Air pollution, neighborhood deprivation, and autism spectrum disorder in the Study to Explore Early Development

Laura A. McGuinn[a,b*], Gayle C. Windham[c], Lynne C. Messer[d], Qian Di[e], Joel Schwartz[e], Lisa A. Croen[f], Eric J. Moody[g], Ana G. Rappold[h], David B. Richardson[b], Lucas M. Neas[h], Marilie D. Gammon[b], Laura A. Schieve[i], Julie L. Daniels[b]

Background: To examine whether neighborhood deprivation modifies the association between early life air pollution exposure and autism spectrum disorder (ASD), we used resources from a multisite case–control study, the Study to Explore Early Development.
Methods: Cases were 674 children with confirmed ASD born in 2003–2006; controls were 855 randomly sampled children born during the same time period and residents of the same geographic areas as cases. Air pollution was assessed by roadway proximity and particulate matter <2.5 µm ($PM_{2.5}$) exposure during pregnancy and first year of life. To characterize neighborhood deprivation, an index was created based on eight census tract-level socioeconomic status-related parameters. The continuous index was categorized into tertiles, representing low, moderate, and high deprivation. Logistic regression was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs).
Results: Neighborhood deprivation modified ($P_{for\ interaction}$ = 0.08) the association between $PM_{2.5}$ exposure during the first year of life and ASD, with a stronger association for those living in high (OR = 2.42, 95% CI = 1.20, 4.86) rather than moderate (OR=1.21, 95% CI = 0.67, 2.17) or low (OR=1.46, 95% CI = 0.80, 2.65) deprivation neighborhoods. Departure from additivity or multiplicativity was not observed for roadway proximity or exposures during pregnancy.
Conclusion: These results provide suggestive evidence of interaction between neighborhood deprivation and $PM_{2.5}$ exposure during the first year of life in association with ASD.

Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders marked by impairments in social interaction and communication, and repetitive behaviors.[1] ASD is a highly heterogeneous condition, with multiple underlying causes, including genetic and environmental factors.[2] Additionally, strong evidence exists for a prenatal and early postnatal window of susceptibility for ASD risk.[3–5] Several epidemiologic studies have reported associations between prenatal and early postnatal air pollution exposure and ASD,[6] specifically for particulate matter <2.5 µm in diameter ($PM_{2.5}$)[7,8] and other measures of traffic-related air pollution.[9] Early life air pollution exposure may increase risk of ASD through an inflammatory response pathway impacting brain development.[10]

Maternal stress has also been hypothesized to alter inflammatory response[11] and has been associated with ASD in a few previous studies.[12–14] Factors at the neighborhood level, such as crime and poverty, have been implicated as social stressors in previous studies,[15,16] with one study finding associations between neighborhood level stressors and cortisol reactivity among women.[17] Environmental toxicants, such as air pollution, and social stressors are often spatially correlated, and in general, both of these exposures tend to cluster in more deprived areas.[18–20] Given this relationship, individual and area level socioeconomic status (SES) may confound the association between air pollution and ASD, but air pollution and area level SES may

[a]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, New York; [b]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [c]California Department of Public Health, Environmental Health Investigations Branch, Richmond, California; [d]School of Community Health, College of Urban and Public Affairs, Portland State University, Portland, Oregon; [e]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Department of Environmental Health, Boston, Massachusetts; [f]Division of Research, Kaiser Permanente, Oakland, California; [g]Wyoming Institute for Disabilities, University of Wyoming, Laramie, Wyoming; [h]National Health and Environmental Effects Research Laboratory, Environmental Public Health Division, U.S. Environmental Protection Agency, Chapel Hill, North Carolina; and [i]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

*Corresponding author. Address: Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1057, New York, NY 10029. E-mail Address: laura.mcguinn@mssm. edu (L.A. McGuinn).The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the Centers for Disease Control and Prevention or the US Environmental Protection Agency (EPA). Any mention of trade names, products, or services does not imply an endorsement by the US Government or the US Environmental Protection Agency. The EPA does not endorse any commercial products, services, or enterprises.

What this study adds

Previous studies have identified associations between air pollution exposure and ASD; however, the extent to which neighborhood deprivation modifies these associations remains largely unknown. In order to address this limitation, we investigated the modifying role of neighborhood deprivation on the association between early life air pollution exposure and ASD using data from the Study to Explore Early Development. The findings from our study showed that neighborhood deprivation modified the association between $PM_{2.5}$ exposure during the first year of life and ASD, with a stronger association for those living in high rather than low/moderate deprivation neighborhoods.

also have synergistic effects on ASD development, working through a shared inflammatory pathway.

