Title
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Journal
Epidemiology, 25(6)

ISSN
1044-3983

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Publication Date
2014-11-01

DOI
10.1097/ede.0000000000000150

Peer reviewed

HHS Public Access

Author manuscript

Epidemiology. Author manuscript; available in PMC 2016 January 02.

Published in final edited form as:

Epidemiology. 2014 November ; 25(6): 851–858. doi:10.1097/EDE.0000000000000150.

In Utero Exposure to Toxic Air Pollutants and Risk of Childhood Autism

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Abstract

Background—Genetic and environmental factors are believed to contribute to the development of autism, but relatively few studies have considered potential environmental risks. Here we examine risks for autism in children related to in utero exposure to monitored ambient air toxics from urban emissions.

Methods—Among the cohort of children born in Los Angeles County, California 1995–2006, those whose mothers resided during pregnancy in a 5km buffer around air-toxics monitoring stations were included (n=148,722). To identify autism cases in this cohort, birth records were linked to records of children diagnosed with primary autistic disorder at the California Department of Developmental Services between 1998 and 2009 (n=768). We calculated monthly average exposures during pregnancy for 24 air toxics selected based on suspected or known neurotoxicity or neurodevelopmental toxicity. Factor analysis helped us identify the correlational structure among air toxics, and we estimated odds ratios (ORs) for autism from logistic regression analyses.

Results—Autism risks were increased per interquartile-range increase in average concentrations during pregnancy of several correlated toxics mostly loading on one factor, including 1,3-butadiene (OR=1.59 [95% confidence interval=1.18–2.15]), meta/para-xylene (1.51 [1.26–182]), other aromatic solvents, lead (1.49 [1.23–1.81]), perchloroethylene (1.40 [1.09–1.80]), and formaldehyde (1.34 [1.17–1.52]), adjusting for maternal age, race/ethnicity, nativity, education, insurance type, maternal birth place, parity, child sex, and birth year.

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Conclusions—Risks for autism in children may increase following in utero exposure to ambient air toxics from urban traffic and industry emissions, as measured by community-based air - monitoring stations.

Autism is a severe neurodevelopmental condition characterized by problems in social interaction and communication, restricted interests or repetitive stereotyped behaviors.[1] Recently, 14.7 in 1,000 children have been diagnosed with autism spectrum disorder by the age of 8 years.[2] The etiology of autism is heterogeneous, and underlying biological mechanisms remain insufficiently understood. Little is known about non-genetic [3] causes, even though environmental factors have been suggested as major contributors, [4] possibly accounting for at least part of the increase in autism observed over the last decades.[5]

A few studies have investigated autism related to air pollution, focusing on road traffic. [6–8] In the only large population-based study (7,603 cases) to date, we previously reported 7%–12% increases in risks for autistic disorder per interquartile range (IQR) increase in measured particulate matter less than 2.5μg per m^3 and ozone, as well as nitrogen oxides (NO, NO_2), our marker of traffic pollutants derived from land-use regression.[7]

Air toxics, also known as hazardous air pollutants, are defined by the Environmental Protection Agency (EPA) as pollutants that may cause serious health effects or adverse environmental and ecological effects. To date only three studies have investigated the influence of toxic air pollutants on autism spectrum disorder. [9–11] These studies were limited in sample size, and relied solely on modeled annual average pollutant concentrations at the county or census-tract level, which are created every few years (i.e., 1996, 1999, 2002,).[12] Thus, estimated exposures did not directly correspond to the time of the pregnancy period, as births were linked with annual averages up to several years before or after the actual pregnancy time period and thus assumed temporal stability of the modeled exposures. This approach may have resulted in considerable exposure misclassification, as air pollution exposure changes over time. Nevertheless, associations with these modeled hazardous air pollutants have been suggested for chlorinated solvents, [9–11] cadmium,[10,11] quinolone,[9] styrene, [9,10] diesel [10] and an index of metal exposure. [10]

Several air toxics (e.g. lead or organic solvents) not only are common in urban air mixtures, but are suspected or known to have adverse effects on the developing central nervous system.[13,14] A number of underlying mechanisms contributing to neurological pathology have been suggested, including the initiation of inflammatory processes, oxidative stress, microglial activation, cerebrovascular dysfunction, and alterations in the blood-brain barrier.[14] Small pathology studies have reported increases in inflammatory and oxidative stress markers in the brains of children who had been exposed to high levels of toxic ambient air pollution prior to accidental death.[15] Inflammatory or immunological processes similar to those seen in response to air pollutants have been hypothesized to play a role in the development of autism.[16] However, whether toxic air-pollutant-induced response pathways also affect prenatal neurodevelopment and lead to autism is currently unknown. We investigated risks for autism in children related to in utero exposure to toxic air pollutants based on monitored ambient concentrations of common air toxics, including aromatic and chlorinated solvents, metals, and polycyclic aromatic hydrocarbons (PAHs).

