity to major roadway can be a reasonable indicator of exposure.[13] A few studies have linked proximity to freeways with autism[14] and lower cognitive function (e.g., verbal/nonverbal intelligence, visual and motor performance, and visual memory) in children,[15] but research on the relationship between both prenatal and postnatal traffic exposures and early developmental outcomes is limited.[16]

Given a large proportion of the US population lives close to major roadways or are exposed to unhealthy levels of air pollution, we aim to investigate whether residential proximity to major roadways or exposures to $PM_{2.5}$ and ozone during pregnancy and early life are associated with developmental screening failure during the first three years of life.

MATERIALS AND METHODS

Study settings and participants.

The Upstate KIDS study is a population-based birth cohort from New York State (excluding New York City) born between 2008 and 2010. The cohort was originally designed to evaluate the long-term impact of infertility treatment on child development.[17] Infants who were conceived by infertility treatment, as indicated on their birth certificate, were frequency-matched based on region of residence and plurality to a random sample of infants conceived without infertility treatment at a 1:3 ratio (total n=18,479). Participants were recruited by mail at approximately 4-month post-partum. Mothers of all multiple births (twins, triplets, etc.) were invited to participate regardless of mode of conception. The original cohort enrolled 6,171 infants whose mothers agreed to participate, including 3,905 singletons, 2,312 twins, and 134 higher order multiples.[17] Higher order births were excluded from the present study due to small numbers. Our analyses include all singleton and twin births who had geocodable addresses and had at least one measurement of early development during the study period (n=5,825). The study was approved by Institutional Review Boards from all involved institutions. All participants provided written informed consent.

Exposure Assessment.

Proximity to major roadways was calculated by first overlaying geocoded Upstate KIDS addresses on the roadway network dataset made available by the New York State

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Department of Transportation (NYSDOT, https://www.dot.ny.gov/tdv). The roadway network locations monitored between 2007 and 2013 were used to calculate the Euclidean distance from each address to the nearest major roadway (major interstate, US and state highways, excluding local, neighborhood or rural roads).

Air pollution exposures were estimated using the Environmental Protection Agency's Downscaler model (available at: https://www.epa.gov/air-research/downscaler-model-predicting-daily-air-pollution). A detailed description of this model has been previously published.[18] Briefly, the Downscaler model estimates census-track level daily concentrations of $PM_{2.5}$ and ozone at the census-tract level using inputs from multiple sources including observed data from local air monitors, meteorological factors, local emission as well as photochemical properties of the pollutants. To assign prenatal air pollution exposures, residential addresses and maternal work location(s) during pregnancy for each participant were geocoded and spatiotemporally linked with the Downscaler outputs. Exposures for each mother/child pair or triad were assigned as the average daily concentrations of air pollutants within the census tract in which they lived/worked across several exposure time windows of interest: each trimester and whole pregnancy. Postnatal exposures were calculated as time-varying daily average concentrations of each pollutant from date of delivery through follow-up assessment to ensure that exposures preceded the outcome. For example, in analyses for outcomes assessed at 24 months postpartum, only exposures before this period were used.

Many previous studies on this topic do not account for residential mobility or daily activity patterns (e.g., work location) which may introduce exposure misclassification given many pregnant woman work outside the home and up to 32% relocate during pregnancy[19]. Our exposure assessment accounts for residential history and maternal work location(s). Specifically, exposures during a specific time window were an average based on all addresses in which participants lived or worked during that window. For postnatal exposure, the child's daycare address was also used when available. An address that was not updated at a given visit was assumed to be unchanged.

Outcome Assessment.

The developmental outcomes of interest include fine motor, gross motor, communication, personal-social functioning, and problem-solving ability. In Upstate KIDS, these outcomes were assessed using the Ages and Stages Questionnaire (ASQ), which is a validated developmental screening instrument recommended for early identification of developmental delays.[20] Parents completed the ASQ at 8, 12, 18, 24, 30, and 36 months of age, corrected for gestational age. Each domain listed above contained 6 items, each of which was scored from 0 to 10 with 0 corresponding to "not yet", 5 as "sometimes", and 10 as "yes", giving a sum ranging from 0 to 60 points for each domain. These scores were used to determine whether a child failed any of the domains (binary outcome), which was defined as scores 2 standard deviations below the means from age-specific reference of over 15,000 U.S. children established by the makers of the ASQ.[21]

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Effect modifiers and covariates.