Neighborhood deprivation is a multi-component measure of area level SES[21] that has been used in previous epidemiological studies to evaluate the impact of stressors at the neighborhood level on air pollution and health associations.[22,23] There are several plausible pathways for air pollution and neighborhood deprivation to contribute to health outcomes. Morello-Frosch and Shenassa[24] theorized that stressors at the neighborhood level can contribute to individual chronic stress, which can influence individual susceptibility, and this stress-induced susceptibility can shape response to environmental exposures. Using this framework, we hypothesize that chronic stress from neighborhood deprivation could influence individual susceptibility by impairing the body's ability to maintain allostasis, leading to compromised immune function and, ultimately, shaping maternal and infant responses to air pollution exposure.[18,25]

The goal of the current study was to investigate the modifying role of neighborhood deprivation on the association between prenatal and postnatal roadway proximity and $PM_{2.5}$ exposure and ASD using data from the Study to Explore Early Development (SEED).

Methods

Study Population

Details of the recruitment and enrollment processes, and data-collection components for SEED, have been reported elsewhere.[26] Briefly, the SEED catchment area includes six geographically diverse sites across the United States within California, Colorado, Georgia, North Carolina, Pennsylvania, and Maryland (eTable 1; http://links.lww.com/EE/A60). Individuals were eligible to participate in SEED if they were born in a study catchment area between September 1, 2003 and August 31, 2006, still resided there at 30–68 months of age,[26] and lived with an English (all sites) or Spanish (California and Colorado sites) speaking caregiver. Children with possible ASD were ascertained through multiple sources serving or evaluating children with developmental problems. Population controls were identified from a random sample of state birth records within a site's catchment area. Institutional review boards at each study site and at the Centers for Disease Control and Prevention approved the SEED study. Informed consent was obtained from all enrolled participants.

Outcome Ascertainment

The Social Communication Questionnaire was administered to the caregivers of both cases and controls as an initial autism symptom screening tool.[27] Any child who had a positive Social Communication Questionnaire screen of above 11 or previous ASD diagnosis received a comprehensive developmental assessment to determine final ASD classification. Controls were moved to the autism workflow if they scored ≥11 on the Social Communication Questionnaire or if suspected of autism during the clinical exam. Potential ASD cases were administered the Autism Diagnostic Observation Schedule,[28] and their caregivers were administered the Autism Diagnostic Interview-Revised.[29,30] Final ASD case classification was based on the results from the Autism Diagnostic Observation Schedule and Autism Diagnostic Interview-Revised.[30] Children who did not have an indication of possible ASD (negative Social Communication Questionnaire screen, no previous ASD diagnosis, and no ASD-specific service classification) received a general developmental assessment only.

Exposure Assessment

Each participant's date of birth and residential address at birth was obtained from electronic birth certificates. Birth addresses were geocoded in ArcGIS using the ESRI StreetMap database.[31] Geocoding match rates ranged from 95% to 100% across study sites.

Start date of pregnancy was calculated by subtracting the clinical estimate of the child's gestational age, recorded on the birth certificate, from the child's date of birth. To ensure the privacy of all participants, all dates related to the date of birth were randomly shifted—in a manner maintaining the relationship between dates—by up to 2 weeks in either direction.

Roadway proximity was used to capture the mixture of chemicals from traffic-related air pollution. Road networks for the entire United States were obtained from ESRI StreetMap. US major roads include national and state highways, major streets, and other major thoroughfares within the US. Local residential roads were not included in this assessment. Each participant's address at birth was matched to the nearest major road/highway using ArcGIS to calculate an individual distance measure (in meters).[31] Distance to major roadway was dichotomized at the 10th percentile level in controls (<45m vs. ≥45m).

We used a previously developed exposure prediction model to characterize $PM_{2.5}$ exposure for the study period years (2002–2007).[32] Briefly, the hybrid prediction model incorporated satellite-based aerosol optical depth measurements, simulated outputs from a chemical transport model, monitored data, land use terms, and meteorological variables. The model used a neural network to calibrate the predictors to monitored $PM_{2.5}$ and was trained and validated with ten-fold cross-validation. Predictions were available at a daily temporal resolution and a 1×1 km spatial resolution. Participants were matched to the centroid of the nearest grid cell based on their residence at birth. Exposure averages were created for the entire pregnancy period and the year post birth. $PM_{2.5}$ exposure during pregnancy and first year of life was modeled continuously, and also was dichotomized at the $PM_{2.5}$ National Ambient Air Quality Standard level of 12.0 µg/m³ (≥12.0 µg/m³ vs. <12.0 µg/m³).

Neighborhood Deprivation

Neighborhood level deprivation was characterized using a neighborhood deprivation index (NDI) measure developed by Messer et al.[33] This index has previously been used to describe relationships between neighborhood deprivation and several pregnancy outcomes, including low birth weight, small for gestational age, and preterm birth.[34–36] To create the index, eight area-level SES-related parameters were obtained from the 2000 US Census at the census tract level: percentage of males and females with less than a high school education; percentage of males and females unemployed; percentage of households defined as crowded (housing units with more than one occupant per room); percentage of males that are not in management and professional occupations; percentage of households in poverty; percentage of female-headed households with dependent children; percentage of households earning <$30,000 per year; and percentage of households on public assistance (eTable 2; http://links.lww.com/EE/A60, for a detailed description of these measures).