Methods

Study design and population

We successfully geocoded 1,522,267 birth addresses for the entire cohort of 1,745,754 children born in Los Angeles County, California in 1995–2006, as previously described.[17] The California Air Resources Board maintains 4 air toxics monitoring stations in Los Angeles County, collecting 24-hour integrated samples every 12 days at each monitoring site (see map, eFigure 1). Using locations' latitude/longitude provided by the California Air Resources Board, we determined the distance from each air monitor to each family's home, and participants were assigned pollutant values based upon the measurements at the nearest monitor. Here, we included all geocoded addresses within <5km (~3.1 miles) of a California Air Resources Board monitoring station in the Los Angeles Basin to balance exposure misclassification with increasing distance from a station against sample size limitations. For sensitivity analyses, we further restricted the buffer size to <3.5km (~2.2miles). We excluded 1,436 records with missing or implausible gestational ages (< 21 weeks or > 46 weeks) or birth weights (< 500 g or > 6,800 g), and 492 deaths before age 6 years identified by linkage to the California death registry data using Link Plus software, [18] yielding a cohort of 148,722 births.

This research was approved by the University of California Los Angeles Office of the Human Research Protection Program and the California Committee for the Protection of Human Subjects, and was exempted from informed consent requirements.

Case ascertainment and record linkage

Autism cases were identified through records maintained by the California Department of Developmental Services, which contracts with seven regional centers in Los Angeles County. We included only cases with a primary diagnosis of autistic disorder (the most severe among the autism spectrum disorder diagnoses) diagnosed at ages 36–71 months during 1998–2009 with the information recorded by a Los Angeles regional center. Eligibility for the Department of Developmental Services' services does not depend on citizenship or financial status, i.e. services are available to all children. Diagnosis of autistic disorder was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-R)[1] (code 299.00) reported on the Client Development Evaluation Report throughout the study period. Validation studies have established the reliability and validity of the Client Development Evaluation Report in California.[19]

We investigated phenotypic severity among 5-year-old children (n=419), who we grouped based on Department of Developmental Services evaluation records as either "impaired" (child does not use words, uses simple words only, or uses two-word sentences) or "less impaired" expressive language abilities (child uses sentences of 3 words or more, or can engage at least in basic conversation). Intelligence quotient data was not used because this information was available only for children diagnosed with "mental retardation".

We previously described the linkage of 10,821 Department of Developmental Services autistic disorder records to birth records in Los Angeles County based on child identifiers, resulting in 8,600 successfully linked records (80% of all cases).[7] We further excluded 41

children whose mothers did not reside in Los Angeles County during pregnancy, 508 records with missing or implausible gestational ages or birth weights, and children who did not have a primary diagnosis of autistic disorder (n=448). Restricting the cohort to those whose mothers' resided in the 5km buffer around air monitoring stations at the time of birth resulted in 768 cases (3.5km buffer: 380 cases; 69,415 non-cases).

Exposure assessment

We initially considered 35 pollutants for which measurement data in Los Angeles County are available [20] and for which there is some previous indication for neurodevelopmental or neurotoxic effects.[21–23] We first created monthly averages for each month of pregnancy; then monthly averages were used to calculate averages across each trimester (eTable 3). We included children for whom we had at least 50% of possible readings for each pregnancy month and the last 30 days of pregnancy, considering that the last month of pregnancy rarely is exactly one month in length. We excluded from the analyses pollutants for which at least 30% of values were missing for more than a third of the monitoring time. Based on this criterion we excluded styrene, arsenic, cadmium, and methyl bromide, among others. Three stations (downtown Los Angeles, Burbank, and North Long Beach) were active throughout the entire study period, while the Azusa station provided measurements only in 2004 and 2005 for PAHs, only 2000–2003 for metals, and only 2000–2006 for all other toxics. Since monitoring for metals at all stations ceased in January 2003, we considered metal exposures only for the birth years 1995–2002. Mercury and cobalt lacked variability in measurements and were excluded. Thus, we retained for analyses 24 toxic air pollutants, including aromatic solvents, chlorinated solvents, volatile organics, total polycyclic aromatic hydrocarbons, and several metals (eTables 1, 2). Exposure measures were created for the entire pregnancy and for the first (first day of the last menstrual period to day 92), second (days 93–185) and third (day 186 to birth) trimesters, based on birth dates and gestational ages. Trimester-specific means are displayed in eTable 3.

