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In utero exposure to near-roadway air pollution and autism spectrum disorder in children

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Data Statement:

KPSC Institutional Review Board approved this study, with waiver of informed consent with the condition that raw data remains confidential and would not be shared. Thus, due to the sensitive nature of this data, the data is not available to be shared.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

Importance: Previous studies have reported associations between *in utero* exposure to regional air pollution and autism spectrum disorders (ASD). *In utero* exposure to components of near-roadway air pollution (NRAP) has been linked to adverse neurodevelopment in animal models, but few studies have investigated NRAP association with ASD risk.

Objective: To identify ASD risk associated with *in utero* exposure to NRAP in a large, representative birth cohort.

Design, Setting, and Participants: This retrospective pregnancy cohort study included 314,391 mother-child pairs of singletons born between 2001–2014 at Kaiser Permanente Southern California (KPSC) hospitals. Maternal and child data were extracted from KPSC electronic medical records. Children were followed until: clinical diagnosis of ASD, non-KPSC membership, death, or December 31, 2019, whichever came first. Exposure to the complex NRAP mixture during pregnancy was assessed using line-source dispersion models to estimate fresh vehicle emissions from freeway and non-freeway sources at maternal addresses during pregnancy. Vehicular traffic load exposure was characterized using advanced telematic models combining traditional traffic counts and travel-demand models with cell phone and vehicle GPS data. Cox proportional-hazard models estimated hazard ratios (HR) of ASD associated with near-roadway traffic load and dispersion-modeled NRAP during pregnancy, adjusted for covariates. Non-freeway NRAP was analyzed using quintile distribution due to nonlinear associations with ASD.

Exposures: Average NRAP and traffic load exposure during pregnancy at maternal residential addresses.

Main Outcomes: Clinical diagnosis of ASD.

Results: A total of 6,291 children (5,114 boys, 1,177 girls) were diagnosed with ASD. The risk of ASD was associated with pregnancy-average exposure to total NRAP [HR(95% CI): 1.03(1.00,1.05) per 5 ppb increase in dispersion-modeled NOx] and to non-freeway NRAP [HR(95% CI) comparing the highest to the lowest quintile: 1.19(1.11, 1.27)]. Total NRAP had a stronger association in boys than in girls, but the association with non-freeway NRAP did not differ by sex. The association of freeway NRAP with ASD risk was not statistically significant. Non-freeway traffic load exposure demonstrated associations with ASD consistent with those of NRAP and ASD.

Conclusions: *In utero* exposure to near-roadway air pollution, particularly from non-freeway sources, may increase ASD risk in children.

Keywords

near roadway air pollution; NOx; autism spectrum disorders; in utero exposures; sex differences

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome characterized by impaired communication, social behavior, and sensory processing[1]. ASD etiology is likely multifactorial, including genetic, perinatal and environmental influences [2–4]. One emerging area of ASD etiologic research concerns *in utero* air pollution exposure.

Several studies have demonstrated associations between ASD and *in utero* regional air pollution exposures, especially particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) [5–8], but also particulate matter ≤ 10 μm (PM_{10})[8], ozone (O_3)[5, 9], and nitrogen dioxide (NO_2)[10] [11]. Although biological mechanisms underlying air pollution exposure and ASD risk remain unclear, some studies have demonstrated stronger relationships between $PM_{2.5}$ and ASD diagnosis in boys than in girls[12, 13] and in males in mouse studies of $PM_{2.5}$ and ultrafine particles (UFP)[6, 14].

