ORIGINAL ARTICLE

Traffic-Related Air Pollution, Particulate Matter, and Autism

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Context: Autism is a heterogeneous disorder with genetic and environmental factors likely contributing to its origins. Examination of hazardous pollutants has suggested the importance of air toxics in the etiology of autism, yet little research has examined its association with local levels of air pollution using residence-specific exposure assignments.

Objective: To examine the relationship between traffic-related air pollution, air quality, and autism.

Design: This population-based case-control study includes data obtained from children with autism and control children with typical development who were enrolled in the Childhood Autism Risks from Genetics and the Environment study in California. The mother's address from the birth certificate and addresses reported from a residential history questionnaire were used to estimate exposure for each trimester of pregnancy and first year of life. Traffic-related air pollution was assigned to each location using a line-source air-quality dispersion model. Regional air pollutant measures were based on the Environmental Protection Agency's Air Quality System data. Logistic regression models compared estimated and measured pollutant levels for children with autism and for control children with typical development.

Setting: Case-control study from California.

Participants: A total of 279 children with autism and a total of 245 control children with typical development.

Main Outcome Measures: Crude and multivariable adjusted odds ratios (AORs) for autism.

Results: Children with autism were more likely to live at residences that had the highest quartile of exposure to traffic-related air pollution, during gestation (AOR, 1.98 [95% CI, 1.20-3.31]) and during the first year of life (AOR, 3.10 [95% CI, 1.76-5.57]), compared with control children. Regional exposure measures of nitrogen dioxide and particulate matter less than 2.5 and 10 μm in diameter ($PM_{2.5}$ and PM_{10}) were also associated with autism during gestation (exposure to nitrogen dioxide: AOR, 1.81 [95% CI, 1.37-3.09]; exposure to $PM_{2.5}$: AOR, 2.08 [95% CI, 1.93-2.25]; exposure to PM_{10}: AOR, 2.17 [95% CI, 1.49-3.16) and during the first year of life (exposure to nitrogen dioxide: AOR, 2.06 [95% CI, 1.37-3.09]; exposure to $PM_{2.5}$: AOR, 2.12 [95% CI, 1.45-3.10]; exposure to PM_{10}: AOR, 2.14 [95% CI, 1.46-3.12]). All regional pollutant estimates were scaled to twice the standard deviation of the distribution for all pregnancy estimates.

Conclusions: Exposure to traffic-related air pollution, nitrogen dioxide, $PM_{2.5}$, and PM_{10} during pregnancy and during the first year of life was associated with autism. Further epidemiological and toxicological examinations of likely biological pathways will help determine whether these associations are causal.

JAMA Psychiatry. 2013;70(1):71-77.
Published online November 26, 2012.
doi:10.1001/jamapsychiatry.2013.266

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AUTISM SPECTRUM DISORDERS are a group of developmental disorders commonly characterized by problems in communication, social interaction, and repetitive behaviors or restricted interests.[1] Although the severity of impairment for the autism spectrum disorders varies across the spectrum (full syndrome autism being the most severe), the incidence rate of all autism spectrum disorders is now reported to be as high as 1 in 110 children.[2] Emerging evidence suggests that environment plays a role in autism, yet at this stage, only limited information is available as to what exposures are relevant, their mechanisms of action, the stages of development in which they act, and the development of effective preventive measures.

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Recently, air pollution has been examined as a potential risk factor for autism.

Table 1. Spearman Correlations of Traffic-Related Air Pollution (TRP) and Regional Pollutants for 524 Children[a]

First Year of Life Estimates	All Pregnancy Estimates				
	TRP	$PM_{2.5}$	PM_{10}	Ozone	Nitrogen Dioxide
TRP	0.92[b]	0.36[c]	0.33[c]	–0.36[c]	0.60[c]
$PM_{2.5}$	0.25[d]	0.67[b]	0.77[c]	–0.11[c]	0.63[c]
PM_{10}	0.27[d]	0.84[d]	0.82[b]	0.13[c]	0.66[c]
Ozone	–0.31[d]	0.26[d]	0.27[d]	0.74[b]	–0.29[c]
Nitrogen dioxide	0.58[d]	0.60[d]	0.64[d]	–0.19[d]	0.89[b]

Abbreviations: $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter less than 10 μm in aerodynamic diameter.
[a] All correlation measures were statistically significant ($P < .05$).
[b] Correlations of the same pollutant across time periods.
[c] Correlations across pollutants within pregnancy.
[d] Correlations across pollutants within the first year of life.