Statistical analysis

We plotted 12-day 24-hour pollutant measurements to examine trends across time and by monitoring station (eFigure 2) and employed Pearson's correlation coefficients to examine collinearity across pollutants and pregnancy periods. With factor analysis (varimax rotation), we examined the correlation structure of pollutants further. Unconditional logistic regression was used to estimate odds ratios (ORs) per IQR increase in pregnancy exposures for each toxic. We adjusted all models for birth year, and further adjusted models for a priori selected potential confounders including maternal age, race/ethnicity, place of birth (US vs. non-US), education, parity, type of insurance (a measure of socioeconomic status in our population [24]), and offspring sex (definitions shown in Table 1). Additional adjustment for paternal age and education, pregnancy complications, birth weight, and type of birth (caesarean/vaginal) did not change the estimates of interest by more than 5% and thus were not retained in the final models. In 2- and 3-pollutant models, we included pollutants that showed the strongest associations with autistic disorder and that loaded either on the same or on different factors or did not load on any factor. We conducted sensitivity analyses stratifying by sex, by expressive language abilities (restricted to 5-year-olds to reduce differences related to age-dependent development), and by regional center catchment area

(cases were assigned by place of recorded diagnosis, non-cases based on birth address zip code linked with regional center catchment area zip codes), as well as restricted to term births. Analyses were conducted with SAS 9.3.

Results

Population characteristics are shown in Table 1. Compared with non-case mothers, mothers of cases were more often older than 35 years, tended to be more educated, and had their prenatal care paid by private insurance. The boy-to-girl ratio among cases was 4.3:1. The correlation matrix and the means, standard deviation, IQRs, and factor load of the air pollutants that loaded >0.6 on four main factors, and the trimester-specific means, are displayed in eTables 1–3; eTable 4 displays very similar population characteristics in 10 mile distance as in 5km, and eTable 5 shows the distribution of cases/non-cases by air monitor.

In the 5 km and 3.5 km buffers, adjusted ORs were consistently increased by 30%–60% for most pollutants loading on factor 1 (Table 2) but there were no associations for PAHs and methylene chloride. Effect estimates were generally stronger in the 3.5 km than the 5 km buffer. An inverse association for vanadium in the 5 km buffer was not retained in the 3.5 km buffer. Effect estimates were also increased for formaldehyde and acetaldehyde (factor 3) and similarly strengthened in the 3.5 km buffer but were weaker than the effect estimates for the correlated aromatic solvents benzene, toluene, ethyl-benzene, xylenes and 1,3-butadiene (factor 1). For substances loading onto factors 2 or 4, point estimates were close to 1.0 and 95% CIs were wide. Among pollutants not loading on a factor, trichloroethylene and copper slightly increased risks in the 5 km but not in the 3.5 km buffer.

We examined pollutants with the strongest associations with autistic disorder loading on factor 1, or loading on different factors, or not loading on any factor (5 km buffer) in 2- and 3-toxics models (eTable 6). The association with 1,3-butadiene disappeared while the estimated effect strengthened for meta-para-xylene in the 2-pollutant model including both pollutants. Adding lead to the model weakened estimates for both lead and meta-para-xylene, and the association became null for butadiene. In models combining the 3 substances with the strongest associations from factors 1 and 3 and not loading on any factor, respectively, resulted in weakened estimates for meta-para-xylene and lead, while estimates changed minimally for formaldehyde and trichloroethylene (eTable 6).

Stratifying by impairment in expressive language, we estimated stronger associations for autistic disorder with “less impaired” expressive language for benzene, 1,3-butadiene, perchloroethylene, formaldehyde, acetaldehyde, and copper, while effect estimate sizes for lead and other aromatic solvents were similar in both groups (Table 3). In contrast with the full sample, PAH exposures in the “less impaired” group increased autistic disorder risk by almost 50%, although confidence intervals were wide.

Models stratified by offspring sex resulted in similar estimates for most pollutants, except lead and PAHs (eTable 7). Positive associations were seen for lead only in boys, and for PAHs only in girls, but this was based on a small number of female cases.