Despite evidence that regional air pollution affects child neurodevelopment, fewer studies have investigated associations between *in utero* exposure to near-roadway air pollution (NRAP) and ASD diagnosis. Some epidemiological studies have examined associations with air pollution from vehicular sources, and effects have not been consistent [5, 13, 15–18]. These have often mixed effects of NRAP with those of primary traffic-related pollution at larger spatial scale. Elemental carbon, nitrogen dioxide (NO_2) and oxides of nitrogen (NOx) using land use regression models, for example, are sometimes used interchangeably as markers for pollution with vehicular sources and as surrogates for the near-roadway mixture. Models of residential exposure to these pollutants generally will not estimate well concentrations of the dynamic mixture of pollutants in fresh tailpipe exhaust, because the estimates include the near-roadway plus the urban background concentrations. The urban background pollutant mixtures can be chemically and physically very different than fresh tailpipe mixture [19–21], which declines nearly to background levels within 300m of the roadway[22]. NRAP is better estimated from roadway dispersion models that capture the steep near-roadway gradient in pollutants, often incorporating measures of traffic volume, vehicle emissions, and meteorological data [23, 24]. Limited research has found ASD associations with NRAP exposure, based on proximity to major vehicular corridors[25] and dispersion models of exposure with steep gradients from nearby roadways[11].

The purpose of this study is to examine the association of *in utero* residential NRAP exposure with risk of ASD in children and potential sexual dimorphism of these relationships. Some studies of other health outcomes found different associations with exposure to NRAP from traffic on freeways, where heavy duty vehicles powered by diesel fuel are common, and with exposure to NRAP from arterial and local streets, which in the USA are in general almost exclusively vehicles powered by gasoline[24–29].

Therefore, we have distinguished freeway from nonfreeway NRAP. As a secondary analysis we examined associations of residential traffic load with risk of ASD to see if results were consistent.

Materials and Methods

Study Population

This population-based retrospective birth cohort study included mother-child pairs of singleton deliveries at Kaiser Permanente Southern California (KPSC) hospitals between January 1, 2001 and December 31, 2014. KPSC is a large integrated healthcare system currently with over 4.5 million members across Southern California, which is approximately 20% of the entire population of the region (eFigure 1). KPSC membership is diverse and similar in socioeconomic characteristics to the region's census demographics[30]. Maternal sociodemographic, pregnancy health information, and residential address history were extracted from KPSC's integrated electronic medical records (EMR) system. Children were followed from birth through EMR until: clinical diagnosis of ASD, no longer a KPSC health plan member, death, or December 31, 2019, whichever came first. Maternal addresses during pregnancy were geocoded using ArcGIS [31]. Derivation and description of study sample is shown in eFigure 2 and accompanying Supplemental Material. The final analysis dataset included 314,391 mother-child pairs. This study received approval from the KPSC and University of Southern California Institutional Review Boards, with waiver of individual subject consent.

ASD

ASD diagnosis was established based on corresponding International Classification of Diseases codes on at least two occasions in the EMR, as described previously and in Supplemental Material, an approach previously shown to have positive predictive value of 88%[12, 32–34].

NRAP exposure assessment

The exposure assessment approach is designed to characterize the population's pregnancy-average exposure to fresh emissions from local traffic, rather than from transported primary traffic-related air pollution. The California line-source dispersion model (CALINE4) was applied to estimate monthly average concentrations of NOx from local vehicle emissions at residential addresses[35]. In this application, the model provides point estimates, rather than grid average estimates, of concentration at the geometric center of each residential parcel, which helps distinguish the spatial gradients in the near-road environment. Changes of subject locations during pregnancy were accounted for by time-weighting their exposures. Numerous observation studies indicate the components of traffic-related air pollution are a complex mixture of highly correlated gases and particles[36, 37]. Fresh vehicle NOx emissions were selected as a surrogate for this traffic mixture because NOx is ubiquitous in NRAP mixtures and the vehicle emission factor model employed for this study, CARB's EMFAC2017, is more accurate for NOx than PM emissions. It is not possible to distinguish the effects of these highly correlated markers of the near-roadway mixture, which is referred to as NRAP for brevity. The CALINE4-modeled NRAP declines nearly to background within 300 meters from roadways, with the steepest gradients within 75m of the source. Therefore, the estimate, expressed in ppb of NOx, was just the incremental NRAP contribution to the background NOx concentrations.