Given the known oxidative stress effects of air pollution, and that male fetus are more vulnerable to this mechanism, we assessed fetal sex and prenatal multivitamin intake as potential effect modifiers[22,23] Covariates of interest included maternal age, maternal education, maternal race/ethnicity, history of smoking, pregnancy alcohol consumption, previous live birth, plurality, gestational age, birthweight, season of conception, insurance status, gestational hypertension, gestational diabetes, and fertility treatment. These variables are obtained from birth certificate or questionnaire. Average annual daily traffic was also obtained from NYSDOT to account for traffic density in the analysis of residential proximity to the nearest road.

Statistical analyses.

Generalized mixed models estimated the relative risk (RR) and 95% confidence intervals (CI) for the associations between exposure levels during each exposure window and the risk of failing the overall ASQ screening or any of the domains up to 3 years of age. Higher order terms for air pollution were not significant and linearity assumptions were met so we assumed a linear relationship and obtained effect estimates for each 10 unit increase in exposure for ozone and $PM_{2.5}$. A separate model was used to determine the RR and 95% CI for living <50, 50–100, 100–500, and 500–1000 m away from a major roadway (reference: >1000m). All models included an infant-level random intercept to account for repeated measures of infants, and a mother-level random intercept to account for the twins/siblings within the same mother. Models for air pollution also include time-varying exposures and can be described as follows:

$$Log\left(Y_{ijk}\right) = \beta_0 + \beta_1 \text{covariates}_{ijk} + \delta^1_{j(k)} + \delta^2_k + \varepsilon_{ijk}$$

where i represents time, j represents infant, and k represents mother, and the random effects ε_{ijk}, $\delta^1_{j(k)}$ and δ^2_k are assumed to be uncorrelated and having the following distributions:

$$\varepsilon_{ijk} \sim N\left(0, \varphi_1\right); \quad \delta^1_{j(k)} \sim N\left(0, \varphi_2\right); \quad \delta^2_k \sim N\left(0, \varphi_3\right)$$

An interaction term was created between the air pollutants and infant sex and prenatal multivitamin intake; however, none was statistically significant, so only main effects were reported. For postnatal exposure, we also tested for potential interaction with gestational complication, low birthweight, and preterm birth but none was significant. Sampling weights accounting for the study design were applied to all analyses.[24] Analyses were adjusted for covariates previously mentioned and exposure during other sensitive windows (i.e., prenatal analyses were adjusted for postnatal exposure and vice versa). However, due to moderate to high correlation between prenatal and postnatal exposures, we also ran the models without adjustment and results remained relatively unchanged.

Analyses were performed for all births, and separately for singleton and twin births. Two-pollutant models were also applied to assess robustness of findings. In addition, we

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conducted sensitivity analyses where we restricted our sample to families who did not relocate during the study period (n=1,971). All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $\alpha<0.01$ to account for multiple comparisons in the air pollutant analyses, and $\alpha<0.05$ for the distance to highway analyses.

RESULTS

The final analyses included 4,809 (82.6%) singletons and 1,016 (17.4%) twins (Table 1). The proportion of children failing any ASQ screening was 22.8% (n=1329). The average birthweight and gestational age (including twins) were 3,046.8 grams (SD: 731.4), and 37.6 weeks (SD 2.7). Most were conceived during the spring or summer, had mothers who were on average 30.6 years old, non-Hispanic White, had some college education or advanced degree, had private insurance, were married, and used daily multivitamins during pregnancy. The majority lived 100–500 meters away from a major roadway. The distributions of air pollutants during each exposure window, and their correlations are presented in Supplemental Tables 1 and 2, respectively. The average concentrations of $PM_{2.5}$ and ozone during the prenatal period were 9.7 $\mu g/m^3$ (SD: 2.0) and 36.2 ppb (SD: 3.9), respectively. In general, $PM_{2.5}$ and ozone were either inversely or weakly correlated with Spearman's correlation coefficients ranging from -0.56 to 0.12. Characteristics of participants by distance from major roadways are also provided in Supplemental Table 3.