To create the weighted NDI, tract-level data from all six study sites were pooled and the data reduction technique principal components analysis was used; to represent the correlation between the components, the eight area-level SES parameters were used as the loadings.[37] The first principal component was retained because it accounted for the largest proportion of the total variability in the component measures. SES-related variable values were weighted according to final factor loadings to create a continuous index score for each census tract. The index score was standardized by dividing the index by the square of the eigenvalue, resulting in a deprivation index with a mean of zero and an SD of one. Higher values of the NDI indicate higher

levels of neighborhood disadvantage. Census tracts of the SEED study areas were categorized as having high, moderate, or low deprivation based on tertile cut points of the continuous index. The deprivation index was then linked to SEED participants based on the birth residence census tract.

Confounders

Information to assess potential confounders was obtained from a caregiver interview, medical records, and birth certificates. A directed acyclic graph was used to identify the covariate set to be included in the model that would result in the least biased estimate. The final adjustment set consisted of the following variables: study site, year of birth, month of birth (as a proxy for season of birth), maternal age (continuous), maternal race/ethnicity (non-Hispanic-white, other race/ethnicity), maternal education (<bachelor's degree, ≥bachelor's degree), and maternal smoking (any smoking 3 months before conception or during pregnancy).

Statistical Analyses

Multivariable logistic regression was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the associations between roadway proximity, $PM_{2.5}$, and ASD, with the population group serving as the control group for all analyses. We first report results for the main associations of each of the exposures in relation to ASD.

Effect measure modification by neighborhood deprivation was first evaluated on the multiplicative scale for continuous measures of $PM_{2.5}$ exposure and categorized measures of distance to roadway (<45m vs. ≥45m) and $PM_{2.5}$ exposure (≥12.0 vs. <12.0 µg/m³). We assessed departure from multiplicativity by including an interaction term between the deprivation index and exposure metrics and compared models with and without interaction terms. Multiplicative interaction was assessed using the likelihood ratio test, with a significance level of 0.10. We additionally evaluated effect measure modification on the additive scale by constructing single-referent models for each of the categorized exposures and computed the relative excess risk due to interaction (RERI) for each exposure.[38] Corresponding 95% CIs were calculated using the delta method.[39] The RERI measure indicates whether there is positive, negative, or no interaction on the additive scale.[38]

Results

Case–control characteristics of the SEED study population, stratified by neighborhood deprivation level, are presented in Table 1. Overall, compared with controls, children with ASD were more likely to be boys, born preterm, and born to non-white, lower educated mothers. In our study population, 187 cases (28%) and 159 controls (19%) were categorized as residing at birth in a highly deprived census tract. Compared to those in the lowest deprivation group, controls in the high deprivation group were more likely to be non-white and to have mothers with lower educations and lower incomes. Their mothers were also more likely to report tobacco use during pregnancy.

$PM_{2.5}$ averages in controls during the pregancy period were 13.3 µg/m³ in the highest deprivation group and 12.6 and 12.4 µg/m³ in the moderate and low deprivation groups, respectively. Those in the highest deprivation group were additionally more

Table 1

Distribution of participant characteristics [n (%)] in SEED by case-control status and neighborhood deprivation level

Characteristic	Low deprivation		Moderate deprivation		High deprivation	
	ASD Case	Control	ASD Case	Control	ASD Case	Control
Total	252 (37)	427 (50)	235 (35)	269 (31)	187 (28)	159 (19)
Sex						
Male	203 (81)	228 (53)	194 (83)	150 (56)	154 (82)	75 (47)
Female	49 (19)	199 (47)	41 (17)	119 (44)	33 (18)	84 (53)
Maternal race/ethnicity						
Non-Hispanic white	190 (75)	364 (85)	142 (60)	182 (68)	46 (25)	65 (41)
Other[a]	62 (25)	63 (15)	93 (40)	87 (32)	141 (75)	94 (59)
Maternal education						
<Bachelor's	76 (30)	84 (20)	112 (48)	105 (39)	143 (76)	100 (63)
≥Bachelor's	176 (70)	343 (80)	123 (52)	164 (61)	44 (24)	59 (37)
Maternal income						
<$50,000	38 (15)	46 (11)	94 (41)	74 (28)	123 (72)	94 (61)
≥$50,000	210 (85)	369 (89)	133 (59)	191 (72)	49 (28)	60 (39)
Maternal age at delivery						
<35 years	165 (65)	262 (61)	177 (75)	194 (72)	144 (77)	133 (84)
≥35	87 (35)	165 (39)	58 (25)	75 (28)	43 (23)	26 (16)
Maternal smoking						
Yes	24 (10)	27 (6)	47 (20)	25 (9)	41 (22)	27 (17)
No	228 (90)	400 (94)	188 (80)	244 (91)	146 (78)	132 (83)
Preterm						
Yes	37 (15)	39 (9)	37 (16)	21 (8)	37 (20)	22 (14)
No	215 (85)	388 (91)	198 (84)	248 (92)	150 (80)	137 (86)
SEED study site						
California	27 (11)	58 (14)	44 (19)	51 (19)	25 (13)	25 (16)
Colorado	65 (26)	99 (23)	46 (20)	52 (19)	28 (15)	34 (21)
Georgia	53 (21)	73 (17)	34 (14)	46 (17)	43 (23)	41 (26)
Maryland	39 (15)	70 (16)	46 (20)	41 (15)	22 (12)	15 (9)
North Carolina	38 (15)	65 (15)	43 (18)	55 (20)	19 (10)	26 (16)
Pennsylvania	30 (12)	62 (15)	22 (9)	24 (9)	50 (27)	18 (11)
$PM_{2.5}$ pregnancy mean (SD)	12.4 (2.9)	12.4 (2.7)	12.5 (2.5)	12.6 (2.4)	13.5 (2.5)	13.3 (2.6)
Distance to major road (meters) mean (SD)	404 (420)	458 (595)	386 (556)	423 (564)	264 (284)	247 (338)