Discussion

Our population-based findings suggest that in utero exposure to several correlated air pollutants, (including 1,3-butadiene, lead, benzene, toluene, ethyl-benzene, and xylenes, formaldehyde, and chlorinated solvents) increases risks for developing autistic disorder. Using the expressive-language phenotype as a measure of severity, several substances were more strongly associated with increased risk in less-impaired autistic disorder, while some were associated with both phenotypes (lead, aromatic solvents). While these differences might be due to chance and random variation, they could also suggest that certain groups of air toxics may affect more or less severe phenotypes of autistic disorder, possibly indicating an opportunity for further investigation of biological mechanisms underlying autism etiology. Due to the high correlations among pollutants in ambient air, we cannot disentangle effects of single substances. Most toxics associated with autistic disorder loaded on 2 factors, one representing urban road traffic and the other, industrial-emission sources. It is possible that certain mixtures generated by road traffic and industry in combination are associated with the observed autistic disorder risks.

Several pollutants for which we found the strongest associations with autistic disorder are generated by road traffic. This finding corroborates earlier studies reporting increased autism risks in relation to markers of road traffic, i.e., land use regression-based and monitored nitrogen exposures, [6,7] diesel exhaust, [10] and distance to major roadways. [8] Markers of traffic exposure that increase autistic disorder risk in our current study are 1,3-butadiene (not examined previously) and benzene, toluene, ethyl-benzene, and xylenes, which were not related to autism spectrum disorder risk in the earlier Bay Area study. [11] Differences among studies may in part be due to different exposure assessment methods. For example, air monitoring may capture exposure to highly volatile substances such as butadiene, benzene, toluene, ethyl-benzene, and xylenes better than the modeled exposures, especially for homes located in closer proximity to an air monitoring station, while modeling may smooth exposure surfaces more strongly across larger areas. We found stronger associations within the smaller buffer size, supporting the notion that exposure misclassification increases with distance from the monitoring station.

Chlorinated solvents have previously been suggested as risk factors for autism spectrum disorder, [9,11] in line with our findings, indicating increased risks related to the chlorinated solvents perchloroethylene and trichloroethylene. These toxics are generated in dry cleaning and other industrial stationary cleaning or degreasing operations. Parental occupation in dry cleaning using perchloroethylene was reported to increase offspring's risk for schizophrenia,[25] and study results for perinatal exposure to perchloroethylene-contaminated water suggested increased risks for neuropsychological disorders.[26] Perinatal exposure to perchloroethylene caused "autistic-like" behaviors, in male but not female mice.[27] We did not see such sex differences.

Lead, with aircraft as the dominant source in Los Angeles, [28] was associated with autistic disorder and correlated with other pollutants loading on factor 1. Our findings for lead are supported by the recent smaller autism spectrum disorder study among offspring of the Nurses' Health Study, showing increased risks related to lead using the EPA hazardous air

pollution model; a sex difference for several metals together was reported in that study but not for lead alone. [10] Our data suggested increased autistic disorder risks related to lead, particularly for boys. Another metal that was related to small increases in autistic disorder risks in our Los Angeles study was copper, which was also moderately correlated with road-traffic-related substances loading on factor 1, but correlated minimally with lead. Copper is used in vehicle brakes, thus it may also be an indicator for road-traffic exposures.[29]

Other toxics we found related to autistic disorder were formaldehyde and acetaldehyde (highly correlated in our data), which may result from industrial sources and from road-traffic emissions. High levels of formaldehyde (a volatile organic compound which is known to be neurotoxic) and acetaldehyde were reported in potential "hot spots" in truck terminals.[30] While formaldehyde may have stronger effects in children than adults, data on neurodevelopment is largely lacking. Similarly, while developmental toxicity from ambient acetaldehyde is suspected,[31] little is known about neurodevelopmental effects.