Estimates at maternal address were further categorized as contributions of “freeway NRAP” for emission from freeways and highways and “non-freeway NRAP” for emission from arterials, collectors, and local roads. Total NRAP estimates were the sum of these estimates. Vehicle emission factors were calculated annually for each roadway link based on the Streetlytics’ volumes and speeds, and heavy-duty truck portion of volume, providing more accurate and complete data for moderate and smaller roads than traditional traffic data sources[38]. Wind speeds and directions were obtained from NOAA/NCEP’s Real-Time Mesoscale Analysis model, a high-spatial (5×5 km) and temporal (1-hour) resolution analysis/assimilation system for near-surface weather conditions[39].

Traffic Load Data

Residential traffic load during pregnancy was assigned as an additional near-road traffic exposure metric that does not depend on meteorology or vehicle emission factors. Traffic load was defined as vehicle kilometers travelled per day within 150-and 300-meter circular buffers around each residential address. This indirect measure of exposure incorporates proximity to roadways and traffic volume. The distances from residences to the nearest freeways, highways, and other roads were computed using GIS tools to assess proximity. Additional description of traffic load is in the Supplemental Material.

Covariates

Covariates were selected *a priori* based on their known association with ASD in prior studies[32, 40] and included maternal age, parity, self-reported education and race/ethnicity, smoking behavior in pregnancy, comorbidity history (≥=1 diagnosis of heart, lung, kidney, liver disease, or cancer). Further adjustments were made for maternal pre-pregnancy diabetes mellitus and obesity (BMI ≥ 30kg/m^2), as both were shown to be risk factors for ASD in a subset of our study cohort[32]. Exploratory analyses demonstrated that average NRAP NOx levels decreased over the study years, as would be expected based on California’s emission control policies[41] (eFigure 3). There were known temporal trends of increasing ASD prevalence over the same period[12], so models adjusted for birth year as a potential confounder. Birth year was modelled both as a linear and non-linear relationship, and the non-linear model was chosen based on Akaike Information Criterion (AIC). Cox proportional hazard models with a penalized spline on the birth year term were utilized. Additional adjustment was made for confounding by season of conception and KPSC birth medical center, to control for potential geographic variation in ASD rates. The thirteen medical centers ranged in location from San Diego in the south to Panorama City in the north and from West Los Angeles to Ontario, Fontana, and Riverside in the east. The distance between nearest medical centers ranges from 10 to 111 km. Further adjustment for income was based on Census tract-level household income at child’s first birthday.

We have previously reported associations of ASD with particulate matter < 2.5 microns in aerodynamic diameter ($PM_{2.5}$) in this cohort[12]. Therefore, we estimated $PM_{2.5}$ exposure to assess confounding of ASD associations with NRAP. $PM_{2.5}$ exposure assignments were derived from the Di et al (2019) gridded model, described in Rahman et al (2021)[42].

Statistical analyses

Associations of *in utero* NRAP exposure and of roadway traffic load with risk of ASD were examined using Cox regression models in which the time variable was follow-up from one year of age. Associations were quantified using hazard ratios (HRs) with 95% confidence intervals (95% CI). Linearity of associations between total, freeway, and non-freeway NRAP estimates and risk of ASD was examined using general additive Cox models with a smoothing spline. No significant deviations from linearity were found for total and freeway NRAP. However, there was significant non-linear association with non-freeway NRAP ($p=0.001$). Therefore, analyses were conducted treating freeway and total NRAP as continuous variables with linear associations. Non-freeway NRAP was categorized based on quintiles of CALINE4-modeled non-freeway NOx. Similar analytical approaches were applied for traffic load. The quintiles for non-freeway NRAP were Quintile 1: ≤0.89 ppb CALINE NOx, Quintile 2: 0.89–1.66 ppb, Quintile 3: 1.66–2.51 ppb, Quintile 4: 2.51–3.80 ppb, and Quintile 5: >3.80 ppb for full quintile analyses, and Quintiles 1–4: ≤3.80 ppb CALINE NOx and Quintile 5: >3.80 ppb in dichotomous NRAP models. Traffic load quintiles were defined as Quintile 1: ≤0.76 vehicle-1000km/day, Quintile 2: 0.76–1.42 vehicle-1000km/day, Quintile 3: 1.42–2.90 vehicle-1000km/day, Quintile 4: 2.90–5.99 vehicle-1000km/day, and Quintile 5: 5.99–139.0 vehicle-1000km/day for 150m buffer models, and Quintile 1: ≤4.64 vehicle-1000km/day, Quintile 2: 4.64–9.0 vehicle-1000km/day, Quintile 3: 9.0–15.2 vehicle-1000km/day, Quintile 4: 15.2–26.0 vehicle-1000km/day, and Quintile 5: 26.0–290.0 vehicle-1000km/day for 300m buffer models.