[a]Includes African American, Asian, Hispanic, and multiracial.

likely to live closer to a major road/highway. $PM_{2.5}$ levels additionally varied across study sites, ranging from a mean of 8.7 μg/m^3 among participants from the Colorado study site, to 15.5 μg/m^3 for participants from the Georgia study site (eTable 3; http://links.lww.com/EE/A60). Finally, deprivation levels additionally ranged across study sites (eTable 4; http://links.lww.com/EE/A60). The Pennsylvania study site had a higher percentage of participants that lived in more deprived census tracts, while the Colorado, Georgia, and Maryland study sites had a higher percentage that lived in less deprived census tracts.

There was moderate variability in the census indicators by study site (eTable 5; http://links.lww.com/EE/A60). Participants from the Colorado and North Carolina study sites tended to live in census tracts of higher SES compared with those from the Georgia and Pennsylvania sites. For example, SEED participants from the Pennsylvania study site resided in census tracts with a greater percentage of households in poverty (9.9%), compared with those from the Colorado study site (4.9%). Continuous deprivation index levels of SEED participants also varied by study site (eTable 5; http://links.lww.com/EE/A60). Mean neighborhood deprivation of study participants varied by site, with a lower mean NDI for Colorado participants (mean: −0.35, range: −1.3 to 2.1) and higher deprivation for participants from the Pennsylvania study site (mean: 0.14, range: −1.2 to 4.3).

Childhood ASD was associated with $PM_{2.5}$ exposure in the first year of life when measured on a continuous scale (Table 2) (OR = 2.08 per 5-μg/m^3, 95% CI = 1.05, 4.10) and when considered as a dichotomous variable (OR = 1.46, 95% CI = 0.86, 2.46 for $PM_{2.5}$ levels >12.0 μg/m^3 in the first year of life compared with ≤12.0 μg/m^3), although CIs for dichotomized results included the null value. Residence at birth within 45 m of a major road was also associated with childhood ASD (OR = 1.21, 95% CI = 0.88, 1.68). There additionally appeared to be a slight inverse association for $PM_{2.5}$ exposure during pregnancy when exposures were dichotomized; however, CIs for both of these exposure metrics included the null value.

There was suggestive modification by neighborhood deprivation for the association between $PM_{2.5}$ during the first year of life and ASD on the additive (RERI: 0.81, 95% CI = −0.88, 2.47) and multiplicative ($P_{for\ interaction}$ = 0.08) scales when $PM_{2.5}$ was dichotomized at 12.0 μg/m^3 (Table 3). The association between $PM_{2.5}$ exposure and ASD was strongest in regions of high deprivation (OR = 2.42, 95% CI = 1.20, 4.86), compared with moderate (OR = 1.21, 95% CI = 0.67, 2.17) or low (OR = 1.46, 95% CI = 0.80, 2.65) deprivation groups (Table 3). Although there was no evidence of modification by neighborhood deprivation for the association between roadway proximity and ASD, there was some heterogeneity in this association by deprivation level. The association for living within 45 m of a major road was strongest for

those in the moderate deprivation group (OR = 1.65, 95% CI = 0.95, 2.86), compared with the low and high groups (Table 3). We did not observe any modification by neighborhood deprivation on the multiplicative scale when using continuous measures of $PM_{2.5}$ exposure (eTable 6; http://links.lww.com/EE/A60).