Using the Environmental Protection Agency's dispersion-model estimates of ambient concentrations of hazardous air pollutants, Windham and colleagues[3] identified an increased risk of autism based on exposure to diesel exhaust particles, metals (mercury, cadmium, and nickel), and chlorinated solvents in Northern California census tracts. Additional research using dispersion-model estimates of hazardous air pollutants also reported associations between autism and air toxics at the birth residences of children from North Carolina and West Virginia.[4] These epidemiologic findings on autism are supported by additional research[5,6] describing other physical and developmental effects of air pollution due to prenatal and early life exposure. For example, high levels of air pollutants have been associated with poor birth outcomes, immunologic changes, and decreased cognitive abilities.[5,6]

Recently, we reported an association between the risk of autism and an early life residence within 309 m of a freeway in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study.[7] The near-source traffic-related air pollutant mixture has a large spatial variation, returning to near-background daytime levels beyond this distance.[8,9] Herein, we report associations of autism with estimates of exposure to the mixture of traffic-related air pollution and with regional measures of nitrogen dioxide, particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), and particulate matter less than 10 μm in aerodynamic diameter (PM_{10}) in the CHARGE sample.

METHODS

The CHARGE study is a population-based case-control study of preschool children. The study design is described in detail elsewhere.[10] In brief, the participants in the CHARGE study were between the ages of 24 and 60 months at the time of recruitment, lived with at least one English- or Spanish-speaking biologic parent, were born in California, and lived in one of the study catchment areas. Recruitment was facilitated by the California Department of Developmental Services, the regional centers with which they contract to coordinate services for persons with developmental disabilities, and referrals from the MIND (Medical Investigation of Neurodevelopmental Disorders) Institute clinic at the University of California, Davis, and from other research studies. Population-based control children were recruited from the sampling frame of birth files from the state of California and were frequency matched by sex, age, and broad geographic area to the children with autism.

Each participating family was evaluated. Children with a previous diagnosis of autism were evaluated using the Autism Diagnostic Observation Schedules, and parents were administered the Autism Diagnostic Interview–Revised.[11,12] Children who received a diagnosis of developmental delay and control children from the general population were given the Social Communication Questionnaire to screen for the presence of autistic features.[13] If the Social Communication Questionnaire score was 15 or greater, the child was then evaluated using the Autism Diagnostic Observation Schedules, and the parent was administered the Autism Diagnostic Interview–Revised. In our study, autism cases were children with a diagnosis of full syndrome autism from both the Autism Diagnostic Observation Schedules and the Autism Diagnostic Interview–Revised. All children were also assessed using the Mullen Scales of Early Learning and the Vineland Adaptive Behavior Scales to collect information on motor skills, language, socialization, and daily living skills.[14,15] Controls were children from the general population who received a Social Communication Questionnaire score of less than 15 and who also showed no evidence of other types of delay (cognitive or adaptive).

Parents were interviewed to obtain, among other factors, demographic and medical information and residential histories. Race/ethnicity data were collected by self-report in categories defined by the US Census (**Table 1**). The residential data captured addresses and corresponding dates the mother and child lived at each location beginning 3 months before conception and extending to the most recent place of residence. Further details about the collection of clinical and exposure data have been previously reported.[10]