The increased risks we saw for PAHs in girls only and among those with "less impaired" language abilities might be a chance finding but should be investigated further. Associations between PAHs and autism spectrum disorder were not reported in earlier studies, [9,11] but some studies suggested adverse behavior in children subsequent to prenatal exposure to PAHs. [32,33]

A number of the substances found to be strongly associated with autistic disorder – including benzene, lead, and chlorinated solvents – have exhibited neurodevelopmental toxicity in experimental and human studies. Lead is an established neurodevelopmental toxicant, with neurodevelopmental effects even at trace levels.[34] Maternal benzene exposure increased risks for spina bifida[35] and was associated with reductions in a mental development index.[36] Possible mechanisms of neurodevelopmental toxicity for toluene, based on studies of abusive use, include suppressed immune functions[37] and oxidative-stress mechanisms,[38] as well as morphological [39] and functional brain receptor interferences that during brain development may lead to neurobehavioral disturbances.[40] Thus, several of the pollutants we found to be related to autistic disorder plausibly interfere with the developing nervous system in utero.

We computed 2- and 3-pollutant models that included toxics with the strongest associations with autistic disorder loading on factor 1 (butadiene, meta-para-xylene, lead); in the model including these 3 toxics, the estimates for the latter 2 toxics were weakened and the effect estimate for butadiene became null. Including in one model pollutants loading on different factors or not loading on any factor, the estimate for butadiene was weakened, while there was little change for formaldehyde and trichloroethylene. Including meta-para-xylene as representative from factor 1 with formaldehyde and trichloroethylene weakened only the estimate for meta-para-xylene. However, our ability to disentangle associations with single pollutants is severely limited due to the inherent correlation structure of pollutants in ambient air. Structurally or functionally related toxicants may affect similar biological processes, pathways or outcomes. Substances may also be acting as indicators for other unmeasured toxics or criteria pollutants. In the Los Angeles air basin, we showed previously moderate correlation between some air toxics including benzene and criteria pollutants. [41]

While associations between criteria air pollutants and autism have been found in prior studies, [6,7] it is unknown whether any of the criteria pollutants are causally related to autism or act as proxies for air toxics from the same sources. Current epidemiological/statistical methods are considered inadequate for assessing the health risks of multiple co-pollutants. [42] It is also possible that mixtures of ambient air pollutants, rather than single pollutants, are related to autistic disorder, due to possible synergistic effects. This needs to be further examined in mechanistic studies aimed at underlying biological pathways related to neurodevelopment.

Several effect sizes we observed are relatively large compared with those reported for birth outcomes and air pollution. [43] They are also larger than our previous findings for criteria pollutants and autism, [7] but similar to those recently reported for hazardous air pollutants and autism.[10] In contrast to the studies using criteria pollutants, we examined agents suspected to have neurodevelopmental toxicity, while criteria pollutants are possibly just indicators correlated with (or proxies for) sources of such toxicants. Estimates based on criteria pollutants would be expected to be affected more strongly by non-differential exposure misclassification.

Our study has several limitations. Although we used measured pollutant concentrations assessed by month of pregnancy, non-differential exposure misclassification is likely. Nevertheless our exposure assessment is based on measurement data related to exposure occurring during the actual months of pregnancy in close proximity of the mother's residence. While autistic-disorder diagnosis rates increased over time in our study period, most pollutants decreased; thus it is unlikely that systematic bias would explain our findings. Our findings are likely driven in part by spatial patterns, and thus neighborhood socioeconomic status may be a concern. While autism diagnoses were reported to vary spatially in California related to socioeconomic status,[44] air pollution concentrations did not differ by maternal education (<high school vs. ≥high school) in our study, in line with previous findings.[45] No spatial neighborhood-level factor is known to cause autism, and so there is no good candidate for a confounder. Unaccounted diagnostic differences among regional centers may be another limitation. Stratifying by the catchment areas of the three largest regional centers indicated increased risks predominantly in two of the three larger centers; thus we cannot exclude likely non-differential diagnostic biases due to differences in practices in the study area.

While we controlled for a range of potential confounders with detailed information from birth certificates, and conducted extensive sensitivity analyses, residual confounding due to unmeasured factors is always possible. The largest change between the unadjusted and adjusted risk estimates resulted from the socioeconomic status-related variables and maternal age. Confounding by criteria pollutants is also possible. However, the 7%–12% increase in risk per IQR we previously estimated for two criteria pollutants in our study area [7] suggests that confounding due to these pollutants would not explain our current findings. Moreover, criteria pollutants would need to be causally related to autism, rather than being proxies for toxics from common sources, in order to operate as confounders. Co-pollutant confounding by measured or by unmeasured substances is possible and cannot be resolved by currently available methods. [42] Associations between maternal smoking and

autism are thus far inconclusive, [4647] but our lack of information on maternal smoking is a weakness. However, our previous population-based study in Los Angeles found that only about 5% of women smoked during pregnancy, with lower rates among Hispanic women [48] in the early 2000s.[24]

Strengths include the large number of autistic-disorder cases diagnosed according to strict criteria using the Diagnostic and Statistical Manual of Mental Disorders-IV, provided in the California Department of Developmental Services data base, and previously validated.[5] Specificity is high;[19] however, we may be missing autistic disorder-cases, as only about 80% of cases are captured in the Department of Developmental Services data-base.[49] As our study was record-linkage-based only, non-participation bias due to non-response of participants is not an issue.