Discussion

We observed modification by neighborhood deprivation for the association between $PM_{2.5}$ exposure during the first year of life and ASD, with the strongest association observed for the joint effect between high neighborhood deprivation and $PM_{2.5}$ levels above 12.0 μg/m^3. Our study was the first US-based study to address the combined effect of neighborhood deprivation and air pollution on risk of ASD. One previous study in Sweden assessed the modifying role of neighborhood deprivation on air pollution and ASD associations and found no differences by level of deprivation.[40] The role of neighborhood deprivation may differ between the United States and Sweden, given the overall differences in access to healthcare and childcare between the two countries. Previous US-based epidemiological studies have shown that psychological stress and social disadvantage can modify air pollution and health associations,[23,41–44] with several showing synergistic effects of air pollution and social disadvantage in relation to pregnancy outcomes.[22,23]

We used distance to major roadway as a marker of the mixture of chemicals from traffic-related air pollution. Our cutoff for living in close proximity to a major road was based on the distribution in the controls (closest 10%), which is similar to the distribution in a previous study of roadway proximity and ASD.[45] Although mothers in the most deprived census tracts of our study were more likely to live in close proximity to a major road, we observed elevated odds of ASD in relation to roadway proximity only for those in the moderate deprivation group. Thus, modification by neighborhood deprivation differed for exposure to roadway proximity and exposure to $PM_{2.5}$ in the first year of life. The distance to roadway measure is a proxy for local traffic particles,[46] whereas $PM_{2.5}$ represents both local and regional transported particles,[47] thus differences in the results may be due to the difference in the two exposures.

Neighborhood deprivation may impact health outcomes in multiple ways. First, living in a deprived area may limit access to resources (e.g., healthcare, parks, and other places for physical activity). Alternatively, stressors at the neighborhood level could contribute to individual chronic stress. The hypotheses of our study were based on the second pathway, although it is plausible that living in a more deprived neighborhood could reduce access to healthcare, with particular implications for ascertainment of ASD. Neighborhood deprivation has been implicated as a social stressor in previous studies,[15,16] with one study finding associations between neighborhood deprivation and cortisol reactivity among women.[17] There are several theories relating the combined effects of social and environmental stressors to health outcomes. One in particular theorizes that stressors at the neighborhood level can contribute to individual chronic stress, which can influence individual susceptibility, and this stress-induced susceptibility can shape response to environmental exposures.[24] Using this framework, we hypothesized in our study that chronic stress from neighborhood deprivation could influence individual susceptibility and, ultimately, shape maternal and infant responses to air pollution exposure.

A synergistic association between air pollution and maternal stress in relation to disease development is biologically plausible given their potentially shared inflammatory pathway. Recent animal studies have investigated the combined effect of maternal stress and air pollution exposure on health outcomes in offspring. Findings in mice showed a combined effect of maternal stress during pregnancy and air pollution exposure on neuroinflammation, microglia activation, and neurobehavioral

Adjusted[a] ORs and 95% CIs for the association between proximity to roadway, $PM_{2.5}$ exposure, neighborhood deprivation, and ASD

	ASD (N)	Controls (N)	OR (95% CI)
Distance to major road			
>45 m	582	767	1.00 (ref)
≤45 m	92	88	1.21 (0.88, 1.68)
Pregnancy $PM_{2.5}$			
5-μg/m^3 increase	674	855	1.08 (0.67, 1.72)
≤12.0 μg/m^3	238	309	1.00 (ref)
>12.0 μg/m^3	436	546	0.83 (0.57, 1.20)
First year of life $PM_{2.5}$			
5-μg/m^3 increase	674	855	2.08 (1.05, 4.10)
≤12.0 μg/m^3	226	318	1.00 (ref)
>12.0 μg/m^3	448	537	1.46 (0.86, 2.46)

[a]All models are adjusted for study site, year of birth, month of birth, maternal education, maternal race/ethnicity, maternal age, and maternal smoking.

Adjusted[a] ORs and 95% CIs for the joint effects of neighborhood deprivation and proximity to roadway and $PM_{2.5}$ exposure in relation to ASD

NDI Levels	Exposure	ASD (N)	Controls (N)	Single referent ORs (95% CI)	RERI (95% CI)	Stratified ORs (95% CI)	LRT P
	Distance to major road						
Low	>45m	230	397	1.00 (ref)		1.00 (ref)	
	≤45m	22	30	1.19 (0.66, 2.14)		1.18 (0.66, 2.14)	
Moderate	>45m	198	242	1.18 (0.91, 1.54)		1.00 (ref)	
	≤45m	37	27	1.94 (1.13, 3.36)	0.57 (−0.41, 1.19)	1.65 (0.95, 2.86)	
High	>45m	154	128	1.32 (0.94, 1.83)		1.00 (ref)	
	≤45m	33	31	1.13 (0.64, 1.99)	−0.38 (−1.10, 0.52)	0.86 (0.49, 1.51)	0.27
	Pregnancy $PM_{2.5}$						
Low	≤12.0 μg/m³	99	165	1.00 (ref)		1.00 (ref)	
	>12.0 μg/m³	153	262	0.81 (0.52, 1.26)		0.81 (0.52, 1.26)	
Moderate	≤12.0 μg/m³	92	96	1.33 (0.89, 1.98)		1.00 (ref)	
	>12.0 μg/m³	143	173	0.96 (0.61, 1.52)	−0.18 (−0.68, 0.32)	0.73 (0.45, 1.16)	
High	≤12.0 μg/m³	47	48	1.06 (0.64, 1.77)		1.00 (ref)	
	>12.0 μg/m³	140	111	1.12 (0.68, 1.84)	0.28 (−0.23, 0.73)	1.05 (0.58, 1.90)	0.50
	First year of life $PM_{2.5}$						
Low	≤12.0 μg/m³	89	160	1.00 (ref)		1.00 (ref)	
	>12.0 μg/m³	163	267	1.46 (0.80, 2.65)		1.46 (0.80, 2.65)	
Moderate	≤12.0 μg/m³	91	98	1.40 (0.93, 2.10)		1.00 (ref)	
	>12.0 μg/m³	144	171	1.69 (0.93, 3.07)	−0.17 (−1.71, 1.37)	1.21 (0.67, 2.17)	
High	≤12.0 μg/m³	46	60	0.90 (0.54, 1.49)		1.00 (ref)	
	>12.0 μg/m³	141	99	2.17 (1.14, 4.15)	0.81 (−0.88, 2.47)	2.42 (1.20, 4.86)	0.08