In all models, birth year, season of conception, KPSC medical centers, maternal age, parity, self-reported education and race/ethnicity, tract-level household income at child's first birthday, history of comorbidity, smoking in pregnancy, pre-pregnancy obesity status and diabetes status, and child's sex were considered as covariates. To assess potential sexual dimorphism, we tested for interactions of exposure with child's sex and presented sex-stratified results. Since average pregnancy exposure to regional $PM_{2.5}$ has been associated with increased ASD risk and the risk was larger in boys [12, 43, 44], we assessed whether the NRAP association with ASD risk was independent of the pregnancy-average $PM_{2.5}$ exposure in the sex-stratified models.

Statistical significance was set at $p<0.05$. All statistical analyses were performed in R (version 3.6).

Results

Participant demographics are displayed in Table 1. Over the course of follow-up (median boys: 9.0 years; median girls: 9.1 years), 6,267 children (2.0%) were diagnosed with ASD; boys were >4 times more likely to be diagnosed than girls [boys: 5,114; girls: 1,177]. Children with ASD were more likely to have older, nulliparous mothers with maternal comorbidities, pre-pregnancy diabetes, and pre-pregnancy obesity than children without ASD. Greater proportions of children with ASD had mothers reporting Asian/Pacific Island and non-Hispanic Black ethnicity and college or higher educational qualifications.

Levels of NRAP expressed as CALINE4 NOx decreased every year over the study period from each source (eFigure 3). Median estimated pregnancy NOx exposure (based on maternal residence) was 4.6 ppb (IQR=2.5–7.5 ppb) for total NRAP, 2.0 ppb (IQR=0.8–4.0 ppb) for freeway NRAP, and 2.1 ppb (IQR=1.1–3.4 ppb) for non-freeway NRAP. Total, freeway, and non-freeway NRAP exposure levels were all significantly higher (all $p<0.005$) for children with ASD diagnoses than for children without ASD.

Total NRAP exposure was associated with child's ASD (HR of 1.03, 95% CI (1.00, 1.05) per 5 ppb increase in CALINE4 NOx) and was almost statistically significant ($p=0.06$; Table 2). Freeway NRAP was not associated with ASD risk [HR (95% CI): 1.01 (0.98, 1.04) per 5 ppb, $p=0.52$]. Non-freeway NRAP exposure during pregnancy in the highest exposure quintile was associated with child's ASD risk [HR (95% CI): CI 1.20 (1.08, 1.34)] compared to the lowest quintile of non-freeway NOx exposure. In contrast, children born to mothers living in areas with non-freeway NRAP in the 2nd −4th quintiles had no greater risk of ASD than children with the lowest quintile non-freeway NOx exposure. The HR (95% CI) of ASD risk comparing the highest quintile of non-freeway NRAP exposure to the combined lower 4 quintiles was 1.19 (1.11, 1.27).

Total NRAP association with ASD was modified by sex (interaction $p=0.01$); Table 3. After adjustment for $PM_{2.5}$, total *in utero* NRAP exposure remained associated with ASD diagnosis in boys [before adjustment for $PM_{2.5}$: HR (95% CI): 1.04 (1.01, 1.07); after adjustment: HR (95% CI): 1.04 (1.00, 1.06)]. (Correlations of regional $PM_{2.5}$ with freeway and non-freeway NRAP were 0.21 and 0.43, respectively). Total NRAP exposure was not associated with ASD in girls. Freeway NRAP was not associated with ASD in either boys or girls. The association between non-freeway NRAP and ASD did not differ between boys and girls. Exposure to the top quintile of non-freeway NRAP, compared with the lower 4 quintiles, was significantly associated with risk of ASD in both boys and girls and was robust to adjustment for $PM_{2.5}$ exposure [boys: HR (95% CI): 1.18 (1.09, 1.27), $p<0.001$; girls: HR (95% CI): 1.23 (1.04, 1.46), $p=0.01$].