To obtain model-based estimates of exposure to traffic-related air pollution, we applied the CALINE4 line-source air-quality dispersion model.[16] The dispersion model was used to estimate average concentrations for the specific locations and time periods (trimesters of gestation and first year of life) for each participant. The principal model inputs are roadway geometry, link-based traffic volumes, period-specific meteorological conditions (wind speed and direction, atmospheric stability, and mixing heights), and vehicle emission rates. Detailed roadway geometry data and annual average daily traffic counts were obtained from Tele Atlas/Geographic Data Technology in 2005. These data represent an integration of state-, county-, and city-level traffic counts collected between 1995 and 2000. Because our period of interest was from 1997 to 2008, the counts were scaled to represent individual years based on estimated growth in county average vehicle-miles-traveled data.[17] Traffic counts were assigned to roadways based on location and street names. Traffic volumes on roadways without count data (mostly

small roads) were estimated based on median volumes for similar class roads in small geographic regions. Meteorological data from 56 local monitoring stations were matched to the dates and locations of interest. Vehicle fleet average emission factors were based on the California Air Resource Board's EMFAC2007 (version 2.3) model. Annual average emission factors were calculated by year (1997-2008) for travel on freeways (65 mph), state highways (50 mph), arterials (35 mph), and collector roads (30 mph) (to convert to kilometers, multiply by 1.6). We used the CALINE4 model to estimate locally varying ambient concentrations of nitrogen oxides contributed by freeways, nonfreeways, and all roads located within 5 km of each child's home. Previously, we have used the CALINE4 model to estimate concentrations of other traffic-related pollutants, including elemental carbon and carbon monoxide, and found that they were almost perfectly correlated (around 0.99) with estimates for nitrogen oxides. Thus, our model-based concentrations should be viewed as an indicator of the traffic-related pollutant mixture rather than of any pollutant specifically.

A second approach was to use the regional air quality data for the exposure assignments for $PM_{2.5}$, PM_{10}, ozone, and nitrogen dioxide. These were derived from the US Environmental Protection Agency's Air Quality System data (http://www.epa.gov/ttn/airs/airsaqs) supplemented by University of Southern California Children's Health Study data for 1997 though 2009.[18] The Children's Health Study continuous PM data were used for a given monitoring station when no Federal Reference/Equivalent Method data for PM were available from the Air Quality System. The monthly air quality data from monitoring stations located within 50 km of each residence were made available for spatial interpolation of ambient concentrations. The spatial interpolations were based on inverse distance–squared weighting of data from up to 4 of the closest stations located within 50 km of each participant's residence; however, if 1 or more stations were located within 5 km of a residence, then only data from the stations within 5 km were used for the interpolation. Because special studies have shown large offshore-to-onshore pollutant gradients along the Southern California coast, the interpolations were performed with pseudostations (or theoretical locations used for estimating pollution gradients from extant data when geography did not permit observed data) located approximately 20 to 40 km offshore that had background concentrations based on long-term measurements (1994-2003) at clean coastal locations (ie, Lompoc, California).

Periods and locations relevant to the modeled traffic exposure were identified based on dates and addresses recorded on the child's birth certificate and from the residential history questionnaire. The birth certificate addresses corresponded to the mother's residence at the time of the child's birth, whereas the residential history captures both the mother's residences during pregnancy (required for estimation of prenatal exposure) and the child's residences after birth through the time of study enrollment. We determined the conception date for each child using gestational age from ultrasonographic measurements or the date of last menstrual period, as determined from prenatal records. We used these locations and dates to estimate exposure for the child's first year of life, for the entire pregnancy period, and for each trimester of pregnancy. When more than 1 address fell into a time interval, we created a weighted average to reflect the exposure level of the participant across the time of interest, taking into account changes in residence. Traffic-related air pollution was determined based on the required inputs reflecting change in each address over the study period. For the regional pollutant measures, we assigned $PM_{2.5}$, PM_{10}, and nitrogen dioxide measurements based on average concentrations for the time period of interest. For ozone, we calculated the averages for the period of interest based on the average range of ozone measurements from 1000 to 1800 hours (reflecting the high 8-hour daytime). Based on these methods, we were able to assign traffic-related air pollutant estimates and regional pollutant measures for 524 mother-child pairs.