[a]All models are adjusted for study site, year of birth, month of birth, maternal education, maternal race/ethnicity, maternal age, and maternal smoking.
LRT, likelihood ratio test.

outcomes in offspring.[48] These findings led to the theory that early life maternal stress can induce an inflammatory reaction, sensitize microglia in the offspring, and make individuals more vulnerable to subsequent challenges, such as air pollution exposure.[10] In relation to the development of ASD, alterations in microglial development by early postnatal inflammation may alter synaptic pruning,[49,50] resulting in altered neuronal connectivity and disruption of typical brain development.

Like many other air pollution epidemiologic studies,[51] our modeled air pollution estimates represent outdoor area level ambient concentrations and do not take into consideration indoor exposures or time spent away from home. Further, exposure assessment and linkage with census tract data was based solely on the residential address at birth, which assumes limited mobility during pregnancy and the year after delivery. Previous studies, however, have shown little change in air pollution exposure assignment when using the birth address versus the complete residential history during pregnancy,[52,53] although one study did show somewhat greater exposure misclassification for the pregnancy period than for the first year of life.[54] Residential mobility during pregnancy may also impact the neighborhood deprivation assignment of participants, and this potential misclassification may differ by individual SES.

We used information from the US Census to construct a weighted area-level deprivation index and made no direct measurement of neighborhood physical and social environments. We used this measure of area level neighborhood deprivation in our study as a proxy for differences in access to resources and maternal stress, but made no direct measure of self-reported stress during pregnancy or early life. By using this measure, we make the assumption that those living in more deprived areas would potentially have higher levels of chronic stress; however, social control and other individual characteristics may modify this relationship.[16] Additionally, it is likely that exposure and deprivation levels and resulting estimates could differ by urbanicity. We were unable to assess the impact of urbanicity on our results as over 95% of SEED study participants lived in "urban" areas.

Another potential limitation is the selectivity of the SEED sample. A number of families of potentially eligible children did not respond to the SEED invitation letter. One SEED site was able to assess characteristics of responders and non-responders – their findings showed that maternal education, age, and race/ethnicity were associated with non-response.[55] We adjusted for all three of these variables in our statistical models in order to address this potential limitation. Because of this limitation, we made no direct assessment of neighborhood deprivation and ASD.

Despite these limitations, this study has several strengths. The Clean Air Act required the US Environmental Protection Agency to set National Ambient Air Quality Standards for criteria air pollutants, including $PM_{2.5}$. The primary standard of 12.0 μg/m³ was set to "protect public health, including the health of sensitive populations, such as asthmatics, children, and the elderly."[56] Therefore, we chose this cut-point for our categorized version of $PM_{2.5}$. We additionally assessed associations with continuous measures of $PM_{2.5}$ for comparability with other studies. Our cut-point for living in close proximity to a major road is similar to that of a previous air pollution and ASD study,[45] and other proximity to roadway studies.[57,58]

To our knowledge, the current study is the first US-based study to assess the modifying role of neighborhood deprivation on the association between air pollution and ASD. We assessed modification on both the additive and multiplicative scales using a validated measure of neighborhood deprivation. Our study additionally used rigorous case-classification based on gold-standard outcome ascertainment tools. Finally, we used both roadway proximity and satellite-based modeled $PM_{2.5}$ estimates in order to capture both local near roadway and background $PM_{2.5}$ exposure.

Conclusions

In summary, we observed suggestive evidence of a stronger association between $PM_{2.5}$ exposure in the first year of life and ASD for those living in more deprived neighborhoods. Additional research in this area of the combined effects of environmental and social stressors is warranted to help identify susceptible subgroups that are particularly vulnerable to both of these stressors.