Compared to those living >1000m away from a major roadway, those who lived 50–100m and 100–500m away had more than twice the risk of failing the communication domain after adjusting for important covariates (Table 2). The direction of association was generally consistent for all other developmental domains but these did not reach statistical significance perhaps due to small cell size. Analyses restricted to participants who did not relocate yielded similar effect estimates (Supplemental Table 4).

There were weak but significant associations between prenatal exposures to both pollutants and failing screening for some, but not all, developmental domains (Figure 1, Supplemental Table 5). A 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure during trimesters 1 and 3 was associated with a 1.6% (0.1%-3.2%) and 2.7% (0.6%-4.9%) increased risk of failing the overall developmental screening, respectively. Likewise, a 10ppb increase in ozone exposure during trimester 2 and the whole pregnancy was associated with 0.7% (0.1%-1.4%) and 1.7% (0.6%-2.9%) increased risk for failing any domain. The associations varied for specific domains where we observed slightly positive associations between $PM_{2.5}$ and failure of the communication and problem-solving domains, and between ozone exposures and failing fine motor and personal social domains. It is also important to note that a slightly inverse association was observed for trimester 2 $PM_{2.5}$ exposure and fine motor development [-0.2% (-0.9%--0.4%)].

Postnatal ozone exposures appear to have consistent positive associations with failing the overall ASQ as well as specific domains (Figure 2, Supplemental Table 6). For example, average daily postnatal ozone exposure was positively associated with failing the overall screening by 8 months [3.3% (1.1%-5.5%) increased risk for 10 ppb increase], 24 months

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[17.7% (10.4%-25.5%)], and 30 months [7.6% (1.3%-14.3%)]. In general, the associations were strongest for failing screening by 24 months. For $PM_{2.5}$, the associations were mixed. Positive associations were observed for failing the communication domain at 24 months, personal-social domain from months 8 to 18, and problem-solving domain at 18 months. However, inverse associations were also observed for overall screening at 12 months, gross motor at 24 and 36 months, personal-social at 30 and 36 months, and problem solving 8, 12, and 36 months. We also performed additional analyses where we removed gestational complications, birthweight, and gestational age as covariates as these may be potential mediators in the prenatal models and may not be confounder in the postnatal models. The results remained consistent (Supplemental Tables 5 and 6).

Analyses stratified by plurality (Supplemental Tables 7 and 8) and co-pollutant models (Supplemental Tables 9 and 10) were generally consistent for both prenatal and postnatal exposures. Restricted analyses among participants who did not relocate also produced consistent results, but some associations became stronger (than not excluding them) for postnatal exposures (Supplemental Tables 11 and 12).

DISCUSSION

We found that living closer to a major roadway during pregnancy or early life increased the risk of delayed childhood development although some of our estimates had wide confidence intervals due to the relatively small number of children failing developmental screening in our population-based sample. Proximity to major roadways exposes people to elevated concentrations of air and noise pollution caused by traffic, which have been found to affect health.[25] Although studies on residential proximity to major roadway and childhood development are still scarce, our findings are consistent with existing reports. A prospective cohort study in Massachusetts, USA, found that compared with children living ≥200 m from a major roadway at birth, those living <50 m away had lower nonverbal IQ, verbal IQ, and visual motor abilities.[15] The Childhood Autism Risks from Genetics and the Environment study, a population-based case–control study of preschool children, also found that children within 309 m from a major freeway had 86% increased risk of autism compared to their counterparts.[14] Several other studies also found that people living closer to major roadways have elevated risk of adverse pregnancy outcomes[26] and many other neurodevelopmental outcomes such as autism spectrum disorders, global IQ,[27] and cognitive functions among adults.[28]

Prenatal exposures appeared to have positive associations with the risk of failing developmental screening, but the magnitude of the associations was weak. The literature on neurodevelopmental effects of these air pollutants is mixed with some showing positive associations[29,30] and some no association.[15] These differences are likely due to heterogeneity between study attributes. In particular, $PM_{2.5}$ is a mixture comprised of many constituents whose contribution to total $PM_{2.5}$ may vary geographically depending on specific sources.[31] Our study takes place in Upstate New York, a region with relatively low air pollution.[32] The $PM_{2.5}$ concentrations studied reflected this relatively small range of exposure during the study period. The lack of variability may explain the weak association with prenatal exposures, but the findings also merit attention since we still see evidence of