Spearman correlations were calculated pairwise between traffic-related air pollutant estimates and regional pollution measures for pregnancy and the first year of life to assess the independence of these exposure metrics. We used logistic regression to examine the association between exposure to traffic-related air pollution and the risk of autism. Models of autism risk as a function of traffic-related air pollutant exposure levels from all road types were fitted separately for each time period. Categories of exposure were formed based on quartiles of the traffic-related air pollutant distribution for all pregnancy estimates because this provided the most comprehensive data for each child. Levels of regional pollutants were examined as continuous variables, and effect estimates were scaled to twice the standard deviation of the distribution for all pregnancy estimates. When levels of correlation permitted, we examined both traffic-related air pollutants and regional pollutants in a single model. Pertinent covariates were included in each model to adjust for potential confounding due to sociodemographic and lifestyle characteristics. We included children's sex and ethnicity, maximum education level of the parents, mother's age, and whether the mother smoked during her pregnancy, as described previously.[7] To examine whether our findings were affected by participants living in an urban or rural area, we included population density, which was obtained from Environmental Systems Research Institute Inc 2008 estimates of people per square meter using ArcGIS software version 9.2. We used the US Census Bureau cutoff of 2500 people per square meter to categorize population density into urban vs rural areas and included this variable as a covariate in our analysis of the effects of air pollution from the first year of life because these residences were the most recently recorded.

We also fitted logistic additive models to evaluate the relationship between autism and traffic-related air pollution. These models used the smoothing spline with 3 degrees of freedom for continuous traffic-related air pollution and used the same adjustment variables as in the linear logistic models already described. Statistical tests were conducted using an α level of .05, and 95% CIs were used to measure precision. All analyses were conducted using the R package version 2.9.2 (http://www.r-project.org). The institutional review boards of the University of Southern California and the University of California, Davis, approved the research.

RESULTS

The children in our study were predominantly male (84%), and most were non-Hispanic white (50%) or Hispanic (30%). No differences were found between cases and controls for any demographic, socioeconomic, or lifestyle variables that we examined (eTable, http://www.jamapsych.com). Details regarding the exposure distributions are presented in the eFigure, A and B. The Spearman correlations calculated for the first year of life and the pregnancy time periods are presented in Table 1. During pregnancy and during the first year of life, traffic-related air pollution was moderately correlated with $PM_{2.5}$ and PM_{10}, highly correlated with nitrogen dioxide, but inversely correlated with ozone. Among the regional pollutant measures, $PM_{2.5}$ and PM_{10} were nearly perfectly correlated, and both were highly correlated with nitrogen dioxide. Correlations with ozone were low and often negative, demonstrating an inverse relationship. We also ex-

Table 2. Risk of Autism for 524 Children, by Quartile[a] of Modeled Traffic-Related Air Pollution Exposure From All Road Types

Time Period	Odds Ratio (95% CI)		
	4th Quartile	3rd Quartile	2nd Quartile
First year of life			
Crude	2.97 (1.71-5.27)	1.00 (0.63-1.60)	0.88 (0.55-1.42)
Adjusted[b]	3.10 (1.76-5.57)	1.00 (0.62-1.62)	0.91 (0.56-1.47)
All pregnancy			
Crude	1.99 (1.22-3.28)	1.10 (0.67-1.78)	1.20 (0.74-1.95)
Adjusted[b]	1.98 (1.20-3.31)	1.09 (0.67-1.79)	1.26 (0.77-2.06)
First trimester			
Crude	1.91 (1.67-3.14)	1.28 (0.80-2.06)	1.28 (0.77-2.14)
Adjusted[b]	1.85 (1.11-3.08)	1.28 (0.79-2.08)	1.28 (0.77-2.15)
Second trimester			
Crude	1.69 (1.04-2.78)	1.15 (0.71-1.87)	0.89 (0.54-1.47)
Adjusted[b]	1.65 (1.00-2.74)	1.13 (0.69-1.84)	0.90 (0.54-1.49)
Third trimester			
Crude	2.04 (1.25-3.38)	0.92 (0.57-1.48)	1.12 (0.68-1.84)
Adjusted[b]	2.10 (1.27-3.51)	0.91 (0.56-1.46)	1.17 (0.71-1.93)

[a] Quartile cut points correspond to traffic-related air pollution exposure levels of 31.8 ppb or greater (fourth quartile), 16.9 to 31.8 ppb (third quartile), and 9.7 to 16.9 ppb (second quartile), compared with 9.7 ppb or less (first quartile [reference group]).