In conclusion, mechanisms underlying effects of toxic air pollutants on autism risk are insufficiently understood and should be examined further. The correlation patterns for many air pollutants limit the ability to disentangle potential effects for specific substances. Focusing on different phenotypes might help to elucidate underlying biological mechanisms. Our study provides population-based evidence of increased risks for autism in children, subsequent to in utero exposure to traffic- and industry-related ambient air toxics, including aromatic solvents, butadiene, lead and chlorinated solvents, based for the first time on detailed prenatal monitoring data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was sponsored by the National Institute of Environmental Health Sciences R21ES022389 and the California Center for Population Research, UCLA, supported by infrastructure grant R24HD041022 from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

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Table 1

Characteristics of the Population for Autistic Disorder Cases and Non-cases in 5 km Distance to Four Governmental Air Monitoring Stations, Los Angeles County, Birth Years 1995–2006.

	Cases (n = 768) No. (%)	Non-Cases (n = 147,954) No. (%)
Mother's race/ethnicity		
Non-Hispanic White	123 (16)	17,508 (12)
Hispanic White	499 (65)	103,588 (70)
African American/Black	48 (6)	9,875 (7)
Asian	93 (12)	16,163 (11)
Other/not specified	4 (0.5)	615 (0.4)
Missing	1 (0.1)	205 (0.1)
Mother's age (years)		
≤ 18	35 (5)	11,737 (8)
19–25	186 (24)	52,138 (35)
26–30	226 (29)	38,907 (26)
31–35	185 (24)	28,948 (20)
> 35	136 (18)	16,224 (11)
Source of payment for prenatal care		
Public (Medi-Cal)	391 (51)	92,196 (62)
Private	355 (46)	51,721 (35)
Other	18 (2)	3,540 (2)
Missing	4 (0.5)	497 (0.3)
Parity		
Primapara	300 (39)	54,302 (37)
Second	267 (35)	44,723 (30)
Third	116 (15)	27,159 (18)
More	85 (11)	21,722 (15)
Missing	0 (0)	48 (0)
Maternal education		
Less than high school	251 (33)	68,337 (46)
High school	199 (26)	37,720 (25)
More than high school	315 (41)	40,636 (27)
Missing	3 (0.4)	1,261 (0.9)
Born in the US		
Yes	308 (40)	53,605 (36)
No	460 (60)	94,059 (64)
Missing	0 (0.0)	290 (0.2)
Child sex		
Male	624 (81)	75,401 (51)
Female	144 (19)	72,552 (49)
Missing	0 (0)	1 (0)

Percents may not add to 100% due to rounding.

Table 2

Adjusted Odds Ratios for Pregnancy Exposure to Air Toxics[a] in 5 km and 3.5 km Buffers and Autistic Disorder in Children by Age 6 Years, Birth Years 1995–2006, Los Angeles County.