The median (IQR) residential non-freeway traffic loads per day were 2.04 vehicle-1000km (0.87, 3.89)] within 150m and 11.78 (5.6, 22.50) within 300m; only 6% of the cohort members had freeway traffic load within 150-meters and 13% had no freeway traffic load within 300 meters. Thus, analysis was conducted for nonfreeway traffic load only. Within a 150m buffer, ASD diagnosis was associated with in utero traffic load exposure in the top 20% (Quintile 5: 5.99–139.0 vehicle-1000km/day) compared to those in the lower four exposure quintiles [HR: 1.14 (1.05, 1.24)]. In a 300m buffer, those living in the third [HR: 1.10 (1.01, 1.20); $p=0.03$], fourth [HR: 1.10 (1.01, 1.20); $p=0.03$], and fifth [HR: 1.13 (1.05, 1.26); $p<0.01$] non-freeway traffic load exposure quintiles had higher risk of ASD diagnosis than those living in the lowest quintile (Table 4). No significant sex interactions were found for non-freeway traffic load (eTable 1).

Discussion:

Data from this large birth cohort from Southern California suggest that the complex mixture of pollutants comprising NRAP has effects that are independent of regional $PM_{2.5}$, for which

there is emerging evidence of a causal relationship with ASD[8]. Other novel findings of this study include strong ASD associations with dispersion-modeled NRAP from non-freeway sources. The results from secondary analyses of traffic load associations with ASD, to assess consistency of the two approaches to NRAP, were supportive of the dispersion-modeled results; ASD was associated with near-roadway non-freeway traffic load.

Pollutants in the NRAP mixture that might cause ASD include ultrafine particles (UFP) and associated high particle number concentrations with steep spatial gradients from on-road vehicular sources[22]. UFP are found in blood after inhalation[45]. Exposure has been linked to increased inflammation and pro-inflammatory cytokines[46–49]. Higher levels of oxidative stress and inflammation have been reported in people with ASD[50]. Animal studies have found that *in utero* exposure to UFP can cause neurodevelopmental damage and behaviors suggestive of ASD[51]. Thus, our findings are biologically plausible. However, NRAP is a complex mixture of many chemicals, in addition to UFP. Other studies have shown that offspring of rats exposed to traffic emissions near vehicular tunnels had delayed growth and impaired social behavior[52], and neurodevelopmental dysfunction[53].

A previous California study found association of ASD diagnoses with *in utero* CALINE4 dispersion-modeled exposure to total NRAP, which was specific to the highest quartile of exposure [11]. Some other studies have examined associations of ASD with dispersion-modeled NO_2 exposure or dispersion models in combination with land use regression to estimate NO_2 or NOx and results have not been consistent [13, 17, 54]. However, as implemented, these models did not distinguish the near-roadway component of these pollutants from the contribution from primary traffic pollution at larger spatial scales and in some cases oxides of nitrogen from other sources beside traffic. The CALINE4 modeling approach estimated exclusively exposure to the near-roadway mixture, rather than a combination of NRAP, transported primary traffic pollution and secondary regional contributions to NO_2 and NOx.

Because ASD primarily affects boys, sexually dimorphic effects may provide clues to reasons for this difference and to potential avenues for prevention. Studies of UFP found male sex-specific effects on neuropathological and behavioral phenotypes found in ASD in mice[55], and in a few human studies larger regional $PM_{2.5}$ associations with ASD have been observed in boys than in girls, including in a subset of this cohort[12]. In the current study, total *in utero* NRAP exposure was more strongly associated with ASD diagnosis in boys, and larger effects of freeway NRAP were observed for boys than girls. However, non-freeway NRAP had similar associations with ASD in boys and girls. To our knowledge, this is the first study to examine effects of NRAP from different roadway types on ASD; further investigation of sexually dimorphic effects is needed.