Conflicts of interest

As data used in this study contain personally identifiable information, these data will not be made available. Analytic code may be requested from the corresponding author.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. *5th ed*. Arlington, VA: American Psychiatric Publishing; 2013.
2. Newschaffer CJ, Croen LA, Daniels J, et al. The epidemiology of autism spectrum disorders. *Annu Rev Public Health*. 2007;28:235–258.
3. Hultman CM, Sparén P, Cnattingius S. Perinatal risk factors for infantile autism. *Epidemiology*. 2002;13:417–423.
4. Rodier PM. The early origins of autism. *Sci Am*. 2000;282:56–63.
5. Stoner R, Chow ML, Boyle MP, et al. Patches of disorganization in the neocortex of children with autism. *N Engl J Med*. 2014;370:1209–1219.
6. Flores-Pajot MC, Ofner M, Do MT, Lavigne E, Villeneuve PJ. Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: a review and meta-analysis. *Environ Res*. 2016;151:763–776.
7. Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient air pollution and autism in Los Angeles county, California. *Environ Health Perspect*. 2013;121:380–386.
8. Raz R, Roberts AL, Lyall K, et al. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case-control analysis within the Nurses' Health Study II Cohort. *Environ Health Perspect*. 2015;123:264–270.
9. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry*. 2013;70:71–77.
10. Bilbo SD, Block CL, Bolton JL, Hanamsagar R, Tran PK. Beyond infection - maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. *Exp Neurol*. 2018;299(pt A):241–251.
11. Diz-Chaves Y, Pernía O, Carrero P, Garcia-Segura LM. Prenatal stress causes alterations in the morphology of microglia and the inflammatory response of the hippocampus of adult female mice. *J Neuroinflammation*. 2012;9:71.
12. Kinney DK, Miller AM, Crowley DJ, Huang E, Gerber E. Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. *J Autism Dev Disord*. 2008;38:481–488.
13. Li J, Vestergaard M, Obel C, et al. A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. *Pediatrics*. 2009;123:1102–1107.
14. Roberts AL, Lyall K, Rich-Edwards JW, Ascherio A, Weisskopf MG. Maternal exposure to intimate partner abuse before birth is associated with autism spectrum disorder in offspring. *Autism*. 2016;20:26–36.
15. Brenner AB, Zimmerman MA, Bauermeister JA, Caldwell CH. Neighborhood context and perceptions of stress over time: an ecological model of neighborhood stressors and intrapersonal and interpersonal resources. *Am J Community Psychol*. 2013;51:544–556.
16. Diez Roux AV, Mair C. Neighborhoods and health. *Ann N Y Acad Sci*. 2010;1186:125–145.
17. Barrington WE, Stafford M, Hamer M, Beresford SA, Koepsell T, Steptoe A. Neighborhood socioeconomic deprivation, perceived neighborhood factors, and cortisol responses to induced stress among healthy adults. *Health Place*. 2014;27:120–126.
18. Clougherty JE, Kubzansky LD. A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environ Health Perspect*. 2009;117:1351–1358.
19. Hajat A, Diez-Roux AV, Adar SD, et al. Air pollution and individual and neighborhood socioeconomic status: evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect*. 2013;121:1325–1333.
20. Gray SC, Edwards SE, Miranda ML. Race, socioeconomic status, and air pollution exposure in North Carolina. *Environ Res*. 2013;126:152–158.
21. Steptoe A, Feldman PJ. Neighborhood problems as sources of chronic stress: development of a measure of neighborhood problems, and associations with socioeconomic status and health. *Ann Behav Med*. 2001;23:177–185.
22. Padula AM, Yang W, Carmichael SL, et al. Air pollution, neighbourhood socioeconomic factors, and neural tube defects in the San Joaquin Valley of California. *Paediatr Perinat Epidemiol*. 2015;29:536–545.
23. Shmool JL, Bobb JF, Ito K, et al. Area-level socioeconomic deprivation, nitrogen dioxide exposure, and term birth weight in New York City. *Environ Res*. 2015;142:624–632.
24. Morello-Frosch R, Shenassa ED. The environmental "riskscape" and social inequality: implications for explaining maternal and child health disparities. *Environ Health Perspect*. 2006;114:1150–1153.
25. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Ann N Y Acad Sci*. 1999;896:30–47.
26. Schendel DE, Diguiseppi C, Croen LA, et al. The Study to Explore Early Development (SEED): a multisite epidemiologic study of autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) network. *J Autism Dev Disord*. 2012;42:2121–2140.
27. Rutter M, Bailey A, Lord C. *SCQ: Social Communication Questionnaire*. Los Angeles, CA: *Western Psychological Services*; 2003.
28. Gotham K, Risi S, Pickles A, Lord C. The autism diagnostic observation schedule: revised algorithms for improved diagnostic validity. *J Autism Dev Disord*. 2007;37:613–627.
29. Rutter M, LeCouteur A, Lord C. *ADI-R: The Autism Diagnostic Interview-Revised*. Los Angeles, CA: *Western Psychological Services*; 2003.
30. Wiggins LD, Reynolds A, Rice CE, et al. Using standardized diagnostic instruments to classify children with autism in the study to explore early development. *J Autism Dev Disord*. 2015;45:1271–1280.
31. ESRI. *ArcGIS Desktop: Release 10.3*. Redlands, CA: Environmental Systems Research Institute; 2015.
32. Di Q, Koutrakis P, Schwartz J. A hybrid prediction model for PM2.5 mass and components using a chemical transport model and land use regression. *Atmos Environ*. 2016;131:390–399.
33. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health*. 2006;83:1041–1062.
34. Janevic T, Stein CR, Savitz DA, Kaufman JS, Mason SM, Herring AH. Neighborhood deprivation and adverse birth outcomes among diverse ethnic groups. *Ann Epidemiol*. 2010;20:445–451.
35. Elo IT, Culhane JF, Kohler IV, et al. Neighbourhood deprivation and small-for-gestational-age term births in the United States. *Paediatr Perinat Epidemiol*. 2009;23:87–96.
36. O'Campo P, Burke JG, Culhane J, et al. Neighborhood deprivation and preterm birth among non-hispanic black and white women in eight geographic areas in the United States. *Am J Epidemiol*. 2008;167:155–163.
37. Oakes JM, Kaufman JS. *Methods in Social Epidemiology*. 1st ed. San Francisco, CA: Jossey-Bass; 2006:478.
38. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012;41:514–520.
39. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*. 1992;3:452–456.
40. Gong T, Dalman C, Wicks S, et al. Perinatal exposure to traffic-related air pollution and autism spectrum disorders. *Environ Health Perspect*. 2017;125:119–126.
41. Islam T, Urman R, Gauderman WJ, et al. Parental stress increases the detrimental effect of traffic exposure on children's lung function. *Am J Respir Crit Care Med*. 2011;184:822–827.
42. Hicken MT, Adar SD, Diez Roux AV, et al. Do psychosocial stress and social disadvantage modify the association between air pollution and blood pressure?: the multi-ethnic study of atherosclerosis. *Am J Epidemiol*. 2013;178:1550–1562.
43. Vinikoor-Imler LC, Gray SC, Edwards SE, Miranda ML. The effects of exposure to particulate matter and neighbourhood deprivation on gestational hypertension. *Paediatr Perinat Epidemiol*. 2012;26:91–100.
44. Clougherty JE, Levy JI, Kubzansky LD, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ Health Perspect*. 2007;115:1140–1146.
45. Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. Residential proximity to freeways and autism in the CHARGE study. *Environ Health Perspect*. 2011;119:873–877.
46. Jerrett M, Arain A, Kanaroglou P, et al. A review and evaluation of intraurban air pollution exposure models. *J Expo Anal Environ Epidemiol*. 2005;15:185–204.