		5km				3.5 km				
Air Toxic	**IQR**	**No. Cases**	**Total No.**	**OR[b]**	**OR[c]**	**(95% CI)[d]**	**No. Cases**	**Total No.**	**OR[b]**	**OR[c]**	**(95% CI)[d]**
Factor 1											
Benzene	0.78 ppbV	651	126,402	1.69	1.46	(1.12–1.89)	326	60,229	1.93	1.58	(1.10–2.27)
Perchloroethylene	0.24 ppbV	619	117,290	1.77	1.40	(1.09–1.80)	312	55,977	2.08	1.61	(1.14–2.26)
1,3-Butadiene	0.28 ppbV	651	126,402	1.75	1.59	(1.18–2.15)	326	60,229	1.98	1.70	(1.12–2.57)
Toluene	1.68 ppbV	631	120,870	1.62	1.37	(1.12–1.67)	320	57,954	1.71	1.42	(1.08–1.88)
Ortho-Xylene	0.28 ppbV	619	120,059	1.61	1.42	(1.19–1.70)	314	57,512	1.80	1.54	(1.20–1.97)
Meta/para-Xylene	0.88 ppbV	641	120,714	1.70	1.51	(1.26–1.82)	318	57,572	1.86	1.60	(1.24–2.07)
Ethyl Benzene	0.19 ppbV	615	120,154	1.60	1.48	(1.25–1.75)	308	57,403	1.80	1.64	(1.29–2.08)
Methylene Chloride~	0.54 ppbV	641	121,972	1.17	1.08	(0.93–1.26)	319	57,985	1.01	0.96	(0.77–1.20)
PAH	0.79 ppbV	557	108,505	1.15	1.03	(0.84–1.26)	268	49,993	1.23	1.05	(0.79–1.39)
Lead	13.6 ng/m3	348	78,373	1.35	1.49	(1.23–1.81)	178	36,719	1.36	1.65	(1.22–2.23)
Vanadium	6.58 ng/m3	348	78,373	0.69	0.67	(0.54–0.83)	178	36,719	0.86	0.85	(0.64–1.13)
Factor 2											
Chromium	1.74 ng/m3	348	78,373	1.02	1.01	(0.97–1.06)	178	36,719	0.99	1.00	(0.94–1.06)
Manganese	5.62 ng/m3	348	78,373	1.03	1.03	(0.98–1.07)	178	36,719	1.00	1.01	(0.96–1.07)
Nickel	1.82 ng/m3	348	78,373	0.97	0.97	(0.89–1.05)	178	36,719	0.96	0.99	(0.89–1.10)
Selenium	0.59 ng/m3	348	78,373	1.04	1.05	(0.95–1.16)	178	36,719	0.99	1.05	(0.92–1.20)
Factor 3											
Acetaldehyde	0.50 ppbV	641	121,793	1.33	1.20	(1.07–1.34)	317	57,361	1.50	1.34	(1.15–1.56)
Formaldehyde	1.93 ppbV	641	121,793	1.37	1.34	(1.17–1.52)	317	57,361	1.42	1.41	(1.17–1.71)
Factor 4											
Ortho-dichlorobenz.	0.02 ppbV	558	103,869	1.07	1.04	(0.96–1.14)	286	49,657	1.04	1.01	(0.90–1.14)
Para-dichlorobenzene	0.02 ppbV	552	103,533	0.94	0.96	(0.91–1.01)	283	49,445	0.95	0.97	(0.90–1.05)
Not loading											
Chloroform	0.01 ppbV	636	122,121	1.19	1.06	(0.95–1.17)	321	58,302	1.26	1.09	(0.95–1.25)
Trichloroethylene	0.14 ppbV	624	118,781	1.06	1.14	(1.03–1.27)	314	56,657	0.92	1.06	(0.90–1.25)

		5km					3.5 km				
Air Toxic	**IQR**	**No. Cases**	**Total No.**	**OR[b]**	**OR[c]**	**(95% CI)[d]**	**No. Cases**	**Total No.**	**OR[b]**	**OR[c]**	**(95% CI)[d]**
Copper	22.8 ng/m3	348/78,373		1.08	1.09	(1.02–1.16)	178/36,719		1.04	1.05	(0.94–1.18)
Hexavalent-chromium	0.10 ng/m3	282/72,962		1.05	0.97	(0.86–1.09)	135/34,131		1.09	1.00	(0.86–1.16)
Molybdenum	0.82 ng/m3	348/78,373		0.97	0.91	(0.69–1.19)	178/36,719		0.96	0.92	(0.63–1.34)

[a] Entire pregnancy average. Numbers refer to “n” used in fully adjusted regression models.

[b] Adjusted for birth year.

[c] Adjusted for: birth year, maternal race/ethnicity, maternal age and education, type of insurance, place of birth mother (US vs. non US), child sex, parity (primapara, 2, 3 or more births).

[d] based on multivariable adjusted models.

PAH: Includes sum of average concentrations of six hydrocarbons: benzo[a]pyrene, benzo[b]flouranthene, benzo[ghi]perylene, benzo[k]flouranthene, dibenz[a, h]anthracene, and indeno[1, 2, 3-c,d]pyren.

Table 3

Adjusted Odds Ratios for Pregnancy Exposure to Air Toxics[a] and Diagnosis of Autistic Disorder by Expressive Language Skills at Age 5 Years, Los Angeles County.