[b] Model adjusted for male sex of child, child's ethnicity (Hispanic vs white; black/Asian/other vs white), maximum education of parents (parent with highest of 4 levels: college degree or higher vs some high school, high school degree, or some college education), maternal age (>35 years vs ≤35 years), and prenatal smoking (mother's self-report of ever vs never smoked while pregnant).

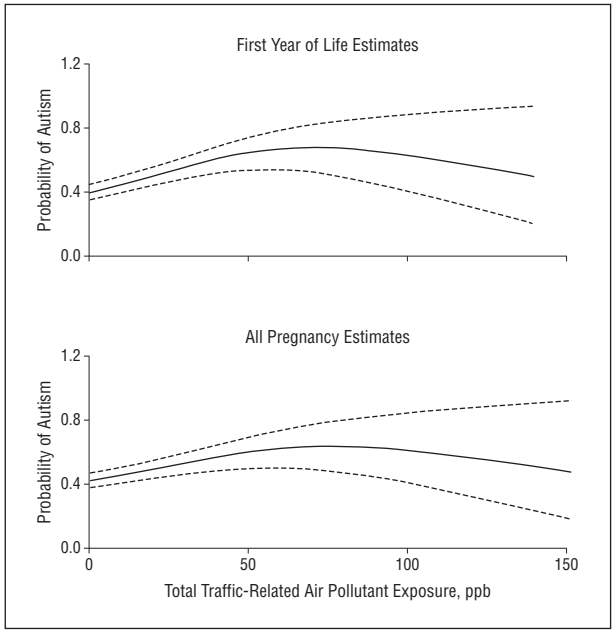

Figure. Probability of autism by increasing level of children's exposure to traffic-related air pollution during the first year of life and during gestation. The dashed lines indicate the 95% CI.

amined correlations of each pollutant across time periods, and high levels of correlation were identified.

EXPOSURE TO TRAFFIC-RELATED AIR POLLUTION

An increased risk of autism was associated with exposure to traffic-related air pollution during a child's first year of life. Children residing in homes with the highest levels of modeled traffic-related air pollution were 3 times as likely to have autism compared with children residing in homes with the lowest levels of exposure (**Table 2**). Exposure in the middle quartile groups (second and third quartiles) was not associated with an increased risk of autism. In our analysis, which included population density, this association with the highest quartile of exposure was still evident (adjusted odds ratio [AOR], 3.48 [95% CI, 1.81-6.83]), and living in an urban area, compared with living in a rural area, was not associated with autism (AOR, 0.86 [95% CI, 0.56-1.31]). When we examined traffic-related air pollutant exposures during pregnancy, the highest quartile was also associated with autism risk (AOR, 1.98 [95% CI, 1.20-3.31]) compared with the lowest quartile. We further divided the pregnancy into 3 trimesters and modeled traffic-related air pollution based on these intervals. During all 3 trimesters of pregnancy, we found associations with the highest quartile of exposure (≥31.8 ppb), compared with the lowest quartile (≤9.7 ppb), and autism (Table 2). Inclusion of demographic and socioeconomic variables in the models did not greatly alter these associations (Table 2).

Because our quartile-based categories indicated that there is a threshold upon which traffic-related air pollutant exposure is detrimental, we also examined the relationship between traffic-related air pollutant exposure and autism using smoothed models for the first year of life and all of pregnancy. An increasing probability of autism was seen with increasing traffic-related air pollutant estimates, with the odds reaching a plateau when these estimates were above 25 to 30 ppb (**Figure**).