The vehicular fleet on non-freeway roads in Southern California is almost exclusively fueled with gasoline, and the diesel-fueled contribution to NRAP comes from freeways [24]. Therefore, the observed associations of ASD with dispersion-modeled NRAP are not plausibly produced by diesel exhaust. Gasoline exhaust effects are little studied, and an important implication of our results is that gasoline exhaust merits further toxicological investigation. Prior studies from Southern California have also reported stronger non-

freeway NRAP associations with BMI[26, 27] and other outcomes[56]. Thus, an important implication of our results is that gasoline exhaust merits further toxicological investigation.

Possible reasons for the absence of freeway dispersion-modeled NRAP associations with ASD are the steep spatial gradient of the NRAP mixture and the typically shorter distance of residences from non-freeway roadways compared with freeways. Differences in the pollutant mixture near fast moving freeway vehicles compared with stop-and-go traffic and cold starts more common on secondary roadways may also explain these differences in effect estimates. Brake dust and metals produced in stop-and-go traffic typical of non-freeway roads are highly toxic in cellular systems[57]. Residential distribution around freeways in Southern California may differ from other places; thus, our results may not be generalizable to other places. The absence of dispersion-modeled freeway NRAP effects should be interpreted with caution because a relatively small proportion of participants lived within 300m of a freeway. In contrast, virtually all subject's residences were located within 300m of an arterial, collector, or local road. Rapid dispersion and changes in the particle size distribution and chemical composition occur within this 300m zone that transforms the fresh emissions to more typical urban mixtures[58]. Studies have identified associations of other outcomes with freeway NRAP[24, 29].

Strengths and limitations

A large, diverse cohort provided longitudinal health and residential data for mother-child pairs across Southern California and relevant confounders, available in the EMR. The KPSC cohort is representative of the study population, and therefore, results can be generalized to Southern California. The results may not be generalizable to other cities and countries, for example to European cities where the passenger vehicle fleet has a much larger proportion of diesel-fueled vehicles. While information about individual vehicle type was not available in traffic load measurements, our use of novel telematic traffic data, linking traffic count, vehicle GIS, travel demand model, and cell phone information, provided more accurate and complete information for moderate and smaller roads. The generally consistent associations of ASD with little-studied dispersion-modeled NRAP and traffic load from non-freeway roads strengthens the inference that the NRAP mixture can have adverse effects on child neurodevelopment. The study did not consider sensitive exposure windows during pregnancy. However, the exposure estimates were monthly aggregates and pregnancy trimester estimates were highly correlated with the pregnancy-average estimates (R=0.8–0.9 for freeway, non-freeway, and total dispersion-modeled NRAP). Therefore, the use of average exposures across the nine months of pregnancy are appropriate.

Conclusion

In utero exposure to NRAP from non-freeway roadways was associated with increased risk of ASD diagnosis in this large, representative retrospective birth cohort study. NRAP effects on ASD and gasoline-fueled emissions characteristic of non-freeway roads merit further toxicological study. Sexual dimorphism of total NRAP effects also warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Cohort characteristics and comparison between children without and with ASD*