	IQR	Impaired expressive language				Less impaired expressive language			
Air Toxic		**No. Cases**	**Total No.**	**OR[b]**	**(95% CI)**	**No. Cases**	**Total No.**	**OR[b]**	**(95% CI)**
Factor 1									
Benzene	0.78 ppbV	218/125,969		1.32	(0.87–1.99)	132/125,883		1.89	(1.08–3.31)
Perchloroethylene	0.24 ppbV	204/116,875		1.11	(0.74–1.67)	126/116,797		2.25	(1.35–3.77)
1,3-Butadiene	0.28 ppbV	218/125,969		1.36	(0.85–2.18)	132/125,883		2.25	(1.18–4.28)
Toluene	1.68 ppbV	209/120,448		1.21	(0.88–1.66)	126/120,365		1.48	(0.95–2.31)
Ortho-Xylene	0.28 ppbV	199/119,639		1.39	(1.03–1.87)	128/119,568		1.55	(1.05–2.28)
Meta/para-Xylene	0.88 ppbV	214/120,287		1.43	(1.07–1.91)	130/120,203		1.68	(1.13–2.48)
Ethyl Benzene	0.19 ppbV	200/119,739		1.46	(1.10–1.93)	124/119,663		1.47	(1.00–2.16)
Methylene Chloride~	0.54 ppbV	214/121,545		1.29	(0.98–1.71)	129/121,460		0.95	(0.65–1.37)
PAHs	0.79 ppbV	240/108,188		1.02	(0.75–1.37)	138/108,086		1.48	(0.95–2.31)
Lead	13.6 ng/m3	173/78,198		1.58	(1.19–2.08)	80/78,105		1.64	(1.05–2.58)
Vanadium	6.58 ng/m3	173/78,198		0.74	(0.55–0.98)	80/78,105		0.61	(0.39–0.97)
Factor 2									
Chromium	1.74 ng/m3	173/78,198		1.03	(0.98–1.09)	80/78,105		0.99	(0.91–1.08)
Manganese	5.62 ng/m3	173/78,198		1.04	(0.98–1.10)	80/78,105		1.00	(0.93–1.09)
Nickel	1.82 ng/m3	173/78,198		1.02	(0.92–1.13)	80/78,105		0.92	(0.78–1.10)
Selenium	0.59 ng/m3	173/78,198		1.08	(0.95–1.24)	80/78,105		0.98	(0.79–1.21)
Factor 3									
Acetaldehyde	0.50 ppbV	206/121,358		1.03	(0.85–1.25)	127/121,279		1.56	(1.23–1.97)
Formaldehyde	1.93 ppbV	206/121,358		1.19	(0.87–1.62)	127/121,279		1.89	(1.29–2.76)
Factor 4									
Ortho-dichlorobenz.	0.02 ppbV	174/103,485		1.08	(0.95–1.21)	116/103,427		0.90	(0.76–1.07)
Para-dichlorobenzene	0.02 ppbV	173/103,154		0.96	(0.89–1.04)	113/103,094		0.86	(0.75–0.97)
Not loading									
Chloroform	0.01 ppbV	211/121,696		0.92	(0.75–1.12)	127/121,612		1.09	(0.86–1.37)
Trichloroethylene	0.14 ppbV	205/118,362		1.19	(1.02–1.39)	127/118,284		0.99	(0.77–1.28)

Air Toxic	IQR	Impaired expressive language				Less impaired expressive language			
		No. Cases	Total No.	OR[b]	(95% CI)	No. Cases	Total No.	OR[b]	(95% CI)
Copper	22.8 ng/m3	173/78,198		1.01	(0.90–1.14)	80/78,105		1.18	(1.03–1.36)
Hexavalent-chromium	0.10 ng/m3	143/72,823		0.84	(0.61–1.16)	58/72,738		0.96	(0.74–1.26)
Molybdenum	0.82 ng/m3	173/78,198		1.24	(0.85–1.80)	80/78,105		0.76	(0.44–1.31)

[a] Entire pregnancy average. Numbers refer to “n” used in fully adjusted regression models.

[b] Adjusted for: birth year, maternal race/ethnicity, maternal age and education, type of insurance, place of birth mother (US vs. non US), child sex, parity (primapara, 2, 3 or more births).

PAH: Includes sum of average concentrations of six hydrocarbons: benzo[a]pyrene, benzo[b]flouranthene, benzo[ghi]perylene, benzo[k]flouranthene, dibenz[a, h]anthracene, and indeno[1, 2, 3-c,d]pyren.