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some effect even in an area with low levels of pollution. Looking at potential sensitive exposure windows, it appears that the effects from exposure during the entire pregnancy are more consistent, suggesting that chronic exposure may be important and merits attention. For $PM_{2.5}$, exposures during the third trimester may be more implicated, which is consistent with the literature.[27] This window is also commonly explored in the literature given the relatively rapid neurodevelopment during this part of pregnancy. We also note that we could have underestimated the effects of air pollutants if the critical windows of exposure are narrower than those we explored.

Postnatal exposures to ozone had stronger positive associations while $PM_{2.5}$ showed some mixed effects. The effects of ozone on neurodevelopmental outcomes are less explored compared to $PM_{2.5}$ in the literature but our findings are generally consistent with previous findings.[27] Although we did not find any pattern of association suggesting that one developmental domain is more affected than others, we observed that postnatal exposure to ozone had the strongest effects for developmental delay at 2 years of age. It is important to note here that some kids drop out of the study at various time, so our analyses at each time point do not necessarily include the same group of kids. On the other hand, the reason for increased risk at 2 years is not clear but it could be speculated that kids around this age start to play outdoors more often and thus are more affected. We also note here that the daily exposure ranges for ozone and $PM_{2.5}$ during our study period was relatively small (i.e., 9.6 to 77.0 ppb, and 2.2 to 35.5 $\mu g/m^3$, respectively), and their average concentrations (36.0 ppb and 10.2 $\mu g/m^3$) were below the federal standards (i.e., 70.0 ppb and 35.0 $\mu g/m^3$, respectively). Our findings for $PM_{2.5}$ demonstrate no consistent negative effect on development with some measures showing a protective association, including a lower risk of overall screening failure at 12 months. In contrast, ozone exposures were associated with significant increase in developmental screening failures in all domains at some point in infancy/childhood including an overall risk of screening failure at 8, 24 and 30 months. At 24 months, ozone was also associated with developmental screening fails for the communication, fine and gross motor, and problem-solving domains. This consistent evidence of neurodevelopmental effects of ozone even at moderate levels of air pollution merits further attention. Given the findings were consistent with and without adjustment for gestational complications, gestational age, and birthweight, air pollution appears to affect development independent of these characteristics.

The biologic mechanisms linking air pollution and brain development remain unclear. Considering the evidence on the effects of air pollution on cardiorespiratory health, inflammation and oxidative stress are likely mechanisms through which air pollution can interfere with neurodevelopment[33]. Air pollutants can invade deep in the lungs and trigger oxidative stress, which in turn causes systemic inflammation.[34] Circulating markers (e.g., cytokines) can pass the maternal-fetal blood barrier and ultimately perturb *in utero* fetal neurodevelopment.[35,36] Postnatal exposure to fine and ultrafine particulate matter can also affect the CNS through direct translocation along the olfactory nerve into the olfactory bulb, or direct diffusion of induced oxidative stress and inflammatory markers across the impaired blood brain barrier.[37–39] Once pollutants enter the CNS, they can directly affect it through activation of innate immune cells such as microglia.[40] Neuropathological changes caused by air pollution have been reported by animal and human studies.[41] The mixed findings

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between postnatal exposure to $PM_{2.5}$ and childhood developmental outcome do not consistently support these biologic mechanisms; however, as previously discussed, $PM_{2.5}$ is comprised of many constituents whose proportion vary across geographic sites. Since we do not have comprehensive data on $PM_{2.5}$ constituents which provide geographic coverage for the study area, we recommend that future studies explore these associations. The reason for the stronger associations with postnatal exposure is unclear and warrants further investigation. However, we speculate that postnatal exposure affects children in a more direct manner compared to prenatal exposure since it is not subject to maternal defense. Secondly, the postnatal period is also a time with rapid neurodevelopment while the immune system is not fully developed, making it a particularly vulnerable window for environmental insults.