REGIONAL AIR POLLUTANT EXPOSURE

The higher levels of exposure to $PM_{2.5}$, PM_{10}, and nitrogen dioxide based on the Environmental Protection Agency's regional air quality monitoring program were associated with an increased risk of autism (**Table 3**). Specifically, for an 8.7-unit increase (micrograms per cubic meter) in $PM_{2.5}$ (corresponding to twice the standard deviation of the $PM_{2.5}$ distribution) exposure during the first year of life, children were 2.12 times more likely to have autism. Increases were also present for pregnancy and trimester-specific estimates of $PM_{2.5}$, with the smallest effects present in the first trimester. For PM_{10}, a 14.6-unit increase (micrograms per cubic meter) during the first year was associated with twice the risk of autism (Table 3). Associations were present for pregnancy and for each trimester, with the first trimester having the smallest magnitude. We did not find associations between levels of regional ozone and autism. Regional nitrogen dioxide exposure during the first year was associated with a 2-fold risk of autism. Similar effects were identified for nitrogen dioxide exposure during pregnancy. Although exposure during each of the 3 trimesters was associated with autism, the effects of the first trimester were the smallest. For all regional pollutant measures, adjustment for demographic and socioeconomic

Table 3. Risk of Autism for 524 Children Based on Continuous Regional Pollutant Exposure[a]

Time Period	Odds Ratio (95% CI)			
	$PM_{2.5}$	PM_{10}	Ozone	Nitrogen Dioxide
First year				
Crude	2.14 (1.48-3.09)	2.14 (1.47-3.10)	1.15 (0.72-1.84)	2.06 (1.39-3.06)
Adjusted[b]	2.12 (1.45-3.10)	2.14 (1.46-3.12)	1.15 (0.72-1.86)	2.06 (1.37-3.09)
All pregnancy				
Crude	2.11 (1.46-3.03)	2.17 (1.50-3.13)	1.08 (0.76-1.52)	1.82 (1.26-2.64)
Adjusted[b]	2.08 (1.93-2.25)	2.17 (1.49-3.16)	1.09 (0.76-1.55)	1.81 (1.23-2.65)
First trimester				
Crude	1.24 (0.99-1.56)	1.47 (1.10-1.98)	1.07 (0.86-1.33)	1.47 (1.07-2.01)
Adjusted[b]	1.22 (0.96-1.53)	1.44 (1.07-1.96)	1.08 (0.86-1.35)	1.44 (1.05-1.20)
Second trimester				
Crude	1.50 (1.16-1.93)	1.82 (1.35-2.45)	1.03 (0.84-1.27)	1.62 (1.17-2.25)
Adjusted[b]	1.48 (1.40-1.57)	1.83 (1.35-2.47)	1.04 (0.84-1.29)	1.61 (1.15-2.25)
Third trimester				
Crude	1.39 (1.11-1.75)	1.61 (1.21-2.13)	1.03 (0.84-1.27)	1.65 (1.19-2.27)
Adjusted[b]	1.40 (1.11-1.77)	1.61 (1.20-2.14)	1.03 (0.83-1.26)	1.64 (1.18-2.29)

Abbreviations: $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter less than 10 μm in aerodynamic diameter.

[a] Regional pollution effects reflect risk of autism based on 2 SDs from the mean value, specifically per increase of 8.7 μg/m^3 of $PM_{2.5}$, 14.6 μg/m^3 of PM_{10}, 14.1 ppb of nitrogen dioxide, and 16.1 ppb of ozone.

[b] Models adjusted for male sex of child, child's ethnicity (Hispanic vs white; black/Asian/other vs white), maximum education of parents (parent with highest of 4 levels: college degree or higher vs some high school, high school degree, or some college education), maternal age (>35 years vs ≤35 years), and prenatal smoking (self-report of ever vs never smoked while pregnant).

variables did not alter the associations. As with traffic-related air pollution, when we included population density in the models that included exposure during the first year of life, the associations with $PM_{2.5}$, PM_{10}, and nitrogen dioxide did not change, nor did they change when living in an urban area vs a rural area was included (data not shown).