	Overall (n= 314,391)	No ASD (n= 308,124)	ASD (n= 6,267)
Child, N (%)			
Male	161,800 (51.2%)	156,686 (50.6%)	5,114 (81.3%)
Female	154,317 (48.8%)	153,140 (49.4%)	1,177 (18.7%)
Maternal age (yrs), Mean(SD)	30.2 (5.8)	30.2 (5.8)	31.2 (5.7)
Parity, N (%)			
0	110,468 (35.1%)	107,850 (35.0%)	2,618 (41.8%)
1	103,291 (32.9%)	101,280 (32.9%)	2,011 (32.1%)
2 or more	82,893 (26.4%)	81,639 (26.5%)	1,254 (20.0%)
Unknown	17,739 (5.6%)	17,355 (5.6%)	384 (6.1%)
Maternal educational qualifications, N (%)			
High School or Less	110,126 (35.0%)	108,257 (35.1%)	1,869 (29.8%)
Some College	93,194 (29.6%)	91,181 (29.6%)	2,013 (32.1%)
College graduate or higher	108,063 (34.4%)	105,724 (34.3%)	2,339 (37.3%)
Unknown	3,008 (1.0%)	2,962 (1.0%)	46 (0.7%)
Census tract household annual income	60,690.3 (25,707.2)	60,696.3 (25,703.9)	60,394.5 (25,868.6)
Maternal ethnicity, N (%)			
Non-Hispanic white	79,938 (25.4%)	78,515 (25.5%)	1,423 (22.7%)
Non-Hispanic black	29,378 (9.3%)	28,747 (9.3%)	631 (10.1%)
Hispanic	158,897 (50.5%)	155,770 (50.6%)	3,127 (49.9%)
Other	6,450 (2.1%)	6,294 (2.0%)	156 (2.5%)
API	39,728 (12.6%)	38,798 (12.6%)	930 (14.8%)
Maternal comorbidity[1], N (%)			
Yes	46,066 (14.7%)	44,942 (14.6%)	1,124 (17.9%)
Smoking during pregnancy, N (%)			
No	199,814 (63.6%)	195,586 (63.5%)	4,228 (67.5%)
Yes	6,706 (2.1%)	6,576 (2.1%)	130 (2.1%)
Unknown	107,871 (34.3%)	105,962 (34.4%)	1,909 (30.5%)
Pre-pregnancy diabetes diagnosis, N (%),			

	Overall (n= 314,391)	**No ASD (n= 308,124)**	**ASD (n= 6,267)**
Yes	10,075 (3.2%)	9,747 (3.2%)	328 (5.2%)
Pre-pregnancy obesity (BMI ≥ 30kg/m2), N (%)			
No	147,472 (46.9%)	144,616 (46.9%)	2,856 (45.6%)
Yes	52,485 (16.7%)	51,122 (16.6%)	1,363 (21.7%)
Unknown	114,434 (36.4%)	112,386 (36.5%)	2,048 (32.7%)
Total NRAP (as ppb CALINE NOx), Median (IQR)	4.6 (2.5, 7.5)	4.5 (2.5, 7.5)	4.8 (2.7, 7.8)
Freeway NRAP (as ppb CALINE NOx), Median (IQR)	2.0 (0.8, 4.0)	2.0 (0.8, 4.0)	2.1 (0.9, 4.1)
Non-freeway NRAP (as ppb CALINE NOx), Median (IQR)	2.1 (1.1, 3.4)	2.1 (1.1, 3.4)	2.2 (1.2, 3.6)

*All tests for differences by ASD diagnosis were statistically significant (all p<0.005) except for household income (p=0.36)

1Maternal comorbidity was defined as ≥=1 diagnosis of heart, lung, kidney, liver disease, or cancer.

Table 2:

Associations between *in utero* total, freeway, and non-freeway NRAP exposure and risk of ASD in children[1]

	HR (95% CI)	P-value
Total NRAP[2]	1.03 (1.00, 1.05)	0.06
Freeway NRAP[2]	1.01 (0.98, 1.04)	0.52
Non-freeway NRAP[3]		<0.01[4]
Quintile 1 [Reference]	Reference	Reference
Quintile 2	1.02 (0.94, 1.12)	
Quintile 3	0.99 (0.91, 1.09)	
Quintile 4	1.02 (0.93, 1.13)	
Quintile 5	1.20 (1.08, 1.34)	
Non-freeway NRAP[5]		p<0.01
Quintiles 1–4 [Reference]	Reference	Reference
Quintile 5	1.19 (1.11, 1.27)	

[1]Adjusted for birth year, medical center, maternal age, maternal ethnicity, maternal education, parity, history of comorbidity, income at age one, season of conception, pre-pregnancy diabetes mellitus, pre-pregnancy obesity, smoking in pregnancy, and child's sex