This study has several limitations. We did not have personal monitoring data or daily activity patterns from the participants, which could introduce some non-differential misclassification bias towards the null. Since the Downscaler models only predict $PM_{2.5}$ and ozone concentrations, we were unable to analyze other pollutants. Furthermore, although we attempted to control for traffic density by including average annual daily traffic as a covariate but were unable to account for traffic type. Lastly, although it is unlikely that air pollution exposure during pregnancy and after delivery would have been causally related to maternal intelligence, we did not have data on maternal intelligence to explore. Despite limitations, this study has many strengths. First, our population-based, prospective design allows us to establish temporality and to assess incident outcomes. Second, the longitudinal follow-up allowed us to collect residential history as well as location information on work and daycare addresses, which improved the accuracy of our exposure assessment. Finally, although the main outcome of interest is completed by parents, the instrument has been well-validated and has been shown to predict clinical developmental delays.[20,42,43]

CONCLUSION

In summary, proximity to major roadways as well as pre- and postnatal exposures to common air pollutants may increase the risk of developmental delays. It appears that postnatal exposures were more important. Air pollution and roadway emissions are potentially modifiable risks for developmental delay and our findings suggest that these associations are present even at levels of exposure below current regulatory standards. Meanwhile, there is a need for larger prospective studies with detailed personal assessment of air pollution exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Proximity to major roadway appears to affect early childhood development
- Prenatal and early-life exposures to fine particles and ozone are also related to risk
- The role of postnatal exposure to ozone seems to be more consistent.

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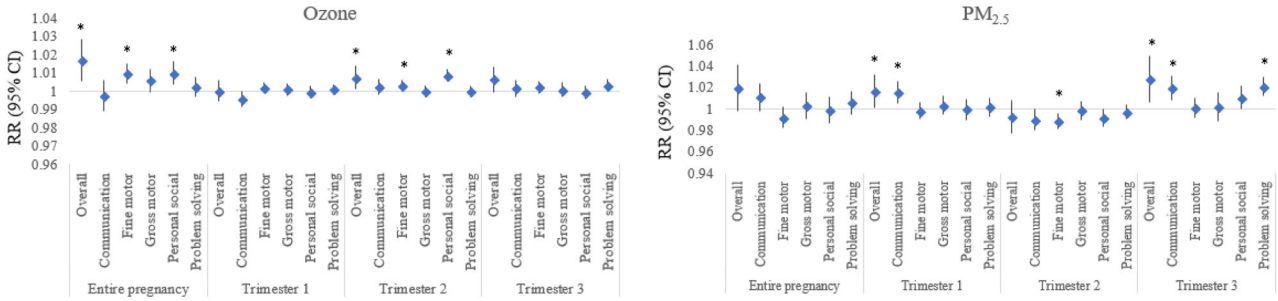

Figure 1.

Associations between prenatal exposures to air pollutants and failure of developmental screening by age 3

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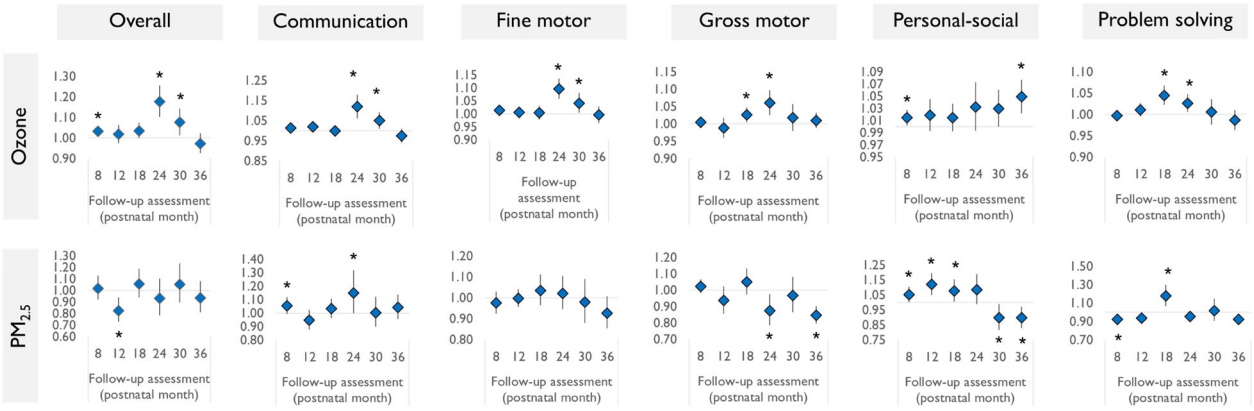

Figure 2.