TRAFFIC-RELATED AIR POLLUTION, $PM_{2.5}$, AND PM_{10}

Because pairwise correlations between traffic-related air pollution and $PM_{2.5}$ and between traffic-related air pollution and PM_{10} were moderate, we included both in models to examine whether local pollution estimates (traffic-related air pollution) and regional pollution measures ($PM_{2.5}$ and PM_{10}) were independently associated with autism. In these analyses, we included the same set of covariates already described in the single pollutant analysis. When examined in the same model, the top quartile of traffic-related air pollutant exposure (AOR, 2.37 [95% CI, 1.28-4.45]) and the exposure to $PM_{2.5}$ (AOR, 1.58 [95% CI, 1.03-2.42]) during the first year of life remained associated with autism. Examining both traffic-related air pollution and PM_{10}, we found that the top quartile of traffic-related air pollutant exposure (AOR, 2.36 [95% CI, 1.28-4.43]) and the exposure to PM_{10} (AOR, 1.61 [95% CI, 1.06-2.47]) remained associated with autism. For the all pregnancy time interval, we found that the top quartile of traffic-related air pollutant exposure (AOR, 2.42 [95% CI, 1.32-4.50]) and the exposure to $PM_{2.5}$ (AOR, 1.60 [95% CI, 1.07-2.40]) were associated with autism when examined in the same model. Similarly, both the top quartile of traffic-related air pollutant exposure (AOR, 2.33 [95% CI, 1.27-4.36]) and the exposure to PM_{10} (AOR, 1.68 [95% CI, 1.11-2.53]) remained associated with autism when examined jointly.

COMMENT

Our study found that local estimates of traffic-related air pollution and regional measures of $PM_{2.5}$, PM_{10}, and nitrogen dioxide at residences were higher in children with autism. The magnitude of these associations appear to be most pronounced during late gestation and early life, although it was not possible to adequately distinguish a period critical to exposure. Children with autism were 3 times as likely to have been exposed during the first year of life to higher modeled traffic-related air pollution compared with control children with typical development. Similarly, exposure to traffic-related air pollution during pregnancy was also associated with autism. Examination of traffic-related air pollution using an additive logistic model demonstrated a potential threshold near 25 to 30 ppb beyond which the probability of autism did not increase. Exposure to high levels of regional $PM_{2.5}$, PM_{10}, and nitrogen dioxide were also associated with autism. When we examined $PM_{2.5}$ or PM_{10} exposure jointly with traffic-related air pollutant exposure, both regional and local pollutants remained associated with autism, although the magnitude of the effects decreased.

We previously reported an association between living near a freeway (based on the location of the birth and third trimester address) and autism.[7] That result relied on simple distance metrics as a proxy for exposure to traffic-related air pollution. The present study builds on that result, demonstrating associations with both regional particulate and nitrogen dioxide exposure and to dispersion-modeled exposure to the near-roadway traffic mixture accounting for traffic volume, fleet emission factors, and wind speed and direction, in addition to traffic proximity. The results provide more convincing evidence that exposure to local air pollution from traffic may increase

the risk of autism. Demographic or socioeconomic factors did not explain these associations.

Toxicological and genetic research suggests possible biologically plausible pathways to explain these results. Concentrations of many air pollutants, including diesel exhaust particles and other PM constituents, are increased near freeways and other major roads, and diesel exhaust particles and polycyclic aromatic hydrocarbons (commonly present in diesel exhaust particles) have been shown to affect brain function and activity in toxicological studies.[19-23] Polycyclic aromatic hydrocarbons have been shown to reduce expression of the *MET* receptor tyrosine kinase gene, which is important in early life neurodevelopment and is markedly reduced in autistic brains.[24,25] Other research indicates that traffic-related air pollution induces inflammation and oxidative stress after both short- and long-term exposure, processes that mediate the effects of air pollution on respiratory and cardiovascular disease and other neurological outcomes.[26-29] Data examining biomarkers suggest that oxidative stress and inflammation may also be involved in the pathogenesis of autism.[30-33]