[2]Near-roadway air pollution (NRAP) scaled per 5 ppb CALINE NOx

[3]Near-roadway air pollution (NRAP) reference category is Quintile 1 (≤0.89 ppb CALINE NOx); Quintile 2: 0.89–1.66 ppb; Quintile 3: 1.66–2.51 ppb; Quintile 4: 2.51–3.80 ppb; Quintile 5: >3.80 ppb

[4]4 degrees of freedom p-value for any association of non-freeway NRAP with ASD diagnosis

[5]Near-roadway air pollution (NRAP) reference category is Quintiles 1–4 (≤3.80 ppb CALINE NOx); Quintile 5 (>3.80 ppb)

Table 3:

Sex-stratified results for the associations between total, freeway, and non-freeway NRAP exposure during pregnancy and risk of ASD in children[1]

	Male		Female	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Total NRAP[2], (sex interaction p=0.01)				
Unadjusted for $PM_{2.5}$	1.04 (1.01, 1.07)	0.01	0.98 (0.91, 1.04)	0.46
Adjusted for $PM_{2.5}$	1.04 (1.00, 1.06)	0.02	0.98 (0.92, 1.05)	0.55
Freeway NRAP[2], (sex interaction p=0.08)				
Unadjusted for $PM_{2.5}$	1.02 (0.99, 1.05)	0.23	0.96 (0.89, 1.04)	0.37
Adjusted for $PM_{2.5}$	1.02 (0.98, 1.05)	0.29	0.96 (0.89, 1.05)	0.42
Non-freeway NRAP[3], (sex interaction p=0.37)				
Unadjusted for $PM_{2.5}$	1.18 (1.09, 1.28)	<0.001	1.22 (1.03, 1.44)	0.02
Adjusted for $PM_{2.5}$	1.18 (1.09, 1.27)	<0.001	1.23 (1.04, 1.46)	0.01

[1]Adjusted for birth year, medical center, maternal age, maternal ethnicity, maternal education, parity, history of comorbidity, income at age one, season of conception, pre-pregnancy diabetes mellitus, pre-pregnancy obesity, smoking in pregnancy, and child's sex

[2]Near-roadway air pollution (NRAP) scaled per 5 ppb CALINE NOx

[3]Reference category is Quintiles 1–4

Table 4:

Associations between non-freeway traffic load exposure during pregnancy and risk of ASD in children, by quintile[1]

	HR (95% CI)	P-value
Non-freeway 150m [2]		
Quintile 1 [Reference]	Reference	Reference
Quintile 2	1.00 (0.93, 1.10)	0.83
Quintile 3	1.02 (0.94, 1.11)	0.65
Quintile 4	1.08 (1.00, 1.18)	0.06
Quintile 5	1.14 (1.05, 1.24)	0.002
Non-freeway 300m [3]		
Quintile 1 [Reference]	Reference	Reference
Quintile 2	1.06 (0.98, 1.16)	0.16
Quintile 3	1.10 (1.01, 1.20)	0.03
Quintile 4	1.10 (1.01, 1.20)	0.03
Quintile 5	1.13 (1.05, 1.26)	<0.01

[1]Adjusted for birth year, medical center, maternal age, maternal ethnicity, maternal education, parity, history of comorbidity, income at age one, season of conception, pre-pregnancy diabetes mellitus, pre-pregnancy obesity, smoking in pregnancy, and child's sex

[2]Traffic load reference category is Quintile 1 (≤0.76 vehicle-1000km/day); Quintile 2: 0.76–1.42 vehicle-1000km/day; Quintile 3: 1.42–2.90 vehicle-1000km/day; Quintile 4: 2.90–5.99 vehicle-1000km/day; Quintile 5: 5.99–139.0 vehicle-1000km/day

[3]Traffic load reference category is Quintile 1 (≤4.64 vehicle-1000km/day); Quintile 2: 4.64–9.0 vehicle-1000km/day; Quintile 3: 9.0–15.2 vehicle-1000km/day; Quintile 4: 15.2–26.0 vehicle-1000km/day; Quintile 5: 26.0–290.0 vehicle-1000km/day