Associations between postnatal exposures (time varying daily average from date of delivery to follow-up assessment) to air pollutants and failure of developmental screening by age 3

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Table 1.

Characteristics of study infants (n=5,825)

Characteristics	N	%
Maternal age (year, mean, SD)	30.6	6.0
Maternal race/ethnicity		
Non-Hispanic White	4699	80.7
Non-Hispanic Black	284	4.9
Asian	153	2.6
Hispanic	335	5.8
Mixed race or ethnicity / Other	354	6.1
Maternal education		
Less than high school	343	5.9
HS or GED equivalent	730	12.5
Some college	1738	29.8
College	1321	22.7
Advanced degree	1693	29.1
Private Insurance	4416	75.8
Married	4915	84.4
Nulliparous	2634	45.2
Any alcohol during pregnancy	689	11.8
Smoked during pregnancy	796	13.7
Gestational diabetes	560	9.6
Gestational hypertension	356	6.1
Daily pregnancy multivitamin use	4253	73.0
Birthweight (grams, mean, SD)		
Overall	3047	731
Singletons	3325	522
Gestational age (weeks, mean, SD)		
Overall	37.6	2.7
Singletons	39.0	1.2
Plurality		
Singleton	4809	82.6
Twin	1016	17.4
Season of conception		
Spring (March-May)	1679	28.8
Summer (July-August)	1622	27.9
Fall (September-November)	1062	18.2
Winter (December-February)	1461	25.1
Any ASQ failure within the first 3 years		
Overall	1329	22.8

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Characteristics	N	%
Fine motor	521	8.9
Gross motor	525	9.0
Communication	600	10.3
Personal social	567	9.7
Problem solving	472	8.1
Distance from major roadway (meter)		
<50	745	12.8
50–100	890	15.3
100–500	3,321	57.0
500–1000	588	10.1
>1000	280	4.8

Abbreviations: ASQ, Ages and Stages Questionnaires; GED, general education diploma; HS, high school; SD, standard deviation;

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Table 2.

Associations between distance to major roadway and failure of childhood developmental milestone by 3 years of age

	Any domain		Fine motor		Gross motor		Communication		Personal-social		Problem solving	
Distance (meter)	**n**	**Adjusted[a] RR (95% CI)**	**n**	**Adjusted[a] RR (95% CI)**	**n**	**Adjusted[a] RR (95% CI)**	**n**	**Adjusted[a] RR (95% CI)**	**n**	**Adjusted[a] RR (95% CI)**	**n**	**Adjusted[a] RR (95% CI)**
<50	182	1.18(0.75,1.86)	68	1.56(0.74,3.29)	75	1.19(0.60,2.38)	82	1.74(0.80,3.77)	78	2.05(0.96,4.37)	60	1.32(0.61,2.86)
50–100	204	1.20(0.77,1.86)	75	1.60(0.78,3.27)	80	0.88(0.44,1.77)	101	2.12(1.00,4.52) *	93	1.87(0.88,3.98)	72	1.41(0.69,2.89)
100–500	760	1.16(0.76,1.75)	316	1.66(0.86,3.22)	300	0.84(0.46,1.54)	337	2.07(1.02,4.22) *	318	1.73(0.84,3.53)	281	1.50(0.77,2.92)
500–1000	125	1.16(0.72,1.88)	46	1.46(0.59,3.60)	45	0.94(0.41,2.18)	58	2.07(0.93,4.62)	57	1.57(0.70,3.52)	40	0.89(0.37,2.15)
>1000	58	Reference	16	Reference	25	Reference	22	Reference	21	Reference	19	Reference

Abbreviations: CI, confidence intervals; RR, relative risk

[a]Adjusted for maternal age, maternal education, maternal race/ethnicity, maternal smoking, pregnancy alcohol consumption, insurance status, plurality, gestational complications, gestational age, birthweight, season of conception, average annual daily traffic, and fertility treatment status.

*Indicates significance at $\alpha<0.05$