47. Kinney PL, Aggarwal M, Northridge ME, Janssen NA, Shepard P. Airborne concentrations of PM(2.5) and diesel exhaust particles on Harlem sidewalks: a community-based pilot study. *Environ Health Perspect*. 2000;108:213–218.

48. Bolton JL, Huff NC, Smith SH, et al. Maternal stress and effects of prenatal air pollution on offspring mental health outcomes in mice. *Environ Health Perspect*. 2013;121:1075–1082.

49. Paolicelli RC, Ferretti MT. Function and dysfunction of microglia during brain development: consequences for synapses and neural circuits. *Front Synaptic Neurosci*. 2017;9:9.

50. Paolicelli RC, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. *Science*. 2011;333:1456–1458.

51. Zeger SL, Thomas D, Dominici F, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect*. 2000;108:419–426.

52. Bell ML, Belanger K. Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures. *J Expo Sci Environ Epidemiol*. 2012;22:429–438.

53. Chen L, Bell EM, Caton AR, Druschel CM, Lin S. Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. *Environ Res*. 2010;110:162–168.

54. Saadeh FB, Clark MA, Rogers ML, et al. Pregnant and moving: understanding residential mobility during pregnancy and in the first year of life using a prospective birth cohort. *Matern Child Health J*. 2013;17:330–343.

55. DiGuiseppi CG, Daniels JL, Fallin DM, et al. Demographic profile of families and children in the Study to Explore Early Development (SEED): case-control study of autism spectrum disorder. *Disabil Health J*. 2016;9:544–551.

56. U.S. EPA. Criteria Air Pollutants: NAAQS Table 2017. Available from: https://www.epa.gov/criteria-air-pollutants/naaqs-table. Accessed 17 May 2017.

57. Gan WQ, Tamburic L, Davies HW, Demers PA, Koehoorn M, Brauer M. Changes in residential proximity to road traffic and the risk of death from coronary heart disease. *Epidemiology*. 2010;21:642–649.

58. Kingsley SL, Eliot MN, Whitsel EA, et al. Maternal residential proximity to major roadways, birth weight, and placental DNA methylation. *Environ Int*. 2016;92-93:43–49.