Emerging evidence suggests that systemic inflammation may also result in damage to endothelial cells in the brain and may compromise the blood-brain barrier.[29] Systemic inflammatory mediators may cross the blood-brain barrier, activating brain microglia, and peripheral monocytes may migrate into the pool of microglia.[34-36] In addition, ultrafine particles ($PM_{0.1}$) may penetrate cellular membranes.[37,38] These particles translocate indirectly through the lungs and from the systemic circulation or directly via the nasal mucosa and the olfactory bulb into the brain.[39,40] Toxicity may be mediated by the physical properties of PM or by the diverse mixture of organic compounds, including polycyclic aromatic hydrocarbons, and oxidant metals adsorbed to the surface.[29] Neurodevelopmental effects of polycyclic aromatic hydrocarbons may be mediated by aryl hydrocarbon hydroxylase induction in the placenta, decreased exchange of oxygen secondary to disruption of placental growth factor receptors, endocrine disruption, activation of apoptotic pathways, inhibition of the brain antioxidant-scavenging system resulting in oxidative stress, or epigenetic effects.[21]

Our study draws on a rich record of residential locations of children with typical development and children with autism across California, allowing us to assign modeled pollutant exposures for developmentally relevant time points. However, our results could also be affected by unmeasured confounding factors associated with both autism and exposure to traffic-related air pollution. Although we did not find that including demographic or socioeconomic variables altered our estimates of effect, confounding by other factors could still occur. These might include lifestyle, nutritional, or other residential exposures, if they were associated with traffic-related air pollution or PM. We have also not explored indoor sources of pollution, such as indoor nitrogen oxide or secondhand tobacco smoke, although prenatal smoking was examined and did not influence the associations of ambient pollution with autism. In addition, confounding could have occurred if proximity to diagnosing physicians or treatment centers was also associated with exposure. We included population density as an adjustment in an analysis using estimates from the first year of life to examine the sensitivity of our results to urban or rural locations, for which population density is a surrogate. We did not find that living in a more densely populated area altered the association between risk of autism and exposure to traffic-related air pollution or regional pollutants. Despite our attempts to use residential history to examine specific time windows of vulnerability, to incorporate meteorology into our traffic-related air pollutant models, and to include pollutants with seasonal variation, we are currently unable to disentangle the trimester-specific effects during the first year of life because of the high level of correlation across these time periods.

Exposures to traffic-related air pollution, PM, and nitrogen dioxide were associated with an increased risk of autism. These effects were observed using measures of air pollution with variation on both local and regional levels, suggesting the need for further study to understand both individual pollutant contributions and the effects of pollutant mixtures on disease. Research on the effects of exposure to pollutants and their interaction with susceptibility factors may lead to the identification of the biologic pathways that are activated in autism and to improved prevention and therapeutic strategies. Although additional research to replicate these findings is needed, the public health implications of these findings are large because air pollution exposure is common and may have lasting neurological effects.

Submitted for Publication: December 9, 2011; final revision received March 30, 2012; accepted April 3, 2012.
Published Online: November 26, 2012. doi:10.1001/jamapsychiatry.2013.266
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Author Contributions: Dr Volk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conflict of Interest Disclosures: Dr Volk received support from Autism Speaks to present research findings at the International Society for Environmental Epidemiology Meeting in 2012. Messrs Lurmann and Penfold are employed by Sonoma Technology, Inc. Dr McConnell has received support from an air quality violations settlement agreement between the South Coast Air Quality Management District (a California state regulatory agency) and British Petroleum.
Funding/Support: This work was supported by National Institute of Environmental Health Sciences grants

ES019002, ES013578, ES007048, ES11269, ES015359, EPA Star-R-823392, and EPA Star-R-833292 and by the MIND Institute's matching funds and pilot grant program.
Role of the Sponsor: The sponsors did not participate in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Previous Presentations: Presented in part at the International Meeting for Autism Research; May 14, 2011; San Diego, California; and the Meeting of the International Society for Environmental Epidemiology; September 16, 2011; Barcelona, Spain.
Online-Only Material: The eTable and eFigure are available at http://www.jamapsych.com.

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